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A COMPREHENSIVE REVIEW OF CONTROLLED DRUG RELEASE DELIVERY SYSTEMS: CURRENT STATUS AND FUTURE DIRECTIONS

K. Mary Swarnalatha[1*], V.T.Iswariya[1],Banoth Akash[2], Sneha Bhandari[2], Ramavath Shirisha[2], T.Ramarao[3]

[1-] Assistant Professor ,Department of Pharmaceutics, CMR College of Pharmacy ,Hyderabad, Telangana, India.
[2-] Department of Pharmaceutics, CMR College of Pharmacy, Hyderabad, Telangana, India
[3-] Principal &Professor Department of Pharmaceutics, CMR College of Pharmacy, Hyderabad,
Telangana, India
Email: iswariyapharma@gmail.com

ABSTRACT:

Controlled-release systems regulate drug plasma concentration after administration through pre determine patterns over a fixed period. The release rate should determine drug absorption and concentration. These formulations reduce daily dosing frequency. This article discusses ideal requirements, advantages, properties, and approaches for developing controlled-release formulations to improve drug delivery. Controlled drug delivery involves delivering drugs at a predetermined rate for a specified period, either locally or systemically. This method, utilizing drug-encapsulating devices, offers advantages over traditional methods, including tailored release rates, drug protection, and increased patient comfort. Controlled release drug delivery systems maintain a uniform plasma concentration within the therapeutic range, minimizing side effects and administration frequency. Oral sustained-release (SR) products optimize drug properties, reducing dosing frequency and ensuring maximum drug utility, reduced side effects, and quicker cure or control conditions. Technological advancements have revolutionized medication methods with controlled drug delivery systems, offering therapeutic benefits like multiple dosing and single doses. Oral controlled- release drug delivery provides continuous oral delivery of drugs at predictable kinetics for a predetermined period, targeting specific regions within the gastrointestinal tract for local or systemic action. This technique reduces drug administration frequency and maintains constant drug levels in the patient's bloodstream, increasing its therapeutic effectiveness.

Keywords: Controlled release, Dosing frequency, Drug concentration, Plasma concentration, zero order.

Introduction:

Controlled drug delivery systems offer benefits such as desired drug levels. However, they also face potential disadvantages such as toxicity, undesirable by-products, surgery, patient discomfort, and potential side effects.[1] Controlled-release systems are expensive compared to traditional pharmaceuticals, but ideal systems should be inert, biocompatible, strong, comfortable, safe, easy to administer, and easy to fabricate, aiming to maintain high drug levels over time.

The ideal polymer balances swelling, erosion, and dissolution processes. However, achieving high gel-state viscosity and maintaining a constant gel layer for linear drug release over prolonged periods remains a challenge due to various dynamic phases in polymer relaxation, disentanglement, and erosion.[2] Controlled release drug delivery systems maintain plasma concentration within the therapeutic range, minimizing side effects and administration frequency by providing uniform drug concentration to the absorption site.[3]

Sustained release systems aim to reduce dosing frequency or increase drug effectiveness by localizing at the action site, reducing the required dose, or providing uniform drug delivery. These systems provide medications over extended periods, while controlled release systems provide therapeutic control. Sustained release dosage forms are increasingly being studied for improved patient compliance and decreased adverse drug reactions. Research in this field has yielded numerous discoveries, with new and sophisticated controlled release and sustained release delivery systems constantly being developed and tested.[4] The introduction of orally administered once-daily products raises concerns about testing and clinical assessment. This presentation provides an overview of extended-release products, their theoretical base, typical formulation approaches, and current issues in the field.[5]

Historically, alkaline compounds or buffers have been used in solid oral formulations of acidic drugs to overcome dissolution rate-limited absorption. However, no strategy has been developed for a simple, compressible, monolithic, and controlled-release system with zero-order kinetics, primarily aimed at minimizing gastrointestinal tract and pH solubility dependency.

