Chapter

Fundamentals Applications of Controlled Release Drug Delivery

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Abstract

The advancement of pharmacology and pharmacokinetics highlighted the important role of drug release kinetics in the determination of therapeutic outcomes of treatments. The advent of modified release dosage forms marked a significant innovation. Technological progressions in coating methods gained momentum in the late 1800s, encompassing innovations like sugar and enteric coatings applied to pills and tablets. Subsequent advancements led to the refinement of enteric coatings for tablets, which eventually evolved into the incorporation of a secondary drug within the sugar coating layer. However, the initial patent for oral-sustained release formulations was awarded to Lipowski. His formulation comprised miniature-coated beads designed to achieve gradual and consistent drug release. This concept was subsequently refined by Blythe, leading to the introduction of the first commercially available sustained release product. Over the last three decades, the escalating complexities associated with bringing new drugs to market, coupled with the recognized merits of Controlled Release Drug Delivery Systems (CRDDS). Presently, oral controlled drug delivery systems have emerged as significant avenues, particularly for compounds characterized by high water solubility and abbreviated biological half-lives. Beyond oral administration, diverse routes such as transdermal, ocular, vaginal, and parenteral approaches are utilized for controlled release of various therapeutic agents.

Keywords: dose-activity relationship, sustained drug concentration, control drug delivery, drug release rate, transdermal drug delivery

1. Introduction

Controlled drug delivery systems offer various advantages such as regulating drug concentrations effectively, reducing the frequency of administrations, maximizing drug utilization, and enhancing patient adherence [1]. Besides that, these systems also display potential drawbacks including material toxicity or lack of biocompatibility, generation of undesirable degradation by-products, necessity for surgical procedures for system implantation or removal, likelihood of patient discomfort due to the delivery device [2], and the elevated cost associated with controlled-release systems relative to conventional pharmaceutical formulations [3]. The optimal drug delivery system should possess qualities of inertness, biocompatibility, mechanical robustness, patient comfort, high drug loading capacity, prevention of unintended release, ease

of administration and removal, and simplicity in fabrication and sterilization [4]. The primary objective of early controlled-release systems was to establish a drug delivery profile that would sustain elevated drug concentrations in the bloodstream across an extended duration. In conventional drug delivery approaches, blood drug levels exhibit a pattern characterized by post-administration escalation followed by a subsequent decline until the subsequent dose is administered. A fundamental principle of traditional drug administration is to maintain the blood concentration of the drug within a range bounded by an upper threshold, which could signify a toxic concentration, and a lower threshold below which the drug's efficacy diminishes [5].

2. Terminology or definition of control release dosage forms

According to the USP, modified-release (MR) dosage form is a formulation selected to achieve therapeutic or practical goals that surpass the capabilities of conventional dosage forms like solutions, ointments, or rapidly dissolving formulations, based on its tailored drug release attributes concerning temporal progression and/or spatial localization [6]. A category within the domain of modified-release (MR) dosage forms is represented by the extended-release (ER) dosage form [6]. This category is characterized by the capability to achieve a minimum reduction of twice in dosing frequency or substantial enhancements in patient adherence and therapeutic efficacy, in contrast to conventional dosage forms such as solutions or rapid drug-releasing formulations [7]. The nomenclature "controlled release (CR)," "prolonged release," "sustained or slow release (SR)," and "long-acting (LA)" have been interchangeably employed to denote the concept of "extended release." Controlled drug delivery pertains to a mechanism by which a specific drug is administered either locally or systemically at a predetermined and regulated rate over a defined duration [8].

A prolonged-release pharmaceutical formulation administers a therapeutic dose of a medication across an elongated time period [9].

Prolonged release or sustained release systems, designed solely to extend therapeutic drug concentrations within blood or tissues over an extended interval, do not fall under the categorization of controlled-release systems as per this delineation. They are discernible from rate-controlled drug delivery systems, which possess the capacity to accurately determine *in vivo* release rates and durations through straightforward *in vitro* assessments [10].

Controlled drug delivery pertains to the regulated administration of a drug at a predetermined rate over a specified timeframe. Controlled release exhibits a zero-order release profile, signifying consistent drug release over time regardless of concentration fluctuations. Sustained release dosage forms, on the other hand, encompass a specific drug delivery configuration where an initial drug dose is promptly released to achieve a rapid therapeutic response. Subsequently, a gradual release of the remaining maintenance dose ensues, ensuring a prolonged but non-constant therapeutic concentration. Sustained release conveys the gradual dispensation of a drug throughout a designated temporal interval. This characteristic may or may not entail controlled-release attributes [11].

In contrast, drug targeting can be conceptualized as a variant of controlled release due to its capacity to exert localized control over drug release within the physiological context [12].

