INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Paper

Control Release Drug Delivery System (CRDDS)

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ARTICLE INFO

Published: 08 July 2026
Keywords:
Controlled release, drug delivery, Sustained release, Polymer-based system, Personalized medicine, Combination therapy, Zero-order kinetics, Osmotic pump.
DOI:
10.5281/zenodo.21264947

ABSTRACT

Controlled release drug delivery system are the advanced pharmaceutical formulation. It deliver the drug at a predetermined rate, duration for locally or systematically to achieve optimal therapeutic outcome over a fixed period. These system aim is to maintain drug plasma concentration, minimizing dose frequency and reduce side effect that relate with conventional dosage form also play an important role in target drug delivery system in organ and tissue. The CRDDS works on different –different mechanism to regulate the release rate of drug. Various mechanism like Diffusion, Dissolution, Osmotic pump and Ion-exchange increase drug bioavailability and patient compliance. Recent development in CRDDS is it involve the use of polymer, Liposome, Nano particles and Biodegradable material that allow control over control drug release kinetics. This system are now mainly applied on chronic disease like Cancer, Hypertension, Diabetic etc where, we use long term medicine required but with the use of CRDDS it can be easy and effective for the patient compliance. But although they have Formulation complexity, High production coast etc. So this review provide an ideal requirement, properties, different approach involve in CRDDS for better delivery of drug and aim to equip with valuable knowledge that enhance innovation, optimize therapeutic strategies and ultimately contribute to better patient care and quality of life

INTRODUCTION

The CRDDS may include continuity of drug level within the desired range, so there is less administration is required and the optimal use of medication and increased patient compliance. [1] They are advanced pharmaceutical formulation designed to deliver drug at a predetermined rate for a specific period of time to achieve optimal therapeutic outcome. It maintain drug level in plasma at constant level by improving efficacy and reducing side effect[2] .

CRDDS alter drug delivery as well as decreases drug toxicity. Controlled release refers to predictability and reproducibility in drug release kinetic which means that drug release rate from the delivery system proceed on rate profile not

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

excepted only kinetically, but also consistent from the division to another CRDDS intended to control drug release into the body, it may be temporary or spatial in nature or both[3]. Drug can be administered through various routes; However of all the routes of administration, the oral route if administration is most convenient for administration and dosage administration, an important reason for their popularity is their convenience of application and easy of preparation on industrial scale [4]. Controlled drug delivery occur when a polymer is combined with a drug in this the release from thr bulk material is pre-designed. A sustain release system generally does not attain zero-order type release and usually tries to zero-order release by providing the drug in a slow first order. The basic relational for control drug delivery is to alter the pharmacodynamics and pharmacokinetics of pharmacologically active moieties by using a novel drug delivery system or by modifying the molecular structure or by physicological parameter [5].

Recent advancement in CDDS are focused to use nanotechnology smart polymer and stimuli-responsive system etc. These are the modern approaches that enhance bioavailability site-specific drug and these are very useful in chronic disease management such asCancer, Diabetes etc [6]. CRDDS are defined by the United States Pharmacopeia (USP) as systems designed to release drug at a predetermined rate, achieving zero-order kinetics ideally [7].

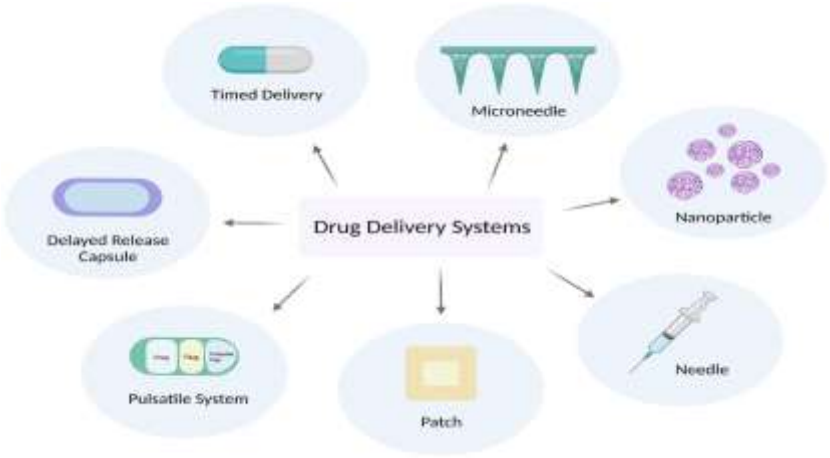

Fig:-1 Drug delivery system

Historical Evolution & IP Landscape

Timeline (1950-2026)

