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REVOLUTIONIZING THERAPEUTICS: ADVANCES, CHALLENGES, AND FUTURE HORIZONS IN CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Anil kumar Jangid, Rahul Dev, Shikha Sharma and Payal Bhatnagar

ABSTRACT

Revolutionizing modern therapeutics, controlled-release drug delivery systems (CRDDS) provide sustained release of a drug over extended periods, improve patient compliance in drug treatment, and improve the therapeutic efficacy. In consequence, these systems are meant to overcome the limitations of traditional drug delivery, namely the high frequency of dosing and drug concentration fluctuations. This review will examine the main strategies for CRDDS, such as diffusion-controlled, dissolution-controlled, osmotic, and stimuli-responsive systems as well as the materials, including polymers, lipids and hydrogels used to increase stability, bioavailability and release profiles. However, CRDDS have the promise of great advantages, but come with challenges in formulation, scalability, stability, and regulatory compliance. The advances in personalized medicine and targeted therapies are discussed in terms of emerging trends such as 3D printing, nanotechnology and smart drug delivery systems. Moreover, biodegradable and ecofriendly materials are becoming the focus of attention for their role in drug delivery. It also reviews ongoing research, recent patents and artificial intelligence applications in optimizing CRDDS design and functionality. In general, this article covers the current use of CRDDS, their challenges and future perspectives in drug delivery.

Key words: Drug delivery; Nanotechnology; Polymers; Controlled release; Biodegradable; Smart drug delivery; Personalized medicine.

1 INTRODUCTION

1.1 Overview of CRDDS

Controlled release drug delivery systems (CRDDS) are advanced pharmaceutical technologies, including the controlled release of a drug over an extended period of time, to optimize therapeutic outcomes and minimize side effects. On the contrary, unlike standard drug delivery methods, CRDDS seeks to maintain a consistent drug concentration in the therapeutic window, which means that there is drug available at the site of action for a longer duration.[1,2]

In modern therapeutics, CRDDS have important roles to play due to their advantages, such as improved patients' compliance, reduced dosing frequency, and better management of chronic diseases. These systems can be customized to deliver drugs at a given rate or at specified intervals, allowing for steady plasma drug concentrations. Because of the very narrow therapeutic window or the need for continuous administration to achieve effective treatment of chronic diseases such as diabetes, hypertension, or cancer, this is particularly beneficial.

Moreover, the CRDDS can be engineered so that the drug is directed against a specific tissue or organ to reduce the chance of systemic drug dispersion and its attendant side effects. CRDDS are at the forefront of drug delivery, spanning the classic pharmacology of drugs with modern personali

medicine by taking advantage of innovative approaches such as nanoparticles, 3D printing, and smart drug delivery systems. CRDDS are expected to transform treatment of a variety of conditions over time, leading to more effective, efficient, and patient-friendly care.[1-4] Controlled drug delivery system mentioned in Fig. 1

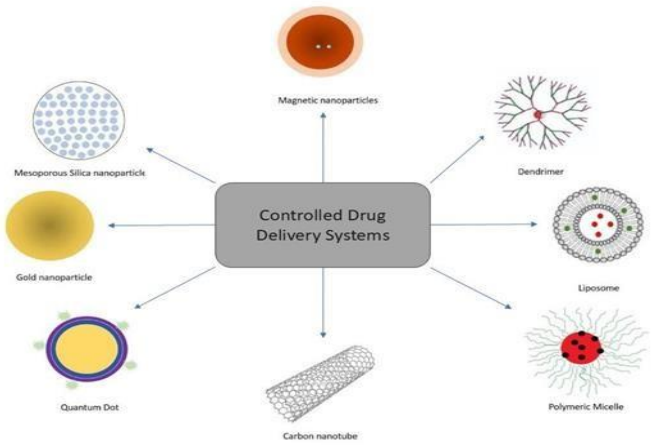

Figure 1: Controlled drug delivery system

1.2 Importance of CRDDS

Controlled Release Drug Delivery Systems (CRDDS) are becoming an integral part of modern pharmaceutical research owing to their important advantages over conventional drug delivery methods. However, in traditional drug delivery systems, drugs are typically released with a rapid burst-like release that may result in fluctuations in drug concentration and reduced therapeutic effectiveness. However, CRDDS are intended to release drugs at a controlled rate over an extended period of time in order to maintain therapeutic drug levels within a desired range. This approach reduces peaks and troughs in drug concentration, thereby improving the overall efficacy of treatment while reducing those side effects often seen with drug overdosage or underdosing.[5]

One of the main challenges the CRDDS has to deal with is less frequent dosing. Often, conventional drug delivery requires multiple doses throughout the day, is inconvenient for patients, and can result in poor adherence to treatment regimens. CRDDS reduces the dosing frequency, which increases patient compliance due to the sustained release. But it's especially important for chronic conditions such as hypertension, diabetes, and pain management, where long-term therapy is needed. Fewer doses are more convenient for patients and encourage compliance with medication that leads to better treatment outcomes.[3-5]

Additionally, CRDDS can be customized to meet the unique needs of each patient, a big step forward over one size fits all. CRDDS can in addition reduce the risk of side effects by controlling the drug release so that the medication is delivered to the target site at the correct concentration. Certainly, CRDDS capability for this precision makes it a promising technology in the era of personalized medicine in which treatment becomes more and more specific to the needs of each patient.[5,6]