3. Rationale

The fundamental principle behind a controlled-release drug delivery system is to enhance the drug's biopharmaceutical, pharmacokinetic, and pharmacodynamics attributes to optimize its efficacy. This optimization aims to minimize adverse effects while achieving disease management or cure in the swiftest feasible duration, utilizing the smallest feasible drug quantity, and selecting the most appropriate administration route. Immediate release drug delivery systems exhibit certain limitations, including the absence of dose maintenance, lack of controlled-release kinetics, and inability to precisely target specific sites within the body [13]. An ideal drug delivery system should ensure the drug's dispensation aligns with the body's requirements throughout a designated treatment period. This entails delivering the drug at a rate that corresponds to the body's needs while considering the specific duration of therapy [14].

4. Advantages of controlled-release dosage forms

4.1 Clinical advantages

- Reduces the frequency of drug administration
- Improvement in the compliance of a patient
- Minimizing fluctuation of drug level in the blood
- Decreasing drug utilization as compared with conventional therapy
- Diminished drug accumulation during chronic treatment
- Decrease in the toxicity of the drug whether local or systemic
- Stabilized patient's medical condition due to the achievement of uniform drug levels
- Enhanced bioavailability for specific drugs due to spatial regulation
- Cost-effectiveness for both healthcare provider and the patient (**Figures 1** and **2**)

4.2 Commercial/industrial advantages

- Demonstration of innovative and technological forefront
- Extension of product life cycle
- Establishment of product distinctiveness
- Broadening of market reach

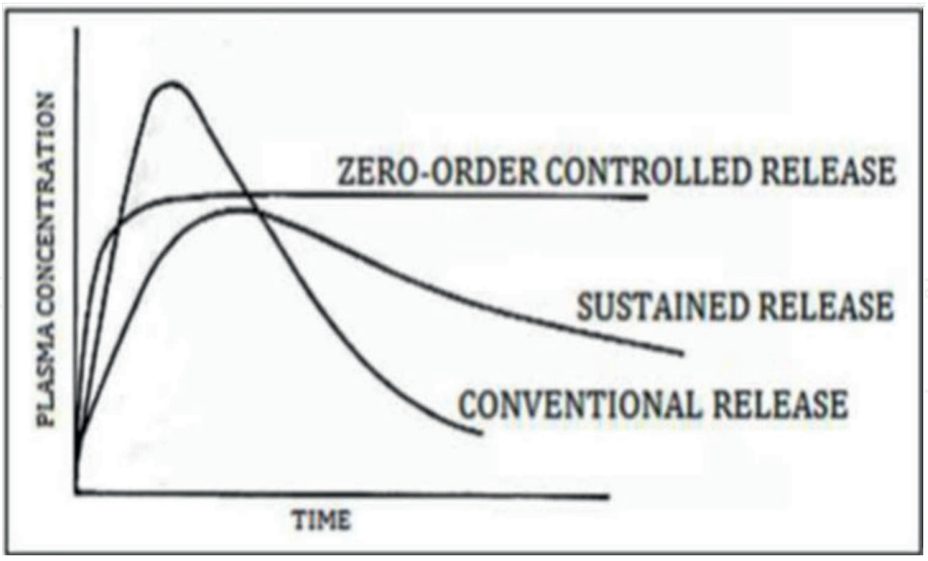

Figure 1.
Plasma drug concentration-time profile [15].

- Extension of Patent protection

4.3 Disadvantages of CRDDS

- Delayed initiation of drug effects
- Potential risk of dose release surge with inadequate formulation strategy

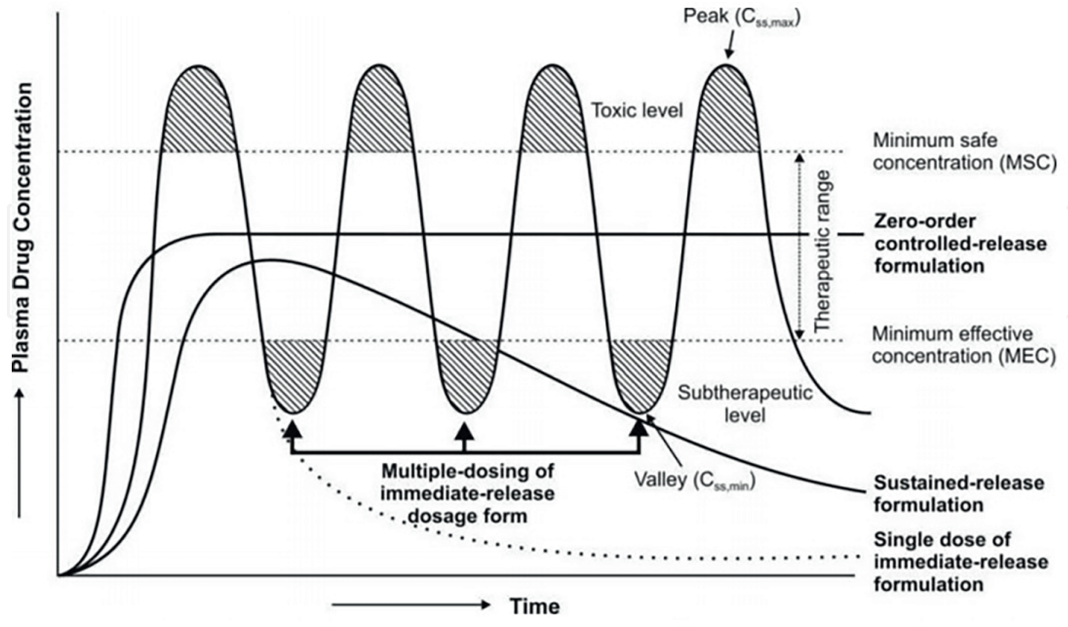

Figure 2.
A hypothetical plasma concentration-time profile from conventional multiple dosing and an ideal controlled delivery formulation [16].

