Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2026, Volume 14, Issue 05
ISSN: 2321–3647(online)

Control Drug Delivery System – Recent Technological Developments

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ABSTRACT

The drug delivery system enables the release of the active pharmaceutical ingredient to achieve a desired therapeutic response. Conventional drug delivery systems (tablets, capsules, syrups, ointments, etc.) suffer from poor bioavailability and fluctuations in plasma drug level and are unable to achieve sustained release. Without an efficient delivery mechanism, the whole therapeutic process can be rendered useless. Moreover, the drug has to be delivered at a specified controlled rate and at the target site as precisely as possible to achieve maximum efficacy and safety. Controlled drug delivery systems are developed to combat the problems associated with conventional drug delivery. There has been a tremendous evolution in controlled drug delivery systems from the past two decades ranging from macro scale and nano scale to intelligent targeted delivery. The most recent breakthroughs in controlled drug delivery systems (2025–2026) include wirelessly controlled bioelectronic devices, advanced nanocarriers, and smart polymers that allow precise, patient-specific dosing and targeted release. These innovations aim to improve treatment accuracy, reduce side effects, and enhance patient compliance. Recent advancements in controlled drug delivery systems (CDDS) focus on enhancing precision, patient compliance, and efficacy through nanotechnology, stimuli-responsive materials, and smart, wearable devices. Key developments include lipid nanoparticles (LNPs) for nucleic acid delivery, stimuli-responsive systems that release drugs based on pH or temperature, wearable pumps, and microneedles for painless, transdermal administration. The paper concludes with the challenges faced and future directions in controlled drug delivery.

Keywords: controlled bioelectronic devices, stimuli-responsive systems, wearable pumps, intelligent targeted delivery, etc.

*Corresponding Author Name: Dr. Sunisha Kulkarni
Received 14 April 2026, Accepted 13 May 2026

Please cite this article as: Kulkarni S *et al*., Control Drug Delivery System – Recent Technological Developments. American Journal of Pharmacy & Health Research 2026.

INTRODUCTION

Controlled drug delivery system (CDDS) is an advanced method of administering therapeutic agents in which the drug is released at a predetermined rate, for a specified period of time, and at a specific target site to achieve optimal therapeutic effect. Unlike conventional dosage forms, such as tablets or injections, that release drugs immediately after administration, controlled drug delivery systems are designed to maintain consistent drug levels in the bloodstream, thereby improving treatment efficacy and patient compliance.[1, 2]

The primary objective of controlled drug delivery is to enhance the safety, effectiveness, and reliability of drug therapy. By regulating the rate and location of drug release, these systems minimize fluctuations in plasma drug concentration, reduce dosing frequency, and lower the risk of side effects and toxicity. This approach is particularly beneficial for drugs with short half-lives, narrow therapeutic indices, or those requiring long-term administration.

Controlled drug delivery systems utilize various technologies and carriers, including polymers, hydrogels, nanoparticles, liposomes, and transdermal patches, to achieve sustained, targeted, or stimuli- responsive drug release. Advances in material science, biotechnology, and nanotechnology have further expanded the scope of CDDS, enabling site-specific delivery and personalized medicine.

Figure 1: Dosage Form Design

Overall, controlled drug delivery systems represent a significant advancement in pharmaceutical sciences, offering improved therapeutic outcomes, better patient adherence, and enhanced quality of life compared to conventional drug delivery methods.

Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or implant or remove the

system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations.

The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration.

The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect on disease. Conventional dosages mean oral delivery and injection are the predominant routes for drug administration. The main drawbacks of these types of dosage are non-local treatment and toxicity to healthy tissues. An ideal drug delivery would be controlled for high efficiency treatment and local drug release to minimize toxicity. With the development of micro/nano drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect on disease. Conventional dosages mean oral delivery and injection are the predominant routes for drug administration. The main drawbacks of these types of dosage are non-local treatment and toxicity to healthy tissues. An ideal drug delivery would be controlled for high efficiency treatment and local drug release to minimize toxicity. With the development of micro/nano electromechanical system (MEMS/NEMS) technology and material science, a variety of devices have been developed to achieve drug delivery for disease treatment over the years. The devices with micro/nanostructures, as powerful platforms, can provide better drug therapy because they allow precise, local, and controlled dosing with lower toxicity. These devices can offer opportunities to address unmet medical needs related to disease therapy.[3, 4]

An ideally controlled drug delivery system requires simultaneous consideration of several factors, such as the mechanism of drug release, the route of administration, and capability of targeting. The approach of drug release has a significant effect on therapeutic efficacy. An ideal approach should maintain drug levels within the therapeutic window to avoid potential health hazards, maximize therapeutic efficiency, and provide a well-controlled drug release triggered

by stimuli. Drug concentration above the therapeutic window is toxic, and below the therapeutic window will lose therapeutic efficacy. Conventional drug delivery systems, such as oral and injection, generally have a high initial level of the drug after the first administration, followed by sharp decrease in blood concentration. Controlled drug release helps to address this issue, shows two profiles of most common time dependent release, sustained release, and pulsatile release. Sustained release can offer a constant drug concentration within the therapeutic window. However, pulsatile release provides a consecutive burst drug delivery. [5,6]

To improve treatment efficiency of the disease, controlled drug delivery can be achieved in different approaches based on different compounds or different therapeutic needs. Most treatments request a sustained release of drug at a constant rate over long periods of time. For some specific drugs, such as insulin and hormones, the drug release should mimic the body's natural pulsatile. A variety of controlled drug delivery devices have been developed to achieve a good therapeutic effect over the years. Controlled drug release can be triggered by different stimuli, such as temperature, pH, magnetic and electric field, etc. These devices use different routes of administration, and different methods and materials for device fabrication, typically including polymer- and silicon-based micropumps, microneedles, microreservoirs, and microfluidic systems.

Significance of CDDS

Controlled drug delivery systems (CDDS) are required to overcome the critical limitations of conventional medications, such as standard tablets or injections, which often cause rapid fluctuations in drug levels and require frequent dosing. By regulating the release rate, these systems ensure a more stable, safe, and effective therapeutic experience. [7, 8, 9]

The primary requirements for these systems include:

- **Maintaining the Therapeutic Window**

  Conventional drugs often create "peaks" (potentially toxic) and "troughs" (ineffective) in the bloodstream. CDDS maintain a constant drug concentration within the therapeutic window—the range where the drug is effective without being harmful. Many systems aim for a zero-order release profile, where the drug is released at a constant rate over time, independent of its remaining concentration.

