Drug Release Mechanisms from Controlled Release Systems

7. WEEK

Drug Release Mechanisms from Controlled Release Systems

There are several mechanism types in the controlled release systems:

1. Diffusion Controlled Release Systems,
2. Dissolution Controlled Release Systems,
3. Dissolution and Diffusion Controlled Release Systems

5. Water Penetration Controlled Release Systems,
6. Ion Exchange Controlled Release Systems,
7. Magnetically Controlled Release Systems,
8. Mechanically Controlled Release Systems

1.Diffusion Controlled Release Systems

Diffusion is described as the migration of a substance from a region of higher concentration to a region of lower concentration.

In diffusion controlled release systems, drugs are trapped in and released via diffusion through inert water-insoluble polymeric membranes (reservoir systems) or polymeric matrices (monolithic systems or matrix systems).

- **Matrix Systems:**

The drug is dispersed in an insoluble matrix of rigid nonswellable hydrophobic materials or swellable hydrophilic substances.

- **Reservoir Systems:**

These system are hollow containing an inner core of drug surrounded in a water insoluble polymer membrane.

❖In matrix type diffusion controlled drug delivery systems, the system is prepared by homogenously dispersing drug particle in rate controlling polymer matrix from either a lipophilic or a hydrophilic polymer.

❖The drug dispersion in the polymer matrix is accomplished by either,

- ✓ blending therapeutic dose of drug with polymer or highly viscous base polymer, followed by cross linking of polymer chains,
- ✓ mixing drug solid with rubbery polymer at elevated temperatures.

The drug release form matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in:

a) a lipophilic, nonswellable polymer matrix with a growing thickness of the drug depletion zone
b) a hydrophilic, swellable polymer matrix with a growing thickness of the drug-depleted gel layer, which resulted from drug release from the drug dispersing polymer matrix
c) an inert polymer matrix, excreted unchanged after release of the drug.

- The resultant drug-polymer dispersion is then molded or extruded to form a drug delivery device of various shapes and sizes designed for specific application.

- It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum.

The rate of the drug release from this system,

$$\frac{Q}{t^{1/2}} = (2AC_R Dp)^{1/2}$$

Where,

- $Q/t_{1/2}$: rate of release of drug
- A : initial drug loading dose in the polymer matrix
- C_R : drug solubility in polymer
- D_P : diffusivity of drug in polymer matrix

In matrix systems, the rate controlling steps are

- ❖ Diffusion of dissolved drug in matrix structure,
- ❖ Loading dose,
- ❖ Drug solubility in polymeric matrix structure.

- In the reservoir type diffusion controlled drug delivery systems, drug is totally or partially encapsulated within drug reservoir.
- Its drug release surface is covered by a rate-controlling polymeric membrane having a specific permeability.
- Drug reservoir may exist in solid, suspension or solution form.
- Polymeric membrane can be fabricated from a nonporous (homogenous or heterogeneous) polymeric material or a microporous (or semipermeable) membrane.
- The encapsulation of drug formulation inside the reservoir compartment is accomplished by injection molding, spray coating, capsulation, microencapsulation, or other techniques.
- For this concept, different shapes and sizes of drug delivery systems can be fabricated.

❖The rate of drug release defined by

$$\frac{Q}{t} = \frac{K_{m/r} K_{a/m} D_d D_m}{K_{m/r} D_m h_d + K_{a/m} D_d h_m} C_R$$

$K_{m/r}$ & $K_{a/m}$: Partition coefficient of the drug molecule from reservoir to rate controlling membrane & from membrane to aqueous layer, respectively.

D_d & D_m : Diffusion coefficient of rate controlling membrane and aqueous diffusion layer, respectively.

hm & hd : Thickness of rate controlling membrane and aqueous diffusion layer, respectively.

C_R : Drug concentration in the reservoir compartment.

In reservoir systems, the rate controlling steps are

- Polymeric content in the coating,
- Thickness of the polymer (membrane) coating,
- Partition coefficient of the drug,
- Diffusivity of the drug,
- Hardness of the system.

The diffusion controlled release systems possess many advantages such as

- the potential to obtain zero-order release kinetics with a constant drug source,
- the ease to control release rate by adjusting the physicochemical properties of polymeric carriers, and
- the low cost of the system.

However, this is not completely safe because of dose dumping from accidentally damaged systems, which may be toxic. In some cases, a surgical procedure may be necessary to remove the device. Obtaining perfect zero-order release kinetics and releasing high-molecular-weight drugs can also be challenging.

