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CONTROLLED DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW OF RECENT ADVANCES, CHALLENGES, AND FUTURE DIRECTIONS

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ABSTRACT

Controlled drug delivery systems (CDDS) represent a significant advancement in the field of pharmaceutical sciences, aiming to deliver therapeutic agents at a predetermined rate for a specified period, thereby maximizing therapeutic outcomes while minimizing adverse effects. Over the past few decades, CDDS have transitioned from conventional formulations to highly sophisticated, targeted platforms utilizing smart materials and innovative engineering techniques. This comprehensive review explores recent progress in CDDS, encompassing polymer-based carriers, lipid-based vesicles, nanoparticles, nanosponges, hydrogels, and implantable systems. Emerging technologies such as stimuli-responsive systems—triggered by pH, temperature, enzymes, or magnetic fields—and bioresponsive carriers for site-specific release are also discussed. Furthermore, the review critically examines the formulation strategies, pharmacokinetic benefits, and clinical translation of these systems, along with the technological, regulatory, and scalability challenges that hinder their widespread adoption. Particular attention is given to the integration of CDDS with digital health tools, biosensors, and artificial intelligence, which are paving the way toward personalized and precision drug delivery. Despite the notable progress, hurdles such as drug degradation, limited bioavailability for certain APIs, immunogenicity, and high production costs remain critical concerns. The paper concludes by highlighting future directions, including advances in nanotechnology, 3D printing, and responsive biomaterials, which hold immense potential for the next generation of CDDS. Overall, this review provides a robust foundation for understanding the current landscape, unresolved challenges, and forward-looking innovations in controlled drug delivery.

KEYWORDS: Controlled raelease, Nanoparticle, Diffusion controlled release.

INTRODUCTION

In the 1940s and early 1950s, oral sustained release products were developed, which served as the foundation for the science of controlled release (AS., 2008). First, there was just one use for the controlled release of fertilizer in the 1970s and the controlled release of marine antifoulants in the 1950s in the field of soul science (Acharya G, 2006). The advancement of pharmacology and pharmacokinetics brought to light the significance of drug release rate in assessing the efficacy of treatment. The development of controlled release is prompted by this (AS., 2008) (Uhrich KE, 1999). These novel modified release dose formulations are completely unique. Rhozes initially created mucilage-coated pills around the year 900 A.D. The drug release rates are altered by this coating, which was frequently used by European nations in the tenth century to create tablets coated in gold, silver, and pearl. The late 1800s saw advancements in coating technology, such as the use of sugar and enteric coating on pills and tablets. Around 1938, the second medication was included into the sugar-coating layer, and the subsequent coating progressed to the enteric coating of tablets. Lipowski, however, was granted the first patent for an oral sustained release preparation; his formulation included tiny coated beads that released the medication gradually and continuously (Rekhi GS, 1995). Blythe later refined this concept and introduced the first sustained release product on the market in 1952. More focus has been placed on this area over the last 30 years as the difficulties associated with new medication marketing have grown and the benefits of controlled release drug delivery systems (CRDDS) have been acknowledged. [Nowadays, oral controlled drug administration is a popular method for delivering medications, namely those with short biological half-lives and high-water solubility (Pandya D, 2015). Other than oral, different routes such as transdermal, ophthalmic, vaginal, and parenteral are used to release different drugs in a regulated manner (Tibbitt MW, 2016).

Controlled Release

A medication therapy dosage schedule that quickly reaches the necessary plasma concentration and is

sustained throughout the course of treatment is desirable. The biological half-life of the drug and mean residential time (MRT) are the main factors influencing the frequency of drug administration. Because of their variable drug release pattern, conventional drug delivery systems frequently result in over- or under-medication adverse drug reactions (ADRs). In addition to reducing medication toxicity, the CRDDS modifies drug distribution (Fan L, 2012). Drug release from the delivery system proceeds at the rate profile that is not only predictable kinetically but also reproducible from one division to another, as implied by the term-controlled release (CR), which also indicates predictability and reproducibility in the drug release kinetics. The purpose of CRDDS is to regulate the body's drug release, which can be either spatial or temporal in character, or both (Gibson JW, 2014). When discussing controlled release, the term "sustained release" was also brought up (JR, 1978). A pharmaceutical dosage form designed to delay the release of API such that its appearance in the systemic circulation is postponed or prolonged and its plasma concentration is maintained throughout time is referred to as sustained release (SR). The length of the therapeutic impact is maintained, and the commencement of pharmacological activity is postponed (JW., 1991).