- Elevated susceptibility to first-pass metabolism
- Augmented reliance on gastrointestinal residence duration of dosage form
- Possible challenge in precise dose adaptation in certain scenarios
- Elevated cost per individual dose compared to conventional formulations
- Not all drugs are amenable to extended-release formulation
- Drug selection of drug for the preparation of extended-release dosage form is the crucial step. Drugs having following characteristics are not suitable for extended-release formulations.

5. Designing controlled release per oral drug delivery systems: Biopharmaceutic and pharmacokinetic aspects

Controlled-release oral medication delivery systems are of paramount importance in enhancing the therapeutic effectiveness and ensuring patient adherence to pharmaceutical goods. The design of these systems must take into account important factors related to biopharmaceutics and pharmacokinetics, as these factors govern the processes of drug absorption, distribution, metabolism, and elimination in the human body [17].

5.1 Biological half-life (t ½)

The biological half-life, commonly known as the "half-life," is a pharmacokinetic variable that characterizes the duration required for the concentration of a medicine or chemical within the organism to diminish by 50%. The topic being discussed holds significant importance in the fields of pharmacology and medicine, as it plays a pivotal role in determining the duration of a drug's activity within the body and the frequency at which it needs be provided to sustain therapeutic levels. The shorter the half-life (t ½) of a drug, the greater the variations observed between the highest steady-state concentration and the minimum steady-state concentration upon repeated administration. Therefore, it is necessary to increase the frequency of administration of the medication product [18].

5.2 Minimum effective concentration (MEC)

The term "minimum effective concentration" (MEC) pertains to the lowest concentration of a chemical or treatment within the human body that is necessary to elicit a therapeutic response. Stated differently, the minimal concentration of a pharmaceutical substance that elicits the intended therapeutic effect is referred to as the minimum effective concentration. This notion holds significant importance within the fields of pharmacology and medicine, as it aids healthcare practitioners in ascertaining the suitable dosage and administration regimen for a certain prescription [19].

Beyond the minimum effective concentration (MEC), the medicine may fail to manifest its intended therapeutic efficacy, resulting in insufficient treatment. Conversely, concentrations over the minimum effective concentration (MEC) may lead to an elevated likelihood of unfavorable consequences, without necessarily yielding any supplementary therapeutic advantages. The objective is to sustain the concentration of the medicine within a therapeutic range, wherein the advantages surpass the potential drawbacks [20].

5.3 Dose size and extent of duration

As the period of treatment increases, there is a corresponding need for an increased total dose per unit delivery method. Therefore, there exists a constraint on the quantity of medication that may feasibly be included into such a system [21].

5.4 Relatively long $t_{1/2}$ or fluctuation desired at steady state

There exists a perspective among certain individuals that medications with a half-life of 12 h or longer do not require or provide any utility for either a sustained release (SR) or a controlled-release drug delivery system (CRDDS). This assertion is unfounded as there exist two scenarios in which a 12 or 24 CRDDS appears to be warranted:

1. A pharmaceutical compound with a half-life ranging from 12 to 72 h could potentially be developed for a controlled-release drug delivery system (CRDDS) that allows for administration every two to three days. The rate at which the blood level time curve decreases following the elimination of the medication from the body is contingent upon the drug's half-life (t ½). The natural variation between the maximum and minimum concentrations of Css can result in a rather significant impact, specifically by introducing a slow-release mechanism that prolongs the elimination process [22].

2. Certain drugs having a half-life (t1/2) ranging from 20 to 100 h, which are intended for extended administration, exhibit a preference for minimizing fluctuations between peak and trough concentrations under steady-state circumstances. States may prescribe medications either with the intention of attaining a specific treatment outcome or due to the limited breadth of the therapeutic range [23].

6. Required biopharmaceutical characteristics of the drug to meet CDDS criteria

6.1 Molecular weight

Convective transport enables the passage of small molecules across membrane holes. This phenomenon is relevant to both the liberation of drugs from the pharmaceutical formulation and their passage across a biological membrane. In the context of biological membranes, it has been observed that spherical molecules are often limited

to a molecular weight of 150, whereas chain-like compounds are limited to a molecular weight of 400 [24].

