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REVIEW ARTICLE

Overview of Controlled Drug Delivery System

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ABSTRACT
Drug supply is the process by which a medicinal substance is administered to have clinical efficacy in humans or animals. Traditional drug delivery has no control over its release and virtually no control over its successful target concentration. This kind of medicating strategy may lead to changes in plasma concentrations that are often unpredictable. Controlled drug distribution technology has advanced over the last 60 years. The regulated method for the distribution of medicinal goods guarantees protection, quality, and patient adherence. Any distribution system that accomplishes the gradual discharge of the medication over a long period is used in a controlled release system. The first controlled release system was introduced in 1952.In designing many controlled oral and transdermal release formulations for biological benefits, the first generation has been highly productive. Generally, controlled-release products by either path are engineered to ensure that the absorption rate of the medication is comparable to the elimination rate of the medication. These systems offer many advantages compared with traditional methods, including adjusting drug release rates, safeguarding fragile drugs, and enhancing patient convenience and compliance.
Keywords: *Traditional drug delivery, Controlled release system, Drug, Patient convenience, Drug release rate, drug distribution.*

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INTRODUCTION

Conventional drug delivery systems (DDS) have a very limited command of their distribution of the drugs and nearly no command of successful target concentration. This form of dosage will result in ever-changing plasma concentrations which are unpredictable[1]. To achieve a fast and full systemic drug absorption, several of the regular oral drugs, such as capsules and tablets, are designed for the discharge of the active medication directly following administration by oral route [2]. These traditional delivery types have some drawbacks, such as 1) Short-term prescriptions need regular administration, raising the risk of missed delivery of medications due to bad patient adherence. 2) Typical concentration of plasma peak. The period is acquired making it impossible to reach a steady state. 3) Inevitable variations in the concentration of drugs can result in the presence or use of drugs as the values of CSS fall or rise above the therapeutic range[3]. Oral drugs absorbed quickly in the food pipe and quickly lost from the blood are normally film-coated or prolonged microencapsulated to the period of distribution and the action of drugs. Most of these types, however, have some physiological shortcomings such as transit periods for gastrointestinal (GI), partial releases of drugs from devices, or the prolonged duration of prescription residence in small intestine upper location contributing to low bioprotein-dosage forms of the long-term release[4].

The development of DDS involving, such as, the use of several carrier membranes to manage extended delivery time with minimal changes in delivery speed has been given great consideration in recent years[5]. DDS, which has an enormous health system impact and can accurately monitor discharge or target drugs at a specific body site[6]. Due to their significant therapeutic advantages, oral controlled release (CR) forms have been developing from the last four decades[7]. Simple pills and injections are recognized for a long time to be not the best method of medicinal use. To develop methods of drug management, attempts have been increased to design efficient DDS, with cooperation between polymer

physicists, pharmacologists, engineers, chemists, and medical researchers, and important advances have been made in managed delivery since research began several decades ago[8].
The intrinsic features of formulation design, GI physiology, pharmacodynamic ,and, pharmacokinetics are essential to achieve a uniform distribution via oral administration, irregular mode of delivery, and design of dosage forms[9]. Scientific and technological advances in the last few years have been made by overcoming physiological barriers, such as the unpredictable gastric emptying time (GET) and short residence time in the development of rate-controlled pharmaco-support systems[10].One of medical research, chemistry, the sciences of materials, manufacturing, and the pharmaceutical industry, as well as other associated bio-science, is the field of controlled drug delivery. DDS continuity in achieving a better living quality and human health is the reason for recent increasing interest and efforts by researchers in this area. Its scope also includes various areas from medicine, agriculture, and biotechnology[11].CR dosage forms provide a wide variety of delayed action formulations which have a pre-determined rate and pre-determined sustained release of its active ingredients. For this method, the primary goal is to include an extended length of action to ensure better compliance with patient conditions[12]. The purpose of the CR mechanism is to create a product that can release drugs continuously at zero-order for a longer period. As the technology available for producing such products progressed considerably, more sellers offer excipients for CR. more and more oral products have been manufactured and sold as CR[13].