- **Improving Patient Compliance and Safety**

  Because the drug is released slowly over hours, days, or even months, patients do not need to take multiple daily doses, which is especially vital for chronic conditions like diabetes or hypertension. By avoiding high initial concentration "spikes," CDDS reduce

the risk of systemic or local adverse effects. These systems can protect delicate molecules (like proteins or peptides) from being degraded by stomach acid or enzymes before they reach their target.

- **Precision and Targeted Delivery**

CDDS can be engineered to release medication only at a specific site (e.g., a tumor or inflamed joint), which increases efficacy at the diseased area while sparing healthy tissues from exposure. Advanced "smart" systems can be triggered to release a drug in response to specific environmental changes, such as pH, temperature, or the presence of specific enzymes.

Overcoming Biological and Chemical Barriers

For drugs with a very short biological half-life, CDDS provide a continuous supply to keep them active in the body longer. They can improve the absorption of poorly soluble drugs by keeping the tract.

Some other significant points of CDDS are –

1. Help in early identification of developmental delays in children
2. Enable early intervention, which improves long-term outcomes
3. Prevent permanent disability and reduce severity of impairments
4. Support normal growth and development of the child
5. Guide parents and caregivers for timely referral and management
6. Reduce emotional, social, and economic burden on families
7. Improve school readiness and learning abilities
8. Assist health workers in planning child health services
9. Contribute to better quality **of life** for affected children

Different Approaches of CDDS [10, 11, 12]

Controlled release (CR) drug delivery system is a sophisticated formulation designed to administer medication at a predetermined and consistent rate over an extended period. The primary objective is to maintain a stable, optimal concentration of the drug within the bloodstream or targeted tissues, ensuring maximum therapeutic efficacy while minimizing potential side effects associated with fluctuating drug levels.

This is the drug delivery system in which a constant level of a drug is maintained in blood and tissue for an extended period. Pharmacokinetics (PK) curves of plasma concentration of a drug versus time for two types of delivery systems, conventional and controlled. In a conventional delivery system, there is typical bolus PK for multiple dosing with oral tablets or injections,

where the drug level fluctuates above and below the minimum effective concentration. The controlled delivery system, on the other hand, shows zero-order PK with just a single dose of controlled drug delivery from a specific formulation or device. The drug levels are maintained constantly within the therapeutic window

Sustained release (SR) drug delivery system is a pharmaceutical formulation designed to release medication slowly and continuously over an extended period after a single administration. The primary goal is to provide a prolonged therapeutic effect, reduce dosing frequency, and minimize fluctuations in the drug's concentration in the bloodstream (the "peaks and valleys" associated with conventional immediate-release doses).

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.

Delayed-release (DR) drug delivery system i s a type of modified-release formulation that is designed to release its active ingredient at a time other than immediately after administration, typically at a specific location in the gastrointestinal (GI) tract. The immediate release drug delivery systems are particularly used to produce fast therapeutic drug plasma levels. These results in reduction or loss in drug effectiveness or also increased incidence of side effects. Modified release drug delivery systems include the systems with pH dependent, extended, delayed or pulsed drug release.

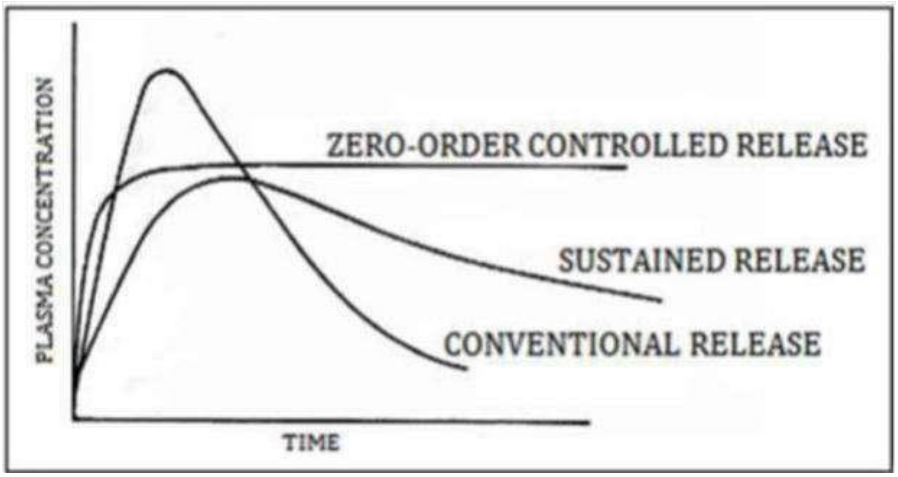

Figure. 2: Plasma concentration vs. time profile

Sustained, extended or prolonged release drug delivery devices, by contrast, are delayed release dosage forms have to be distinguished from the ones mentioned as they exhibit a more or less

pronounced lag time before drug release. A delayed Release dosage form is designed to release the drug at a time other than promptly after administration. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location.

Dissolution controlled - A dissolution-controlled drug delivery system is a type of controlled release system in which the rate of drug release is governed by the dissolution of a drug or its coating in the surrounding biological fluid. In this system, the drug is released only after the barrier material or matrix dissolves, making dissolution the rate-limiting step.[1, 13, 14]

There are two ways to prepare dissolution-controlled preparation:

1. Reservoir-Controlled Drug Delivery System
2. Matrix-Controlled Drug Delivery System

Reservoir-Controlled Drug Delivery System

A reservoir-controlled drug delivery system is a type of controlled release system in which the drug is contained in a core (reservoir) surrounded by a rate-controlling polymeric membrane. The drug release occurs by diffusion through this membrane, which controls the rate at which the drug enters the body. In this system, the polymer membrane is the key component that regulates drug release. As bodily fluids penetrate the membrane, the drug dissolves in the core and then diffuses outward at a controlled, nearly constant rate. The release rate depends on factors such as membrane thickness, permeability, surface area, and drug concentration.

Examples of reservoir-controlled systems include transdermal patches, implantable devices.