Controlled release dosage form:

The USP defines modified-release forms as those that use drug release characteristics to achieve therapeutic or convenience objectives not offered by conventional dosage forms. Extended-release (ER) dosage forms allow for a 2-fold reduction in dosing frequency or a significant increase in patient compliance or therapeutic performance. Most marketed monolithic oral ER dosage forms fall into two technologies: hydrophilic, hydrophobic, or inert matrix systems, and reservoir (coated) systems. These systems involve simple diffusion/erosion systems or osmotic systems, where the drug core is enclosed within a polymer membrane. [6,7]

Polymers used in control drug delivery system:

Polymers play a crucial role in drug delivery, serving as binders in tablets, viscosity and flow controlling agents in liquids, suspensions, and emulsions. They can also be used as film coatings to disguise drug taste, enhance stability, and modify release characteristics. Controlled drug delivery (CDD) involves combining a polymer with a drug or active agent to release the active agent in a predesigned manner, achieving more effective therapies and reducing under and overdosing.[8]

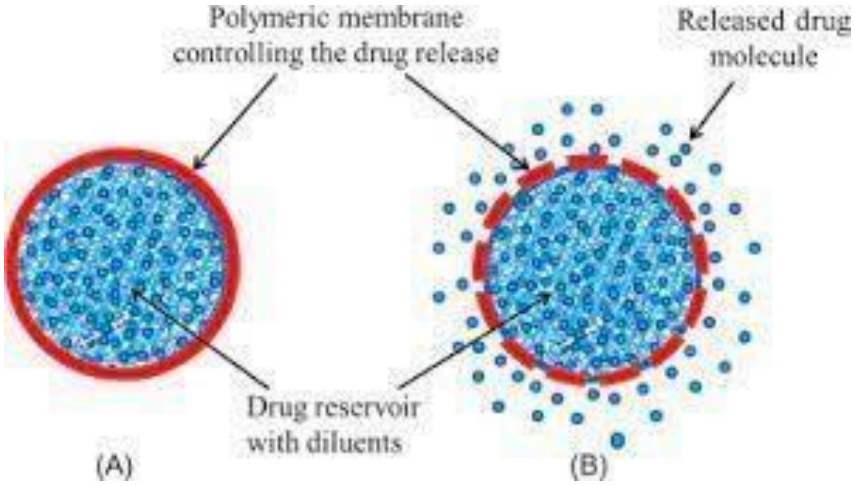

Fig 1: Polymer-controlled drug delivery.

Characteristics of drugs suitable for controlled release:

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the GI tract.
3. Administered in relatively small doses.
4. Possess a good margin of safety.

Advantages:

1. Reduced dose and frequency.
2. Reduce fluctuations.
3. Effect of less drug minimizes local and systemic side effects.
4. Minimize drug accumulation.
5. Reduce chronic drug activity.

Disadvantages:

1. Sustained release dosage forms (SRDS) has drawbacks such like increased costs and less flexibility in dosage adjustments.
2. Risk of dose dumping, reduced drug absorption, delayed action onset, and potential for first-pass clearance.
3. They also require more costly manufacturing processes and equipment and cannot be used for drugs absorbed at specific times in GIT.
4. Effective drug release in oral formulations is influenced by gastrointestinal resistance time and is designed for normal populations.
5. However, disease states and interpatient variability are not considered.
6. Enzymatic breakdown and product failure can make effective antidotes difficult to use. [9,10]

Types of controlled drug delivery systems:

Controlled drug delivery systems are broadly classified as follows:

1. Oral controlled release system
2. Targeted delivery system
3. Dental systems
4. Ocular systems
5. Transdermal systems
6. Vaginal and uterine systems
7. Injections and implants [11].

Factors affecting formulation.

There are two major factors. They are:

1. Biological factor
2. Physiochemical factor

1. Biological Factors:

Absorption: The rates, extent, and uniformity of absorption of the drug are important factors when considering its formulation into an extended-release system. The most critical in the case of oral administration is Kr<<.

Distribution: Drug distribution in the body is crucial for elimination kinetics. The apparent volume of distribution and the ratio of drug in tissue to plasma (T/P) concentration describe drug distribution characteristics. Drugs with a higher apparent volume of distribution decrease the elimination half--life, but the drug's elimination rate is limited by tissue binding sites. Larger distribution volumes concentrate more drugs in tissues compared to blood, limiting clearance mechanisms. The T/P ratio is used to estimate the drug amount in the body, based on the known amount in central and peripheral compartments.

Metabolism: Drug metabolism can either inactivate an active drug or convert an inactive drug to an active metabolite, making S.R/C. R. design difficult. Two areas related to metabolism are maintaining uniform blood levels and addressing variable blood levels through intestinal or tissue or first-pass effects. Fluctuating drug blood levels due to intestinal metabolism or first-pass hepatic metabolism are poor candidates for sustained/controlled release dosage forms. [12]

Side effects: Side effects of drugs are primarily caused by fluctuating plasma concentrations. Controlling concentration within the therapeutic range can minimize these effects. SR drug delivery is commonly used for local gastrointestinal side effects, incorporating controlled-release mechanisms.