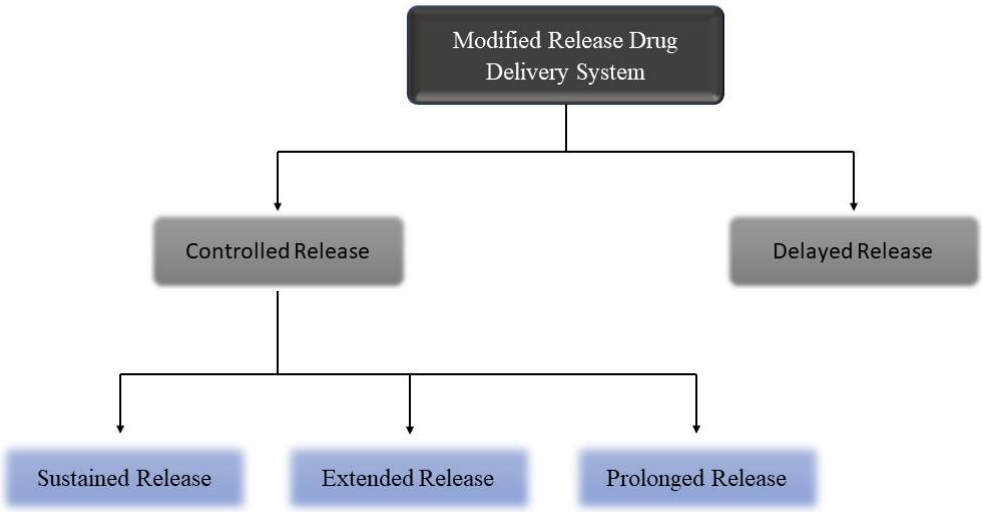

Figure 1: Classification of Modified Release Drug Delivery System.

Table 1:Background from 1950 on drug delivery technologies and technology needed for the future[14].

1950	1980	2010
1st Generation	2nd Generation	3rd Generation
Basics of Controlled Release	Smart Delivery System	Modulated Delivery System
Oral • Once-a-day or twice a day	Zero-order • zero-order vs First-order	Poorly soluble drug • Non-toxic excipients
Transdermal Once-a-day, once-a-week	Peptide & protein Durable depot with biodegradable polymers Delivery to pulmonary sites	Peptide & protein • Delivery for >6 months • Control of release kinetics • Non-invasive delivery
Drug release mechanisms Dissolution Diffusion Osmosis Ion-exchange	Smart polymers & hydrogels Responsive to the condition Auto-release	Smart polymers & hydrogels • Signal specificity &sensitivity • Rapid response kinetics
	Nanoparticles • Tumor-specific delivery	Targeted drug delivery • Non-toxic to non-targetcells • Overcoming the barrier of blood-brain
Successful control of physicochemical properties of delivery	Cannot overcome the biological barriers	Should surmount both biological and physiochemical barriers

Classification of modified DDS has demonstrated in figure 1. CR technology's history is split into three periods: the era of sustained release of drugs was from 1950 to 1970, the needs for controlled drug delivery were established between 1970 and 1990, and modern CR technology was introduced after 1990 (Table 1) [14]. Meanwhile, figure 2 explains the general mechanism of CDDS.

Advantages of CDDS[15-17].

CDDS has many benefits over traditional therapy:

- Good plasma level
- Improved compliance with patients
- Lower dosage and toxicity
- Possibility of targeting
- Medication management frequency is decreased.
- Patient compliance should be enhanced.
- Better control can be achieved of drug absorption
- Optimizing minimum dosage supply
- Reduce or remove locally adverse effects
- Reduce or suppress systemic side effects
- Minimize chronically dosed drug accumulation.
- Improve treatment effectiveness
- Quicker cure or tracking of condition
- Improve/control means that fluctuations in the level of drugs are reduced.
- Enhance the bioavailability of certain drugs
- Use special effects, for example, continued release of aspirin, until bedtime for the morning arthritis relief by dosing.
- Difficult medication delivery: the sluggish release of soluble water medicines, quick release oflow solutions medicines.
- Healthcare costs reduction

Disadvantages of CDDS[18]

- Drug action delay
- Potential to dump the dose in the event of a bad formulation approach Improved metabolic capacity in the first-pass metabolism
- Increased dependence on GI dosage residence time
- The right to change dosage less reliably in some situations
- Unit dose costs are higher compared to standard doses
- Not all prescriptions are appropriate for ER dose formulation.