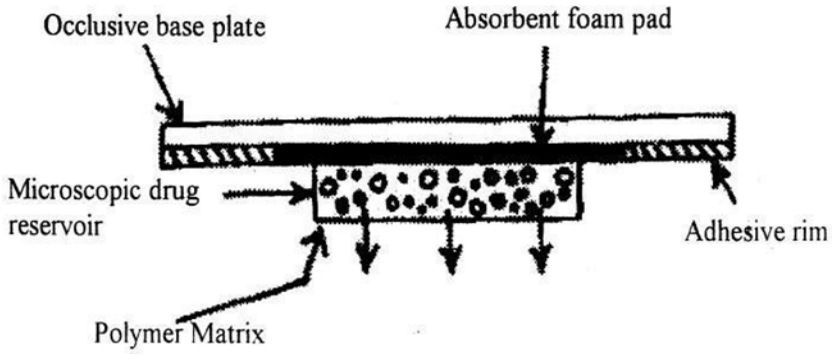

Figure 3: Reservoir-Controlled DDS

Matrix-Controlled Drug Delivery System

A matrix-controlled drug delivery system is a type of controlled release system in which the drug is uniformly dispersed or dissolved within a polymeric matrix. Drug release occurs as the drug diffuses through the matrix and/or as the matrix swells or erodes when it comes in contact with biological fluids. In this system, there is no separate rate-controlling membrane. Instead, the matrix itself controls the drug release rate. As the outer layer of the matrix becomes

hydrated, the drug near the surface is released first, followed by the gradual release of drug from the inner layers.

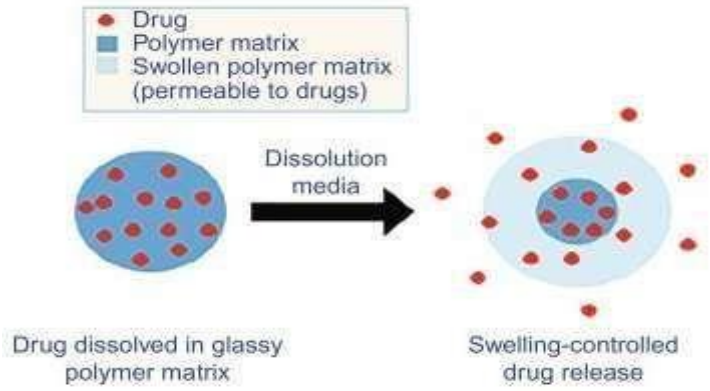

Figure 4: Matrix-Controlled DDS

TYPES OF MATRIX SYSTEMS:

Hydrophobic matrix systems – Use insoluble polymers (e.g., ethyl cellulose) where drug release occurs mainly by diffusion.

Hydrophilic matrix systems – Use swellable polymers (e.g., HPMC) where drug release occurs by diffusion and erosion.

Biodegradable matrix systems – The matrix gradually degrades, releasing the drug.

Diffusion controlled – A diffusion-controlled drug delivery system is a type of controlled release system in which the drug release occurs by diffusion from a dosage form into the surrounding biological fluid. The movement of drug molecules takes place from a region of higher concentration to lower concentration, and diffusion is the rate-limiting step.[15, 16]

Diffusion-controlled systems are mainly of two types:

1. **Reservoir Diffusion System**

   The drug is present in a central core (reservoir) surrounded by a polymeric rate-controlling membrane. The drug diffuses through this membrane at a controlled rate.

   Example: Transdermal patches, implantable devices.

2. **Matrix Diffusion System**

   The drug is uniformly dispersed throughout a polymer matrix. When the matrix comes in contact with bodily fluids, the drug diffuses out through the pores or polymer network.

   Example: Sustained-release tablets.