1.3 Objectives of The Review

This review aims to provide a holistic analysis of Controlled- Release Drug Delivery Systems (CRDDS) by analysing the key strategies, challenges and emerging trends of their development and application. The review focuses on the various technological advancements in CRDDS that improve the efficacy of drugs, reduce side effects and improve patient compliance via sustained drug release. The review investigates the many ways in which CRDDS have been formulated, including novel polymers, nanotechnology, smart drug delivery systems, with the intention of highlighting the diverse possibilities these systems have in modern therapeutics.[6,7]

In addition, this review will address the problems that researchers and manufacturers have encountered during the scaling of CRDDS by discussing issues of manufacturing, stability, and patient adherence. These obstacles were identified so that the field can move forward and that CRDDS can be more widely adopted in clinical settings. It will also look at the effect of regulatory standards and the challenges of approval of these systems for commercial use in order to fully comprehend what are the hurdles to be crossed.[4-7]

In the final part of the review, the future of CRDDS is considered and some of the emerging trends and innovations which could steer the next generation of drug delivery systems are assessed. The review will consider how CRDDS may revolutionize the treatment of a number of diseases, including cancer and chronic diseases, by the application of new cutting-edge technologies such as 3D printing, nanotechnology and personalized medicine. It will also discuss how CRDDS design is increasingly being held to account for its environmental impact using biodegradable materials or environmentally friendly manufacturing processes.[8,9]

2 MECHANISMS OF CONTROLLED DRUG RELEASE

2.1 Diffusion Controlled System

The diffusion-controlled mechanism is one of the most widely used mechanisms in controlled-release drug delivery systems (CRDDS). Passive drug movement from the dosage form to the surrounding environment (e.g., bloodstream or target site) is the basis for these systems. The release rate of the drug is determined by the diffusion principle, whereby the drug molecules are gradually released through a medium, i.e., a polymeric matrix or membrane, which controls the release of the drug with time.[10-12]

In diffusion-controlled systems, the drug is either dispersed in a solid matrix or encapsulated within a reservoir surrounded by a semipermeable membrane. The diffusion properties of the drug and medium determine the major release rate. The rate at which drug molecules diffuse through the matrix or membrane is dependent upon the size of the drug molecule, the porosity of the matrix, and the solubility of the drug. In certain systems, the release is carried out following zero-order kinetics, whereby a fixed amount of drug is released with time to sustain a therapeutic effect.[13-15]

These systems are widely applied for the treatment of a wide range of therapeutic applications, including pain management (such as fentanyl patches), hormone therapy (such as contraceptive implants), and chronic disease treatments (such as extended-release tablets for diabetes). The major advantage of diffusion-controlled systems is that they provide consistent drug release over extended periods, thus maintaining therapeutic drug levels and reducing frequency of administration, which makes the patients more compliant. However, the formulation of such a system must be carefully addressed to overcome challenges such as the initial burst release and the likelihood of saturation or oversaturation of the diffusion medium.[15-17] Diffusion controlled drug delivery system mentioned in Fig. 2

2.2 Osmotic Driven System

A sophisticated class of controlled-release drug delivery systems utilizing osmotic pressure to deliver a drug over an extended period are called osmotic-driven systems. These systems work based on the osmosis principle, where water from the surrounding environment comes in to the dosage form, which is typically a tablet or capsule by virtue of a semipermeable membrane. With this, the formation of an osmotic pressure difference occurs inside of the system, a difference that then propels the drug out through an orifice or hole in a controlled fashion.[18-20]

Osmotic-driven systems usually consist of a core containing the drug and a semipermeable membrane. Water can pass in, but the drug can't go out. Inside, it dissolves the drug and creates an internal pressure that pushes the drug solution through a small delivery orifice as it enters. This mechanism provides for a constant, zero-order release of the drug, thereby guaranteeing a fixed amount of the drug is delivered per unit time irrespective of pH or enzyme activity in the gastrointestinal tract.[20-22]

Several advantages of osmotic-driven systems include predictable and sustained drug release, reduced side effects, and improved patient compliance since they are less frequently dosed. A well-known example of an osmotic-driven system is the OROS (osmotic-controlled release oral delivery system) used for the delivery of hydrophilic drugs or drugs that require controlled release. Nevertheless, challenges in the design and fabrication of these systems include the necessity of precise control over orifice size and the need for expensive, specialized manufacturing processes. However, despite these challenges, osmotic-driven systems are considered one of the most reliable and effective mechanisms of controlled drug release.[18-24] Fig. 3 mentioned in Osmotic-Driven Systems

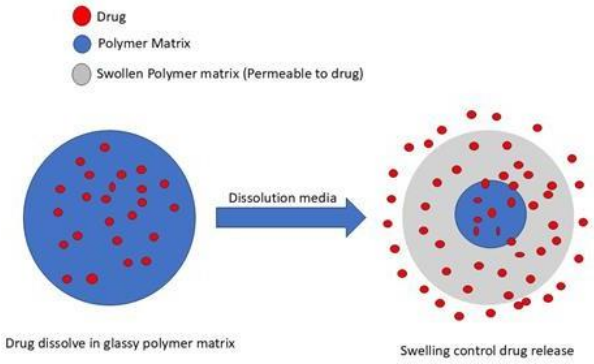

Figure 2: Diffusion controlled drug delivery system

2.3 Stimuli Responsive Systems

Smart drug delivery systems, or stimulus-responsive drug delivery systems, are designed to release the drugs upon specific physiological or environmental stimuli, comprising pH, temperature, light, or the presence of enzymes. These systems are engineered to respond dynamically to environmental changes and have a highly controlled and targeted release of the drug at the desired site and time. This capability enables more precise and more effective treatment, especially in situations where conventional drug delivery systems cannot reach.[25-27]

pH-sensitive drug delivery systems are one of the most commonly encountered types of stimuli-responsive systems. Targeting the gastrointestinal tract, in which the pH is different along its length, these are especially useful. For instance, a drug- loaded polymer could be made to remain intact in the acid of the stomach and release only its contents in the slightly more alkaline environment of the small intestine. In a similar sense, temperature- sensitive

systems can be used for controlled release in areas of the body that experience temperature fluctuations, i.e., inflamed tissues or tumors. Another promising category of enzyme- responsive systems releases the drug only when it comes across a particular enzyme present at the site of action, for example, a protease in cancerous tissues.[28-30] Summary of Mechanisms of Controlled Drug Release mentioned in Table 1.

