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Engineering Controlled Drug Delivery Systems: Design Strategies, Release Kinetics and Emerging Therapeutic Perspective

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Abstract
Controlled pharmaceutical delivery systems (CDDSs) have progressed from traditional sustained-release formulations to engineered platforms with the ability to modulate drug release in a spatial, temporal and physiological or externally applied stimuli-responsive manner. Recent advances in biomaterials, nanotechnology, microfabrication, additive manufacturing, and bioengineering have enabled precise control over drug loading, transport, degradation, and therapeutic exposure. This review critically discusses the engineering principles that govern the design of CDDSs with special emphasis on polymer selection, carrier architecture, drug-material interactions, surface engineering, encapsulation strategies and physicochemical parameters influencing release performance. It covers the basic and sophisticated drug-release mechanisms including diffusion, dissolution, swelling, erosion, degradation, osmosis and stimuli-responsive release. It also covers the mathematical models to describe and forecast release kinetics. Emerging platforms, such as long-acting injectable and implantable systems, nanocarriers, microneedles, 3D-printed dosage forms, mechanically and remotely triggered systems, and smart responsive carriers, demonstrate the potential of personalized and on-demand therapy. Scalability, reproducibility, biocompatibility, stability, regulatory considerations and patient-centric design are taken into consideration in translating engineered delivery platforms from laboratory-scale development to clinical application. Finally, the combination of artificial intelligence, machine learning, advanced manufacturing and precision medicine is discussed as a potential pathway to rationally optimize drug release and therapeutic outcomes

Keywords: Controlled drug delivery; Drug release kinetics; Pharmaceutical engineering; Stimuli-responsive delivery; Long-acting drug delivery; Smart drug delivery systems; Precision therapeutics

I. Introduction to Controlled Drug Delivery Systems

A Controlled Drug Delivery System (CDDS) is engineered to regulate the rate, duration, and sometimes the site of drug release, ensuring that drug concentrations remain within the desired therapeutic range over an extended period. This system contrasts with conventional dosing forms, like tablets and injections, which can lead to significant fluctuations in plasma drug levels and necessitate repeated dosing. Such frequent administrations may diminish patient compliance and lead to uneven drug concentrations.

A CDDS maintains drug concentration at the action site by delivering medication at a controlled rate for a specific duration. Various mechanisms can regulate this delivery, including diffusion, osmotic pressure, and chemical reactions. Key terminology includes controlled release (steady drug release), sustained release (prolonged action), and targeted delivery (specific site delivery). Critical concepts also encompass the therapeutic window (optimal drug concentration range), loading dose (initial high dose), maintenance dose (subsequent doses), and zero-order release (constant drug output).

The rationale for implementing CDDS includes maintaining therapeutic drug concentration, minimizing variations in drug levels, reducing dosing frequency, enhancing patient adherence, and limiting adverse effects. CDDS allows for extended drug release from a single administration, ideal for long-term treatments, promoting consistent pharmacological responses while avoiding excessively high drug concentrations.

Controlled drug delivery systems (CDDS) aim to achieve regulated drug delivery, prolonged therapeutic impact, and sustained drug concentration, thereby minimizing adverse effects. They focus on maintaining drug levels over time, reducing plasma concentration fluctuations, and enhancing patient adherence through less frequent dosing. By ensuring

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steady medication delivery and enhancing drug stability and bioavailability, CDDS improve treatment efficacy while providing targeted distribution when required. This approach addresses the limitations of conventional dosage forms, which often require repeated doses that can lead to fluctuating therapeutic levels. [1,2,3]

Advantage of CDDS

- decreased frequency of dosage
- Enhanced adherence to treatment
- preservation of the therapeutic drug's concentration
- Decreased drug variations in plasma
- Decreased negative consequences
- Extended therapeutic effect
- Enhanced bioavailability when appropriate
- Improved management of medication release
- Possibility of targeted medication administration
- Decreased discomfort from repeated administration

Limitation of CDDS

- Controlled medication delivery systems have many drawbacks despite their benefits:
- more expensive to produce than many traditional dosage formulations.
- intricate manufacturing and formulation procedure.
- Dose dumping could occur if the system malfunctions.
- Certain materials or polymers may raise issues with biocompatibility or toxicity.
- Not all medications can be administered under regulated conditions.
- Certain oral systems may be impacted by gastrointestinal disorders.
- Consistently attaining the intended release profile could be challenging.
- The implantation or removal of certain implantable systems may necessitate an intrusive surgery.

Drug Selection and Design Considerations

Physico Chemical and biological properties of drugs

The development of an efficient controlled drug delivery system requires a comprehensive understanding of the drug's physicochemical and biological characteristics. These factors, including solubility, dissolution, membrane penetration, stability, absorption, distribution, metabolism, elimination, and therapeutic response, influence the drug's effectiveness. Hence, the selection of a drug for controlled release should consider its physicochemical properties alongside its pharmacological efficacy.

1. Physical and Chemical Characteristics

1.1 Solubility in Water

One key factor influencing medication dissolution and bioavailability is aqueous solubility. Medications must dissolve in biological fluids before entering systemic circulation. Highly soluble drugs may release quickly, necessitating special formulation strategies for extended release, while poorly soluble drugs can exhibit delayed dissolution and variable absorption. Therefore, solubility is vital in drug selection and controlled release formulation, with moderately soluble drugs often being more suitable as they balance release rates, avoiding rapid release or incomplete dissolution.

1.2 Lipophilicity and Partition Coefficient

A popular indication of lipophilicity, the partition coefficient shows a drug's relative affinity for lipid and aqueous phases. Lipophilicity has a significant impact on tissue distribution, membrane penetration, and a drug's capacity to overcome biological barriers. The lipophilicity of a drug can also affect how it interacts with lipids, polymers, membranes, and other elements of the delivery system in controlled drug delivery. As a result, when choosing the formulation and release mechanism, partitioning properties should be taken into account.

1.3 pKa and Ionisation Degree

A drug's degree of ionisation at a specific pH is determined by its pKa. The water solubility and membrane permeability of a medication might vary significantly between its ionised and unionised forms. While the ionised form is typically more soluble in water, the unionised form is typically better able to traverse lipid membranes.

Therefore, medication dissolution, membrane penetration, absorption, and release can be affected by the pH of the formulation and the biological milieu. Because the pH varies significantly throughout the gastrointestinal tract, it is especially crucial to comprehend pKa and ionisation behaviour for medications supplied thru the gastrointestinal tract.

1.4 Molecular Weight and Size

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Diffusion, dissolution, membrane permeability, distribution, and elimination are all impacted by molecular weight and size. In general, smaller drug molecules penetrate thru biological membranes more easily than larger ones. Therefore, while creating diffusion-controlled and membrane-controlled drug delivery systems, molecular size is a crucial factor to take into account.

Molecular size can also affect how quickly a drug diffuses via the polymer matrix in polymeric controlled release systems. In general, larger molecules diffuse thru a polymeric network more slowly than smaller molecules.

1.5 Stability of Drugs

A controlled release formulation must have both chemical and physical stability since the medicine may stay in touch with formulation ingredients for an extended amount of time. When stored or released from the dosage form, medications that are vulnerable to hydrolysis, oxidation, photodegradation, or other degrading processes may lose their efficacy.

Therefore, before creating a controlled release system, the drug's stability under formulation, storage, and physiological circumstances should be assessed. One of the essential physicochemical characteristics that must be taken into account while developing drug delivery systems is stability.

1.6 Solid-State Properties and Melting Point

A drug's solubility, rate of dissolution, stability, and interactions with excipients can all be affected by its melting point and solid-state properties. Different crystalline forms, polymorphs, hydrates, and amorphous states of drugs can have distinct physicochemical and biologic characteristics.

Because variations in crystallinity or amorphous content can significantly impact solubility and bioavailability, the solid state is especially crucial for poorly soluble medicines.

1.7 Characteristics of Diffusion

A key component of many controlled release systems is diffusion. A hydrogel, membrane, polymer matrix, or other carrier material may allow drug molecules to diffuse. Molecular size, drug–polymer interaction, polymer structure, drug concentration, and environmental circumstances are some of the variables that affect the rate of diffusion. In order to comprehend and regulate the release rate from controlled medication delivery systems, transport and diffusion properties are crucial.

1.8 Complexation and Drug-Excipient Properties

Drug solubility, stability, release, and bioavailability can all be impacted by interactions between the drug and formulation ingredients. Drug molecules can interact chemically or physically with proteins, polymers, lipids, cyclodextrins, and other excipients. For instance, complexation with appropriate carrier molecules can change the release characteristics of poorly soluble medicines and increase their apparent solubility.

II. Properties of Biology and Biopharmaceuticals

2.1 Half-Life in Biology

The biological half-life of a drug is the time required for its concentration in the body to decrease by approximately 50%. This factor is crucial in determining the suitability of a medication for controlled release, as drugs with shorter half-lives can benefit from extended delivery to reduce administration frequency and maintain therapeutic levels. Conversely, drugs with very long half-lives typically do not require controlled release, while those with very short half-lives might necessitate higher delivery rates. Therefore, understanding pharmacokinetic characteristics is vital for designing controlled release formulations.

2.2 Features of Absorption

The effectiveness of controlled release formulations depends on medication absorption, which requires liberation from the dosage form, dissolution in biological fluid, and passage through biological membranes. Factors such as solubility, lipophilicity, ionization, molecular size, permeability, gastrointestinal conditions, and transport pathways influence absorption. Medications with optimal absorption properties are more appropriate for controlled release development.

2.3 Distribution

Drugs are distributed in the bloodstream and tissues post-absorption, influenced by physicochemical properties, blood flow, tissue permeability, molecular size, lipophilicity, and protein binding. The volume of distribution indicates the extent of a drug's dispersion beyond plasma, which is crucial for designing systems that maintain therapeutic concentrations over time, impacting the concentration–time profile.

2.4 Binding of Plasma Proteins

Numerous medications bind reversibly to plasma proteins like albumin and α1-acid glycoprotein,

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affecting their unbound percentage, which is crucial for pharmacological activity, metabolism, excretion, and tissue diffusion. Protein binding significantly influences drug distribution, clearance, volume of distribution, and half-life, making it a vital factor in predicting a drug's pharmacokinetic behavior.