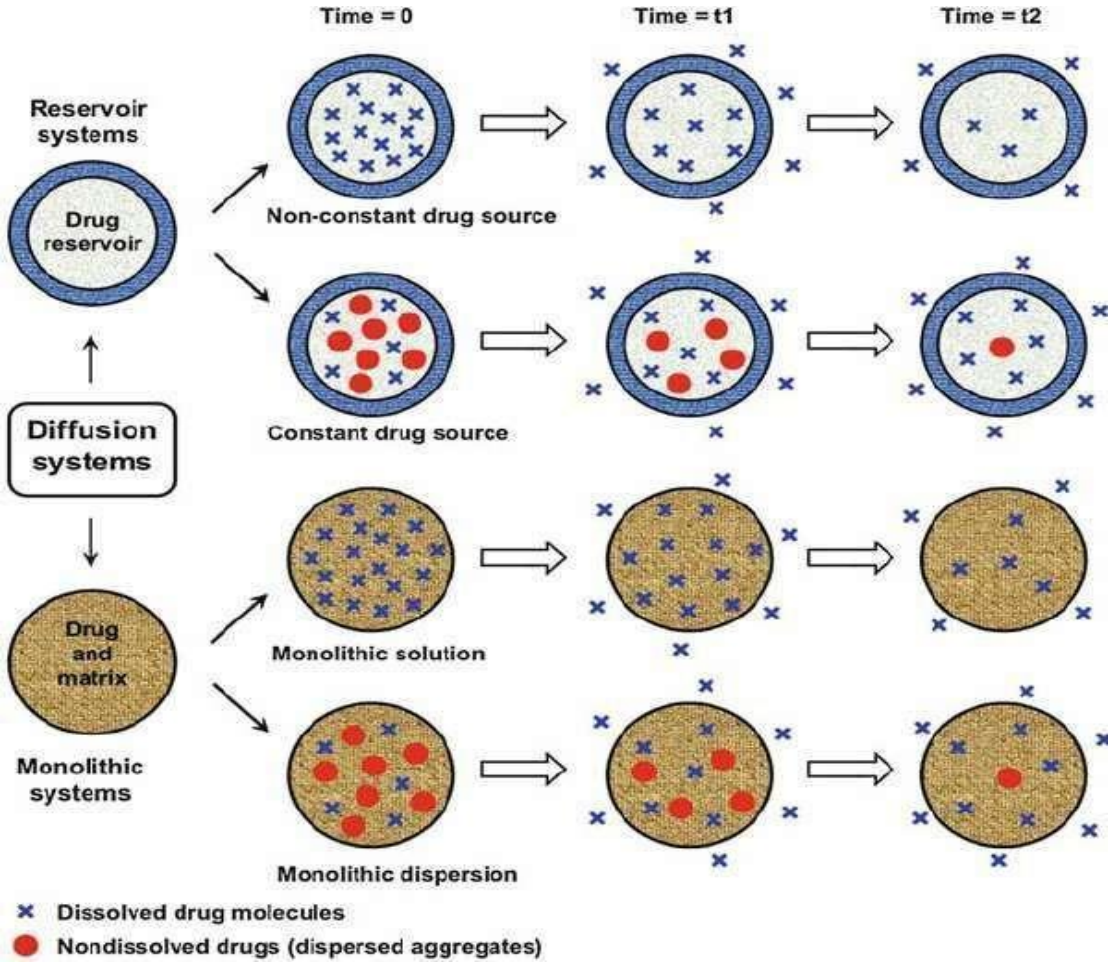

Figure 5 : Reservoir Diffusion System and Matrix Diffusion System

Diffusion–Dissolution Controlled Drug Delivery System

A diffusion–dissolution-controlled drug delivery system is a combined controlled release system in which both diffusion and dissolution mechanisms regulate the release of a drug. In this system, the drug release occurs when the drug or polymer first dissolves, followed by diffusion of the dissolved drug through a polymeric membrane or matrix into the surrounding biological fluid. Typically, the drug is either coated with a slowly dissolving polymer or embedded in a polymer matrix. As the coating or matrix dissolves gradually, the drug becomes available and then diffuses out at a controlled rate. Thus, both dissolution of the material and diffusion of the drug act as rate-limiting steps here.

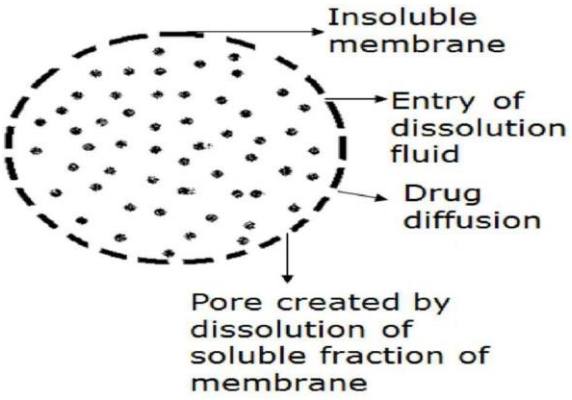

Figure 6: Diffusion–Dissolution Controlled Drug Delivery System

Water penetration controlled - A water penetration-controlled drug delivery system is a type of controlled release system in which the rate of drug release is regulated by the penetration of water into the dosage form. This system is often used for hydrophilic matrix tablets or swellable polymers.

Mechanism - When the dosage form comes in contact with bodily fluids, water penetrates the system. The water hydrates or swells the polymer, forming a gel layer around the drug core. The drug then diffuses through the gel layer at a controlled rate into the surrounding medium. As water continues to penetrate, the gel layer may gradually erode, allowing more drugs to be released.

Main Characteristics - The rate of drug release depends on: Polymer type (hydrophilic or hydrophobic), Swelling behavior, Tablet geometry and size. It often produces sustained or extended drug release.

Examples

- Hydrophilic matrix tablets (e.g., HPMC-based sustained-release tablets)
- Certain osmotic pump tablets

These are of two types: -

a) - Osmotically controlled

An osmotic-controlled drug delivery system is a controlled release system in which the drug is released at a predetermined and constant rate through a semi-permeable membrane, driven by osmotic pressure. In this system, water from the surrounding biological fluids enters the dosage form, dissolves the drug, and the resulting solution is pushed out through a small orifice, ensuring predictable.[17, 18, 19]

The osmotic pump system is similar in construction to a reservoir device but contains an osmotic agent that acts to imbibe water from the surrounding medium via a semipermeable membrane which is permeable to water but impermeable to drug. Such a device, called the

elementary osmotic pump (EOP), was first described by Theeuwes and Higuchi (1975). The delivery of the active agent from the device is controlled by water influx across the semipermeable membrane. The drug is forced out of an orifice in the device by the osmotic pressure generated by the device. The size of the orifice is designed to minimize solute diffusion, while preventing the build-up of a hydrostatic pressure head that has the effect of decreasing the osmotic pressure and changing the volume of the device. Therefore, the drug release rate remains constant delivering a volume equal to the volume of osmotic water uptake.

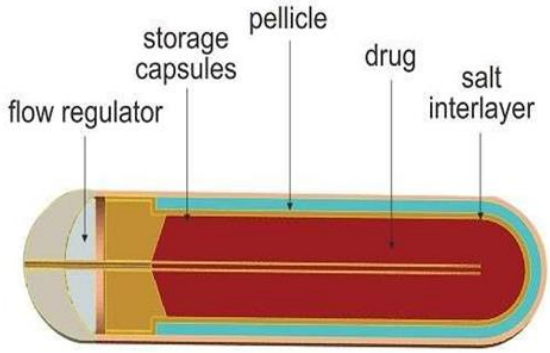

Figure 7: Osmotic Pump

b) Swelling Controlled-[20, 21]

- Polymer mess size is increased
- Drug diffuses outside
- Swelling polymer
- Hydrophillic polymer

Method using ion exchange resins

Using ion exchange resins (IER) for controlled drug release (CRDDS) involves binding charged drugs to the insoluble polymer beads, forming a drug-resin complex (resinate), and then slowly releasing the drug in the body as its ions exchange with physiological ions (like in the stomach), allowing for sustained release, taste masking, or targeted delivery, often with techniques like coating or bead formulation for enhanced properties like floating.

Key Steps & Methods

Drug Loading (Complexation):

Batch Process: Mix drug solution with resin beads in a vessel, allowing ions to exchange until equilibrium, forming the resinate.

Column Process: Pass the drug solution through a resin-packed column, often with a buffer wash to ensure deep loading.

Mechanism: Cationic drugs bind to acidic resins (like sulfonate groups), while anionic drugs

bind to basic resins, replacing the resin's mobile ions.

FORMULATION TECHNIQUES FOR CONTROLLED RELEASE:

Coating: Beads are coated (e.g., with ethyl cellulose) to control the rate of drug release, often creating floating systems (FDDs) by trapping CO2.