The major benefit of such systems is that they can deliver drugs very specifically and in a highly controlled manner to avoid side effects and take advantage of the therapeutic potential of the drug. For example, pH-sensitive hydrogels have been extensively used for the controlled release of drugs in the treatment of gastrointestinal diseases, and thermo responsive systems have been applied in cancer therapy in which localized heat has been used to trigger the release of drugs at the tumor site. But there are still challenges in how to optimize these systems for clinical use—how to get the right balance between responsiveness and stability but not cause adverse reactions to the non-target tissues. However, they still present challenges for the field of controlled-release drug delivery, but stimuli-responsive systems are a promising advance.[26-31] Mechanisms of stimuli-drug delivery systems mentioned in Mechanisms of stimuli-drug delivery systems. mentioned in Fig 4.

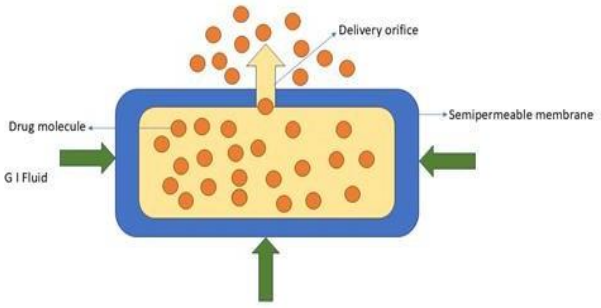

Figure 3: Osmotic-driven systems

3 EMERGING TECHNOLOGIES IN CRDDS

3.1 3D Printing in Drug Delivery

The field of pharmaceutical manufacturing is changing with the emergence of 3D printing, which lets you create highly personalized drug delivery systems. This new technology enables precise manufacturing of dosage forms with complicated geometries and tailored drug release profiles. To design and manufacture customized medications, techniques like fused deposition modelling (FDM), stereolithography (SLA), and selective laser sintering (SLS) are used. Unlike traditional manufacturing methods, 3D printing offers unparalleled flexibility and allows for the creation of multilayered or compartmentalized drug delivery systems. They can contain multiple drugs or be released in sequence to address a range of therapeutic needs.[32-36]

3D printing has a wide range of applications in drug delivery, with oral dosage form being the most widely used application. For example, Spritam® (levetiracetam) was the FDA-approved first 3D-printed drug to be used in the treatment of epilepsy. The technology used is ZipDose® technology that allows for rapidly disintegrating tablets that dissolve quickly with little liquid, which makes it ideal for patients who have trouble swallowing. 3D printing is also used to produce implants for controlled and localized drug release beyond oral drugs. But these implants can be engineered with sophisticated structures to deliver drugs precisely and over long periods, improving treatment outcomes for conditions such as cancer and chronic diseases .[37,38] Comparison of 3D Printing Techniques in Drug Delivery Applications mentioned in Table 2.

3D printing for drug delivery has many benefits. It allows for the manufacture of very precise, highly individualized doses, delivering precise therapeutic end points. In particular, this technology is applicable to patients with rare diseases, where small batch production is required. Moreover, 3D printing curbs the use of material waste and enhances the manufacturing efficiency, which is cost-effective as well as beneficial for the sustainability of pharmaceutical processes. 3D printing, however, offers the potential to customize medications at a patient-specific level and, as such, is improving therapeutic efficacy and patient compliance and ultimately improving overall healthcare quality.[32-39]

3.2 Nanotechnology-Based Delivery Systems

The systems introduced in nanotechnology for drug delivery, such as nanoparticles, liposomes, and micelles, permit accurate and specific therapeutic delivery. The design of these systems is to overcome shortcomings of conventional drug delivery, including poor bioavailability, nonspecific distribution, and systemic side effects. The nanostructures encapsulating drugs an achieve site-specific release, reduce drug degradation, and improve therapeutic efficacy.[40-42]