2.5 Metabolism

The activity of a medication is influenced by drug metabolism, particularly in the liver, affecting its strength, clearance, and half-life. First-pass metabolism can reduce the bioavailability of orally administered drugs, while controlled drug delivery systems can modify pharmacokinetic behavior by adjusting the rate and route of exposure.

2.6 Removal and Clearance

The process of drug elimination from the body, primarily through metabolism and excretion, is termed elimination, while the efficiency of this process in plasma is known as clearance. Both renal and hepatic clearance significantly affect drug concentration and duration of action. For medications with rapid clearance requiring frequent administration, a controlled release method for prolonged drug input may be beneficial.

2.7 The Therapeutic Window

The therapeutic window is the range of drug concentrations between the minimum required for therapeutic effect and where toxicity occurs. Controlled medication delivery aims to maintain drug concentrations within this range, as both excessive and insufficient release pose risks of side effects and inadequate therapeutic activity, respectively.

2.8 Dosage Dimensions

When developing controlled release formulations, the dosage necessary to provide a therapeutic effect is crucial. It could be challenging to incorporate medications that require extremely high dosages into a dosage form that is practical in size. Therefore, it is usually easier to include medications that require relatively tiny or moderate doses into controlled release systems.

2.9 Window of Absorption

Certain medications are effectively absorbed from a specific area of the gastrointestinal tract. If the controlled release formulation releases the medication after it has moved past the primary absorption site, such medications may exhibit decreased bioavailability. Therefore, while creating gastroprotective or prolonged-release formulations, the position and duration of the absorption window should be taken into account.

2.10 Administration Route

The design of a controlled delivery system is influenced by the chosen route of administration, which impacts drug absorption, distribution, metabolism, and excretion. Each route, including oral, transdermal, parenteral, pulmonary, and ophthalmic, presents unique physiological barriers and formulation requirements. Key considerations in selecting a route include the therapeutic goal, drug characteristics, patient needs, and desired duration of drug release. [1,4 - 8]

Drug candidates suitable for controlled release potential Drugs for Controlled Release

Pharmacokinetic, physicochemical, and biopharmaceutical characteristics are crucial for a drug's suitability for controlled-release systems. Ideal candidates have a biological half-life of 2–8 hours, a tolerable therapeutic index, small dose requirements, and predictable absorption and elimination. Controlled release can lower dose frequency and plasma level volatility for medications requiring consistent administration. Drugs must also exhibit good gastrointestinal absorption, with important traits including predictable pharmacokinetic profiles, sufficient therapeutic index, excellent absorption, appropriate solubility, and stability in gastric conditions. [9 - 13]

Dose, half-life, therapeutic index and bioavailability

Important pharmacokinetic and pharmacological factors affecting medication efficacy and safety include dose, half-life, therapeutic index, and bioavailability. The dose determines the therapeutic response, with effective dosing crucial for minimizing side effects. Factors like administration method, clearance, distribution, and patient characteristics can influence optimal dosing. Half-life (t½) reflects the time taken for plasma concentration to reduce by 50%, critical for establishing dosage intervals and achieving steady-state concentrations, influenced by volume of distribution and clearance. The therapeutic index (TI) indicates the safety margin between effective and toxic doses, necessitating careful monitoring for drugs with a narrow TI. Bioavailability is the extent a drug reaches systemic circulation, affected by route of administration and metabolic processes,

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significantly impacting drug delivery system design and therapeutic efficacy. [14 - 18]

III. Approaches for Designing Controlled Release System

3.1 Diffusion/ Dissolution controlled systems:

Diffusion and dissolution are the two earliest and most widely used mechanisms for controlled drug release, forming the foundation of first-generation controlled release technology developed between 1950 and 1980 (1) Both mechanisms can be engineered as reservoir type or matrix type systems, and in practice, the two mechanisms frequently coexist within same dosage form [19]

3.1.1. Diffusion

Controlled System: In diffusion-controlled systems, the drug is entrapped within a water-insoluble polymeric membrane (reservoir system) or dispersed throughout an inert polymeric matrix (monolithic system), with release determined by Fick's diffusion laws rather than polymer degradation. Fick's first law states that drug flux across a membrane or matrix is directly proportional to the concentration gradient; Fick's second law describes how this concentration gradient changes over time and distance within the system. Fickian diffusion refers to releases that follow this relationship, whereas deviations from it are known as non-fickian or anomalous diffusion. [1]

3.1.2. Reservoir membrane-controlled systems:

Reservoir (membrane-controlled) systems include a drug core surrounded by a thin polymeric membrane, which can be porous or non-porous. The release rate in these systems is primarily determined by membrane thickness, porosity, and the drug's physicochemical properties, such as partition coefficient, molecular size, and diffusivity. These systems are relatively simple to design for zero-order release, but membrane rupture poses a risk of dose dumping.[1]

3.1.3. Matrix (monolithic) Systems:

Matrix (monolithic) systems distribute or dissolve the drug directly within the polymer. When the drug is loaded below the polymer's solubility limit, it is fully dissolved in the matrix and released with non-zero-order kinetics that decrease as the diffusional path length increases over time. When drug loading exceeds the solubility limit, the drug is dispersed throughout the matrix, making it more suitable for long-term delivery.

Matrix systems eliminate the dose-dumping risk associated with reservoir rupture and are compatible with both degradable and non-degradable polymers; however, not all drugs are chemically compatible with a given polymeric matrix. [1]

Loading above saturation ensures a constant release by replenishing the dissolved drug, resulting in near zero-order release until depleted. A declining release rate is caused by drug depletion and an increase in diffusion distance. [19]

3..1.4. Dissolution Controlled System:

Dissolution-controlled systems control drug release by gradually solubilizing a polymer coating or matrix, rather than diffusion thru an intact barrier.(1)In reservoir-type dissolution systems, the drug core is surrounded by a slowly dissolving polymeric membrane; the release rate is determined by the coating's thickness and dissolution rate.(19)In matrix-type dissolution systems, the drug is encapsulated in a polymer that dissolves over time, releasing the drug as the matrix around it erodes(1,19)Because dissolution rate is the rate-limiting step, polymer solubility is the primary formulation variable that controls release in these systems.(19)Many conventional immediate-release tablets, effervescent tablets, and pills use dissolution-controlled mechanisms.[1]

Table1: Difference between Diffusion and Dissolution controlled systems

Parameters	Diffusion controlled	Dissolution controlled
Driving force	Concentration gradient across membrane or matrix (Fick's law)	Rate of polymer/coating solubilization
Rate-limiting step	Diffusion of drug through intact polymer barrier	Dissolution/erosion of the polymer itself
Reservoir subtype	Drug core surrounded by water-insoluble membrane (porous or non-	Drug core coated with a slowly dissolving polymer membrane

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	porous)	
Matrix subtype	Drug dissolved/dispersed in an inert, non-dissolving polymer	Drug encapsulated within a polymer that itself dissolves over time
Key formulation variable	Membrane thickness, porosity, drug partition coefficient and diffusivity	Polymer solubility and coating/matrix thickness
Effect of drug loading vs. solubility limit	Loading above solubility limit sustains near-zero-order release; below it, release declines over time	Less directly applicable — rate governed primarily by polymer dissolution, not drug loading level
Ease of achieving zero-order release	Achievable in reservoir form; more difficult in matrix form	Governed by dissolution kinetics of polymer; typically declining unless designed with a constant-dissolving geometry
Dose-dumping risk	Present in reservoir form if membrane ruptures; absent in matrix form	Generally lower, as release depends on gradual solubilization rather than a single barrier failure
Degradable/non-degradable polymer compatibility	Degradable systems can be difficult to design; matrix form compatible with both	Requires a polymer with a defined, predictable solubility profile
Typical dosage forms	Membrane-coated reservoir tablets, monolithic matrix tablets	Coated pellets/beads, immediate-release and effervescent tablets
Interplay with the other mechanism	Diffusion often becomes dominant once dissolution creates pores permitting water ingress	Dissolution often initiates the process that transitions release into a diffusion-controlled phase

3.1.5 Design Considerations for Diffusion- and Dissolution-Controlled CRDDS:

In order to achieve a desired release profile, designing a diffusion- or dissolution-based CRDDS involves more than just choosing a mechanism; it also involves adjusting a number of interdependent formulation variables. [1]

Polymer selection: The formulator's main lever is the choice of polymer. Since the dissolution rate directly determines the drug release rate, the polymer must be selected for a defined and predictable solubility or erosion profile when a dissolution-controlled release is desired. If a diffusion-controlled release is preferred, the polymer should stay mostly intact during the release time, and control will be applied thru the thickness, porosity, and permeability of the membrane. Before any other parameter is adjusted, this distinction directs the first mechanistic decision. [1]

Drug loading relative to the polymer's solubility limit: Drug loading in relation to the polymer's solubility limit provides a second independent design parameter. Loading the drug below its solubility limit within the matrix results in fully dissolved drug and a decreasing, non-zero-order release profile, whereas loading above the solubility limit leaves a reserve of dispersed, undissolved drug that continuously replenishes the diffusing fraction, maintaining a near-zero-order release until the reserve is depleted. This means that formulators can change the release order of a matrix system without changing the polymer itself, simply by adjusting the drug-to-polymer ratio relative to saturation. [1,19]

The choice between reservoir and matrix architecture: The decision between reservoir and matrix architecture is a risk-tradeoff rather than purely kinetic. Reservoir systems are relatively simple to design for true zero-order kinetics, but they have an inherent dose-dumping risk if the rate-controlling membrane ruptures. Matrix systems lose some kinetic precision but completely eliminate this risk because the drug is distributed throughout the bulk rather than concentrated behind a single barrier. This tradeoff is especially important when the

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therapeutic index of the drug in question is limited. [1]

Membrane or coating thickness: Membrane or coating thickness allows for additional tunable control in both diffusion- and dissolution-based reservoir systems. Increasing coating thickness slows diffusive transport or delays the onset of dissolution, allowing formulators to fine-tune the duration of release for a specific dosing interval while leaving the underlying polymer chemistry unchanged. [1,19]