Matrix Formulation: Incorporating resins into tablets or suspensions to provide sustained release over time.

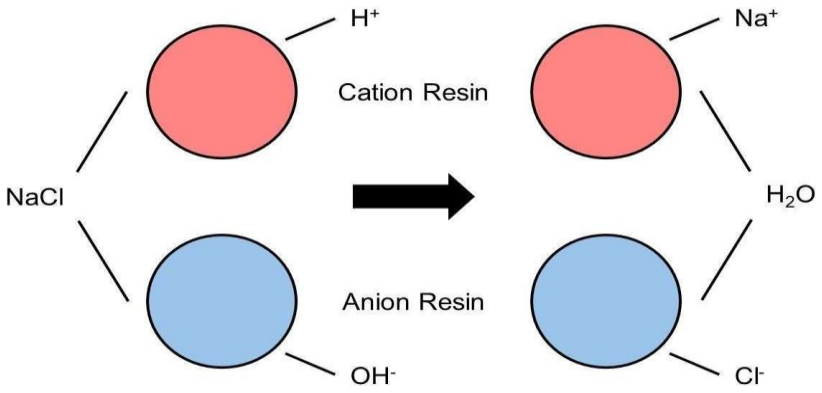

Figure 8: Method Using Ion Exchange Resins

Chemically controlled release system

A chemically controlled release system is a type of drug delivery technology where the release rate of an active agent is primarily governed by chemical reactions, such as the degradation or dissolution of the polymer matrix or the cleavage of chemical bonds linking the drug to a carrier. This contrasts with physical mechanisms (like simple diffusion or osmosis) where the polymer system itself remains largely unchanged during the release process.[22]

Chemically controlled systems typically fall into two main categories:

- **Erosion/Degradation Controlled Systems:** In these systems, the drug is omogeneously dispersed within a polymer matrix that gradually degrades or dissolves in the presence of water or biological fluids (e.g., enzymes).

  Mechanism: As the polymer breaks down into smaller, soluble, non-toxic units, the embedded drug is simultaneously released.

  Examples: Biodegradable polymers like poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and their copolymers (PLGA) are commonly used, especially for implantable devices like the Gliadel wafer for brain cancer treatment. The body metabolizes and eliminates the degradation products, so device retrieval is unnecessary.
- **Pendent Chain Systems (Polymer-Drug Conjugates):** In this approach, drug molecules are not simply embedded but are chemically attached (conjugated) to the

backbone of a polymer through a reactive bond.

Mechanism: The drug is released when the chemical bond linking it to the polymer chain is broken, typically through hydrolysis or enzymatic degradation at the target site. This strategy is often used for targeted delivery, as specific enzymes found in diseased tissues (like tumors) can trigger the release.

- **pH independent formulation**

  pH-independent Controlled Release Drug Delivery Systems (CRDDS) are designed to provide a uniform drug release rate regardless of the varying pH levels throughout the gastrointestinal (GI) tract (pH 1.2 to 8.0). These systems are primarily developed for drugs with pH-dependent solubility, such as weak acids or weak bases, which otherwise would dissolve too quickly in one region and precipitate in another.[23]

Core Mechanisms and Approaches

pH-Modifying Excipients: The most common strategy involves adding acidic or basic "pH modifiers" to the dosage form to create a constant micro-environmental pH within the drug delivery matrix.

- **For Weak Bases:** Acidic excipients (e.g., citric acid, succinic acid) are added to lower the intestinal tract, preventing drug precipitation and maintaining release.
- **For Weak Acids:** Basic excipients (e.g., sodium carbonate, calcium phosphate) are used to raise the in the stomach, increasing solubility in acidic environments.
- **Polymer Selection:** Non-ionic polymers, such as Hydroxypropyl Methylcellulose (HPMC**)**, are frequently used because their hydration and drug-release kinetics are relatively unaffected by pH.
- **Osmotic Pump Systems:** These systems use osmotic pressure to pump drug out of a semi-permeable membrane. The release rate is governed by the osmotic pressure gradient rather than external pH.
- **Floating Systems:** For weakly basic drugs that are highly soluble in the stomach, gastro-retentive (floating) systems are used to keep the drug in the low-pH gastric environment longer to ensure complete absorption.

Advantages-

- **Predictable Pharmacokinetics:** Ensures a stable drug release profile, reducing "peak and valley" plasma levels and inter-subject variability caused by differing gastric emptying times or GI pH.

- **Improved Bioavailability:** Prevents drugs from precipitating into insoluble forms as they move from the acidic stomach to the alkaline intestine.
- **Patient Compliance:** Facilitates once- or twice-daily dosing for chronic conditions, reducing the burden of frequent administration.

Typical Candidates for pH-Independent CRDDS

- Weakly basic drugs (e.g., Verapamil, Dipyridamole, Ondansetron).
- Weakly acidic drugs (e.g., Divalproex sodium).
- Drugs with a short half-life or narrow therapeutic window.
- Medications requiring long-term therapy for chronic inflammatory or cardiovascular diseases.
- Drugs with good solubility across a wide pH range
- Drugs having moderate dose size
- Drugs with short biological half-life
- Drugs requiring constant plasma concentration
- Drugs stable in both acidic and alkaline environments
- Drugs absorbed throughout the entire gastrointestinal tract
- Drugs not affected by food or gastric pH changes
- Drugs with high therapeutic index
- Drugs suitable for long-term therapy