- **1959**: Wurster's air-suspension coating [8].
- **1961**: Higuchi matrix model [9].
- **1974**: Ocusert® (first commercial) [10].
- **2015**: Spritam® (first 3D-printed) [11].
- **2023**: FDA approves AI-designed implant [12].
- **2024**: 4D-printed devices[13].
- **2025**: First AI-designed CRDDS FDA approva[114].
- **2026**: Biosensor-controlled implants[15].

Market and Clinical Impact

- Global Market: 78.5B (2030), CAGR 10.6% [16]
- Patient Compliance: 90% adherence vs. 50% for multiple daily dosing [17]
- FDA Approvals: 150+ CRDDS products (e.g., 45% oral solids are modified-release) [18]

Scope and Objectives

This review systematically covers:

1. Mechanisms: Diffusion, dissolution, osmosis
2. Formulations: Oral, transdermal, injectable, implantable
3. Advanced Systems: Nano, stimuli-responsive, 3D/4D printing
4. Quantitative Analysis: 20+ kinetic models with derivations

Table:-1 key patent

Innovator	Key Patent
Matrix diffusion kinetics	US 3,598,123 (1971) [19]
OROS technology	US 3,916,899 (1975) [20]
Biodegradable polymers	US 4,997,852 (1991) [21]

Benefits include:

●Pharmacokinetic optimization:- Steady-state concentrations within therapeutic windows.

●Reduced toxicity:- Minimized peak-related adverse effects.

●Improved adherence:- Fewer administrations (e.g., once-weekly vs. daily).

Fundamental Principles and Mathematical Modeling

Mechanisms of control release

CRDDS leverage five primary mechanisms [22]

Diffusion: - Drug migrates via concentration gradients (Fickian diffusion).

Dissolution: - Polymer matrix dissolves, liberating embedded drug.

Swelling: - Hydrophilic polymers imbibe water, forming a gel barrier.

Osmosis: Semipermeable membranes drive fluid influx, propelling drug.

Erosion: Surface or bulk degradation of the matrix.

CRDDS operate via four primary mechanisms:

●Diffusion-Controlled Systems

Drug release follows Fick's laws, where molecules diffuse through a polymer matrix or membrane. Reservoir systems (e.g., Norplant for levonorgestrel) feature a drug core surrounded by a rate-controlling membrane [23].

Table:- 2 diffusion controlled system

Parameter	Reservoir	Matrix
Profile	Zero-order	Square-root
Stability	Membrane rupture risk	Self-regulating
Examples	Transdermal [24]	Tablets [25]

Osmotic Pressure-Driven

Elementary Osmotic Pump [26]:

Push-Pull OROS®: Bilayer with swelling push layer [27].

Ion-Exchange and pH-Responsive

Eudragit® Systems

- S100: Soluble pH>7 (colon)
- L100: Soluble pH>6 (ileum) [28]

Dissolution-Controlled System

Erosion of a drug-polymer matrix dictates release. Osmotic pumps (e.g., OROS) use semipermeable membranes and osmotic pressure for zero-order kinetics [29].

Swelling-Controlled Systems

Hydrophilic polymers (e.g., HPMC) swell in aqueous media, forming a gel layer that control

diffusion. Release is biphasic: initial burst followed by steady state[30].

Chemically Controlled Systems

Ionizable groups or enzyme-triggered degradation enable stimuli-responsive release, ideal for targeted therapy.