The overlap between diffusion and dissolution mechanisms: The overlap of diffusion and dissolution mechanisms can also be viewed as a deliberate design strategy rather than an unintended limitation. Because partial dissolution of a matrix or coating creates pores that allow water to enter, formulators can choose a polymer that dissolves just enough to form a porous network, after which diffusion thru the resulting water-filled channels becomes the dominant and more controllable release mechanism. This hybrid approach combines the predictability of diffusion-controlled kinetics with the reduced formulation requirements of a dissolution-based system. [1,19]

drug physicochemical properties: Drug physicochemical properties limit which mechanisms are possible for a given active pharmaceutical ingredient. Partition coefficient, molecular size, and diffusivity determine whether a candidate drug is suitable for diffusion-controlled delivery, regardless of polymer choice, and should thus be considered alongside polymer selection during early formulation design. [1]

2)Ion-exchange systems:

Ion exchange resins (IER) are insoluble, cross-linked polymers (usually polystyrene or polymethacrylate) having ionizable functional groups attached to their backbone. These resins, when in contact with an aqueous solution, will exchange their mobile counter-ions for ions of opposite charge in the surrounding fluid, in a reversible and stoichiometric process governed by electroneutrality. [20]

IERs are classified as cation exchangers (bearing acidic groups like SO_3H or COOH) or anion exchangers (bearing basic groups like NR_3^+ or NH_2). Each of these is further classified as strong or weak based on how their ionization responds to pH — strong resins remain ionized throughout the pH range, whereas weak resins are ionized only under specific pH conditions, making their exchange capacity pH-dependent. [21]

Factors influencing the choice and performance of ion exchange resins (IERs):

The choice of an appropriate IER for controlled drug delivery is influenced by a number of resin, drug, and environmental considerations. Important resin properties include ion exchange capacity, swelling ratio, particle size, degree of cross-linking, regulatory status, and biocompatibility/biodegradability. Drug properties such as pKa, lipophilicity, molecular size, and ionic nature all have an impact on the strength and efficiency of drug-resin interactions. Furthermore, external conditions such as pH, temperature, and agitation have a significant impact on ion-exchange kinetics and drug release behavior. As a result, these parameters should be carefully tuned to achieve the desired drug loading, stability, and controlled-release profile. [20]

Table2: Some recent application of IER in Controlled drug delivery systems

Application Category	Example Resins Used	Representative Drug(s)	Design Outcome
Sustained/extended oral release	Dowe 50WX series, Dowe 50W×4/×8, Indian 254	Battistini, Diltiazem	Once-daily dosing achieved via resinate microcapsules; release extended up to 15 h with dual cross-linking
Fast-disintegrating + sustained release tablets	Dowe WX2-400, Indian 234/Tulsi on 343	Dextromethorphan, Diphenhydramine	Combines rapid tablet disintegration with prolonged drug release from the resinate core
Combination/dual-drug delivery	Dowe 50Wx2/x4/x8	Dextromethorphan + Diphenhydramine	Two drugs co-loaded on resin for extended, balanced

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			combined release
Site-specific/enteric delivery	Cholestyramine	Potassium diclofenac	Resin protects drug through GI transit for targeted enteric release
Mucoadhesive delivery	Poly (ethylene-g-styrene-trimethylammonium chloride)	Riboflavin-5-phosphate	Resin imparts mucoadhesive properties confirmed in vivo
Transdermal/iontophoretic delivery	Poly (propylene-g-vinyl benzyl trimethylammonium chloride)	Ketoprofen	Enhanced ion-assisted transport across skin
Reduced toxicity carriers	Amine 50W-X4	Adenovirus-liposome conjugates	Resin binding lowers systemic toxicity of the complex
Gastroretentive/floating systems	Amberlite IRA-900	Diclofenac	Resin-based buoyancy enables oral floating drug delivery
Adsorption-enhanced systems	Acrylic copolymers, Sulfonated styrene-DVB copolymer	Cefotaxime sodium, Chlorpheniramine	Higher drug adsorption and binding onto resin surface
Hydrophobicity-tuned release	Carboxyalkyl methacrylates	Propranolol, Diltiazem, Verapamil	Release kinetics adjusted through resin-drug hydrophobic interact
Self-propelled release	SP-Sephadex	Tetracycline	Novel self-propelled release mechanism demonstrated

Design strategy for Controlled release:

- Coating/microencapsulation: polymer coating (e.g., PVA, Eudragit) over resinate to slow diffusion. [20]
- Dual/combination resinates- co-loading two drugs on one resin for combination therapy. [20]
- Gastroretentive systems use resin and bicarbonate to create buoyancy thru CO_2. [20]
- Mucoadhesive systems are resin-encapsulated bioadhesive polymers used for site-specific GI delivery. [20]

3) Osmotically controlled systems:

Among the numerous approaches available for the design of controlled-release pharmaceutical delivery systems (CRDDS), osmotic pump technology is one of the most reliable methods because the drug release occurs at a constant zero-order rate, which is not significantly affected by physiological variables, such as stomach pH, intestinal motility, food intake or the hydrodynamic conditions of the dissolution fluid. The release mechanism of this system is independent of the biological environment, and osmotic systems show a high correlation between in vitro and in vivo behavior, making their performance much more predictable than conventional dosage forms that release drugs instantaneously, but are not able to sustain a steady plasma concentration over time. [22]

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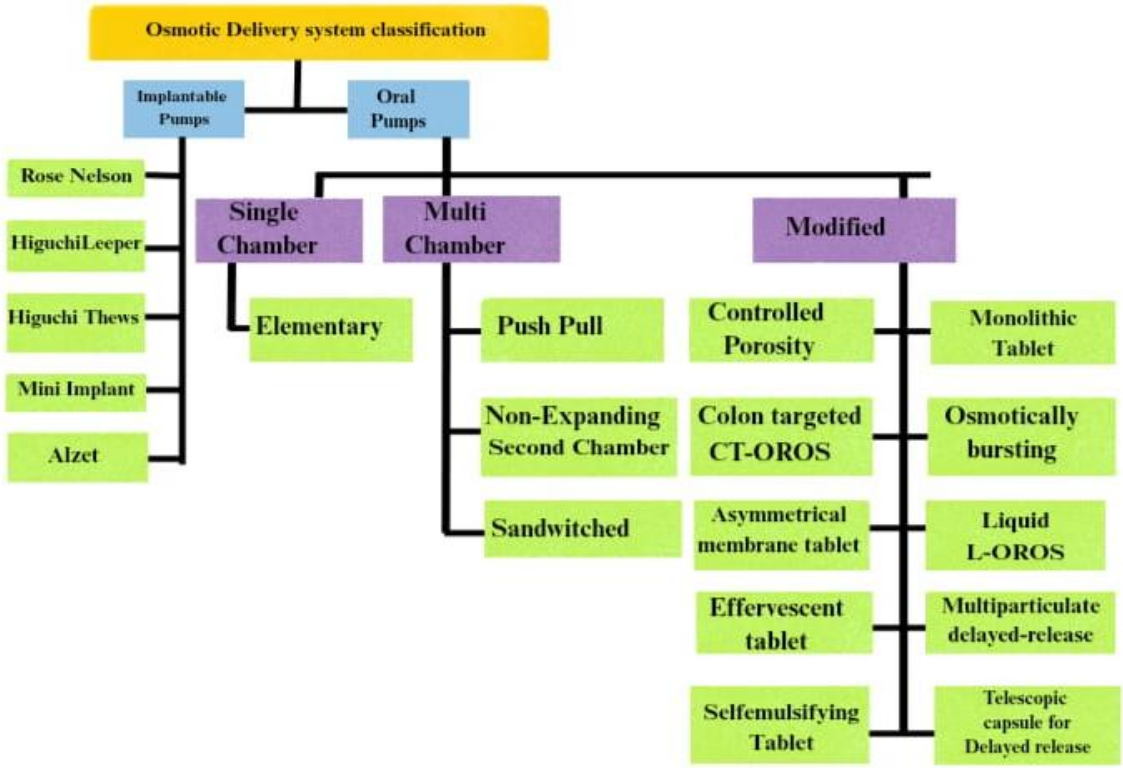

Fig1: Osmotic drug delivery systems

Basic Design and Mechanism

The osmotic pump is composed of a core of drug (often with an osmogen) enclosed in a semipermeable membrane with one or more small openings. Due to the osmotic pressure difference, water enters thru the membrane in an aqueous medium and thereby increases the internal pressure and forces the drug solution or suspension out thru the orifice. The release rate is mainly a function of membrane permeability, orifice size and shape, and internal osmotic pressure and not drug solubility. Highly water-soluble drugs can generate sufficient osmotic pressure themselves, so no additional osmogen is necessary. [22,23]

Design Elements

Drug: Moderate solubility and 1-6 h half-life preferred.

Osmogen: Common agents are lactose, mannitol, NaCl, and sucrose, selected for good solubility and osmotic activity.

Semipermeable membrane: Usually cellulose acetate, selective water permeability, strength and biocompatibility.

Delivery orifice: Generally, 0.5-1.5 mm, to control drug release and avoid excessive pressure or leakage.

Wicking agents or pore-forming agents: Used to enhance water uptake or to create microporous channels in the membrane. [22]

Design Difficulty

Dose dumping due to a faulty membrane coating.

Controlled release requires precise orifice sizing.