Disease state: Disease state and crucial factors in determining a drug for SR, as seen in aspirin for rheumatoid arthritis and asthma attacks. Aspirin SR dosage can maintain therapeutic concentrations, alleviate morning stiffness, and align with oral SR delivery based on circadian rhythm.[13]

2. Physiological Factors:

a) Aqueous solubility
b) Partition coefficient
c) Drug pKa and ionization at physiological pH
d) Drug stability
e) Molecular weight and diffusivity
f) Protein binding
g) Dose size

a) Aqueous solubility: Drugs are typically weak acids or bases, making them difficult to incorporate into the SR mechanism. High solubility drugs dissolve quickly in water or fluid, leading to increased blood drug concentration. Solubility, particularly in physiological pH range, can also pose challenges. The biopharmaceutical classification systems estimate major factors affecting oral absorption. [14,15]

Parameters	**Preferred value**
Molecular weight/size	<1000 Daltons
Solubility	>0.1 mg/ml for pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

b) **Partition coefficient:** The partition coefficient is a measure of a drug's ability to penetrate biological membranes, affecting both permeation and diffusion. It is determined by the ratio of drug in an oil phase to its adjacent aqueous phase. Drugs with a high partition coefficient are oil-soluble and easily partition into membranes. The Hansch correlation is used to determine the relationship of partition coefficient. [15,16]

c) Drug pKa & ionization in physiological pH:

The Henderson-Hasselbalch equation and pH--partition hypothesis explain the impact of pH-pKa crosstalk on drug ionization, absorption, distribution, metabolism, excretion, and toxicity (ADMET). Despite its significant contributions to drug pharmacokinetics, pharmacodynamics, safety, and toxicity, its impact on ADMET has not been effectively linked to physiologically based pharmacokinetic modeling and simulation.

d) **Drug stability:** Drugs undergo acid/base hydrolysis and degradation when administered orally. Stable drugs can developed as slow-release dosage forms, while unstable ones undergo gut wall metabolism and are not suitable for SR systems. [17,18]

Methods using ion-exchange:

The system enables controlled drug release by absorbing an ionized drug on ion-exchange resin, coating them with a water-permeable polymer, and spray-drying them to produce the desired drug. The drug is released from the polymer-coated drug resin preparation by exchanging the charged ions in the GIT, with rate of diffusion controlled by resin properties and ionic environment.

Advantages: For those which highly susceptible to enzymatic since it offers protective by temporarily altering the substrate.

Limitations: The release rate is proportional to the conc. Ions present in the vicinity of the administration site.

Two types:

Cationic drugs: A cationic drug forms a complex with an anionic ion-exchange resin, allowing hydronium ion (H+) to penetrate the gastrointestinal tract, releasing the drug from the resin complex.

Anionic drugs: An anionic drug forms a complex with a cationic ion-exchange resin, activated by chloride ion (Cl-) in the gastrointestinal tract, releasing the drug from the resin complex. [19,20] .

Classification:

The mechanism used to obtain sustained and controlled release of drugs, these systems are classified as follows:

1. Diffusion- controlled systems:

The diffusion process involves drug molecules moving from higher concentration to lower concentration, as per Fick's law. Release rate of a drug depends on diffusion through the membrane barrier. [21,22]

- **a)** **Reservoir type:** Reservoir type delivery systems are produced. This ensures that the drug is slowly diffused out of the delivery vehicle. The rate-limiting step during the release process in these types of delivery systems is the partitioning of the drug molecules within the polymeric membrane.
- **b)** **Matrix** A controlled release matrix system delivers the drug locally or systemically at a predetermined rate for a specified period of time . The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels.