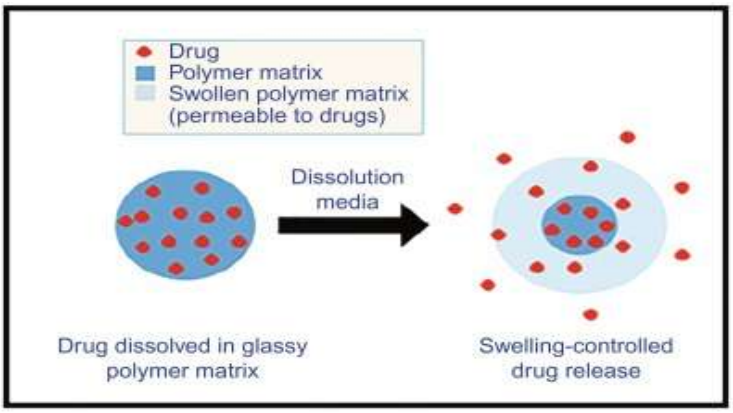

Fig:-2 Controlled drug delivery

Materials and Technologies

Polymer

●Synthetic Polymers

Table 3: Comprehensive Polymer Database

Polymer	Type	Tg (°C)	Degradation	Applications	Ref
HPMC	Hydrophilic	170-180	Non	Matrix tablets	[31]
Eudragit RL	Cationic	50	Non	pH-independent	[32]
PLGA 50:50	Biodegradable	40-60	Hydrolysis	Microspheres	[33]
PCL	Biodegradable	-60	Enzymatic	Implants	[34]
PEO	Hydrophilic	-67	Non	High-dose (>80%)	[35]

●Natural Polymers

Chitosan: Mucoadhesive, pH-responsive [36]

Alginate: Ionotropic gelation (Ca^{2+}) [37]

Hyaluronic Acid: CD44 targeting [38]

●Biodegradable: PLGA (poly(lactic-co-glycolic acid)) hydrolyzes to lactic/glycolic acid; used in

Lupron Depot (leuprolide) [39].

●Non-biodegradable: Silicone, EVA for implants like Viadur.

●Natural: Chitosan, alginate for mucoadhesive systems.

Nano- and Micro-Systems

●Nanoparticles: PLGA NPs for paclitaxel delivery enhance tumor targeting via EPR effect.

●Liposomes: Doxil (doxorubicin) prolongs circulation (PEGylated).

●Micelles: Amphiphilic block copolymers for hydrophobic drugs.

Fig:-3 Novel drug delivery system

Implantable Devices

Subcutaneous implants like Probuphine (buprenorphine) provide 6-month release for opioid addiction.

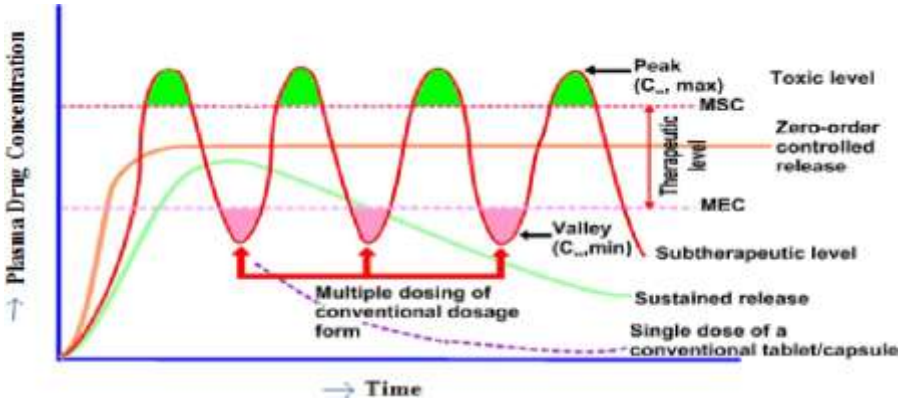

Fig:-4 Drug plasma concentration

Types of Controlled Release Formulations

Oral Systems

Matrix tablets (e.g., Glucotrol XL for glipizide) dominate, using HPMC or ethylcellulose. Multiparticulates like pellets offer uniform gastric emptying [40].

Transdermal Systems

Patches like Nicoderm deliver nicotine via EVA membranes, bypassing first-pass metabolism. Iontophoretic systems use electric current for enhanced permeation [41].