High cost of manufacturing (drilling process in particular)

Irretrievability: The device cannot be stopped after administration in most cases. [22]

The osmotic gradient is reduced by the reverse solute flux (RSF) and concentration polarization, which slows the water influx and thus disturbs the desired zero-order

The choice of a stable, non-toxic and cheap osmogen is still of importance. More recent approaches like magnetic nanoparticle-based draw solutions aim at reducing RSF and regenerating the osmogen efficiently. [23]

5) Erosion controlled system

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Erosion-controlled drug delivery systems regulate drug release through the physical loss of polymer mass, rather than diffusion. This involves two processes: chain scission, which breaks polymer backbones into smaller units, and erosion, which removes the degraded material from the device. [24]
Degradable polymers are categorized based on erosion types: bulk erosion and surface erosion. In bulk erosion, water penetrates faster than hydrolysis, leading to uniform degradation throughout the polymer, exemplified by PLGA, PCL, PGA, and PLLA, which degrade over months to years. In contrast, surface erosion occurs when hydrolysis outpaces water penetration, resulting in degradation limited to the outer layer, analogous to an ice cube melting, with polyanhydrides being a classic example due to their hydrophobic nature and reactive anhydride bonds. [24,25]
Typically, controlled release systems rely on surface erosion because this makes the surface area exposed, and thus the rate of release, predictable over the lifetime of the device. Additionally, the core material, which has not yet eroded, has the same molecular weight and mechanical properties as the initial polymer. This predictability is why erosion-controlled designs are preferred to diffusion-controlled designs for steady, near-zero-order, or otherwise tunable release. [25]

Parameters governing erosion rate:

Several formulation and environmental factors influenced erosion behavior. Lower crosslink density and higher hydrophilicity accelerated erosion, while temperature increases (from 25°C to 37°C) halved the induction period and total erosion time. Tablet size and geometry did not affect the induction period; smaller tablets eroded faster due to less mass. Tablets with the same surface-area-to-volume ratios eroded at similar rates, highlighting that release rates can be adjusted by device shape. pH had minimal impact except in highly alkaline conditions, where base-catalyzed hydrolysis accelerated erosion. Additionally, increased shaking rates enhanced erosion by clearing degradation byproducts effectively. [25]

Broder degradation mechanism:

A broader perspective on degradation behavior across several polymer classes can place polyanhydride specific results into the context of more general design principles of erosion and degradation. [24]
Chemical degradation route: Chain scission occurs either passively thru hydrolysis or actively via enzyme-catalyzed hydrolysis. Certain bond types, such as anhydride, ortho-ester, ester, urea, urethane/carbonate, and amide linkages, are susceptible to passive hydrolytic breakdown under physiological conditions, with anhydride bonds breaking down first, followed by ester bonds and then amide bonds. This reactivity ordering explains why polyanhydrides are preferred when fast, surface-confined erosion is the design objective. [24]

In-vitro characterization approaches:

Several techniques are commonly used to evaluate erosion-controlled systems during development, including gravimetric mass loss measurements, FTIR and Raman spectroscopy for tracking chain scission and compositional changes, SEM and AFM for surface morphology such as pore formation and roughness, and DSC, TGA, and GPC for monitoring shifts in glass transition temperature, decomposition temperature, and molecular weight distribution. [24]

IV. Polymers and formulation strategy:

4.1 Natural, synthetic and biodegradable polymers:

[a] natural polymer:

Natural polymers derived from microorganisms, algae, plants, and mammals include proteins, polyesters, and polysaccharides. [26] They are widely used in pharmaceuticals and biomedical applications due to their biocompatibility and biodegradability, which reduce toxicity and immunological reactivity. Key examples include chitosan, cellulose, chitin, gelatin, alginate, collagen, hyaluronic acid, and silk fibroin, particularly in bone and cartilage tissue engineering. These materials support the differentiation of mesenchymal stem cells and are also utilized in controlled drug delivery systems due to their accessibility and safety. [27][28]

[b] synthetic polymer:

Synthetic polymers, created from monomers via initiators and catalysts, include polyethylene (PE), polystyrene (PS), and polyamides (PA). Their precise chemical modifications allow for tailored properties, making them valuable in biological applications. [26]
Notably, dendrimers and sialyl-based polymers can inhibit viral glycoprotein binding, thus preventing viral attachment to host cells. These polymers serve as drug carriers in controlled delivery systems (CDDSs) due to their mechanical strength and regulated drug release. Additionally, combining synthetic and natural polymers, such as blending PLGA with PCL, enhances material properties for

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flexible and porous drug delivery systems while promoting sustained release during hydrolysis. [28]

[C] Biodegradable polymer:

The development of biomaterials heavily utilizes glutamic acid, a natural and biocompatible amino acid known for its biodegradability and non-toxicity. Its strong cation-chelating properties make it valuable across food, medicine, cosmetics, water treatment, and agriculture. Bacteria like Bacillus subtilis synthesize poly (glutamic acid) (PGA) through peptide bonds of glutamic acid units. [26] PGA's biomedical applications can be enhanced via chemical modifications and cross-linking with other polymers. Additionally, devices utilizing PGA, when exposed to laser radiation, generate reactive oxygen species (ROS) that can help destroy cancer cells and facilitate cellular imaging.

Biodegradable polymers are classified into natural and synthetic types. Natural polymers include polysaccharides like starch and cellulose, and are used in tissue engineering and drug delivery due to their favorable properties. [27] Synthetic biodegradable polymers are advantageous in tissue regeneration and drug delivery as they don't require surgical removal. Polymer blending enhances mechanical and degradation properties, benefiting controlled drug delivery systems by reducing toxicity and enabling prolonged release, although the release mechanisms are more complex than with single polymers. [28]

4.2 Matrix and Reservoir systems:

[a] Matrix System:

Membrane-controlled reservoir systems and monolithic/matrix systems are the main types of diffusion-controlled drug delivery systems, releasing medications via diffusion through water-insoluble polymers. In matrix systems, drugs are distributed within a hydrophilic polymer matrix, allowing gradual release as water causes swelling. [1] Drug release is governed by Fick's laws of diffusion and depends on drug solubility, matrix size, and polymer properties. Reservoir systems employ a polymeric membrane for diffusion, while matrix systems allow drug release through the matrix. Release can be classified as diffusion-controlled or erosion-controlled depending on the relative rates of drug diffusion and polymer erosion. [19]

[b]Reservoir system:

Dissolution is the key phase in dissolution-controlled release systems, involving medication coated or encapsulated in a polymeric matrix that dissolves gradually. These systems may use low-solubility polymeric membranes to enclose medications [1]. In membrane-controlled devices, the drug core is covered by a polymer membrane, affecting release rates based on thickness, porosity, and drug characteristics like molecular size and diffusivity. Reservoir systems consist of a drug core within a hydrogel membrane, where water dissolves the drug, ensuring a constant release rate while solid drug remains. [29] Additionally, microchip drug delivery systems allow for controlled medication release but face challenges with membrane degradation and reservoir opening. [19]

4.3 Polymer drug interactions

Beyond the physical structure of drug delivery systems, molecular interactions between drugs and polymers play a vital role in controlled-release drug delivery systems (CRDDS). By manipulating these interactions, formulators can regulate release kinetics, enhance drug-loading capacity, and increase stability, moving beyond reliance on diffusion barriers or matrix erosion. The interactions can range from strong covalent bonds to weaker non-covalent ones, allowing for release durations from hours to weeks. [30]

4.3.1. Covalent Conjugation:

The strongest polymer-drug interaction involves direct covalent bonding between the drug and the polymer backbone, which can be designed for stability or cleavability. Stable linkages immobilize the drug until network degradation, while cleavable linkages respond to time, pH, or enzymatic activity, allowing for controlled release. Carbodiimide-based amide bonds have been used to attach growth factors to PEG hydrogels, with long-chain PEG spacers reducing steric hindrance. Examples of cleavable linkages include hydrolysable esters, disulfide bonds, and peptide sequences. Notably, tethering the peptide exenatide to a PEG hydrogel with β-elimination-cleavable linkers enables an extended release of about seven days in vivo. Covalent conjugation effectively retains small drug molecules, particularly those smaller than the polymer network's mesh size, which can be adjusted for optimal performance. [30]

4.3.2. Electrostatic Interactions: Electrostatic interaction is a key mechanism for drug delivery, leveraging the attraction between oppositely charged drug and polymer components. This nonspecific interaction enables the controlled release of multiple charged drugs from a single system. Anionic polymers like alginate effectively bind cationic growth factors, such as VEGF, for sustained tissue

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regeneration. When direct interactions are inadequate, intermediaries like heparin can mediate binding, with its sulfation pattern allowing for fine-tuning of release properties. In these systems, drug release is generally triggered by polymer degradation or ionic screening from the surrounding environment. [30]

4.3.3Hydrophobic association: Hydrophobic association plays a crucial role in delivering poorly water-soluble drugs, necessitating the incorporation of hydrophobic domains into hydrophilic polymeric carriers like hydrogels. This is achieved through copolymerization with hydrophobic monomers or adding substances such as cyclodextrin or cholesterol. Cyclodextrins, with their hydrophilic exterior and hydrophobic interior, effectively associate with hydrophobic drugs while keeping the carrier hydrophilic. In these systems, drug release is influenced more by the drug's partitioning equilibrium between the polymer matrix and the surrounding medium than by the mesh size of the network. [30]

4.3.4. Hydrogen bonding:
Intermolecular hydrogen bonding is a significant non-covalent mechanism in polymer-based controlled release drug delivery systems (CRDDS), particularly for amorphous solid dispersions (ASDs) with poorly soluble drugs. In these systems, the polymer can have proton donor groups that bond with the drug's hydrogen bond acceptor groups, influencing the drug's mobility. The extent of this hydrogen bonding, adjustable by the drug-to-polymer ratio, directly affects stability and release kinetics. Lower ratios provide mobility that risks recrystallization, while higher ratios inhibit mobility, enhancing solubility and prolonging release. This molecular interaction exemplifies a broader concept of transitioning release profiles within CRDDS via formulation strategies. Additionally, covalent, electrostatic, hydrophobic, and hydrogen-bonding interactions provide a toolkit for controlling drug release, noting that stronger interactions may compromise drug bioactivity. Therefore, selecting the optimal interaction type involves considering the drug's properties and therapeutic goals. [30,31]

4.4. Formulation and manufacturing approaches

4.4.1 Formulation of Polymers Used in Controlled Release Drug Delivery Systems:_ The functional roles of polymers in Controlled Release Drug Delivery Systems (CRDDS) are categorized into three main types: the primary polymeric matrix for drug encapsulation, coatings for delayed or enteric release, and release modifiers that adjust release kinetics. Selection of polymers is based on functional needs, including pH-dependent solubility, appropriate glass transition temperature for stable processing, mechanical strength for solid dosage forms, and biocompatible degradation. Various formulation techniques are employed to effectively utilize these polymer properties in CRDDS carriers. [32,33]