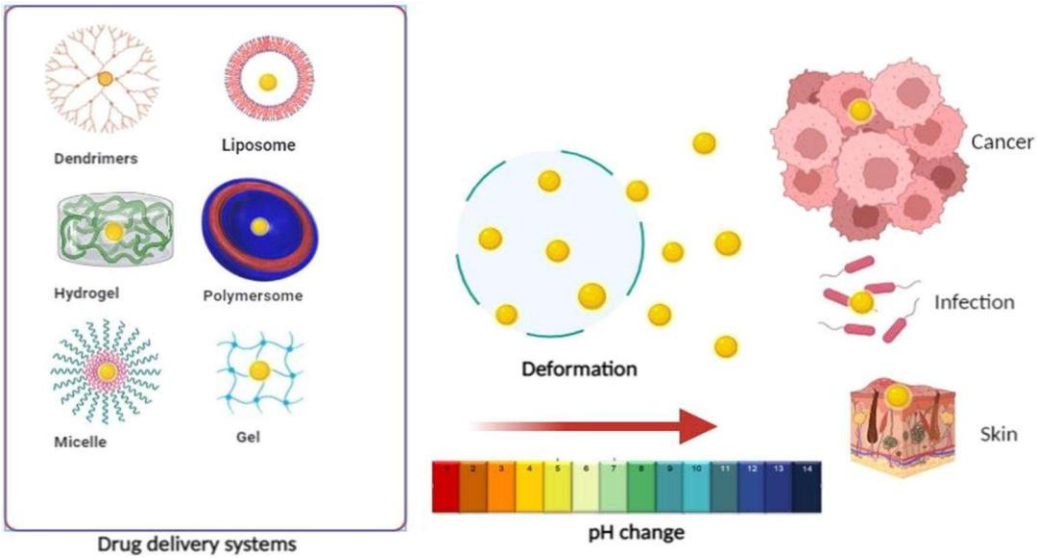

Figure 9: pH Independent Formulation

Altered Density System

The altered density system is a formulation approach in oral Controlled Release Drug Delivery Systems (CRDDS) designed to prolong the drug's residence time in the gastrointestinal (GI) tract, typically the stomach, by modifying the density of the dosage form. This increases the time available for drug absorption and reduces dosing frequency.[24, 25]

This system is generally classified into two main approaches:

1. **High-Density Approach**

   In this method, the density of the pellets is made higher than that of normal stomach contents (which are typically around 1.0 g/cm³), usually at least 1.4 g/cm³. The weighted pellets settle at the bottom of the stomach and remain there for a longer period due to gravity.

   Mechanism

   The dosage form stays in the lower part of the stomach, continuously releasing the drug as stomach contents are emptied in a controlled manner. It relies on making a dosage form denser than stomach contents (over 1.004 g/cm³) so it sinks to the stomach's bottom, gets trapped in the antrum's folds (rugae), and resists peristaltic movement, delaying emptying and prolonging drug release in the stomach. Materials like barium sulfate, iron powder, zinc oxide, and titanium dioxide are used to achieve this high density (around 2.5-3 g/cm³).

   Drugs are coated onto heavy cores or mixed with inert, heavy materials such as barium sulfate, titanium dioxide, iron powder, or zinc oxide. The weighted pellets can then be covered with a diffusion-controlled membrane formulating dosage forms (tablets, pellets) with a density greater than stomach contents (around 1.004 g/cm³), using heavy inert materials like barium sulfate, zinc oxide, or iron powder, causing them to sink to the stomach's bottom, thus staying longer for enhanced absorption, especially for drugs like propranolol or for treating stomach infections. Formulation focuses on incorporating these high- density excipients with controlled-release polymers (HPMC, sodium alginate) to ensure prolonged therapeutic action and resistance to peristaltic emptying.

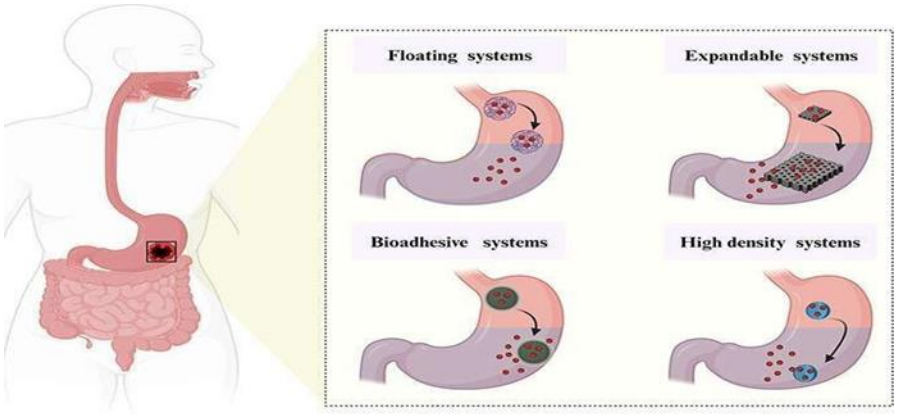

Figure 10: High-Density Drug Delivery System

- **Low-Density Approach (Floating Drug Delivery System)**

  Also known as a floating or hydrodynamically balanced system, this approach uses carriers with an apparent density lower than that of gastric fluid, allowing the dosage form to float on top of the stomach contents.[26, 27]

  Mechanism- The formulation remains buoyant in the gastric fluid for an extended period, slowly releasing the drug while it is in the stomach, and is emptied gradually with the rest of the stomach content

  Formulation: Porous materials with a low bulk density (e.g., polystyrol, pop rice, or popcorn) serve as carriers. These shells are undercoated with a polymer (like methacrylic polymer or cellulose acetate phthalate), followed by a drug layer mixed with release-controlling polymers such as ethyl cellulose or hydroxypropyl cellulose. Effervescent systems that generate gas (like (like CO_2) in situ also fall under this category to achieve buoyancy.

Figure 11: Floating Drug Delivery System

Importance of Floating Drug Delivery System

- Prolongs gastric residence time of the dosage form
- Improves bioavailability of drugs absorbed mainly from the stomach or upper intestine
- Provides sustained and controlled drug release
- Reduces frequency of dosing, improving patient compliance
- Enhances therapeutic effectiveness of drugs with short half-life
- Minimizes drug degradation in the intestinal environment
- Useful for drugs that act locally in the stomach (e.g., antacids, antibiotics for H. pylori)
- Reduces fluctuations in plasma drug concentration
- Improves absorption of drugs with narrow absorption window

Key Recent Developments in Controlled Drug Delivery

1. **Wireless Bioelectronic Drug Delivery Systems (Will-DDSs)** [28]

   Published March 2025 (Nature Reviews Electrical Engineering)

   Uses **wireless signals** to control drug release inside the body.

   Benefits: **real-time adaptability**, precise dosing, and improved patient compliance.

   Applications: chronic diseases (e.g., diabetes, cancer), where dynamic dosing is critical.

2. **Nanotechnology-Based Carriers**

   Nanoparticles, liposomes, and dendrimers are being engineered for **site-specific delivery**.

   Recent patents (2025) highlight **multi-layered nanocarriers** that respond to pH or temperature changes.