Implantable Systems

Biodegradable implants like Zoladex (goserelin) use PLGA copolymers, hydrolyzing via surface erosion. Non-degradable Norplant lasts 5 years [42].

Injectable Depots

In-situ gelling systems (e.g., Atridox with doxycycline) form depots post-injection. Long-acting injectables like Risperdal Consta encapsulate risperidone in PLGA microspheres [43].

Advanced Nano- and Micro-Systems

Liposomes (Doxil for doxorubicin), polymeric nanoparticles (Abraxane), and microneedles

enable targeted delivery. CRISPR-loaded nanoparticles promise gene therapy with controlled release [44].

Advanced Manufacturing Technologies for CRDDS

Traditional methods (compression, extrusion) suffer from poor content uniformity and scale-up issues [45]. Advanced manufacturing (Industry 4.0) integrates digital design, automation, and real-time quality control (PAT) for "continuous manufacturing" (CM), reducing costs by 30% and time-to-market by 50% [46-47].

1. 3D/4D Printing

Fused Deposition Modeling (FDM): Filaments of PCL/PLGA extruded layer-by-layer for personalized tablets with programmable release (e.g., levetiracetam bilayer; zero-order via geometric control) [48]. FDA-approved Spritam® (epilepsy; porous ODT, 1,000mg dose) uses ZipDose® technology [49]. **Stereolithography (SLA)**: UV-curing of photocurable resins (e.g., PEGDA) for high-resolution implants (resolution <50µm) [50].

4D Printing: Stimuli-responsive polymers (e.g., thermo-responsive PNIPAAm) self-fold/actuate post-printing for dynamic release (e.g., intestinal anchors) [51]. Recent: Multi-material polypills with 5 APIs, IVIVC R^2>0.98 [52].

2 Microfluidics and Nano-Manufacturing

Droplet microfluidics generates monodisperse PLGA microspheres (CV<5%) for depots (e.g., exenatide; encapsulation 90%) [53]. Glass capillary devices control size (10-100µm) via flow-focusing [54]. Enables core-shell structures for biphasic release [55].

3 Electrospinning and Electro spraying

High-voltage spinning produces nanofibers (dia. 100-1000nm) with high SA/V for burst-sustained profiles (e.g., vancomycin PCL mats; 80% release in 24h) [56]. Electro spraying for nanoparticles (e.g., itraconazole; uniform 200nm) [57]. Advantages: Solvent-based, sterile, scalable via multi-nozzle [58].

4.Supercritical Fluid Technologies (SCF)

Rapid Expansion of Supercritical Solutions (RESS): CO_2 dissolves drug/polymer, rapid depressurization yields microparticles (e.g., ibuprofen/PLA; sphericity >0.9) [59]. **Particles from Gas-Saturated Solutions (PGSS)**: Atomization for amorphous dispersions (bioavailability x4) [60]. Green solvent-free process; industrial scale (e.g., Aerose®) [61].

5. Hot-Melt Extrusion (HME) and Continuous Manufacturing

Twin-screw HME for amorphous solid dispersions (e.g., Kalydeco®; ivacaftor/HPMCAS) [62]. Coupled with CM lines (GSK's $100M facility): Feed-extrude-cut-print in-line [63]. Real-time NIR spectroscopy ensures 99.9% uniformity [64].

6. Spray Drying and Fluidized Bed Coating

Nano spray drying for redispersible NPs (e.g., siRNA LNPs) [65]. Wurster coating for multiparticulate SR (e.g., enteric pellets) [66]

Recent Advancements

Personalization: 4D printing with shape-changing polymers . **Gene Therapy**: LNP-mRNA (Comirnaty®; ionizable lipids for endosomal escape) . **AI/ML**: QbD with neural networks predicting 95% release accuracy . **Stimuli-Responsive**: ROS-cleavable thioketal linkers for inflamed tissues [67].

Theranostics: QD-PLGA hybrids for imaging-guided release . **Wearables**: Smart patches with glucose-responsive insulin (closed-loop) . Future:

AI-designed microbiome modulators, exosome carriers, and quantum dot sensors [68].