Terminology/Definition

Modified release dosage form

Modified release dosage forms are those in which the drug's release rate and timing varies from those of the standard type. One such illustration of a modified release dosage form is an enteric coated tablet. Erythromycin, for instance, is designed as an enteric-coated tablet because it breaks down in the stomach. A further development of the modified release distribution methods is the multi-layered tablet (Allen LV, 2004).

Sustained release dosage form

To keep the drug concentration in the body roughly constant over an extended period of time, the sustained release dosage form's drug release occurs at a predefined rate. The drug's release rate is determined by first-order kinetics. One dose of an SR dosage form often contains more medication than its conventional or quick release dosage form (Banker SG, 2002).

Extended-release dosage form

An extended-release dosage form is defined as one that lowers the frequency of dose administration by at least two times as compared to an instant release or standard dosage form. This class includes long-acting, controlled-release, and sustained-release dose forms (Bhargava A).

Delayed release dosage form

A delayed release dosage form is one that delivers the medication in increments over a predetermined period of time or at specific times rather than immediately after administration as an instant release or conventional dosage form does. A part of the medication, though, might occasionally be released right once after administration (Chauhan MJ, 2012).

Immediate release dosage form

This class includes the traditional dose forms. To achieve quick and thorough systemic absorption, the medication is released from the dosage form after ingestion. The drug's plasma concentration begins to drop in accordance with its pharmacokinetic profile following absorption from the dose form. Ultimately, therapeutic activity stops when the concentration drops below the minimal therapeutic concentration (MEC). The duration of action is the amount of time that the drug concentration stays within the therapeutic window, while the start of action is the moment that the maximal concentration is reached. The subsequent dose is given in order to keep the concentration at a constant level. Therefore, the drug concentration in plasma and tissue compartments of a standard dose form exhibits a "see-saw" or "peak and valley" pattern. The magnitudes of these oscillations vary according to the drug kinetics, which include the rate of absorption, distribution, elimination, and dosage intervals (Chugh I, 2012).

ADVANTAGE OF CONTROLLED DRUG DELIVERY SYSTEMS (Yadav, 2022)

Reduces the frequency of dosing
2. Eliminates overdosing
3. Prevents or reduces side effects
4. Lowers overall health care costs
5. Improves treatment efficacy
6. Reduces adverse side effects and improves tolerability
7. Improves patient compliance
8. Uses less of the entire drug;
9. Minimizes or eliminates systemic or local side effects;
10. Minimizes drug accumulation during chronic usage

DISADVANTAGE OF CONTROLLED DRUG DELIVERY SYSTEMS (Yadav, 2022)

1. Likely to be expensive
2. Unpredictable and frequently yield subpar in-vitro-in-vivo relationships
3. Could result in dose dumping if the release design fails.
4. Less room for adjusting the dosage
5. Could raise the clearance rate for the first pass
6. Sometimes there is poor systemic availability
7. The gastric residence time affects and restricts the effective drug release duration.

TYPE OF CONTROLLED DRUG DELIVERY SYSTEMS (Rao, 2014)

Controlled drug delivery systems are broadly classified as follows:

Oral controlled release system
Targeted delivery systems
Dental systems
Dental systems
Transdermal systems
Vaginal & uterine systems
Injections & implant

Oral controlled release drug delivery systems
To produce a delayed release of medication into the gastrointestinal tract, most oral controlled release systems use diffusion, dissolution, or a combination of the two.

Dissolution controlled release
In theory, the easiest oral medications to make are sustained release ones that use dissolution as the rate-limiting step.