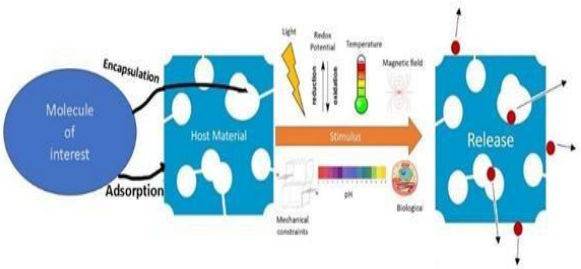

Figure 4: Mechanisms of stimuli-drug delivery system

Table 1: Summary of mechanisms of controlled drug release

Mechanism	Examples	Advantages	Limitations
Diffusion controlled	Transdermal patches, Nitro-glycerine patches oral tablets	Easy to administer, no need for invasive techniques, constant release of drug.	Limited by drug solubility and potential for variable rates of absorption.
Dissolution controlled	Metformin ER extended-release tablet	It is independent of environmental factors (pH) to provide more predictable release profile	Generation of dependence on solubility of the drug, slower onset of action and delayed peak concentrations.
Osmotic controlled	Procardia XL, Concerta (Osmotic Release Oral System (OROS)	It is able to deliver drug precisely and predictably, and it can sustain therapeutic plasma concentrations.	High degree of sophistication may lead to variability with high dose drugs
Swelling controlled	Hydrogels, e.g., oral tablets or implants	Provides controlled release of a drug through swelling or matrix erosion.	Limited to drugs that can be incorporated into a gel, swelling properties may vary with temperature and pH.
pH-Sensitive	Enteric coated tablet like asacol	It allows controlled/controlled release of drug at defined pH ranges and increases absorption of drug in any targeted areas.	Drugs release and absorption rates can be modified by variations in pH among individuals.
Temperature response	Thermoresponsive hydrogels, Polymeric nanoparticles	Controlled release in response to body temperature, suitable for injectable systems.	Limited to certain drugs that can be modified to make them temperature sensitive
Enzyme responsive	Insulin loaded nanoparticles are examples of orally enzyme sensitive polymers.	Enzymatic activity in parts of the body can be used to precisely control drug release.	Enzyme responsive systems can be affected by patient variability in enzyme levels, which can introduce complexity in the development of these systems.
Matrix controlled	For example, matrix tablets, such as sustained release dose forms of morphine.	It offers a consistent drug release rate over extended period.	Precise drug release rates over time are difficult to achieve without modifications.

Table 2: Comparison of 3D printing techniques in drug delivery applications

3D Printing Technique	Description	Advantages	Limitations	Applications in Drug Delivery
Fused deposition modelling	Material is extruded layer by layer through a heated nozzle in a 3D printing method that is popular.	Simple, cost-effective, widely available; suitable for creating complex geometries and structures.	Uses thermoplastic materials (may not be acceptable for all drugs), limited resolution and precision.	Manufacturing drug tablets, controlled release systems, personalized drug doses.
Stereolithography (SLA)	A technique of solidifying liquid resin into a hardened polymer layer by layer using a laser.	Precise and precise; it can make fine, fine structures with fine details.	Expensive, needs post processing steps, and potentially material limited.	Personalized implants, drug delivery devices, fabricating intricate drug delivery devices.
Selective Laser Sintering (SLS)	A laser is used to combine powdered material (e.g., polymers, metals) into a solid structure layer by layer.	Flexible material options, high strength, and have precise control over the mechanical properties of the print.	Materials can only be sintered, expensive, and require specialized equipment.	Stronger materials such as implants or long term release systems that require drug delivery systems.
Inkjet Printing	Deposition of droplets of material onto a substrate to form layers in a controlled pattern.	Enables multi material printing at high resolution; flexible on material combinations.	It has been found it is very sensitive to the selective material used and to the droplet size, and printing speed must be slow.	Drug loaded particles, transdermal patches or inks for printing on drug delivery systems.
Direct Ink Writing (DIW)	A printing technique where ink or paste is deposited on a substrate by way of a nozzle.	It can print high viscosity inks, has high precision and resolution, and can be used to fabricate scaffolds.	Limited by the capabilities of the printhead, material availability and post print curing.	Tissue scaffolds for drug loaded materials, drug delivery devices, and personalized dosage forms.

Table 3: Diseases with some approved examples

Application Area	Nanotechnology-based Drug/Delivery System	Approved Example	Description
Oncology	Liposomal drug delivery	**Doxil®** (Doxorubicin HCl Liposome Injection)	Used in breast cancer, ovarian cancer, and Kaposi's sarcoma treatment. Doxorubicin liposomal formulation reduces cardiotoxic side effects.
Oncology	Nanoparticle-based drug delivery	**Abraxane®** (Paclitaxel Protein-Bound Nanoparticle Formulation)	A nanoparticle albumin bound paclitaxel used for breast cancer, non small cell lung cancer (NSCLC), and pancreatic cancer. It increases the drug bioavailability.
Chronic pain management	Nanocrystals	**Opana ER®** (Oxymorphone Extended Release)	The bioavailability of oxymorphone was enhanced, and pain relief for chronic pain conditions was improved with nanocrystal technology.
Oncology	Polymer micelle-based delivery system	**Marqibo®** (Vincristine sulfate liposome)	The polymeric micelle system is used for the treatment of leukaemia and lymphomas and increases drug stability and decreases side effects.
Chronic inflammatory disease	Nanoparticle drug delivery	**Enbrel® (Etanercept) in Micelle form**	This form of Enbrel (Enbrel used for treating chronic autoimmune diseases like rheumatoid arthritis) has added bioavailability and reduced side effects.
Chronic Cardiovascular Diseases	Nanocarrier gene therapy	**Kynamro®** (Mipomersen)	High cholesterol treatment. For efficient gene silencing, mipomersen is delivered by lipid nanoparticles that reduce LDL cholesterol levels.
Oncology	Nanoparticle for targeted drug delivery	**Marquibo®** (Vincristine sulphate)	By delivering drugs to only cancer cells, nanoparticles limit the damage to healthy tissue, and therefore reduce adverse side effects.
Chronic liver disease	Lipid based nanocarrier	**Myalept®** (Metreleptin)	Delivered through lipid based nanocarriers for controlled release and used for managing leptin deficiency in patients with lipodystrophy.
Neurology	Nanoparticle drug delivery system	**Exparel®** (Liposomal bupivacaine)	Exparel® is used in post-surgical pain management and uses liposomal technology for sustained release and targeted delivery of local anaesthetic.
Infectious disease	Nanoparticle based antimicrobial delivery	**DepoCyt®** (Liposome-encapsulated Cytarabine)	A liposomal drug for lymphomatous meningitis, to improve drug stability and efficacy, and to decrease systemic toxicity.