Interfacial Polymerization: Two reactive monomers in immiscible solvent phases react at the interface, forming a thin polymeric membrane around the drug. The membrane thickness and permeability can be adjusted to control diffusion-based release. [34]
Solvent evaporation: The drug and polymer are co-dissolved in a solvent, emulsified in an aqueous phase, and the solvent evaporated to yield solid drug-loaded particles. [34]
Solvent Casting: Drugs and polymers are co-dissolved and cast onto a flat surface; solvent evaporation produces a uniform drug-loaded film, which is commonly used for transdermal and buccal delivery. [34]
Nanoprecipitation: a surfactant-free method in which rapid solvent diffusion at the interface causes the polymer to precipitate and entrap the drug in nanoparticles. [34]
Emulsion methods: Single emulsions (oil-in-water) encapsulate hydrophobic drugs, whereas double emulsions (water-in-oil-in-water) encapsulate hydrophilic drugs within micro or nanoparticles. [34]
Ionic gelation: Electrostatic cross-linking between an oppositely charged polymer and a counterion produces gels, beads, or nanoparticles that are ideal for charged biomolecules like proteins and peptides. [34]
Coacervation: Phase separation can lead to the formation of micro- or nanocapsules, which can be simple (driven by pH, temperature or non-solvent) or complex (based on electrostatic interaction between oppositely charged polymers). [34]
Microfluidics: The possibility to control fluids very precisely in microscale channels allows for highly reproducible formation of particles of controlled size and composition. [34]
Hot melt extrusion (HME) is frequently used to process drugs and polymers above the Tg and Tm into a homogenous matrix, extrudate, or filament for later tableting or 3D printing for erosion- and diffusion-controlled matrix polymers like Eudragit

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derivatives. By using plasticizers, this solvent-free method can reduce processing temperature and increase flexibility for downstream shaping while avoiding organic solvents. [32]

4.4.2Manufacturing of Polymers Used in Controlled Release Drug Delivery Systems: Degradation rate, drug loading capacity, and release kinetics are all directly impacted by a polymer's molecular weight, monomer composition, and polydispersity index (PDI), all of which are determined by the manufacturing process used to create it. Important manufacturing factors consist of: [33]

Molecular weight distribution: Compared to polymers with a narrow molecular weight distribution, those with a wider molecular weight distribution or high PDI degrade more quickly and exhibit more variability in release behavior, including unwanted initial burst release. [33]

Batch-to-Batch inconsistency: Molecular weight and PDI fluctuate during traditional batch processing due to uneven heat and mass transfer; even small changes in monomer ratios can significantly change degradation kinetics. [33]
Scalability challenges: Hot melt extrusion (HME) is a widely used manufacturing method where polymer and drug are processed at elevated temperatures to create a uniform extrudate for further processing. This solvent-free technique emphasizes simplicity, scalability, and automation, often incorporating plasticizers to reduce temperatures and prevent thermal degradation. However, challenges such as melt fracture, porosity, and residual solvents from laboratory to industrial scale need addressing. Innovative green manufacturing methods are being explored to produce pharmaceutical-grade polymers sustainably while ensuring controlled release properties. [32,33]

Biopolymer production: Polymers with high biocompatibility and biodegradability, like chitosan, alginate, and starch-based derivatives, come from renewable biological sources as opposed to petrochemical feedstocks. [33]

Enzymatic polymerization: Biocatalysts reduce uncontrolled polymerization by enabling highly selective polymer chain formation in mild aqueous conditions without the use of metal catalysts or hazardous solvents. [33]

Microwave-assisted synthesis: Rapid, consistent volumetric heating shortens reaction times and uses less solvent by speeding up the formation of polymer networks. [33]

Supercritical CO2 Processing: Supercritical carbon dioxide, which is recyclable, dissolves and forms polymers into films, gels, or nanoparticles without the use of flammable organic solvents. [33]

Ionic liquids and deep eutectic solvents (DES): Low-vapor-pressure, non-flammable solvents are used as reaction media for the synthesis of nanopolymers and to extract polymers like chitosan from biological waste. [33]

V. Drug release mechanism and kinetics

Maintaining drug levels within the therapeutic window involves keeping concentrations between the minimum effective concentration (MEC) and the minimum toxic concentration (MTC). High single doses can elevate levels above MTC, causing side effects, while levels may rapidly drop below MEC. To address fluctuations, controlled or sustained release drug carriers are desirable, with a focus on achieving a zero-order release profile. However, excessive release can impact efficacy, prompting the exploration of pulsatile or stimuli-responsive systems. Factors influencing drug release include composition, polymer type, additives, their ratios, and preparation methods, with release mechanisms categorized into diffusion, solvent-based, chemical reactions, and stimuli-controlled release. [35]
5.1 Diffusion-Control Release: A capsule-style reservoir system demonstrates diffusion-controlled drug release, where a drug is dissolved or distributed in a core encased in a polymeric membrane. Drug diffusion is caused by variations in the drug's concentration across the membrane. In this case, the medication diffuses through the membrane after first dissolving in the core. Diffusion-controlled release profiles are also seen in matrix-type nanospheres, in which drug molecules are distributed throughout the polymer matrix. Because matrix-type systems lack a membrane that acts as a diffusion barrier, drug molecules inside the carrier typically exhibit high initial release followed by a decreasing release rate as the diffusion distance increases. [35]
5.2 Solvent- controlled release: Osmosis-controlled and swelling-controlled drug release are examples of solvent-controlled drug release, which is controlled by solvent transport into the drug carrier. When a constant concentration gradient is maintained, water

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diffuses from the external low-drug-concentration medium into the drug-loaded core thru a semipermeable polymeric membrane in osmosis-controlled systems, resulting in a zero-order release profile. Water permeates glassy hydrophilic polymers in swelling-controlled systems, resulting in polymer swelling and drug release. Water diffusion and polymer-chain relaxation determine the release rate. Mesh size controls drug release in these systems, which frequently employ three-dimensional crosslinked polymers like hydrogels. The Peppas model **("Mt/M∞ = kt^n)** describes drug release from hydrogels and aids in determining whether diffusion is Fickian or non-Fickian. Swelling-controlled systems can also accomplish zero-order release, depending on drug distribution and polymer composition. [35]

5.3 Degradation-controlled drug release: The hydrolytic or enzymatic breakdown of ester, amide, and hydrazone bonds releases drugs from drug carriers made of biodegradable polymers like polyesters, polyamides, poly (amino acids), and polysaccharides. Because polymer degradation occurs more quickly than water diffusion, polyanhydrides and poly (Ortho esters) usually experience surface erosion, while PLGA, PLA, and PCL usually experience bulk degradation. Rapid water diffusion, however, can speed up degradation in small matrices like nanoparticles and cause bulk degradation instead of the usual surface erosion. The polymer degradation rate, which is impacted by molecular weight, end groups, monomer composition, and crystallinity, determines the kinetics of drug release. Biodegradable polymers are beneficial because they break down into substances that the body can easily get rid of, reducing long-term negative effects. Drug release in drug–polymer conjugates are regulated by hydrolytic or enzymatic cleavage of the drug–polymer linkage; when the relevant enzyme is concentrated in target tissues, enzymatically cleavable conjugates can offer target-specific delivery. [35]

5.4 Stimuli -Controlled Release:

Controlled release by stimuli Temperature, pH, ionic strength, sound, and electric or magnetic fields are examples of internal or external stimuli that regulate drug release from stimuli-responsive nanocarriers (Abdulmajid et al.). These carriers have been investigated for target-specific drug delivery because the stimuli can be localized. For instance, nanocarriers with pH-sensitive linkers have been developed for tumor-specific drug delivery, taking advantage of the weakly acidic pH of many solid tumors. Additionally, pH-sensitive carriers are created to improve the contrast between intracellular and release of drugs outside of cells. Within Drug release in thermosensitive drug carriers is brought on by the polymer's temperature-induced phase transition. [35]

5.2 Fundamental of kinetics of drug release

Model Dependent Methods: ***Model***-dependent approaches describe drug dissolution profiles using mathematical models. Nonlinear regression, typically using least-squares minimization, determines a model's suitability. Zero-order, first-order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas, Baker–Lonsdale, Weibull, Hoffenberg, and Gompertz models are common drug-release kinetic models. [36]

5.2.1 Zero order model

Dissolving drugs from dosage forms that don't the following equation can be used to disaggregate and release the medication gradually: Q0 - Qt = K0t (1) Equation (3) can be rearranged to produce:

Q0 + K0t = Qt (2) where Qt is the quantity of medication dissolved in time t, Q0 is the starting drug concentration in the solution (usually Q0 = 0), and K0 is the zero order release constant given in concentration/time units. Data from in vitro drug release studies were plotted as the cumulative amount of drug released versus time to examine the release kinetics. **Application:** The drug dissolution of various modified release pharmaceutical dosage forms can be described by this relationship, as in the situation of some transdermal systems, osmotic systems, matrix tablets with low soluble medications in coated forms, etc. [36]

5.2.2First order model: Additionally, this model explains the absorption and elimination of medications, although this process is complex. The drug's release follows first-order kinetics expressed by the formula: dC/dt = -kc, where K is the first-order rate constant. The equation log C = log C0 - Kt / 2.303 relates to the drug's concentration over time. When plotting log cumulative percentage of drug remaining against time, the result is a straight line with a slope of -K/2.303.**application:** This relationship can be used to explain how drugs dissolve in pharmaceutical dosage forms, such as those that contain water-soluble medications in porous matrices. [36]

5.2.3 Higuchi model: The Higuchi model, proposed in 1961, explains drug release from matrix systems, initially for planar forms but later adapted to various geometries and porous systems. Key assumptions include low initial drug solubility compared to matrix concentration, one-dimensional diffusion, small drug

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particle size, and consistent ideal sink conditions. The primary equation for release is Ft = Q = √D(2C - Cs)Cs t, where Q is the amount released, C is the initial concentration, Cs is the solubility, and D is the diffusion coefficient. For heterogeneous matrices, an alternate expression takes into account porosity and tortuosity. The simplified Higuchi model is f t = Q = KH X t1/2, with KH as the dissolution constant. This model applies to pharmaceutical dosage forms, such as tablets, where dissolution occurs parallel to the surface as dimensions decrease consistently. [36]

5.2.4 Hixson and Crowell Model:

The particle's regular area is proportional to the cube, as noted by Hixson and Crowell (1931). root of its volume. They arrived at the following equation: W01/3 -Wt1/3 = κ t , where Wt is the pharmaceutical dosage form's starting drug amount, and W0 is the quantity of medication left in the prescription dosage form at time than the surface-volume relation is incorporated into the constant κ (kappa). The release from systems where the diameter and surface area of particles or tablets change is described by the equation [34]. In order to examine the release kinetics, information from in vitro the cube root of the drug percentage that remained in the matrix was plotted against time in drug release studies