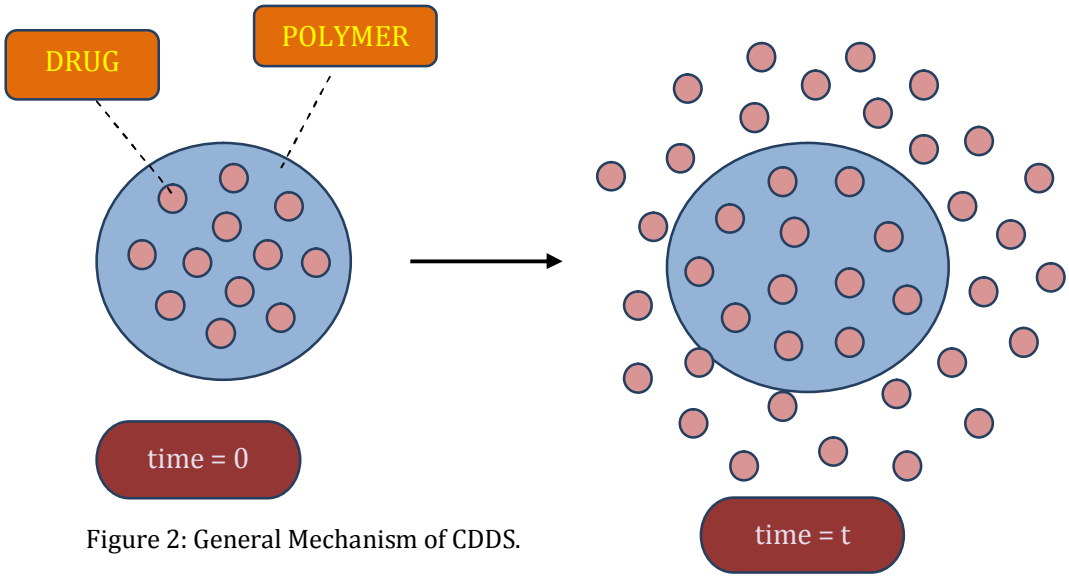

Figure 2: General Mechanism of CDDS.

FACTORS AFFECTING ORAL-CONTROLLED RELEASE PRODUCTS [19-23]

Dose size

The upper range to administer the drugs through the oral route, commonly for a single dose is 0.5-1 gram.

Ionization and Dissociation constant

As per the pH partition hypothesis, unaltered drug species shall be absorbed through various bodily tissues on priority, so it is quite crucial to consider the association between dissociation constant and the environment in which the drug to be absorbed. In traditional dosage forms, the drug completely solubilizes in the stomach and fully absorbs in the small intestine, but in the controlled system, the drug may be in solid form in the intestine, which signifies that the solubility of the drug is prone to alter during its release. Those compounds with lesser solubility, are to be innately controlled because their release periodof dosage form, in the GI tract (GIT), will be restricted by drug dissolution. 0.1 mg/ml is shown to be the minimum limit of solubility for a drug to be formulated for CR.

Partition coefficient

Compounds with greater partition coefficient tend to be lipid-soluble thus having greater bioavailability, whereas lower partition coefficient leads to lesser penetration of compounds to the membrane which means poor bioavailability

Drug stability

Drugs showing instability in the stomach region, are administered in controlled form so that it reaches the intestine with delayed release, this can also be deteriorating for drugs which get degraded in the intestine. Thus, generally drugs unstable in the GIT tract are not suitable for CR.