   Advantage: reduces systemic toxicity by releasing drugs only at diseased tissue. [(29)]

3. **Smart Polymers & Hydrogels**

   Polymers that **respond to stimuli** (temperature, pH, enzymes) are being integrated into drug delivery systems.

   Hydrogels allow **sustained release** and can be implanted for long-term therapy. [30,31]

   Example: Injectable hydrogels for **oncology treatments** that release chemotherapy drugs gradually.

4. Microchip-Based Delivery [32, 33]

   Implantable **micro-reservoir chips** controlled electronically.

   Enables **multi-drug release schedules** tailored to patient needs.

Currently in **clinical trials** for hormone therapy and pain management.

5. ***Challenges & Risks***

Biocompatibility: Ensuring materials don't trigger immune reactions.

Manufacturing complexity: Nanocarriers and microchips are costly to produce.

Regulatory hurdles: Approval processes for novel devices are lengthy.

Patient acceptance: Implantable devices may face resistance due to invasiveness

Comparison of Emerging Technologies

Technology	Key Feature	Advantages	Challenges
Wireless DDS	Remote-controlled release	Precise dosing, adaptable	Requires biocompatible electronics
Nanocarriers	Targeted delivery	Reduced toxicity, site-specific	Complex manufacturing
Smart Polymers	Stimuli-responsive	Sustained release, patient-friendly	Stability issues
Microchips	Programmable reservoirs	Multi-drug scheduling	Surgical implantation needed

CDDS in Global and Indian Market

Market Size & Growth [34,35]

The global Clinical Decision Support Systems market is rapidly expanding as healthcare providers adopt digital tools and AI-enabled solutions. Various estimates project strong growth: Valued at around USD 5.7–6.8 billion in 2024 and expected to reach ~USD 10.7–25.4 billion by 2030–2032, growing at a compound annual growth rate (CAGR) ~11 % to nearly 18 % in the forecast period.

The global controlled release drug delivery market size was estimated at USD 59.8 billion in 2024 and is projected to reach USD 148.6 billion by 2033, growing at a CAGR of 10.7% from 2025 to 2033. Changing prescription patterns of physicians preferring controlled-release drug delivery over conventional systems, owing to the benefits such as high therapeutic efficacy, better patient compliance, and reduced treatment cost, is expected to contribute to the market's growth over the forecast period.

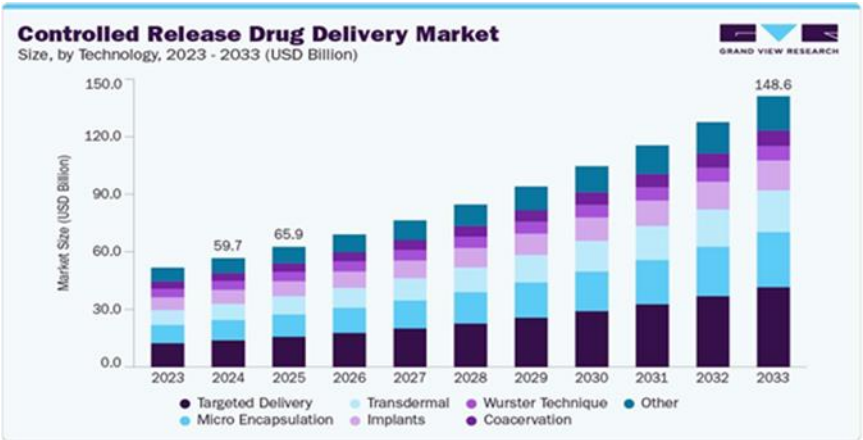

Figure 13: Controlled Release Drug Delivery Market (2025 – 2033)

CDDS in Indian Market

In the Indian market, the term CDDS most commonly refers to Controlled Drug Delivery Systems within the pharmaceutical sector, though it can occasionally refer to financial instruments or specific logistics services depending on the industry context.

- Market Rationale: Indian pharmaceutical companies focus on CDDS to reduce dosing frequency, minimize side effects (by avoiding "peaks and troughs" in blood drug levels), and improve patient compliance for chronic conditions like diabetes and hypertension.
- Technologies Used: Indian manufacturers employ several mechanisms:
- Diffusion-Controlled: Reservoir or monolithic systems where drugs diffuse through a polymer.
- Osmotically Controlled: Tablets that use osmotic pressure to pump the drug out through a laser-drilled hole.
- Targeted Systems: Designing drugs to release specifically in the colon or other target sites.

Regulatory Oversight: In India, these products are regulated by the Central Drugs Standard Control Organization (CDSCO), which oversees the approval of new modified-release formulations.

CDDS in Global Patent and Proprietary Drug Product List

CDDS technologies are categorized within "Novel Drug Delivery Systems" (NDDS) on proprietary and patent lists. These lists track**:**

1. Proprietary Formulations: Drugs using unique CDDS platforms are often listed under proprietary names (trade names) to distinguish them from generic immediate-release

versions.

2. Patent Protection: CDDS formulations frequently hold their own patents, separate from the active ingredient's original patent. This allows manufacturers to extend market exclusivity through "new formulation" or "dosage form" patents.

Common CDDS Technologies

Products on global patent lists often utilize the following CDDS types:

- Sustained/Controlled Release: Maintaining drug concentration within a therapeutic range for extended periods.
- Specialized Systems: Advanced carriers such as bilosomes, dendrimers, nanoparticles, and transferosomes designed for precise transport.
- Layered Tablets: Bilayer or inert core-active coat structures characterized by specific physical forms (e.g., A61K9/2086 patent class).

Global Resources for CDDS/Proprietary Data

- The Orange Book (FDA): Tracks approved drug products with therapeutic equivalence, including many CDDS-based formulations.
- Pat-INFORMED (WIPO): A global gateway to medicine patent information for major therapeutic areas like HIV/AIDS, cardiovascular diseases, and oncology.
- MedsPaL (Medicines Patent Pool): Provides the intellectual property status of priority medicines, specifically those on the WHO Model List of Essential Medicines.
- CDD Vault (Collaborative Drug Discovery): A private/public platform for sharing preclinical and chemical drug discovery data globally.

Market Status (2026)

- **Economic Impact:** The Indian drug delivery systems market is projected to reach approximately USD 0.81 billion by 2026. The broader global market for controlled-release systems is expected to grow significantly, driven by the increasing prevalence of chronic diseases such as diabetes and cardiovascular disorders.