Encapsulation dissolution control (Yadav, 2022)
These techniques often entail applying a slowly dissolving substance to particular medication particles or granules. The coated particles can be put in capsules, like in Spansule Products, or compressed straight into tablets, like in Space Tabs. A limited or wide spectrum of coated particles of varied thickness can be used to achieve repeat or sustained action, as the time needed for the coat to dissolve depends on its thickness and aqueous solubility.

Matrix dissolution control
Compressing the medication into tablet shape with a slowly dissolving carrier of some kind is another strategy. In this case, the pace at which the dissolving fluid penetrates the matrix regulates the rate of medication availability. The tablet matrix's porosity, the presence of hydrophobic additives, and the tablet's and the particles' surface wettability can all regulate this.

DIFFUSION CONTROLLED RELEASE
The release rate of a drug is contingent upon its diffusion through an inert membrane barrier, which is a characteristic of diffusion systems. Typically, an insoluble polymer serves as this barrier. The two main categories of diffusion-controlled systems that have advanced during the last 20 years are matrix devices and reservoir devices.

Reservoir devices
In this approach, a medication core is encased in a water-insoluble polymeric substance. In the fluid around the particle or tablet, the drug will exchange after partitioning into the membrane. More medication will pass through the membrane, spread out to the edges, and interact with the media around it.

Matrix devices
A solid medication is distributed throughout an insoluble matrix in this approach. The rate of solid dissolution has no bearing on the rate of drug release, but the rate of drug diffusion does.

DIFFUSION AND DISSOLUTION CONTROLLED SYSTEMS
This system's primary characteristic is the partially soluble membrane that encloses the drug core. The encapsulated medicine can diffuse through pores in the polymer covering when a portion of the membrane dissolves.

ION-EXCHANGE RESINS
Water-insoluble substances known as resins are made up of repeating cationic or anionic groups along their chain. In order to create the drug-charged resin, the resin is mixed with the drug solution and either repeatedly exposed to the drug in a chromatographic column or left in contact with the drug solution for prolonged periods of time. After being cleaned to get rid of impurities, the drug-resin is dried to create particles or beads. The drug molecules are exchanged and diffuse out of the resin to the bulk solution when a high concentration of an appropriately charged ion comes into contact with the ion-exchange group.

pH-INDEPENDENT FORMULATION
The granules are intended to deliver basic or acidic medications orally at a controlled pace that is not influenced by the pH of the gastrointestinal system (Pederson, A.M., German patent). They are made by combining an acidic or basic medication with one or more buffering agents, granulating it with the proper pharmaceutical excipients, and then covering it with a film-forming polymer that is permeable to gastrointestinal fluid. As the GI fluid passes across the membrane, the buffering agents bring the fluid's pH down to a stable level, which maintains the drug release rate.

OSMOTICALLY CONTROLLED RELEASE
Osmotic pressure is what propels continuous medication release in these kinds of drug delivery systems. This system is created by encircling the core of an osmotically active or osmotically inert medication with a semi-permeable membrane and an osmotically active salt. Each system has a delivery orifice drilled in it using either a laser or a high-speed mechanical drill (Theeuwes, 1983).

Evolution of the Controlled Release Dosage Forms
First-generation: From 1950 to 1980, many dosage forms of controlled release drugs were available. The medicine is released from oral and transdermal formulations of this class of dosage forms more quickly thanks to four different kinds of drug release mechanisms. Osmosis, diffusion, dissolution, and ion exchange are the four categories of processes. The most widely used methods for administering pharmaceuticals involve processes that are regulated by diffusion and dissolution. The invention of the oral and transdermal routes played a major factor in the first generation of medications' success. There were no biological barriers found for this generation of medications, and the relationship between in-vitro and in-vivo formulation was widely recognized (Yun Y.H., 2015).

Second-generation: These are less effective than the first, but they can still carry proteins and peptides by

employing biodegradable polymers in formulations for prolonged release. Systems for delivering insulin to the lungs were created during this period. Due to its poor bioavailability, which has negative consequences, it must be administered at doses that are many times greater than those needed for parenteral injection. Researchers looked examined nanoparticles that target the gene and the tumor in the last ten years of the second generation (K., 2014).