Molecular size

Compounds with high molecular weight are not good candidates to be used for CR. Diffusivity is the function of the drug to penetrate the membrane which depends upon the size and structure of cavities of the membrane.

Biological Half-life

For CR, compounds with a half-life lower than 8 hours area good candidate. Whereas drugs with a half-life lower than 2 hours need greater amounts of the drug for CR. Compounds with a half-lifeof more than 8 hours are not utilized in CR. Thus, drugs with very less or more half-life are not suitable for CR form.

Metabolism

Metabolism of a drug compound is taken into consideration in forming CR products. CR forms can be developed if the location, extent, etc. of metabolic reaction is known

ORAL CONTROLLED – RELEASE PRODUCTS [3,24-26]

Based on their release mechanism these are classified as follows:

1. Diffusion – Controlled products
   The water-insoluble polymer in these systems regulates the water circulation and the resulting release of the dissolved material. Diffusion happens when the material comprising the CR system moves through a drug. Diffusion may occur through pores in the polymer matrix or via polymer chains. The two groups are narrowly divided-

a) Reservoir Devices.
b) Matrix Devices.

   These two processes are radically distinct from the essential mechanisms of drug release.

a) Reservoir Devices: A water-insoluble polymer encloses a core drug in this method. The drug splits into the membrane and exchanges the particles (or tablet) surrounding the liquid. Through the rate-limiting membrane, the active agent is released into the surrounding. The rate of drug distribution is relatively stable in these systems.
b) Matrix devices: The drug or active substance will be distributed into a polymer matrix in the homogeneous system which is called a matrix system. Diffusion happens as the drug travels into the outside environment from the polymer matrix. If the release proceeds, this type of device usually reduces its rate, as the active agent has a gradually greater journey distance and takes more time to release it.

2. Dissolution-controlled products
   In these materials, slow-soluble polymers or microencapsulation regulate the rate at which the drug is dissolving. The drug will be available for dissolution once the coating is dissolved. The drug release rate can be regulated by adjusting the thickness and composition of the coat. Some formulations contain a fraction of the overall dose to provide a pulse dosage soon after administration as an immediate release portion. Diffusion controlled products can be encapsulated or produced as a tablet for pellet dosage forms. Products controlled by dissolution can be categorized into two types-

a) Encapsulation Dissolution controls.
b) Matrix Dissolution control.

a) Encapsulation Dissolution control: This device approach involves the covering with a slow dissolving substance with individual particles (or) granules with drugs. The coated particles may directly be packed (or stored in capsules) into tablets. Micro-encapsulation controls the rate of dissolution of the drug (and hence the availability for absorption). The substance will be available for dissolution until the coating is dissolved. The drug release rate can be regulated by adjusting the thickness and composition of the coat. The coating can be weakened and should not chew these items. One of the benefits of embedded pellets is that it is less susceptible to stomach emptiness to start absorption. The entry of pellets into the small intestine is generally more uniform (where most of the absorption is present) than with non-disintegrating tablets.

b) Matrix Dissolution control: The compression of the drug with a slow dissolving carrier is a different method in this device. This controls the rate of drug release by the dissolution fluid penetration in the matrix, by its porosity, hydrophobic additive presence, and by its moistening system and particle surface.

3. Erosion products
   Drugs or active agents are combined with biodegradable polymers in this method. As a consequence of cellular processes, this substance degrades inside the organism and the release of drugs takes place continuously. The majority of biodegradable polymers are degraded into biologically acceptable, gradually smaller compounds utilizing hydrolysis of the polymer chains. The release of these drugs by the erosion rate of the carrier matrix is regulated. The release rate depends on the erosion rate.
4. Osmotic pump systems
   The osmotic pump is similar to a storage device but has an osmotic agent (e.g. the salt active component), which works through a semi-permeable membrane to absorb water from a surrounding medium. The pressure is created in the system that pushes the active agent out of the system through an orifice (a dimension intended to mitigate the solution's diffusion and at the same time preventing the development of a hydrostatic pressure head that reduces the osmotic pressure and alters the dimensions of this device). The benefit of such medication being that the continuous release stays unaltered by the gastrointestinal tract setting and depends entirely on water movement in the dosage type. By changing the osmotic agent and hole size, the release rate may be changed.
5. Ion exchange resins
   The expansion of medicament-resin complexes was known and commercially utilized. The compound is bound to the resin and released in interaction with the ion exchange groups by transferring properly charged ions. This technique applies to some medicines which, in their relative affinity to the polymers used, have unique features.