Application: This expression is applicable to pharmaceutical dosage forms, like tablets, where the dissolution takes place in planes parallel to the drug surface if the tablet's dimensions decrease proportionately and the initial geometrical form remains constant throughout. [36]

5.2.4 Korsmeyer-Peppas model:

In their 1983 study, Korsmeyer et al. introduced the Korsmeyer-Peppas model, which defines a relationship for drug release from polymeric systems, expressed as Mt/M∞ = KTNQ. Here, Mt/M∞ represents the fraction of drug released at time t, k is the release rate constant, and n denotes the release exponent. This model differentiates drug release mechanisms for cylindrical matrices based on the value of n: Fickian diffusion is characterized by 0.45 ≤ n, non-Fickian transport by 0.45 < n < 0.89, Case II transport by n = 0.89, and super case II transport when n > 0.89. The exponent is determined from the initial 60% of the release data, and log cumulative percentage drug release is plotted against log time to assess the release kinetics. [36]

Table3: Interpretation of diffusional release mechanisms from polymeric films

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.45 < n = 0.89	Non-Fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II transport	t^{n-1}

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6.Advanced and Emerging Controlled Drug Delivery System:

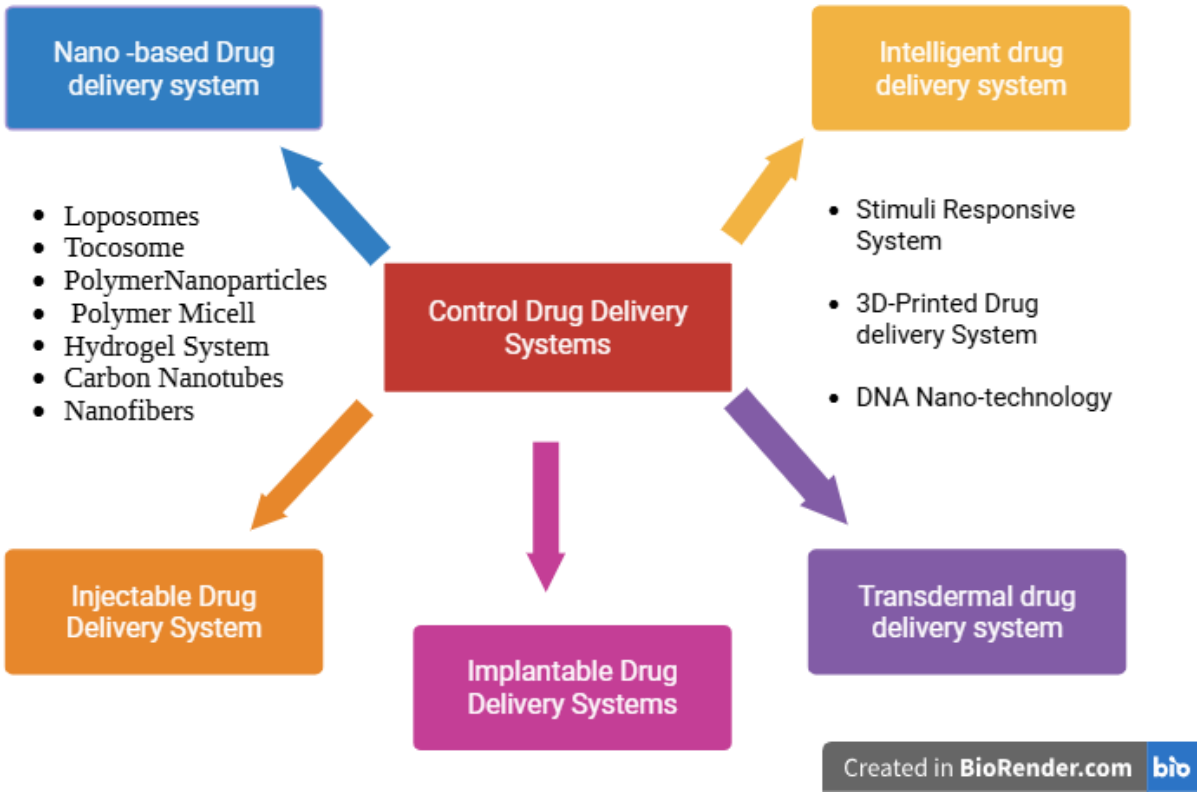

Fig2: Control Drug Delivery system

6.1 Nano-based Drug Delivery Systems:
Nanotechnology originally proposed in 1959, has become a key driver in scientific and industrial advancement, particularly in life sciences. Its unique properties enable the development of innovative nano formulations for biomedicine, including drug delivery systems that enhance solubility, stability, and tumor targeting, while minimizing toxic side effects. Various materials utilized in nano drug delivery systems (NDDS) include liposomes, nanodrugs, polymer micelles, hydrogels, and inorganic systems. [37]

6.1.1 LOPOSOMES: Liposomes are lipid bilayer vesicles, ranging from 20 to 1000 nm, with a hydrophilic core and hydrophobic shell, known for their biocompatibility, biodegradability, and low toxicity. They can encapsulate both hydrophilic and hydrophobic drugs, enhancing solubility and reducing toxicity while protecting drugs from degradation. Over nearly 50 years, liposome-based nanotechnology has advanced various therapeutic applications, including anticancer and antibacterial treatments, benefiting drugs like doxorubicin and rifampicin. Transferrin-modified liposomes effectively deliver drugs to gliomas, while lipid nanoparticles (LNPs) have emerged as significant in nucleic acid therapies, aiding mRNA vaccines like the COVID-19 vaccine. Despite advantages like low toxicity, challenges such as low drug-loading capacity and instability persist, prompting future research towards improved drug targeting and responsiveness. [37]

6.1.2 TOCOSOME:
Tocopherol (TPGS), an FDA-approved vitamin E-derived pharmaceutical excipient, is widely used in drug delivery. Qi et al. developed a cholesterol-modified TPGS carrier (TPGS-CHMC) with a lower critical micelle concentration. TPGS-CHMC/DTX micelles enhanced anticancer activity against paclitaxel-resistant ovarian cancer cells and reduced toxicity compared with free docetaxel
Drug delivery makes extensive use of tocopherol an (TPGS), an FDA-approved pharmaceutical excipient derived from vitamin E. A cholesterol-modified

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TPGS carrier (TPGS-CHMC) with a reduced critical micelle concentration was created by Qi et al. When compared to free docetaxel, TPGS-CHMC/DTX micelles decreased toxicity and increased anticancer activity against paclitaxel-resistant ovarian cancer cells. [37]

6.1.3 POLYMERIC NANOPARTICLE:

Colloidal particles of biodegradable polymers exist as nanocapsules and nanospheres. Nanocapsules consist of a drug core encased in a polymeric membrane, while nanospheres involve drug entrapment in a polymer matrix. A novel one-step self-assembly technique was developed for nanocapsules preparation. Studies showed that doxorubicin hydrochloride and NaYF4: Yb, Er@NaGdF4 were encapsulated in poly (DL-lactic-co-glycolic acid), demonstrating pH-dependent drug release: 35.7% at pH 5 and 14.58% at pH 7.4. Additionally, docetaxel-loaded hyaluronic acid nanocapsules exhibited a 24-hour sustained release. Another study by Das et al. revealed that a mesoporous bioactive glass nanosphere with poly-l-glutamic acid provided greater daunomycin release at pH 5.5 than at pH 7.4, facilitating localized medication delivery. .[38]

6.1.4 POLYMER MICELL

Polymeric micelles (PMs) offer a reliable and stable alternative to lipid-based drug carriers, characterized as biodegradable nanoparticles composed of amphiphilic deblock or triblock copolymers. They feature a hydrophobic interior that accommodates water-insoluble drugs while protecting them with a hydrophilic outer shell, enhancing drug solubility, biocompatibility, permeability, and reducing toxicity. Commonly used hydrophilic segments include PEG and poly-N-isopropyl acrylamide, while hydrophobic segments include polypropylene glycol and polycaprolactone. Innovative self-assembling PMs responsive to glutathione (GSH) and reactive oxygen species (ROS) were developed with PTX and honokiol (HK), effectively inhibiting laryngeal cancer growth by allowing targeted drug loading and release in tumor environments. These micelles demonstrated improved tumor accumulation and prolonged circulation, showcasing the advantages of multi-drug co-delivery and enhancing the nano-drug delivery system's efficacy**.** [39]

6.1.5 HYDROGEL SYSTEM:

Hydrogels are three-dimensional networks of hydrophilic polymers capable of absorbing significant amounts of water, making them crucial biomaterials for various biomedical applications like drug delivery, tissue engineering, and wound healing. Since the creation of poly(hydroxyethyl methacrylate) (pharma) hydrogel in the 1960s, advancements in polymer science have led to the development of customizable hydrogels. These can be natural, synthetic, or semisynthetic and can be tailored for elasticity, porosity, and swelling. A key feature is their ability to respond to stimuli, which enhances their use in smart biomedical devices. While 3D bioprinting and nanotechnology have expanded their applications, challenges such as biocompatibility, mechanical stability, and controlled drug release remain. Current research focuses on improving these attributes for better therapeutic outcomes. .[40]

CLASSIFICATION OF HYDROGEL: Hydrogels can be categorized according to a number of factors, such as their source, cross-linking techniques, ionic charge, composition, degradability, and responsiveness to stimuli. Here, we classify them as chemical and physical hydrogels, which are differentiated by their mechanisms of cross-linking formation, as shown in Figure 2. Hybrid gels with both Chemical and physical cross-linking are not separately categorized here. We then choose and examine a range of representative hydrogels with different gelation mechanisms. [40]