6.2 Solubility

In order for absorption mechanisms to occur, it is important that the drug is available in a solute form at the specific site of absorption. In the preformulation study, it is imperative to ascertain the drug's solubility across different pH levels. When the solubility of a substance is below 0.1 μg/ml in an acidic media, it is anticipated that there will be inconsistent and diminished bioavailability. When the solubility of a substance is below 0.01 μg/ml, it is probable that absorption and availability are mostly governed by limitations in dissolving [25]. Therefore, the underlying factor driving dissemination may be insufficient. Passive diffusion from the small intestine appears to facilitate effective absorption of medicines following oral administration, provided that the non-ionized form constitutes a minimum of 0.1 to 1% of the medication.

6.3 Apparent partition coefficient (APC)

In order for drugs to be absorbed through passive diffusion, it is necessary for them to possess a minimum apparent partition coefficient (APC). There exists a positive correlation between the apparent partition coefficient (APC) in an n-octanol/buffer system and the rate of drug flux over a membrane. The determination of the acid dissociation constant (APC) is necessary across the whole pH spectrum within the gastrointestinal (GI) tract. The application of the apparent partition coefficient (APC) is necessary for the evaluation of drug distribution between controlled-release drug delivery systems (CRDDS) and the biological fluid [26].

6.4 Absorption mechanism

In order for a drug to be considered a viable candidate for per oral controlled-release drug delivery systems (CRDDS), it is imperative that its absorption process occurs *via* diffusion across the entirety of the gastrointestinal (GI) tract. The term "diffusion" in this context pertains to the process of absorption, which occurs through two distinct pathways: partitioning into the lipid membrane (transcellular) or travelling through water-filled channels (paracellular). The occurrence of absorption from all segments of the gastrointestinal (GI) tract is of significant importance, and this process can be influenced by various factors such as the drug's pKa, the pH level in the specific segment, the binding of the drug to mucus, and the rate of blood flow. The absorption process exhibits a strong reliance on the hydrodynamics within the gastrointestinal lumen [27].

6.5 Pharmacokinetic and elimination half life (t ½)

Pharmaceutical substances characterized by a half-life of 8 h are considered highly compatible with controlled-release drug delivery systems (CRDDS). If the half-life (t ½) is shorter than 1 h, it is possible that the required dose size for a dosage form intended to last for 12 or 24 h may be excessively large. If the half-life (t ½) of a substance is significantly lengthy, the use of controlled-release drug delivery systems

(CRDDS) is generally unnecessary, unless the purpose is just to minimize fluctuations in steady-state blood concentrations [28].

6.6 Total clearance (CL)

Clearance (CL) is a pharmacokinetic parameter that quantifies the rate at which a drug is eliminated from the body by measuring the volume of distribution that is cleared of the drug over a specific period of time. The important parameter for evaluating the necessary dose rate for continuous release drug delivery systems and predicting the concentration in a steady state is the subject of discussion [29].

6.7 Terminal disposition rate constant (Ke or λz)

The terminal disposition rate constant, also known as the elimination rate constant, can be derived from the half-life (t ½) and is necessary for the prediction of a time-dependent blood level pattern [30].

6.8 Apparent volume of distribution (Vz)

The Vz is the theoretical volume that a pharmaceutical substance would occupy if it were dissolved at an equivalent concentration to that observed in the bloodstream. The proportionality constant that establishes the relationship between the quantity of a drug present in the body and the observed concentration in the bloodstream. Within the trio of CL, Vz, and t ½, it can be observed that the former two parameters function as independent variables, while the latter parameter serves as the dependent variable [31].

In order to forecast the concentration time profile, it is necessary to determine the volume of distribution (Vz) or clearance (CL).

6.9 Absolute bioavailability (F)

The absolute bioavailability refers to the proportion of a medicine that enters the systemic circulation following given by a route other than intravenous. In order for medications to be deemed appropriate for controlled-release drug delivery systems (CRDDS), it is desirable for the F value to exhibit a proximity to 100% [32].

6.10 Intrinsic absorption rate constant (Ka)

In order to ensure that the method of release is the rate-regulating step, it is normally necessary for the intrinsic absorption rate constant of the drug, when supplied orally in the form of a solution, to be significantly higher, typically by an order of magnitude, than the desired release rate constant of the drug from the dosage form [33].

6.11 Therapeutic concentration (Css)

The therapeutic concentrations encompass the desired or target steady-state peak concentrations (Css max), the desired or target steady-state minimum concentrations (Css min), and the mean steady-state concentration (Css avg). The distinction between CSS max and CSS min lies in the variability. The precision of the dosage form performance must be increased in order to achieve fewer desirable fluctuations. As the value of Css decreases, the magnitude of Vz decreases, resulting in an increase in the duration of t ½. Additionally, there is a corresponding increase in the magnitude

of F. A smaller quantity of medication is necessary for integration into a controlled-release drug delivery system (CRDDS) [34].