Dominant Technologies:

Injectable Systems: Currently hold the largest market share (approx. 82.8%) due to the rise in Biologics and wearable delivery devices. Conditions such as diabetes, cancer, and autoimmune disorders require long-term, precise dosing. Injectable systems offer high bioavailability and accurate delivery, which are critical for managing these life-threatening illnesses. A major shift toward home healthcare is fueling the adoption of wearable injectors and auto-injectors. These

devices allow patients to self-administer large-volume biologics hands-free, reducing the need for frequent hospital visits. The Indian drug delivery devices market is projected to reach approximately USD 0.81 billion by 2026. While other segments like inhalers are large, injection devices are categorized as the most lucrative and fastest-growing segment

Oral Controlled Release: Features technologies like diffusion-controlled and matrix systems, which remain the top pick for chronic condition management. Oral controlled release systems account for approximately 35.3% of the global controlled release market revenue. The Indian oral drug delivery market is a core component of its USD 0.81 billion drug delivery device market, growing rapidly due to heavy investment in R&D and a robust manufacturing base for complex generics. The cardiovascular segment currently holds the largest share of applications for oral drug delivery, followed closely by metabolic disorders like diabetes.

Leading Players: Major Indian companies active in CDDS development include Sun Pharmaceutical Industries, Cipla, Dr. Reddy's Laboratories, Lupin, and Zydus Lifesciences. Leads with a focus on advanced oral controlled-release formulations and vaccine technologies. A leader in oncology and immunology, specializing in biodegradable polymers for sustained release Known for advanced implantable systems for chronic conditions like neuroscience and immunology. Invests heavily in nanotechnology-enabled delivery systems and gene therapies.

Proprietary and Approved CDDS Products in India

Products using CDDS technologies are listed by the Central Drugs Standard Control Organization (CDSCO) as "New Drugs" or "Modified Release" formulations. Examples of proprietary and patented products in the Indian market include:

Chronic Care (Diabetes/Weight):

Semaglutide Injection: Approved for chronic weight management as of January 16, 2026. Generic competition is projected to reduce the cost of semaglutide therapy by 50% to 70%. Monthly treatment costs may fall from the current to approximately. Secured a court ruling in late 2025 allowing them to manufacture and export semaglutide to countries without patent protection, with a planned domestic launch post-March 2026 Partnered with Ajanta Pharma to market semaglutide across 23 emerging markets and is targeting the Indian market post-patent expiry.

Tirzepatide: Proprietary solution for injection (various strengths). A major formulation patent (Indian Patent No. 262697) for semaglutide is scheduled to expire on March 20, 2026. This "patent cliff" is expected to trigger immediate market entry by 10–15 Indian generic players within three months of expiry. Marketed and distributed by Cipla under an agreement with Eli

Lilly, leveraging Cipla's extensive network to reach Tier-2 and Tier-3 cities The current pricing is a barrier for many; however, the impending patent cliff for competitor semaglutide (expected in March 2026) suggests that the overall anti-obesity and diabetes drug market in India is poised for significant price reductions and increased access through generics. Achieved through specific molecular modifications, including a C20 fatty- diacid portion that binds strongly to albumin in the bloodstream, extending the drug's half-life to approximately 5 days.

Dapagliflozin + Metformin ER/SR: Common sustained-release (SR) combinations for glycemic control.

Specialized Proprietary Formulations:

Pancreatin Mini microspheres: Patented proprietary formulation. The small size of the microspheres allows them to pass through the pylorus (the opening from the stomach to the small intestine) simultaneously with chyme (food), even when the pylorus is constricted. The enteric coating protects the enzymes from stomach acid (pH <5.5) and dissolves rapidly once it reaches the duodenum (pH >5.5), ensuring localized delivery where digestion occurs. These products are often "proprietary" because the manufacturing process for stable, acid-resistant enzyme pellets is technically demanding and requires specialized coating equipment to ensure consistent enzyme activity.

Rivastigmine/Donepezil SR: Controlled-release versions for neurological disorders. The 23mg SR dose is specifically designed to provide higher therapeutic concentrations while maintaining a side- effect profile comparable to lower-dose immediate-release versions. (Sun Pharma) and Exelon Capsules: These use specialized enteric-coated pellets or matrix tablets to delay release until the drug passes the stomach, significantly reducing nausea.: By bypassing certain parts of the digestive tract or using transdermal routes, these specialized formulations ensure more of the drug reaches the brain.

Prolonged Release Tablets: Examples include Diviron-SR (Diclofenac) and Mebeverine HCl prolonged-release capsules.

Regulatory Resources

To track specific proprietary drug products and their CDDS status in India, anyone can refer to:

- CDSCO Approved New Drugs List**:** Updated lists of drugs by year (including 2025 and 2026).
- New Drugs Division (SND): Specific lists for subsequent new drug approvals and fixed-dose combinations.
- CSIR-CDRI New Drugs: Repository of drugs developed through Indian research

institutes, such as Gugulipid and Centchroman.

CONCLUSION

The dosage form is a combination of drugs and excipients. Excipients are used to get a structure, enhance stability and mask the taste. Solid, semisolid and liquid dosage forms are the conventional dosage forms that suffer from fluctuations in plasma drug levels which demands high dosing and dosing frequency with poor patient compliance. The bioavailability of a drug is crucial to achieving the desired action from any dosage form. Controlled drug delivery systems have emerged as an alternative to the conventional sort, to improve the bioavailability, extent the drug release and maintain drug plasma levels within the therapeutic window with minimal side effects. Controlled drug delivery increases the drug solubility and stability and offers the selective delivery of drugs with a predictable rate and mechanism to specific organ/tissue/cells. Dissolution, diffusion, water penetration and chemically controlled drug delivery systems are the types of controlled drug delivery systems. Stimuli-responsive delivery systems are useful in various disease conditions (cancer, infections, etc.) to target as well as control the release. Further, nanocarriers with intelligent biomaterials and additive manufacturing techniques can be developed to achieve controlled targeted delivery. The future of drug delivery is focused on patient-specific therapy using microfluidic-based, 3D-printed devices and CRISPR cas9 based delivery systems integrated with quantum sensing.

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