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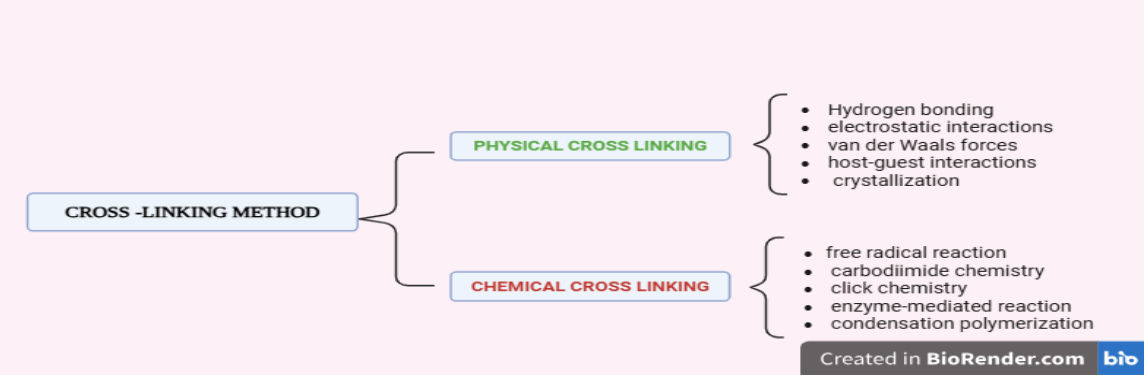

Fig3: Cross- linking method

- **PHYSICAL HYDROGEL:** Hydrogels can be categorized by factors like source, cross-linking techniques, ionic charge, composition, degradability, and responsiveness to stimuli. They are primarily classified into chemical and physical hydrogels based on their cross-linking mechanisms. Hybrid gels, featuring both types of cross-linking, are not separately categorized. This document also examines various representative hydrogels with different gelation mechanisms.[40]

- **CHEMICAL HYDROGEL: Covalent** cross-linking of polymers using techniques like carbodiimide chemistry, free-radical polymerization, click chemistry, enzymatic cross-linking, and electron irradiation creates chemical hydrogels. They offer spatiotemporal precision, controlled gel formation, and stable networks. Chemical hydrogels find extensive use in tissue engineering, drug delivery, and regenerative medicine. [40]

6.1.6 CARBON NANOTUBES

Carbon nanotubes (CNTs), formed from hexagon-shaped graphene sheets, exhibit unique electrical properties due to delocalized π-electrons. They are classified as single-walled (SWCNTs) or multi-walled (MWCNTs) based on the number of walls. CNTs have gained attention for their large surface area, enhancing drug conjugation efficiency. Current research focuses on using CNTs for anti-cancer drug delivery while aiming to reduce toxicity and expand their application for other medications. Functionalized CNTs are noted for their low toxicity and reduced immunogenicity, enabling effective transport of proteins, peptides, nucleic acids, and drugs to targeted cells and tissues. [1]

6.1.7 NANOFIBER

Solid fibers with diameters from a few nanometers to 1000 nm, featuring a high surface-to-volume ratio, are promising as drug delivery carriers. Drug release kinetics can be tailored by adjusting diameter, morphology, and porosity. Nanofibrous systems offer high drug loading efficiency and spatial distribution, with electrospinning being a common production method. Silk fibroin and bacterial cellulose serve as natural alternatives to synthetic fibers. Characterization involves assessing structure, composition, and drug release modes. These nanofibers can enable instant, dual-mode, or prolonged release, influenced by the choice of swellable or biodegradable polymers. The drug release dynamics are affected by the polymers' properties, process variables, and environmental conditions, making formulation complex and variable. [1]

6.2 INTELLIGENT DRUG DELIVERY SYSTEM

6.2.1 Stimuli responsive systems:

Because of their small size, nanoparticles (NPs) can improve drug delivery and get past biological obstacles like intracellular trafficking. High drug-loading capacity and efficient delivery, programmable surfaces for enhanced in vivo stability, low toxicity with progressive biodegradation and excretion, and sustained cellular response without burst release are all characteristics of ideal NPs. Drug delivery systems become more potent, effective, and long-lasting when stimuli-responsive NPs react to particular endogenous stimuli. [41]

a) PH - sensitive responsive nanoparticles:

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The stomach, duodenum, colon, lysosomes, and endosomes demonstrate pH gradients that pH-responsive nanoparticles (NPs) exploit. The tumor extracellular matrix (ECM), with a pH of 6.5–7.2, is a prime target for these NPs, as ECM degradation can enhance drug penetration and reduce hypoxic conditions in tumors. Wang et al. created DEX-Haaser NPs using a pH-sensitive linker, releasing Haaser only in acidic conditions, while pH-sensitive bromelain NPs with doxorubicin (DOX) improve ECM breakdown and DOX release. Additionally, pH-sensitive mesoporous silica nanoparticles show promise for co-delivering unsolid acid and sorafenib, emphasizing their role in targeted drug delivery. [41]

b) **Thermosensitive Nanoparticles for Drug Delivery:**
Thermosensitive nanoparticles (NPs) are advanced drug delivery systems in oncology that integrate chemotherapy and thermotherapy. Stable at body temperature (~37 °C), they release drugs in response to heat at tumor sites (40–42 °C), utilizing near-infrared (NIR) light for precision. These NPs also serve as platforms for imaging and photothermal therapy, exemplified by $Base_3$-based NPs combined with doxorubicin (DOX). Apart from cancer treatment, they aid in wound healing and antibacterial therapy. Emerging research focuses on mitochondrial temperature-responsive delivery to address drug-resistant tumors. Despite challenges regarding temperature sensitivity, biocompatibility, and clinical safety, thermosensitive NPs provide targeted drug release and improved therapeutic outcomes. [41]

c) **photo triggered response: Light-**responsive nanoparticles use UV, visible, or near-infrared (NIR) light for targeted, non-invasive drug release, minimizing toxicity and allowing for controlled timing. They are effective in site-specific therapy for ocular diseases, facilitating drug delivery across the blood-retinal barrier and enabling sequential release for both extracellular and intracellular targeting. Enhanced by magnetic targeting or other stimuli, these nanoparticles demonstrate significant potential in cancer therapy and localized treatments, despite challenges in tissue penetration**.** [41]

D) enzyme-sensitive drug delivery systems:
Enzyme-sensitive drug delivery systems target drug release through enzyme selectivity, capitalizing on differing enzyme levels in tumor versus normal tissues. Key enzymes include proteases, esterases, glycosidases, and hyaluronidase. Approaches involve enzyme-sensitive materials like polymeric nanoparticles, liposomes, and mesoporous silica NPs that either degrade or modify surfaces for drug release. Examples include collagenase-loaded liposomes that improve drug penetration by degrading tumor extracellular matrix and hyaluronidase-sensitive NPs that release drugs via hyaluronic acid degradation. However, clinical use of these systems faces challenges such as poor targeting specificity and slow reaction times. [41]

6.2.2 3D-printed drug delivery systems:
Three-dimensional printing (3DP) is an innovative computer-aided fabrication technology that creates three-dimensional objects layer by layer. It gained prominence in pharmaceuticals due to its ability to produce complex drug formulations with precise dosages and controlled release. Notable applications include Aparecida's Sprites for epilepsy and potential uses in pediatric medicine, biodegradable implants, and personalized healthcare. The integration of advanced materials has led to 4D printing, allowing structures to change in response to stimuli. However, challenges such as excipient selection, formulation design, and regulatory requirements pose hurdles for pharmaceutical 3DP, necessitating further advancements and regulatory refinement for successful commercialization. [37]

6.2.3 DNA NANOTECHNOLOGY:
DNA nanotechnology is an innovative drug-delivery method due to its ability to carry genetic information with precise architecture and low toxicity. However, its application is limited by vulnerability to nuclease degradation. Key categories include DNA origami, tile-based assembly, and DNA wireframes. Tile-based structures consist of double DNA duplexes with crossovers, while DNA origami is formed through thermal annealing of staple and scaffold strands. An example is the delivery of doxorubicin to LNCaP prostate cancer cells using DNA origami. Additionally, wireframe structures are designed using graphical methods and have been improved

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through honeycomb-edged designs to enhance structural fidelity. [38]

6.3 INJECTABLE SYSTEM:
The purpose of injectable drug delivery systems is to deliver medications directly into the body by different methods, including intravenous, subcutaneous, and intramuscular injections. [42]

Injectable Drug Delivery System Types:
1. Needles and Syringes
2. Injectors
3. Injectors for pens
4. Implantable Technology
5. Intravenous Infusion Systems.

Injectable Drug Delivery Systems' Mechanism: The method entails administering medications directly into the body, avoiding the digestive system and enabling regulated release, enhanced bioavailability, and targeted delivery of therapeutic agents. [42]

Benefits: Benefits include quick action, precise dosage management, prevention of gastrointestinal deterioration, and increased patient compliance for People who have trouble swallowing [42]

Drawbacks: The intrusive nature of injections is one drawback. Potential injection site reactions, patient discomfort or needle phobia, and the need for qualified medical professionals for appropriate administration. [42]

6.4 IMPLANTABLE SYSTEM

The purpose of implantable drug delivery systems (IDDS) is to be inserted into the body and offer regulated and targeted medication administration. [42]

6.5 Implantable Drug Delivery System Mechanism:

The method entails the regulated release of medications. From biomaterials or implanted devices, with customized Release kinetics mechanisms and release profiles. [42]

Benefits: Benefits include localized and targeted medication delivery, decreased adverse effects and increased patient compliance because of the regulated dosage.[42]

Drawbacks
The need for surgery is one drawback. Implantation, restricted ability to modify dosages, and possible dangers of infection or implant rejection. [42]

6.5 Transdermal Drug Delivery System:

The purpose of transdermal drug delivery systems (TDDS) is to deliver drugs through the skin at a regulated pace. Benefits from these systems include improved bioavailability, fewer adverse effects, and long-term therapeutic outcomes and enhanced patient adherence. [42]

Transdermal Drug Delivery System Mechanism:
The process entails the spread of medications through the skin's layers, assisted by penetration enhancers and regulated by membranes that limit rate. Skin age, condition, and medication characteristics are important factors. Function in transdermal delivery's efficacy.[42]

Benefits

Benefits include avoiding first-pass metabolism, long-term medication administration and a practical, non-invasive method of administration.[42]
Drawbacks
Some drawbacks include limited appropriateness for specific medications (strong, lipophilic), possible skin irritation, and a gradual onset of action.[42]