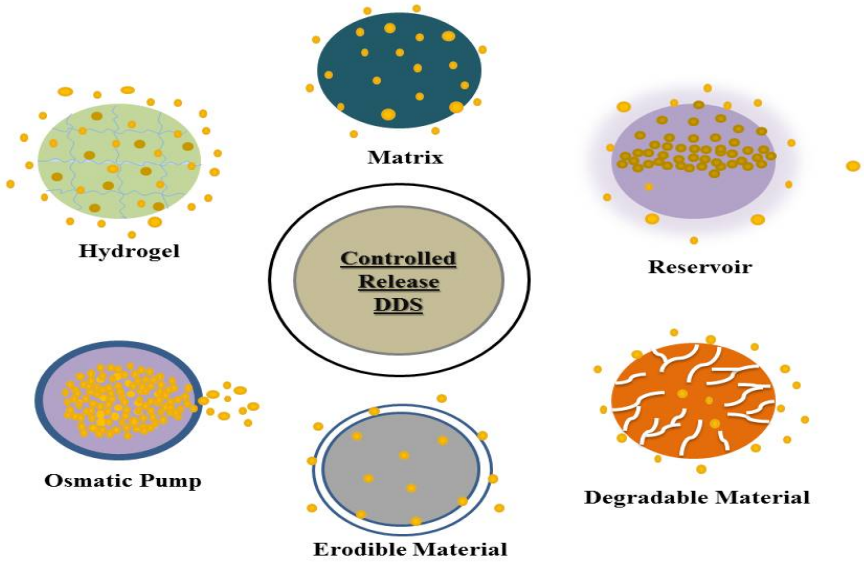

Figure 3: Drug delivery systems were developed with various material techniques to regulate release. For starters, the medication diffuses in a matrix-based system through a windy web of linked pores. The medication moves across a semi-permeable membrane in a tank. When pores are formed when material

degrades in a degradable DDS, the medicine is released. Similarly, the substance is released on the surface during erodible DDS and dissolves. In response to osmotic gradients, the osmotic pumps deliberately release drugs through one or more narrow pores in an impermeable membrane. Finally, hydrogel DDS releases medicines across a restricted network whose mesh size depends on the architecture of hydration and polymer.

Figure 3 shows the different-different release mechanism of CDDS followed by table 2 which shows patented CDDS.

Table 2: Patented controlled release drug delivery systems [27].

Title	Patent number	Year
1. Biodegradable Controlled Release Systems		
Biodegradable polymer matrices for sustained delivery of anaesthetics	US6214389, US6214388	1999 2000
Biodegradable controlled release bioactive agent delivery device	US20060034891, WO/2006/023130	2006
Baclofen and r-baclofen gastroprotective drug delivery systems	US20110091542 A1	2011
2. Bio mucoadhesive Controlled Release Systems		
Biocompatible adhesive system and bio adhesive drug delivery system with controllable release	WO/2000/047644, AU2547900	2000
Controlled regional oral delivery	WO/2006/039022	2006
3. Floating Controlled Release Systems		
Controlled release gastric floating matrix	WO/2006/040779	2006
Metformin hydrochloride intragastric floating sustained-release tablet and preparation method thereof	CN101536989	2009
4. Osmotically Controlled Release Systems		
Floating osmotic device for controlled release drug delivery	US20030064101	2003
Potassium chloride elementary osmotic pump-controlled release tablet and preparation method thereof	CN102144985	2011
5. Multilayer Controlled-Release Tablets		
Multilayer tablet	US6254886	2001
Multilayer omeprazole tablets	US20090280173 A1	2009
6. Diffusion Matrix System		
Mesalazine controlled release oral pharmaceutical compositions	WO/2000/076481	2000
Zero-order sustained release matrix tablet formulations of carbamazepine	US5980942	1999
Controlled-release formulation coated with aqueous dispersion of ethyl cellulose	JP2006188539, JP2006188540	2006
Opioid formulation having extended controlled release	JP2009149681	2009
Controlled release formulation containing vardenafil	JP2012254993	2012