7. Methods for creating controlled-release formulations

1. Controlled-release dissolution
   - Encapsulation dissolution control
   - Seed or granule coated
   - Micro-encapsulation
   - Matrix dissolution control
2. Diffusion controlled release
   - Reservoir-type devices
   - Matrix-type devices
3. Diffusion and dissolution controlled systems
4. Ion exchange resins
5. Osmotically controlled release

8. Factors affecting the design and implementation of controlled-release systems

8.1 Physiological properties

8.1.1 Aqueous solubility's

The majority of active pharmaceutical moieties (APIs) exhibit weak acidic or basic properties, which can impact the solubility of these APIs in water. Designing controlled-release formulations for weak water-soluble medicines might be challenging. Drugs with high solubility in aqueous solutions exhibit an initial burst release, which is thereafter followed by a rapid increase in the concentration of the drug in the plasma. These particular pharmaceutical compounds exhibit favorable characteristics that make them suitable candidates for controlled-release drug delivery systems (CRDDS). The solubility of CRDDS is problematic due to its dependence on pH. BCS class-III and class-IV medicines are deemed unsuitable candidates for this particular sort of formulations [35].

8.1.2 Partition coefficient (P-value)

The p-value represents the proportion of the drug that partitions into the oil and aqueous phases, which is a statistically significant factor influencing the passive diffusion of the medication across the biological membrane. The medications exhibit

varying P values, which may not be conducive for controlled release (CR). Therefore, it is imperative that the drugs possess the ability to dissolve effectively in both aqueous and lipid phases [36].

8.1.3 Drug pKa

The pKa value is a critical determinant of the drug's ionization throughout the gastrointestinal tract at physiological pH. In general, medicines with high ionization are not considered suitable candidates for controlled-release drug delivery systems (CRDDS). The rate of absorption of unionized pharmaceuticals is significantly faster in comparison with ionized drugs while crossing biological membranes. The pKa range for an acidic medicine, whose ionization is pH-dependent, spans from 3.0 to 7.5. Conversely, the pKa range for a basic drug falls within the range of 7 to 11 [37].

8.1.4 Drug stability

Pharmaceutical substances that exhibit stability in acidic or basic environments, as well as resistance to enzymatic degradation and other gastric fluids, are considered favorable candidates for controlled-release drug delivery systems (CRDDS). If a medicine undergoes degradation in the stomach and small intestine, it is not considered ideal for controlled-release formulations due to the potential loss in bioavailability of the drug in question [38].

8.1.5 Molecular size and molecular weight

The molecular size and molecular weight are two critical variables that influence the diffusibility of molecules through a biological membrane. Molecules of a size below 400D exhibit a high degree of diffusibility, but those beyond 400D provide challenges in terms of drug diffusion [39].

8.1.6 Protein binding

The drug-protein combination functions as a reservoir inside the plasma, effectively retaining the drug. Pharmaceutical compounds exhibiting elevated levels of plasma protein binding are deemed unsuitable candidates for controlled-release drug delivery systems (CRDDS) due to the fact that protein binding serves to prolong the biological half-life. Therefore, there is no requirement to maintain the sustained release of the medicine.

8.2 Biological factors

8.2.1 Absorption

The consistency of both the rate and amount of absorption plays a crucial role in the formulation of controlled-release drug delivery systems (CRDDS). Nevertheless, the step that significantly restricts the rate of drug release is the liberation of the drug from the dosage form. In order to prevent dose dumping, it is recommended that the absorption rate be quick while the release rate should be controlled. There are several factors that influence the absorption of medicines, including water solubility, log P, and acid hydrolysis [40].

8.2.2 Biological half-life ($t_{1/2}$)

Typically, the drug exhibits a brief half-life, necessitating frequent administration, making it a viable choice for a controlled-release system. A pharmaceutical compound characterized by a prolonged half-life necessitates administration at extended intervals. Ideally, medicines with a half-life of 2–3 h are considered suitable candidates for controlled-release drug delivery systems (CRDDS). Pharmaceutical substances exhibit a half-life (t1/2) exceeding a duration of 7–8 h when not employed under a regulated release mechanism [41].

8.2.3 Dose size

The CRDDS was developed with the intention of reducing the need for repetitive dosing, necessitating the inclusion of a larger amount compared to standard dosage forms. However, the dosage employed in traditional dosage forms provides a reference for determining the appropriate dosage in controlled-release drug delivery systems (CRDDS). The magnitude of the sustained dose volume should be maximized to ensure compliance with the established acceptance criteria [42].

8.2.4 Therapeutic window

Drugs possessing a limited therapeutic index are deemed unsuitable for controlled-release drug delivery systems (CRDDS). In the event of a failure to regulate the release mechanism, it would result in dose dumping and subsequent toxicity as shown in **Figure 3.**

8.2.5 Absorption window

Pharmaceutical compounds that exhibit absorption from a particular segment in the gastrointestinal tract (GIT) are not considered optimal candidates for controlled-release drug delivery systems (CRDDS). Pharmaceutical substances that undergo absorption within the gastrointestinal tract (GIT) exhibit favorable characteristics for controlled-release applications.

8.2.6 Patient physiology

The release of a drug from its dosage form is directly or indirectly influenced by the physiological condition of the patient, including factors such as gastric emptying rate, residence time, and gastrointestinal illnesses. The pharmacokinetic factors that are considered throughout the drug selection process are shown in **Table 1**.