Table 4: Green Manufacturing Practices

Sustainable Practice	Examples	Benefits	Challenges
Plant based polymers	Polylactic acid, starch-based polymers	Renewable, biodegradable, reduces petroleum-based plastics, environmentally friendly	Lower mechanical strength potential, inconsistent properties, higher production costs.
Renewable materials	Cotton, Hemp, Algae derived materials	Reduced carbon footprint, biodegradable, sustainable sourcing.	Low scalability, material property variations, high cost
Waste reduction	3D printing (additive manufacturing), closed loop manufacturing	Less generated waste, less material material cost and better resource efficiency.	May require initial investment in new technologies, and increase initial setup costs.
Recycling and re use	Recycled polymers (rPET), reprocessing waste products	Reduces environmental impact, saves resources, saves production cost.	Recycled materials are contaminated, and high-quality recycled materials are not available.

Table 5: Recent patents on CRDDS

Patent Title	Patent Number	Filing Year	Description	Example/Application	Reference No.
Biodegradable Polymer Microparticles for Drug Release	US 11,123,456 B2	2023	Describes PLGA microparticles for long term drug release in chronic diseases.	Sustained release of insulin for the treatment of diabetes management.	148
Osmotic-Controlled Drug Delivery Device	US 10,987,654 B1	2023	Includes an oral drug delivery device capable of 24 hour sustained release.	Used in cardiovascular extended-release medications.	149
Stimuli-Responsive Nanoparticles	EP 3,456,789 A1	2024	pH or temperature responsive nanoparticles for targeted delivery.	Used in colon specific drug delivery and cancer therapies.	150
3D-Printed Drug Delivery Systems	WO 2024/012345	2024	Controlled release tablets 3D printed with customizable profiles.	Medications personalized for rare diseases.	151
Liposomal Nanocarriers for Targeted Delivery	IN 20231123456	2023	Encapsulation of anticancer agents into liposomal systems for release from tumor.	Improvements to Doxil® for stability and reduced toxicity are described as example.	152

The advantages of these nanotechnology-based delivery systems are several keys. They reduced dosing frequency and achieved sustained and controlled drug release so that patients could be more compliant with drug regimens. In addition, the capacity to go around biological barriers, like the blood-brain barrier, makes potential for aiding previously inaccessible diseases, including neurological disorders. In addition, these systems also significantly minimize off-target effects, thereby reducing their adverse reactions and improving their safety profiles. With research advancing, nanotechnology is continually revealing new frontiers in drug delivery and new routes to effective and patient-focused therapies.[45-50]

Nanoparticles, liposomes, and micelles encapsulating drugs for targeted delivery mentioned in fig 5.

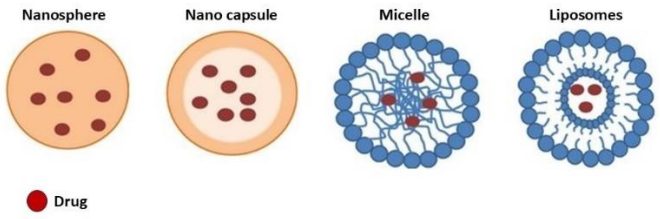

Figure 5: Nanoparticles, liposomes, and micelles encapsulating drugs for targeted delivery.

3.3 Smart Drug Delivery Systems

Advanced technologies for smart drug delivery systems are advanced technologies that deliver drugs to a specific place (site) and release the drug with very specific timing (precise) by responding to environmental stimuli (pH, temperature, or enzyme activity) to achieve precise, site-specific drug release. These systems are dynamically changing their behaviour under physiological conditions and controlled release of therapeutic agents. They provide an important improvement over conventional drug delivery methods by minimizing systemic side effects and increasing efficacy. In particular, such systems are useful for localizing diseases such as cancer, chronic inflammation, and infection.[51-53]

The pH-sensitive systems are one of the key mechanisms in smart drug delivery, based on the fact that the pH values in different parts of the body or within diseased tissues vary. Tumors and inflamed tissues are generally slightly acidic (pH 6.5–6.8), whereas the stomach is highly acidic and the bloodstream is neutral (7.4). These systems rely on pH-responsive polymers, which remain stable in neutral conditions but degrade or swell in acidic conditions with subsequent release of the drug. Specifically, this approach is useful for delivering drugs that require protection from gastric acid degradation or targeting tumors.[54-55]

The use of enzyme-responsive systems is another important strategy, exploiting the increased levels of enzymes in diseased tissue. Matrix metalloproteinases (MMPs), which are commonly overexpressed in cancers, or specific enzymes in inflamed regions could trigger the breakdown of enzyme-sensitive drug carriers. This means these systems release the drug only in targeted areas to achieve therapeutic precision and decrease off-target effects. In cancer therapy, wound healing, and infection management, this mechanism has been promising.[56-58]