OTHER CONTROLLED DRUG DELIVERY SYSTEMS

Oral

Protein and peptide medicinal products, which are suitable for delivering therapeutically agents that are selectively incorporated into the intestine, have to be delivered orally. Gelatin capsules were covered with sodium alginate levels and connected to suitable calcium chloride levels and in vitro for gastric and intestinal resistance tested. For their in vivo gastrointestinal tract activity, gelatin capsules covered with 20 percent w/v of the polymer that provided the most positive in vitro results were tested by human volunteers. The radiographic tests have shown that, while the uncoated gelatin capsules have disintegrated into the stomach within 15 minutes of ingestion, the alginate-coated gelatin capsules have remained unstable as long as they stay in the stomach (up to 3 h) [28].

Parenteral

Kushwaha used a combination of polymer polyvinyl alcohol with natural macromolecule gum Arabica and discovered that the timeframe of drug discharge and release depend on the amount of drug that is loaded into the matrix, the solution, and the medium discharge. The advantage of this system is that it can be adjusted to adjust the plasticizer, homopolymer, and cross-linker composition for the system's release kinetics. Chitosan 45-300 µ microspheres have been used for regulated progesterone delivery[29].

Dental

The ethylcellulose strip was used to reduce sub-gingival microorganisms in periodontal pocketing by Somayaji *et al.* for tetracycline and metronidazole. The patients were subdivided into five groups according to how long the medicine was in place, superficial scaling was given. Tetracycline,

metronidazole, and placebo have been marked at sites. Sites were cleaned and insulated and samples of essential microbiology for gram staining and cultivation methods were taken [30].
In the 1960s multiple controlled distribution systems, including macromolecule-controlled matrices and storage tanks, biodegradable chemically controlled and biodegradable compounds, and solvent-activated hydrogels and osmotic pumps were developing to monitor the release of the macromolecule. Further development has introduced "smart" materials that emit medications to stimulate the environment. Nanotechnology in pharmaceuticals was developed and extended into the liposomes, dendrimers, polymer nanospheres, and polymer micelles. CR technologies including microelectronics to allow pulsative and remote therapeutic releasing[31].

CONCLUSION

Modern technologies including the goal concept for successfully controlled delivery have now emerged. By optimizing the biopharmaceuticals, pharmacokinetics, and pharmacodynamics of drugs, controlled-release products offer benefits over conventional dosing formulas so that dosing frequency is greatly reduced. DDS play the most important role in getting the drugs to the site for sufficient action at the appropriate rate & at the appropriate level. It should therefore conform with other essential requirements such as physical, chemical, and solid-production stability in a way that ensures uniformity of material.
Due to their need to be able to command and find the arrangement in targeted GI areas, the design of CR systems was an obstacle for formulated researchers. The most beneficial remains CR formulations using alternate routes, except the oral method. The advancing effects of many experiments and errors in the drug delivery systems are the results of an evolutionary process. To study drug delivery systems, clinically useful formulations are developed for patients. Clear objectives are required for the development of efficient drug delivery systems. It is not enough to create a new supply system alone. It must work safely and effectively in the human body. There are certain constraints on the objective of clinical applications and it is important to address them from the early stages of development. The creation of clinically beneficial drug delivery systems which many wrong term functional issues are focused on a knowledge of the properties and biological barriers of drug supply systems.

CONFLICTS OF INTERESTS

Declared None.

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