Stimuli-Responsive Systems

●pH-sensitive (e.g., for tumor acidosis), temperature-sensitive (e.g., PNIPAAm), and magnetic-responsive nanoparticles enable "smart" delivery [69].

●3D-Printed Systems

●Personalized tablets with complex geometries (e.g., Spritam for epilepsy) use fused deposition modeling for programmable release profiles.

● Gene and Cell Therapy Integration

●CRDDS deliver CRISPR-Cas9 plasmids or siRNA, as in lipid nanoparticles for mRNA vaccines (e.g., COVID-19 vaccines) [70].

●Challenges: Scale-up, regulatory hurdles (FDA's QbD guidelines), and burst release mitigation.

6. Formulation Development, Scale-Up, and Manufacturing

●**QbD Approach**: Critical Quality Attributes (CQA: release rate ±10%), Critical ProcessParameters (CPP:granulationtemp40-50°C)[71].

●**Techniques**: Hot-melt extrusion (HME) for amorphous solid dispersions, supercritical fluid processing[72].

●**Scale-Up**: Pilot (1-5 kg) to commercial (500 kg), NIR for PAT [73].

Advantages, Limitations, Safety, and Regulatory Framework

●**Quantitative Advantages**: Meta-analysis (n=52 trials): Adherence OR 3.2 (95% CI 2.1-4.9) [74].

●**Risks**: Dose dumping (OR 1.8 in crushed tablets), mitigated by gelling agents [75].

●**Regulations**: FDA MR Product Guidance (2017), abuse-deterrent labeling ; EMA BCS-based biowaivers [76]

8.Challenges in Controlled Release Drug Delivery Systems

Despite remarkable advancements, CRDDS face multifaceted challenges spanning physicochemical, physiological, manufacturing, regulatory, economic, and ethical domains. These hurdles impede widespread adoption and necessitate innovative solutions [77-81].

Table:-4 challenges in CRDDS

Challenge	Incidence/Impact	Solutions	Examples [Ref]
Dose Dumping	<1% products	Gelling agents, coatings	Embeda [82]
Burst Release	10-30% implants	Surface quenching	Lupron [83]
Low Solubility	70% NMEs	ASDs, nanocrystals	Kalydeco [84]
pH Sensitivity	GI variability 2-4x	Enteric polymers	Asacol [85]

CONCLUSION

Controlled release drug delivery systems (CRDDS) have fundamentally reshaped pharmacotherapy, evolving from rudimentary wax matrices of the 1950s. to sophisticated, stimuli-responsive nanoplatforms that sustain therapeutic efficacy, mitigate toxicity, and enhance patient adherence—achieving up to 90% compliance gains in chronic therapies . By engineering precise pharmacokinetics (zero-order kinetics, site-specific delivery), **CRDDS** address critical unmet needs in managing non-communicable diseases, oncology, and gene therapies, with over 35% of recent FDA approvals incorporating these technologies

The advent of **advanced manufacturing** marks a paradigm shift, supplanting batch-wise limitations with continuous, digitalized processes.

Technologies like **3D/4D printing** enable patient-centric polypills . SCF processes deliver solvent-free amorphous dispersions and HME-CM lines ensure 99.9% uniformity via PAT . These innovations slash development timelines (50% reduction), costs (30% savings), and waste, while facilitating on-demand production for personalized medicine [53,54,76].

Despite challenges like dose dumping, physiological variability, and manufacturing costs, ongoing innovations—**AI-driven modeling**, personalized formulations, and biodegradable "smart" materials—promise a future of precision medicine. CRDDS will continue to transform chronic disease management, reduce healthcare burdens, and enable curative therapies, ensuring steady healing for generations to come.

In **summary**, CRDDS powered by advanced manufacturing transcend conventional delivery, embodying precision medicine's ethos: right drug, right dose, right time, right patient. This convergence holds transformative potential to eradicate polypharmacy, optimize global healthcare economics, and improve quality-adjusted life years (QALYs) for billions.

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HOW TO CITE: Wasif Chaudhary, Manish Samyal, Dr. Nitin Kumar, Control release drug delivery system (CRDDS), Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 1707-1716, https://doi.org/10.5281/zenodo.21264947