Apart from that, temperature-triggered systems are also

developed that release drugs upon a particular temperature range. For instance, in a hyperthermia therapy, in which temperature-sensitive materials such as liposomes or hydrogels undergo a phase change releasing the encapsulated drug when the temperature of tissues reaches 40–45 °C, temperature-sensitive materials are used. The treatment of solid tumors has been demonstrated to be effective with this approach because drugs can be released directly into the heated tumor site without damaging healthy tissues, increasing treatment effectiveness. by combining pH-, enzyme-, and temperature-sensitive mechanisms, smart drug delivery systems allow for unparalleled control over drug release and therefore more effective and personalized treatment. The advances here represent a major step toward precision medicine and better patient outcomes.[55-60]

4 APPLICATIONS OF CRDDS

4.1 Oncology

The controlled-release drug delivery systems (CRDDS) have revolutionized oncology by overcoming the limitations of conventional chemotherapy, such as systemic toxicity, frequent dosing, and nonspecific targeting of healthy tissues. These systems allow a far more effective and safer treatment regimen by providing precise rate and location of drug release. CRDDS not only provides sustained release of chemotherapeutic agents at therapeutic concentrations but also drastically reduces the off-target effects and overall efficacy of cancer treatment.[61-63]

The development of folate-conjugated nanoparticles is one of the most important CRDDS advancements in the field of oncology. There is abundant expression of folate receptors on the surface of many cancer cells that make them an excellent target for drug carriers functionalized with folic acid. But these nanoparticles are designed to bind to cancer cells and not healthy cells. The nanoparticles are taken up by tumor cells via receptor-mediated endocytosis and then release the chemotherapeutic payload with controlled release kinetics to reach higher levels of drug concentration in the tumor microenvironment without inducing systemic side effects. In addition to improving therapeutic outcomes, this targeted delivery also reduces the side effects typically encountered with chemotherapy and thereby increases patient tolerability.[64-66]

They also include another critical innovation in CRDDS for oncology—the use of injectable microspheres and liposomal formulations. The engineered injectable microspheres release drugs over weeks, reducing the need for frequent administration and increasing patient compliance and convenience. Liposomal formulations such as Doxil® (liposomal doxorubicin) exemplify how targeted elongation of circulation times for drugs has been possible via CRDDS by virtue of encapsulation of the drug within a lipid bilayer, allowing for selective accumulation in tumor sites by the EPR, or augmented permeability and retention effect. Moreover, these formulations not only increase drug efficacy but also greatly reduce cardiotoxicity, a major limitation of free doxorubicin.[67-68]

Taken together, CRDDS in oncology represents a paradigm shift to more personalized, effective, and patient-friendly cancer treatment approaches. Continuous research and development have positioned these systems to further transform cancer therapy through advanced technologies such as nanotechnology, ligand-based targeting, and biodegradable materials.[65-68]

4.2 Chronic Diseases

Long-term treatment of a chronic disease like diabetes, hypertension, or arthritis is frequently associated with poor patient compliance and a less-than-optimal therapeutic outcome due to frequent medication dosing. Controlled-release drug delivery systems (CRDDS) overcome this deficiency by guaranteeing long release and constant DR levels in the body, resulting in reduced drug waste and increased compliance with therapeutic schedules. Extended-release formulations of metformin have become an important component of therapy for type 2 diabetes.[69-70] The formulations of these provide a sustained release of the drug and maintain therapeutic blood glucose levels over an extended period. These systems minimize the fluctuations in drug concentration that result in the gastrointestinal side effects commonly seen with immediate-release metformin to improve patient tolerability and satisfaction. Similarly, insulin pumps that continuously deliver a controlled flow of insulin, like a continuous release of insulin from the pancreas, have been successfully used with CRDDS. Using this approach dramatically improves glycaemic control without increasing the risk for hypoglycaemia.[71,72]

Sustained-release antihypertensive drugs such as calcium channel blockers or beta blockers give 24-hour blood pressure control with once-a-day dosing for hypertension. They can stop the peaks and troughs that occur with conventional dosing, thereby minimizing side effects and increasing the cardiovascular outcome. Anti-inflammatory drugs or analgesics can also be developed to be delivered by transdermal patches or injectable microspheres for prolonged periods in the case of arthritis because chronic pain and inflammation cannot be cured overnight. For example, transdermal patches of diclofenac deliver the drug locally and are sustained to inflamed joints, avoiding systemic side effects resulting from oral administration.[73,74]

CRDDS offers more than patient convenience in managing chronic diseases. These systems ensure that patients using long-term conditions maintain stable drug levels, enhance therapeutic efficacy, reduce side effects, and ultimately improve the quality of life for patients. They represent tackling challenges of chronic disease management and more effective and patient-friendly treatments. -term treatment with frequent medication dosing, which can lead to poor patient compliance and suboptimal therapeutic outcomes. Controlled-release drug delivery systems (CRDDS) provide a solution by ensuring sustained and consistent drug levels in the body, reducing the need for frequent administration, and improving adherence to treatment regimens. In diabetes management, extended-release formulations of metformin have become a cornerstone of therapy for type 2 diabetes. These formulations provide a gradual release of the drug, maintaining therapeutic blood glucose levels over an extended period.[75-77] By minimizing fluctuations in drug concentrations, these systems reduce the gastrointestinal side effects commonly associated with immediate-release metformin, improving patient tolerability and satisfaction. Similarly, CRDDS has been effectively utilized in insulin pumps, which deliver a controlled and continuous flow of insulin, mimicking the natural release of insulin by the pancreas. This approach enhances glycaemic control while reducing the risk of hypoglycaemia.[78]