2.Dissolution Controlled Release Systems

In dissolution controlled release systems, drugs are coated with or encapsulated within slowly dissolving **polymeric membranes (reservoir systems)** or **matrices (monolithic systems),** respectively.

In monolithic systems, drug aggregates are distributed throughout the polymeric matrices. Dissolution of the drug aggregates and release of the dissolved drug result when the matrices dissolve. However, in reservoir systems, drugs are surrounded through a low soluble polymeric shell in which drugs are protected.

In dissolution controlled release systems, the solubility of the polymeric carriers is a key factor in controlling drug release. These systems are advantageous in that they have the potential to release high-molecular-weight drugs and do not need to be surgically removed.

However, they are also associated with drawbacks including potential toxicity resulting from dose dumping and/or dissolved polymeric materials and difficulty in obtaining perfect zero-order release profiles.

3.Dissolution and Diffusion Controlled Release Systems

In reality, controlled release systems will never be dependent on only dissolution or diffusion. In dissolution and diffusion combination systems, drugs are trapped in partly soluble polymeric membranes or matrices that will dissolve to create pores.

In this systems,

- Drug encased in a partially soluble membrane.
- Pores are created due to dissolution of parts of membrane.
- It permits entry of aqueous medium into core and drug dissolution.
- Diffusion of dissolved drug out of system.
- Ethylcellulose and PVP mixture dissolves in water, and create pores of insoluble ethylcellulose membrane.

The pores allow aqueous media to flow into the core of the system to drive the diffusion of encapsulated drugs. In general, either one mechanism (dissolution or diffusion) or a combination of both can occur during the release process. However, in some cases, one mechanism can be dominant over the other to allow easy mathematical description, such as dissolution rate-limited or diffusion controlled release.

In these systems, the rate controlling steps are

- ❖Diffusivity of drug,
- ❖Partition coefficient of drug,
- ❖Solubility of drug and polymers.

4. Chemically Controlled Release Systems (Erosion and Polymer–Drug Conjugate)

Drug release can be tailored in chemically controlled release systems by changing their chemical structure (such as degradation, group transfer, etc.). They can be divided into two types:

- ❖erosion controlled systems
- ❖polymer–drug conjugate controlled (pendant side chain) systems.

In **erosion controlled systems**, drugs are loaded in erodible polymeric matrices by dispersion and/or molecular interactions (hydrophobic, ionic, etc.) and can be released upon degradation of the matrices and dissolution and diffusion of the drug molecules, as illustrated in the below figure.

In these systems, the diffusion and dissolution of drugs and the erosion of polymeric matrices can control the release profiles. It can be difficult to predict the release kinetics and the eroded polymers may be toxic. However, these systems can release high-molecular-weight drugs, do not require surgical removal, and, in some cases, can allow for zero-order release kinetics.

Erosion controlled release systems employing biodegradable injectable hydrogels for controlled release of chemical drugs or protein drugs such as doxorubicin, insulin, bovine serum albumin, and human growth hormone have been reported. Upon mixing, these drugs can ionically interact with the hydrogel precursor macromolecules. Hydrogels formed after the drug-loaded polymer solutions were injected into rats, and the drugs were released over time upon hydrogel degradation.

Release was controlled by the degradation of the polymeric carrier, and the diffusion of insulin and polymeric degraded products. The initial burst release was observed due to fast diffusion of insulin from the release system without ionic interaction with polymer molecules.

In **polymer–drug conjugate systems**, drugs are covalently linked to polymeric molecules via hydrolytically or enzymatically degradable (or exchangeable) spacers.

These systems can be used for distribution controlled release in which drugs are formulated in colloidal forms and are inactive and stable in circulation.

The environment of the desired target site regulates the mechanism of drug release. The covalent linkages between the drug and polymer are either cleaved via hydrolysis or enzymatic degradation to release and activate the drug.

For example, when such systems are used to deliver drug in the colon, bacteria present in the gastrointestinal tract will produce enzymes that break the covalent linkages.

Polymer–drug conjugate systems provide a way to improve drug efficacy and can be used to control the release of drugs, proteins, targeting moieties, and some imaging agents. They also present higher stability, water solubility, and prolonged half-life of the drug in addition to lower immunogenicity, lower antigenicity, and more specific targeting to tissues or cells.