Third generation: Self-regulating drugs, long-term, non-invasive protein, nucleic acid, or peptide delivery, drug delivery via nanoparticles to the targeted area, and delivery of weakly water-soluble drugs are some of the new drug delivery technologies (Yun Y.H., 2015).

Nanocarriers in Controlled Drug Delivery

Nanoparticle

These are initially solid colloidal particles of fewer than 100 nm composed of macromolecules that allow pharmaceuticals to be chemically bound (covalently bound) or entrapped in them to give controlled release properties and physical stability of the drug. Solid-lipid nanoparticles, metallic, polymeric, and inorganic-clay particles are a few examples. The use of nanoparticles, which can be delivered in a number of ways, increases the therapeutic effect of the medication. It is essential that the nanoparticle be able to transport the drug to a location that is difficult to access. It minimizes adverse effects while efficiently carrying out the medication's regulated release (S, 2021) (M, 2018).

Liposome

These are the colloidal particles that are created when an aqueous compartment is enclosed by lipid bilayers and amphiphilic phospholipids (Sercombe L., 2015). The hydrophobic effect creates a closed bilayered structure by facilitating the arrangement of amphiphilic molecules and minimizing adverse interactions between hydrophobic chains and the surrounding aqueous environment (Allen T.M., 2013). a Phospholipids can be either phosphatidylcholine or phosphatidylserine, depending on the polar head group. The synthesis of liposomes commonly uses phosphatidylcholine. The range of sizes is 25 nm to 200 nm (Dimov N., 2017). The reticuloendothelial system eliminates particles larger than 200 nm, which then momentarily circulate in the bloodstream. Liposomes' enhanced permeability and retention (ERP) makes them ideal for targeting tumor cells (Jain, 2012).

Exosomes

Cells create exosomes, which are membrane-bound, nanoscale vesicles that range in size from 30 to 100 nm. They are used to move materials between cells, both endogenous and external. Exosomes can transport a variety of medicinal substances, including nucleic acids, small proteins, and mRNA. For targeted drug delivery, these molecules can subsequently be delivered to specific cell or tissue types. Due to their strong potential for internalization with cells, they have been used extensively and developed quickly in recent years. Genes and peptides are transferred by exosomes, both natural and artificial (Bunggulawa E.J., 2018).

Nanoemlusion

A nanoemulsion is a heterogeneous mixture of water and oil, two immiscible liquids, stabilized by emulsifiers or surfactants. Drugs that are hydrophobic and delivered in various ways are carried by them. They outperform traditional emulsions in terms of resistance to flocculation, creaming, and sedimentation. Nanoemulsion can effectively deliver a medicine to a specific area because of its increased surface area and other properties (Tayeb H.H., 2018).

Nanofibers

Solid fibers called nanofibers are ideal for use as drug delivery systems because of their increased surface to volume ratio and diameter, which ranges from a few nanometers to 1000 nm. Different drug release kinetics can be achieved by adjusting the diameter, shape, and porosity of nano-fibres (Kajdič S., 2019). Nanofibrous delivery devices enable constant drug distribution and high loading efficiency (Zare M., 2020). The electrospinning method can be used to create nanofibers, and patterning can be used to control drug release (Adepu S. G. M., 2017).Silk fibroin nanofibers are a great substitute for synthetic nanofibers in medication delivery since they are naturally made from a type of bacterium known as bacterial cellulose (Adepu S. K. M., 2021) (arokhi M., 2020). To enable rapid drug release, the polymer employed to make the nanofibrous mesh has a high porosity, an interconnected porous structure, and a large specific surface area. The drug release from the nanofibers can be regulated to be dual-mode/biphasic, prolonged, and stimulus-responsive (Torres-Martinez E.J., 2018).