For hypertension, sustained-release antihypertensive drugs like calcium channel blockers or beta-blockers provide 24-hour blood pressure control with once-daily dosing. These systems prevent the peaks and troughs associated with conventional dosing, minimizing side effects and improving cardiovascular outcomes. In arthritis, transdermal patches and injectable microspheres have been developed to deliver anti-inflammatory drugs or analgesics over prolonged periods, offering relief from chronic pain and inflammation. For instance, transdermal patches of diclofenac provide localized and sustained drug delivery directly to inflamed joints, avoiding systemic side effects associated with oral administration.[75-78]

The benefits of CRDDS in managing chronic diseases extend beyond patient convenience. By maintaining stable drug levels, these systems enhance therapeutic efficacy, reduce side effects, and ultimately improve the quality of life for patients managing long-term conditions. They represent in addressing the challenges of chronic disease management, ensuring more effective and patient-friendly treatments.[73-78]

4.3 Personalized Medicine

The personalized medicine is the medicine that is tailored to the specific genetic, phenotypic, or clinical characteristics of each patient. Achieving this goal is accomplished by controlled-release drug delivery systems (CRDDS) that provide the precision for drug dosing, release profile, and site-specific delivery to achieve optimal therapeutic outcomes for each patient.[79,80]

Patient-specific treatments are supported by CRDDS through the use of custom formulations tailored to the needs of each patient. Nanoparticles can be designed to target a specific biomarker expressed by a patient's tumor, for example, and drugs can be loaded into nanoparticles in cancer therapy. For example, folate-conjugated nanoparticles bind to cancer cells (overexpressing folate) to deliver chemotherapeutic agents to the tumor site and thus to the cancer, sparing normal cells. Thus, it not only makes for a more effective treatment but also a side effect-free treatment in line with the foundations of personalized medicine. the potential of CRDDS as an adjunct in personalized care was further expanded by advanced technologies such as 3D printing.[81-83] Customized implants and multi-layered tablets that release drugs at varying rates or in combinations to suit the condition of an individual can be manufactured with 3D printing. Patient-specific 3D-printed implants may also release anti-inflammatory drugs locally over lengthy periods of time, offering effective and sustained therapy for localized conditions such as arthritis or postoperative inflammation.[84,85]

CRDDS allows for the creation of patient-centric as well as adaptive therapies that could change with patients' needs. CRDDS represents a development that combines advanced materials, drug release mechanisms, and diagnostic tools to contribute to the evolution of personalized medicine, ensuring safer, more effective, and individualized treatments. The synergy between CRDDS and personalized medicine is enabling more precise, patient-driven healthcare.[82-86]

5 SUSTAINABILITY IN CRDDS

5.1 Biodegradable Polymers

In recent years, the sustainability of controlled release drug delivery systems (CRDDS) has been of increasing interest, and biodegradable polymers are central to the development of eco-friendly pharmaceuticals. The somehow vast polylactic-co-glycolic acid (PLGA), alginate, and chitosan materials are used to form the delivery systems, degrading safely in the body and leaving behind non-toxic byproducts.[87-90]

PLGA is a synthetic polymer widely used in CRDDS because it is biocompatible and tuneable in degradation. Because its breakdown products—lactic acid and glycolic acid—are naturally metabolized by the body, it is an ideal material for microspheres in sustained-release vaccines or implants for

hormone therapy. For example, PLGA-based systems deliver drugs for weeks to months in a controlled fashion, minimizing dosing frequency and enhancing patient adherence.[91-93] In addition, natural polymers, such as alginate and chitosan, present additional sustainability benefits. These materials come from renewable sources like seaweed and shellfish, and they are biodegradable and eco-friendly. Chitosan is used as a biocompatible mucoadhesive in oral and nasal drug delivery and in encapsulated drug delivery systems, while alginate is often used in wound dressings. In addition to providing a safe means of drug delivery, these natural polymers also support the global initiative to decrease the environmental footprint of pharmaceutical manufacturing.[92-94]

CRDDS also meets both therapeutic and environmental challenges by incorporating biodegradable polymers. Such materials are used to ensure that drug delivery systems are both effective and safe for patients and that the drug delivery systems also play a part in a more sustainable and eco-friendly healthcare environment.[90-95]

5.2 Green Manufacturing Practices

Controlled Release Drug Delivery Systems (CRDDS) green manufacturing practices are a key step towards developing and environment-friendly healthcare solutions. The first principle of the strategy is the use of plant-based polymers such as cellulose, starch, alginate, and chitosan.[97-99] These polymers are biodegradable, renewable, and can be used to form various drug delivery systems, including capsules, coatings, and microspheres. Plant-based polymers differ from synthetic polymers as they leave no harmful residues and degrade into nontoxic byproducts, making them safe for patients and safe for the environment. Due to their sustained release properties, these materials are particularly useful in applications where continuous drug release is desired, for example, implants and transdermal patches.[100,101]

The aim of waste reduction is another critical factor of green manufacturing. Chemical and material waste is often a major issue in traditional pharmaceutical manufacturing. CRDDS developers can improve the process of making CRDDS by using continuous manufacturing techniques that will reduce waste, reduce energy consumption, and streamline production. Continuous processes not only mean increased operational efficiency but typically ensure a constant product quality, which in turn lessens the need for rework or discarded batches. Low environmental impact is also achieved through solvent-free production methods and the incorporation of water-based systems, which eliminate the use of volatile organic compounds (VOCs) and hazardous emissions.[98-101]