9. Polymer used in controlled drug delivery system

The significance of polymers in medication delivery is progressively growing. Polymers find diverse applications in the field of pharmaceuticals, encompassing their utilization as binders in tablet formulations, as well as agents for controlling viscosity and flow in liquids, suspensions, and emulsions [43]. Polymers have the potential to serve as film coatings in order to mask the unpalatable flavour of pharmaceuticals, improve their stability, and alter their release properties. This review

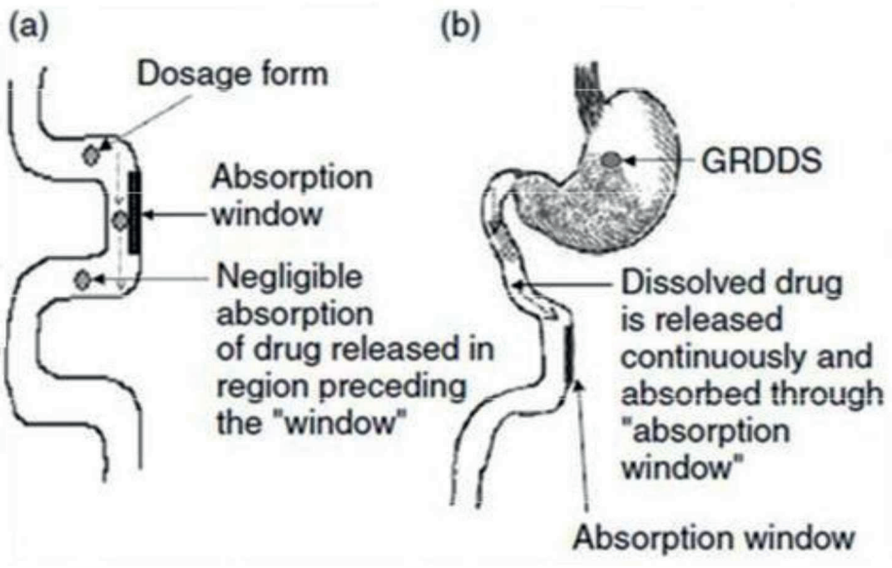

Figure 3.
Absorption pathway of drug delivery system.

centers on the importance of pharmaceutical polymers in the context of controlled drug delivery applications. Currently, a significant number of individuals, estimated at sixty million, experience positive outcomes as a result of utilizing sophisticated drug delivery systems. These systems offer enhanced safety and efficacy in administering appropriate dosages of medications, hence aiding in the treatment of many human afflictions, such as cancer [44]. Controlled drug delivery (CDD) refers to the deliberate combination of a polymer, whether it is of natural or synthetic origin, with a drug or any other active agent. This combination is carefully planned to enable the release of the active ingredient from the material in a predetermined manner. The active agent's release can exhibit constancy, cyclic patterns, or be contingent upon environmental factors or external stimuli over an extended duration. The underlying objective of drug delivery regulation is to enhance the efficacy of medicines while mitigating the risks associated with both suboptimal and excessive doses [45].

Parameter	Comment
Elimination half-life	The recommended duration falls within the range of 2–6 h.
Elimination rate constant(KE)	Design is a fundamental requirement.
Total clearance (CLT)	Dose independent
Intrinsic absorption rate	It ought to be higher than the release pace
Apparent volume of distribution (Vd)	Vd affect the necessary dosage of the drug
Absolute bioavailability	75% or more
Steady state concentration (Css)	Less Css and lesser Vd
Toxic concentration	Therapeutic window must be widened

Table 1.
Pharmacokinetic parameters for drug selection.

10. Polymers as biomaterials for delivery systems

Various materials have been utilized for the purpose of regulating the release of pharmaceutical medicines and other bioactive substances. The initial development of these polymers mostly focused on nonbiological applications, driven by their advantageous physical characteristics.

- Poly(urethanes) were chosen for their flexibility,
- While poly(siloxanes) or silicones were selected for their insulating capabilities.
- Poly(methyl methacrylate) (PMMA) is a polymer that is widely recognized for its exceptional physical strength and transparency.
- Poly(vinyl alcohol) (PVA) is commonly utilized in various applications due to its desirable properties of hydrophilicity and strength.
- Poly(ethylene) is commonly used in various applications due to its desirable properties, such as toughness and resistance to swelling.
- On the other hand, poly(vinyl pyrrolidone) is often chosen for its ability to suspend particles effectively.

In order for a material to be effectively employed in formulations for controlled drug administration, it is imperative that the material possesses chemical inertness and is devoid of any leachable contaminants [46]. In addition, it is imperative for the entity to possess a suitable physical composition, characterized by little undesirable deterioration, and be easily amenable to processing. Several polymers are now employed for regulated drug delivery, including poly(2-hydroxy ethyl methacrylate), poly(N-vinyl pyrrolidone), and poly(methyl methacrylate). Poly(vinyl alcohol) is a polymer that is commonly used in various applications due to its unique properties. Poly(acrylic acid) is a polymer that is commonly used in various applications [47].