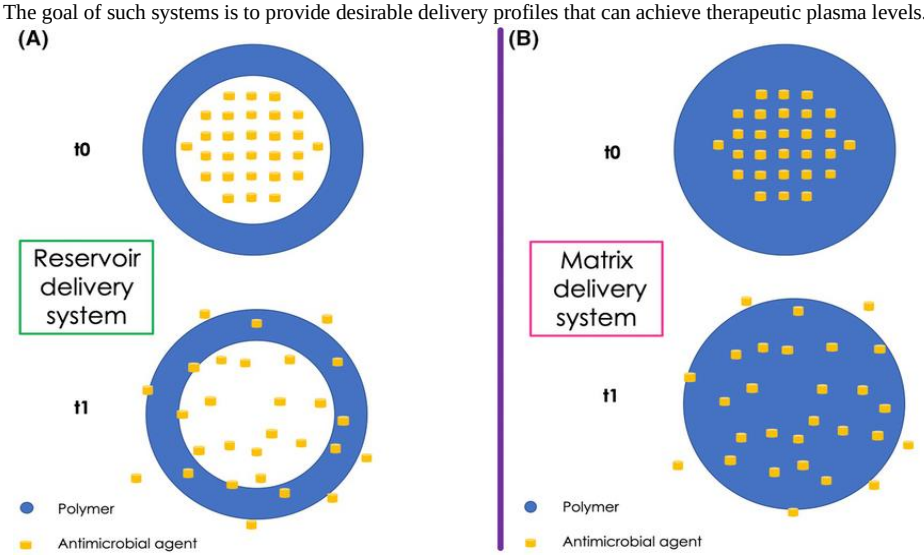

Fig 2: Schematic diagram of reservoir and matrix systems

2. Dissolution-controlled systems:

High aqueous solubilized drugs that face dissolution rate. Controlling dissolution can be achieved by slowing it down, incorporating it in an insoluble polymer, or coating it with polymeric materials. The rate-limiting step is diffusion across the aqueous boundary layer [23,24].

a) **Encapsulation dissolution- controlled systems:** The drug particles are coated or encapsulated by microencapsulation techniques with slowly dissolving materials like cellulose, polyethylene glycols, polymethacrylates, waxes, etc. The dissolution rate of the coating depends on its solubility and thickness of the coating.

b) **b)Matrix dissolution -controlled systems:**
Matrix dissolution systems are the most commonly used technique in controlled delivery system and involve the API being homogeneously distributed throughout a polymer matrix. As the polymer matrix dissolves (typically via an erosion-mediated process), drug molecules are released into the external environment.

3. Water penetration-controlled systems:

It rates control is obtained by the penetration of water into the system [25].

a) **Swelling-controlled systems:**

Swelling-controlled release systems absorb body fluids and swell, increasing solvent content and polymer mesh size, allowing drug diffusion through swollen networks [26].

b) **Osmotic controlled release systems:**

This system encapsulates an osmotic drug with an active drug within the biocompatible membrane. A gradient of osmotic pressure creates a continuous pumping of drug solutes out of the tablet, dispersed at a zero-order rate, independent of the system's environment [27,28]

All the osmotic drug delivery systems have a semi-permeable membrane that controls the flow of water and has an osmotic core. They consist of only one orifice, and the drug is released only in a solution form. Suitable only for water-soluble drugs. Drug release follows zero-order kinetics.

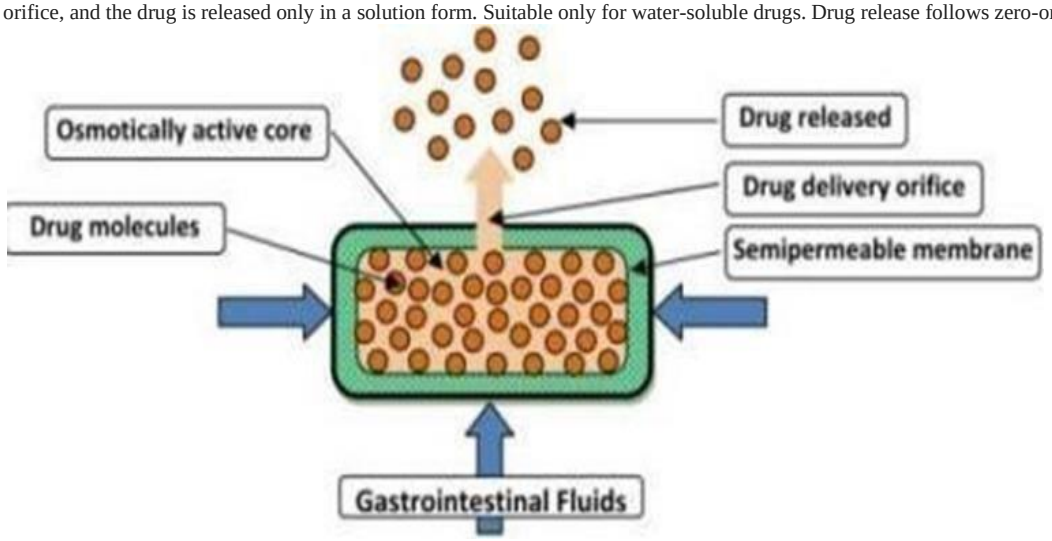

Fig 3: Schematic diagram of EOP osmotic system.