7. Therapeutic Applications and Translational Perspectives

- **Oral, transdermal, parenteral and localized delivery**
  Different dosage forms for drug administration include tablets, capsules, pills, ointments, syrups, and injections, chosen based on the target site, therapy duration, and the drug's properties. Key factors influencing the route of administration are the drug's solubility and permeability, the body part being treated, and the drug's action. Some medications, poorly absorbed when taken orally due to stomach degradation, are administered via injection, ensuring 100% bioavailability when given intravenously. [43]

(a) Oral drug delivery.
Oral drug administration, while practical and cost-effective, faces challenges such as

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proteolytic enzyme degradation, severe GI pH fluctuations, and a mucus barrier that limits drug absorption. Enteric coatings and mucoadhesive polymers can enhance drug stability and interaction with the intestinal surface. [44] Targeting intestinal transporters with small-molecule ligands may enhance drug transport, yet the dynamic GI environment complicates clinical application. Oral tablets are typically immediate-release (IR) or modified-release (MR), with IR often necessitating repeated dosing, impacting patient compliance. Modified-release systems can better maintain drug levels, thus improve compliance and reduce the frequency of dosing and potential side effects. [43]

(b)Transdermal drug delivery

Transdermal drug delivery faces the challenge of the hydrophobic stratum corneum, with techniques like permeation enhancers, deformable nanocarriers (e.g., transferosomes), and microneedles being crucial for enhancing penetration. Benefits include superior systemic safety and localized control. Key research topics involve standardizing penetration evaluation methods, mapping challenges across drug delivery routes, and developing adaptable nanotechnology systems. Future efforts should focus on modifying core nanocarrier designs for specific routes, ensuring biological resilience and scalability, and aligning with regulatory navigation and safety evaluations. [44]

(c) Parenteral drug delivery

Parenteral drug delivery, particularly through IV injections, presents challenges related to interactions with blood components. Key design factors include biocompatibility, toxicity, drug loading and release, and biodistribution, aiming to prevent opsonization and rapid clearance by the reticuloendothelial system. A common technique is "stealth coating," often by PEGylation, to reduce immune detection, and targeting ligands enhance tissue selectivity. However, challenges such as PEG-related immunogenicity and variations in EPR in humans create risks like accelerated blood clearance and hypersensitivity reactions. Future research should focus on developing non-PEG stealth coatings and frameworks for patient immunological risk assessment. [44]

- **Delivery of peptides, proteins and nucleic acids**

In delivery, plant cells receive biomolecules such as peptides, proteins, and nucleic acids through peptide-based foliar spraying technology. This method involves complexing nucleic acids like DNA and siRNA with cell-penetrating peptides (CPPs) to create sub-micrometer-sized nanocomplexes, which are sprayed on plant leaves. Chloroplast-targeting peptides (CTPs) can direct molecules to chloroplasts, while CPPs facilitate cellular entry. This technique effectively delivers siRNA for gene silencing and plasmid DNA for gene expression in plant nuclei and chloroplasts, providing a cost-effective, non-transgenic method for biomolecule transfer into plants. [45]

(a)Peptides:

Peptide and protein medications are pivotal in biomedicine due to their unique biological properties and therapeutic potentials. Peptides, consisting of 2 to 50 amino acids, differ from proteins, which have over 50 and complex structures. Synthetic polymers are often used in drug delivery systems (DDS) to enhance the stability and efficacy of these medications by modifying their properties for better targeted delivery and slow release. Classification of peptide/protein medications is based on structure (single-chain, multi-chain, binding proteins) and function (hormones, enzymes, antibodies, cytokines). This classification aids in understanding their mechanisms of action and guides the development of new therapies, focusing on criteria like cell proliferation inhibition and anti-inflammatory effects.[46]

(b)Proteins:

Polymer-based delivery systems address the challenges of protein antigen breakdown and low immunogenicity in vaccine delivery by enhancing protein stability, absorption, and immune responses. Key strategies include encapsulation in biocompatible nanoparticles like PLGA and PLA for prolonged release and antigen depot formation. Other methods, such as complexation and hydrogel entrapment, improve antigen stability and transport, may enable adjuvant co-delivery, and enhance immune engagement without additional adjuvants. These systems collectively improve stability, controlled release, targeting, and immunogenicity while preventing degradation. [46]

[c] Nucleic acid:

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Nucleic acid vaccines, particularly DNA and mRNA, stimulate immune responses by introducing sequences that enable cells to express antigens independently. They provide long-term antigen expression and evoke both humoral and cellular responses, offering a more comprehensive protective effect compared to traditional protein and peptide vaccines. DNA vaccination was the first investigated, with early studies in 1992 demonstrating increased immune responses. Despite initially sluggish development due to technical challenges, advancements in polymer carriers have enhanced vaccination effectiveness by controlling DNA release rates and targeting. These innovations have shown promise in suppressing tumor growth and eliciting strong immune responses. [46]

Patient-centric and personalized drug delivery

In the pharmaceutical industry, technologies that enable exact control over the rate, time, and location of drug release within the body are referred to as controlled drug delivery systems. These systems have a number of uses and provide advantages like enhanced patient compliance, decreased adverse effects, and enhanced efficacy.

The dose form is a combination of drugs and excipients. Excipients are used to enhance stability, give products structure, and mask flavors. Conventional dosage forms like solid, semisolid, and liquid require high doses and frequent administration while having poor patient compliance due to changes in plasma drug levels. [47]

[A]Patient specific drug delivery:

3D printing is transforming drug delivery by enabling personalized medication tailored to individual patient needs. This technology allows for the precise creation of customized oral dosage forms, surpassing traditional manufacturing limitations. [47] Benefits include improved targeting accuracy, enhanced treatment efficacy, and increased patient satisfaction. Additionally, 3D printing aids in surgical planning and medical education by producing realistic anatomical models. It holds significant potential to revolutionize the biopharma industry through innovative manufacturing techniques and patient-specific formulations. [48]

[B] 3D Printing In Drug Delivery

It is crucial to establish precise rules and regulations for 3D-printed medicinal delivery devices. To guarantee safety, effectiveness, and quality control, industry, regulatory agencies, and researchers must work together.

- Another name for 3D printing is additive manufacturing
- It deposits materials layer by layer to form three-dimensional things.
- It makes it possible to precisely fabricate elaborate and sophisticated structures.
- Customization, which is crucial for individualized treatment delivery, is a significant benefit.
- Because 3D printing may be utilized to create effective and focused treatment delivery systems, it has garnered interest in the healthcare industry.
- It may be used for customized and regulated drug delivery.
- Because the dosage form's structure and characteristics may be customized to meet therapeutic needs, the technology is seen as a promising method for delivering therapeutic agents.
- The review focuses on 3D printing's developments, usage, and potential for medicinal delivery. [48]

[c] Patient Compliance:

Controlled drug delivery systems (DDS) are designed to improve patient compliance by maintaining stable plasma drug levels through a continuous release of medication. Traditional dosage forms lead to fluctuations in drug levels, necessitating multiple doses that often result in toxicity and lower compliance. An optimal controlled DDS reduces dosage frequency and side effects while enhancing drug bioavailability, thereby minimizing toxicity and improving overall treatment effectiveness. [50]

Challenges and future perspectives

[a]Challenges

- Delivery methods using polymers enhance the durability, bioavailability, and targeted release of chemotherapeutic drugs.
- Biodegradable and non-biodegradable polymers, along with modifications and combination treatments, improve specificity and effectiveness in cancer therapy.
- Ongoing research in polymer-based systems shows promise for enhancing precision medicine in cancer treatment.
- Platinum-based drugs, such as cisplatin and carboplatin, cause serious side effects, including neurotoxicity and nephrotoxicity, while also leading to drug resistance.
- Combination therapies are being explored to boost the anticancer effects of platinum drugs and manage associated side effects.

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• Efficient peptide vaccine delivery to antigen-presenting cells (APCs) is critical for initiating immune responses.
• Microfabrication has led to the creation of implantable microchips for drug delivery; however, challenges like biocompatibility and the risks of surgical procedures remain.
• Enzyme-responsive drug delivery can achieve site-specific release at inflammatory tissues, but controlling initial drug release is a challenge.
• In nanomedicine, while nanoparticles provide targeted delivery, their safety and potential toxicity due to accumulation and oxidative stress must be carefully evaluated. [46,49]

[B] Future perspective:
• Organs such as the liver, lungs, and brain can experience stress and inflammation due to the accumulation of nanoparticles in the reticuloendothelial system.
• Nanoparticles' ability to cross the blood-brain barrier may aid in treating brain diseases, but also poses risks of neurotoxicity.
• These nanoparticles may have immunomodulatory effects.
• Inorganic mesoporous nanoparticles exhibit adjustable characteristics (pore size, particle size, shape, surface properties) that are beneficial for controlled drug delivery.
• Stimuli-responsive polymers can enable spatiotemporal control of drug release into target cells. [47]

[C] Prospects for 3D-Printed Controlled Medication Administration in the Future
Personalized medicine: It is possible to create dosages and release schedules that are unique to each patient.

- Controlled release: Allows for sequential, pulsatile, continuous, or instantaneous drug release.
- Precision therapy: By using customized dosage, it may lessen negative effects.
- Complex structures: Enables the creation of complex geometries for sophisticated drug release.
- Multiple medications: A single dosage form may contain a variety of medications and materials.
- Modern technology: Printers that are faster, more accurate, and have higher resolution can increase accuracy.
- Scalability: Future studies should concentrate on large-scale production, cost-effectiveness, and reproducibility.
- Better materials: New photopolymers and biocompatible polymers could get beyond existing restrictions.
- Temperature-sensitive medications: FDM processing of heat-sensitive medications may be made possible via low-temperature printing.
- Safety and stability: Heat and UV radiation must not deteriorate drugs during printing. [49]

8. Conclusion:

Controlled drug delivery systems have evolved from traditional sustained-release formulations into complex platforms capable of regulating drug release based on various stimuli and conditions. Performance is influenced by factors like drug solubility, molecular size, and polymer interactions, utilizing different mechanisms such as diffusion and osmosis. While innovative methods, including 3D printing and nanotechnology, enhance targeted drug administration, challenges persist in translating research to clinical use, particularly concerning biocompatibility and safety. Future developments are expected to focus on integrated platforms combining AI and precision medicine, aiming for personalized dosing and optimal therapeutic outcomes while balancing manufacturing viability and patient safety. Continued interdisciplinary research is essential for realizing the potential of these advanced systems.

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