The following polymers will be discussed: polyacrylamide, poly(ethylene-co-vinyl acetate), poly(ethylene glycol), and poly(methacrylic acid).

Polymers, such as polyethylene, polyvinyl chloride, methyl acrylate, and ethylcellulose, are characterised by their insolubility and inertness [48].

The substances carnauba wax, stearyl alcohol, and castor wax are characterized by their insolubility and erodibility. The hydrophilic substances mentioned include methyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose, and sodium alginate.

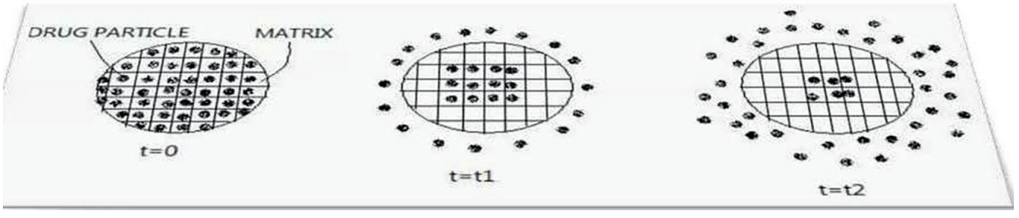

Figure 4.
Porous matrix composed of a water-insoluble polymer.

The medicine is distributed as solid particles within a porous matrix composed of a water-insoluble polymer, such as polyvinyl chloride, in a matrix system as shown in **Figure 4**.

At the onset, the drug particle situated on the surface of the release unit will undergo dissolution, leading to a fast release of the drug. Subsequently, drug particles located at progressively greater distances from the surface of the release unit will undergo dissolution and subsequently be released through diffusion through the pores, ultimately reaching the external environment surrounding the release unit [49]. The primary determinants influencing the release rate from a matrix system include the quantity of drug present inside the matrix, the porosity of the release unit, and the drug's solubility. In recent years, there has been an emergence of additional polymers specifically engineered for medicinal purposes, which have been relevant in the field of controlled release. A few of these materials have been specifically engineered to undergo degradation within the human body. A limited subset of these materials falls within this category [50].

- Polylactides (PLA).
- Polyglycolides (PGA).
- Poly(lactide-co-glycolides) (PLGA).
- Polyanhydrides.
- Polyorthoesters.

Initially, absorbable sutures were fabricated using polylactides and polyglycolides. Consequently, researchers naturally progressed to exploring the application of these polymers in the development of controlled drug delivery systems. One notable benefit of these degradable polymers is in their ability to undergo degradation into biologically acceptable compounds, which can subsequently be metabolized and eliminated from the body by regular metabolic processes. Nevertheless, it is important to acknowledge that biodegradable materials do generate breakdown by-products, which must be accepted within the biological environment without causing significant negative reactions [51].

Thorough testing of both desirable and potentially nondesirable degradation products is necessary, as several factors might influence the biodegradation of the initial materials. The below enumeration presents a comprehensive overview of the significant aspects that contribute to the extensive range of structural, chemical, and processing features that have the potential to influence biodegradable drug delivery systems [52].

- Chemical structure
- Distribution of repeat units in multimers
- Presence of unexpected units or chain defects.
- Molecular weight.
- Morphology (amorphous/semi-crystalline, microstructures, residual stresses).

- Presence of low-molecular-weight compounds.
- Sterilization process.
- Site of implantation.
- Adsorbed and absorbed compounds (water, lipids, ions, etc.)
- Physicochemical factors (ion exchange, ionic strength, pH).

11. Applications of controlled drug delivery system

Controlled drug delivery systems in the pharmaceutical industry refer to technologies that allow for precise control over the rate, time, and place of drug release within the body. These systems have various applications, offering benefits such as improved efficacy, reduced side effects, and increased patient compliance. Here are some pharmaceutical applications along with examples [53–55]:

Oral Drug Delivery:

Extended-Release Tablets: These release the drug over an extended period, maintaining therapeutic levels and reducing dosing frequency. Example: OxyContin (oxycodone).

Gastric Retentive Systems: These systems ensure prolonged drug presence in the stomach, which can enhance absorption or provide a local effect. Example: Proton pump inhibitors like Dexilant (dexlansoprazole).

Colon-Specific Delivery: Utilized for drugs that need to reach the colon for local or systemic effects. Example: Asacol (mesalamine) for treatment of ulcerative colitis.

Transdermal Drug Delivery:

Patches: These deliver drugs through the skin at a controlled rate, offering prolonged systemic effects. Example: Nicotine patches for smoking cessation.

Topical Gels/Creams: Control the release of drugs for localized effects on the skin or underlying tissues. Example: Voltaren Gel (diclofenac) for pain relief.

Intravenous Drug Delivery:

Infusion Pumps: These systems deliver a constant and controlled infusion of drugs directly into the bloodstream. Example: Insulin pumps for diabetic patients.