Applications:

Controlled release medications are beneficial for patients with chronic diseases such as diabetes, hypertension, asthma, and epilepsy, as well as neurological disorders like Alzheimer's and Parkinson's. They are also used in hormone therapy, chronic disease management, and pain management, providing sustained release of pain-relieving medications for improved control and reduced side effects. Controlled drug delivery systems (CDDS) are used in various fields, including cancer treatment, ophthalmology, neurological disorders, cardiovascular diseases, antibiotic therapy, hormone replacement therapy, transplantation medicine, and pediatric medicine. CDDS provide prolonged relief, reduce the need for frequent dosing, and minimize the risk of addiction. They target tumors, improve treatment efficacy, and minimize systemic side effects. CDDS are also used in ophthalmology for sustained drug release, neurological disorders like Parkinsons disease and epilepsy, and in antibiotic therapy for localized infections.[29]

Polymers

Polymers play a significant role in controlled drug delivery systems due to their versatility in modulating drug release rates, targeting specific tissues, and protecting drugs from degradation. Here are a few common types of polymers used in controlled release drug delivery:

1. **Biodegradable Polymers:** These polymers break down into harmless byproducts in the body over time, gradually releasing the drug. Examples include polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer poly (lactic-co-glycolic acid) (PLGA).
2. **Hydrogels:** are three-dimensional networks of hydrophilic polymers capable of absorbing and retaining large amounts of water. They can swell in response to changes in environmental conditions (e.g., pH, temperature) and release drugs accordingly. Examples include polyethylene glycol (PEG) and poly(N-isopropylacrylamide) (PNIPAM).
3. **Micelles:** are self-assembled colloidal structures formed by amphiphilic block copolymers in aqueous solutions. They can encapsulate hydrophobic drugs within their core and release them in a controlled manner. Examples include poly (ethylene oxide)-b-poly (propylene oxide) (PEO-PPO) copolymers.
4. While not strictly polymers, liposomes are composed of phospholipid bilayers and can encapsulate both hydrophilic and hydrophobic drugs. Surface modifications with polymers like PEG can prolong circulation time and enhance drug delivery efficiency.
5. **Dendrimers:** are highly branched polymers with well-defined structures. Dendrimers can encapsulate drugs within their interior or conjugate drugs to their surface, allowing for controlled release kinetics. Examples include polyamidoamine (PAMAM) dendrimers.
6. **Polymeric microspheres/nanoparticles** are solid or porous polymeric particles with drug molecules dispersed or encapsulated within them. They can be designed to release drugs through diffusion, degradation, or a combination of both. Examples include polylactide-co-glycolide (PLGA) microspheres and nanoparticles.
7. Natural polymers like chitosan, alginate, and hyaluronic acid have been extensively investigated for drug delivery applications due to their biocompatibility and biodegradability.

These polymers can be tailored in terms of molecular weight, composition, and structure to achieve specific release profiles, site-specific targeting, and reduced toxicity. Controlled-release drug delivery systems offer numerous advantages over conventional dosage forms, including improved patient compliance, reduced side effects, and enhanced therapeutic efficacy.

Conclusion:

Dosage forms combine drugs and excipients to enhance stability and taste. Conventional dosage forms struggle with fluctuating plasma drug levels, requiring high dosing frequency and patient compliance. Controlled drug delivery systems improve bioavailability, release, and maintain plasma levels with minimal side effects. These systems include dissolution, diffusion, water penetration, and chemically controlled delivery. Stimuli-responsive delivery systems are useful in disease conditions. Future drug delivery focuses on patient-specific therapy using microfluidic-based, 3D printed devices, and CRISPR cas9-based systems. Modern technologies, including targeted concepts, have revolutionized oral controlled delivery, offering advantages over conventional dosage forms. This optimizes drug properties, reduces dosing frequency, and maximizes drug utility through uniform plasma concentration, making it a popular and convenient delivery method.

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