Solid lipid nanoparticle

Solid-lipid nanoparticles (SLNs) are alternatives to conventional colloidal nanocarriers that combine the benefits of liposomes and polymeric nanoparticles without the toxicity. Spherical SLNs range in size from 50 to 1000 nm and are composed of lipids, emulsifiers, and API that are solid at room temperature (Adepu S. K. M., 2020) (Scioli Montoto S., 2020). The biocompatible lipids that make up the foundation of the SLN safety profile are well tolerated by the body and lungs. In addition to proteins and nucleic acids, SLNs have the capacity to transport hydrophilic and lipophilic medications, opening up new avenues for drug and gene delivery (Duan Y., 2020). Because phospholipid fatty molecules are more pliable, thinner, and biologically compatible, they can flow through small fenestrations and arterioles without clotting (.Duan Y., 2020).

Challenges and future direction

Systems for administering controlled medications have advanced significantly over the last 20 years.

Development is still required to get past the constraints and broaden possible futures.

Microfluidies in controlled drug delivery

It seems promising that controlled and implanted microfluidic delivery devices will be the main focus of future studies. Lab-on-a-chip (LOC) technology is commonly used because it uses small microdevices containing chambers and channels (Hassan S., 2019). The fluid flow behaviour is controlled by these tiny devices to better deliver the drug to the intended site (Simutis K., Antibody discovery using microfluidic systems. In: editors. Microfluidics for Pharmaceutical Applications., 2019). Recent studies have proposed polymerizing -amino acid N-carboxy anhydrides (NCAs) to create synthetic polypeptides that can be shaped into nanostructures and deliver the drug exactly to a specific location. Altering the polypeptide structure's chemical and physical characteristics can also control the release of medicinal drugs. (S.A., 2020).

Intelligent Biomaterials

There is a lot of promise for intelligent biomaterials that can sense their environment, adapt to it on their own, and regulate the release of drugs. For example, an intelligent hydrogel may sense the pH or temperature of its immediate environment to determine the blood sugar levels in that environment. The precise amount of insulin needed to sustain such levels would then be provided. Since smaller biosensor hydrogels are more delicate and cannot be given the mechanical strength to carry out the necessary function, it is currently difficult to build smaller hydrogels, despite the fact that doing so is important (Chen R., 2019).

Nanomedicine improvements and challenges

The ability of nanoparticles to cross the blood-brain barrier is beneficial in brain diseases, but it also causes neurotoxicity when the intended site of action is not the brain. Nanoparticles can sometimes have immunomodulatory effects as well. Using this of nanoparticles, inflammatory monocytes can be targeted across the blood-brain barrier to inhibit the progression of auto-immune illnesses encephalomyelitis. One of the many benefits of using nano-drug delivery systems instead of more conventional ones is the ability to administer drugs more effectively and more efficiently. However, toxicology and safety characteristics for nanoparticulate systems need to be mesoporous nanoparticles have sparked interest in regulated drug administration. For better drug targeting and endosomal release, they are hence ideal. To prevent the early release of pharmaceuticals through mesopores, stimuli-responsive polymers can be used to line them and give spatiotemporal control during the release of a particular medicament into the cytoplasm of the target cell (Vallet-Regí M., 2018).

CONCULSION

Controlled drug delivery systems have emerged as transformative tools in pharmaceutical science, offering enhanced therapeutic efficiency, reduced dosing frequency, and improved patient compliance. The evolution from conventional formulations to advanced, intelligent systems—such as stimuli-responsive nanoparticles, polymeric carriers, and implantable devices—demonstrates the remarkable progress in this field. Despite these advances, several challenges persist, including drug stability, manufacturing complexities, regulatory barriers, and biological obstacles that limit clinical translation.

Continued interdisciplinary research integrating material science, nanotechnology, biotechnology, and computational modelling is essential to overcome these limitations. Moreover, the convergence of CDDS with cutting-edge technologies such as artificial intelligence, biosensors, and personalized medicine opens new avenues for individualized and targeted therapies. Future efforts should focus on optimizing system design, ensuring scalability, and enhancing safety and efficacy to facilitate broader clinical adoption. As the field advances, controlled drug delivery is poised to redefine the landscape of modern therapeutics, offering smarter, safer, and more effective treatment options.

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