5. Water Penetration Controlled Release Systems

In water penetration controlled release systems, drug release can be achieved by the penetration of water or body fluids into the systems. These systems can be divided into two types including

- ❖ swelling controlled systems
- ❖ osmotically controlled systems..

In **swelling controlled release systems**, drug aggregates are homogeneously dispersed into a dry swellable 3D polymeric network. When these systems are immersed in water or body fluid, the flow of water into the 3D polymeric network will hydrate the systems. Therefore, the aqueous solvent content within the system and the network mesh size increase, resulting in the dissolution and diffusion of drugs throughout the hydrated polymeric network.

The swelling property of the systems and dissolution and diffusion properties of drugs are key factors to control drug release.

In **osmotically controlled systems**, the osmotic pressure caused by the presence of an osmotic agent (e.g., PEG, PVA) within a semipermeable membrane reservoir, which is permeable to water but not to solutes (loaded drugs), regulates drug release.

There are two types of osmotically controlled release systems:

- Type A contains an osmotic core with drugs (OROS Technology),
- Type B contains a drug reservoir surrounded by an osmotic core (PUSH-PULL OROS Technology).

The release of drugs from osmotically controlled systems is governed by various factors such as

- solubility
- osmotic strength of osmotic agents,
- orifice size,
- water permeability of the semi-permeable membrane,
- surface area of the semi-permeable membrane,
- osmotic pressure difference across the semi-permeable membrane.

Osmotically controlled release systems provide many advantages including

- high drug-loading efficiency,
- release capacity,
- refillability,
- possibility to obtain zero-order release kinetics,
- independence from drug properties and environmental conditions.

However, these systems are

- usually expensive,
- require more extensive quality control,
- are not suitable for drugs with short half-life in aqueous solution,
- need to be surgically implanted into the body in some applications.

6. Ion-Exchange Controlled Release Systems

Ion-exchange controlled release systems generally use resins composed of water-insoluble polymers cross-linked with abundant ionizable functional groups in the polymer backbone.

There are two types of ion-exchange controlled release systems based on the ionic properties of the resin:

- ❖ cationic resin for release of anionic drugs,
- ❖ anionic resin for release of cationic drugs.

Ion-exchange controlled release systems can be used to release ionic drugs. These ionic drugs bind to the resins through electrostatic interactions and are released by exchanging with similarly charged ions in the release environment.

Release rate can be controlled by several factors including

- pH and ionic strength of the release environment,
- molecular weight and charge density of both resin and drugs,
- particle size and cross-linking density of resin.

- ❖ These systems can protect loaded drugs from enzymatic degradation by temporarily altering the substrate.
- ❖ The ion-exchange systems are useful for controlled release of ionic drugs due to their high loading capacity on the resin surface.

7. Magnetically Controlled Release Systems

- In this type controlled release mechanism, drug reservoir is a dispersion of active molecule in polymer matrix from which macromolecular drug can be delivered only at a relatively slow rate.
- This low rate of delivery can be improved by incorporating electromagnetically triggered vibration mechanism into polymeric device combined with a hemispherical design.

- Device is fabricated by positioning a tiny magnet ring in core of hemispherical drug dispersing polymer matrix.
- As the magnet is activated to vibrate by external electromagnetic field, drug molecules are delivered at much higher rate.
- The external surface is coated with drug impermeable polymer (ethylene vinyl acetate or silicon elastomer) except one cavity at the centre of the flat surfaces.

- This delivery used to deliver drugs at a low basal rate, by a simple diffusion process under non triggering condition.

- Another feature of these systems is the possible of target the system to the desired tissue by applying a magnetic field to the area of the body where it is desired to be transported after the preparation is applied to the patient.

8. Mechanically Controlled Release Systems

- In this type controlled release mechanism, drug reservoir is in solution form retained in a container equipped with mechanically activated pumping system.
- A measured dose of the drug formulation is reproducible delivered in to a body cavity.
- For example, the nose through the spray head upon manual activation of the drug delivery pumping system.

Insulin pumps are another mechanically controlled release system. The pump, which is about the size of a smart phone or deck of cards, is worn on the outside of your body and delivers insulin through a tube (catheter), connected to a thin cannula, placed into the layer of fat under your skin, typically around your stomach area.

The pump can be worn around your waist in a pump case or attached to a belt or bra, in a pocket, or on an armband. There are a variety of custom-made accessories available so you can carry your insulin pump with style.

The force that regulates the release of the active substance is the pressure difference, which can be caused by the osmotic effect or by direct mechanical action applied to the tank where the active substance is located.