Liposomes and Nanoparticles: These can encapsulate drugs, allowing for targeted delivery and controlled release. Example: Doxil (liposomal doxorubicin) for cancer treatment.

Intramuscular and Subcutaneous Injections:

Depot Injections: These release the drug slowly from an injected depot, providing sustained effects. Example: Risperdal Consta (risperidone) for schizophrenia.

Ocular Drug Delivery:

Sustained-Release Implants: These implants slowly release drugs into the eye for conditions like macular degeneration. Example: Ozurdex (dexamethasone implant).

Ophthalmic Inserts: These deliver drugs to the eye over an extended period. Example: Dextenza (dexamethasone insert) for postoperative pain and inflammation.

Pulmonary Drug Delivery:

Dry Powder Inhalers (DPIs): These deliver drugs to the lungs in a fine powder form for localized or systemic effects. Example: Advair Diskus (fluticasone/salmeterol) for asthma.

Nebulizers: These convert liquid medication into a mist that can be inhaled for respiratory conditions. Example: Pulmicort Respules (budesonide) for asthma.

Nasal Drug Delivery:

Nasal Sprays: These can provide controlled delivery of drugs for local or systemic effects. Example: Flonase (fluticasone propionate) for allergic rhinitis.

Intrauterine Devices (IUDs):

Hormonal IUDs: These release hormones for contraception over an extended period. Example: Mirena (levonorgestrel-releasing IUD).

Intraperitoneal Drug Delivery:

Chemotherapy: Intraperitoneal delivery can provide controlled release of chemotherapy drugs directly into the abdominal cavity for treating ovarian cancer.

Implantable Devices:

Drug-Eluting Stents: These are used to prevent restenosis (re-narrowing) of arteries after angioplasty. Example: Cypher Stent (sirolimus-eluting stent).

These examples demonstrate the diverse range of controlled drug delivery systems and their applications in the pharmaceutical industry, allowing for more precise and effective treatment options for various medical conditions [56, 57].

12. Discussion

Drugs and excipients are combined in the dose form. Excipients are used to give products structure, improve stability, and cover up their flavors. Conventional dosage forms like solid, semisolid, and liquid require high doses and frequent administration while having poor patient compliance due to variations in plasma drug levels. Any dose form must include a medicine that is bioavailable in order to have the desired effect. Controlled drug delivery systems have become a viable alternative to traditional methods for maintaining drug plasma levels within the therapeutic range while increasing bioavailability, extending drug release, and minimizing negative effects. Controlled drug delivery allows the selective release of medications with a predictable pace and mechanism, as well as increased drug solubility and stability [11].

The several kinds of controlled drug delivery systems include diffusion, water penetration, dissolution, and chemically controlled drug delivery systems. Delivery methods that respond to stimuli can be used to target and regulate the release of substances in a variety of illness situations, including cancer and infections. To further accomplish controlled targeted delivery, nanocarriers with intelligent biomaterials and additive manufacturing processes can be developed. Patient-specific therapy using microfluidic-based, 3D-printed devices, and CRISPR cas9-based delivery systems linked with quantum sensing are the main goals of drug delivery in the future [58].

13. Future prospects

The field of controlled-release technology is still being developed despite the numerous controlled-release appliances that have been studied and/or used recently. Significant improvements in medication research, together with improved and earlier preventive medicine diagnostics, have contributed to an increase in human life expectancy. As a result, more medications are needed to treat a variety of illnesses, including coronary artery disease, diabetes mellitus, chronic pain, chronic lower respiratory

disease, Alzheimer's disease, and Parkinson's disease. The first and most crucial step is to find medications for these illnesses. Drug candidates with poor water solubility can be transformed into therapeutically useful drug formulations, while those with short half-lives can be transformed into formulations for sustained release. The advancement of novel medications will greatly benefit from the drug delivery technology.

To deliver medications with various distinct qualities, a variety of drug delivery methods must be devised. The evolution of medication delivery systems has resulted from many iterations and failures, or trials and errors. It is necessary to test a wide range of medication delivery methods and to iterate on the most promising ones. Until a suitable treatment for a condition is discovered, this procedure must continue. Instead of using the same strategy that others have been doing for a decade or more, it is necessary to try numerous other techniques. For instance, numerous nanoparticle-based medication delivery systems have been created, yet they all use essentially the same methodology and only have minor variations.

It should be emphasized once more that the aim of research into medication delivery systems is to create patient-friendly formulations. Clear objectives are necessary for the development of efficient drug delivery systems. A new delivery method alone is insufficient. It must be safe and effective when used inside the human body. Clinical applications have some limitations, and it is important to get those out of the way early on in the development process. Understanding the characteristics of the drug delivery systems as well as biological barriers is the foundation for developing therapeutically viable drug delivery systems, which many mistakenly refer to as solving practical difficulties. In terms of drug distribution, there is no such thing as a "basic study" and a "practical study." Only the study of creating clinical formulations to treat different ailments exists.

Consent for publication

Not Applicable.

Conflict of interest

The author confirms that this chapter contents have no conflict of interest.

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