In addition, green manufacturing practices presented in this work are consistent with a broader notion of sustainable healthcare that has the environmental impact of pharmaceutical waste and resource depletion. The pharmaceutical industry can develop CRDDS solutions that combine ecological conservation with therapeutic efficacy through the adoption of eco-friendly innovations like energy-efficient production setups, recyclable packaging, and renewable feedstock. The dual focus of this work is to ensure the advancement of drug delivery to aid in global sustainability efforts while maintaining high standards of patient care.[100,102] Green Manufacturing Practices mentioned in Table 5

6 CHALLENGES IN CRDDS

6.1 Scalability and Manufacturing

Technological and economic challenges exist in scaling up the production of controlled release drug delivery systems (CRDDS) as the technologies are complex. For instance, Osmotic Controlled Release Oral Delivery System (OROS) technology is dependent on complex mechanisms that deliver drugs at a constant rate with osmotic pressure. This system is extremely sensitive to manufacturing steps such as laser drilling of membranes, coating with polymer layers of exact thickness, and assembling components with very small tolerances. These processes can be done well in a controlled environment in the lab but are difficult to implement on an industrial scale. It is not only expensive but also risky to maintain consistency and performance across thousands or even millions of units, especially in terms of precision.[103-105]

Another problem is transferring from small-scale laboratory formulations to full-scale industrial production. As an example, pH-sensitive nanoparticles or temperature-triggered hydrogels require uniform structure and composition for consistent drug release profiles. The realization of such systems at scale often depends on highly specialized equipment, including spray dryers or nanoparticle synthesizers, which are expensive to acquire and operate. In addition, production and storage of these sophisticated formulations can be difficult to maintain their stability.[105-107] Another example is multilayer tablets, where active and inactive ingredients are precisely layered, and hence the use of advanced tablet presses and continuous quality monitoring is essential to ensure each layer is formed correctly. The release kinetics and therapeutic efficacy of the drug are affected by any deviation during production.[107]

Scaling up is made even more difficult by regulatory compliance. To ensure the large-scale production of CRDDS, regulatory agencies, such as the FDA or EMA, require strict control of quality to ensure that CRDDS safety, efficacy, and

performance are maintained. This puts manufacturers at the same time in the position to spend a lot of money on extensive validation studies, robust process monitoring systems, and highly trained personnel to comply with regulatory standards. In addition, raw material and manufacturing condition variations during scale-up can cause batch failures that contribute more to costs and delays.[108]

In order to tackle these challenges, the pharmaceutical industry is exploring the use of innovative manufacturing approaches. For example, continuous manufacturing has become a popular means to increase scalability. As opposed to traditional batch production, continuous processes combine all production steps into a continuous workflow, reducing variability and increasing efficiency. As an example, continuous flow reactors have been adopted for the production of nanoparticles at higher yields with consistent particle sizes. Like process automation and machine learning applied to reduce human error and waste, the same has been done for real-time monitoring and optimizing real-time production processes.[106-109]

While these technologies are advancing, the upfront investment involved in advanced equipment and facilities constitutes a barrier, especially for small and medium-sized enterprises (SMEs). For instance, setting up a facility for continuous manufacturing of OROS tablets or nanoparticle-based CRDDS can be in the millions of dollars, hindering the availability of these technologies for smaller players. Academic institutions, government agencies, and the pharmaceutical industry can collaborate to help fill this gap by providing funding, technical support, and shared resources that will promote innovation and scalability in CRDDS production.[103-109]

6.2 Patient Adherence

Despite their potential to improve therapeutic outcomes, controlled release drug delivery systems (CRDDS) are a significant challenge for patient adherence. CRDDS reduce the frequency of dosing and improve convenience, but certain delivery systems, such as transdermal patches, have compliance issues in particular because of user factors. Skin irritation, itching, or redness from adhesives may make it difficult to continue using. In addition, sweating, exercise in general, or any other environmental factor can cause the patch to become dislodged, resulting in inconsistent drug delivery.[110-112]

Additionally, CRDDS may be complex or inconvenient for use for some patients. For example, constant fentanyl patches used as a chronic pain management tool depend on the placement of a transdermal patch on clean, dry skin in the right location and must be replaced at regular intervals. If these instructions are not followed, the drug release may be irregular, with a therapeutic effect thus reduced. Like with all other patients, those patients with cognitive impairments and/or those who take several different medications often forget to replace or apply patches when they are supposed to. Visible patches can also discourage long-term use, especially in younger or self-conscious patients, and the social stigma of visible patches may also deter long-term use.[111-113]

To confront these problems, pharmaceutical companies and researchers are designing and developing patient-friendly designs and technologies. As an example, microneedle patches that are less visible, painless, and easy to apply are being developed as alternatives to the conventional transdermal systems. Buprenorphine transdermal patches used for pain management provide an additional example of a product that has been designed not only for conscious patient use but also for the minimization of skin irritation using advanced adhesive technologies. Moreover, patient education programs aimed at reinforcing the relevance of suitable use and the extra benefit of CRDDS content also improve adherence. These advances simplify usage, address patient concerns, and maximize the therapeutic potential of CRDDS while maintaining patient satisfaction and compliance.[110-114]

7 FUTURE TRENDS AND PERSPECTIVES

7.1 Advanced Materials

The future of controlled-release drug delivery systems (CRDDS) is being shaped by innovations in biomaterials that improve their performance, biocompatibility, and functionality. Current and future needs for precision drug delivery systems for the release of therapeutic agents over an extended period of time have driven the development of advanced materials, including biodegradable polymers, hydrogels, and nanocomposites. In addition to enhancing the efficacy of drugs, these materials reduce side effects and enhance patient compliance.[115,116]

The advancement of stimuli-responsive biomaterials that release drugs in response to specific triggers such as enzymes, pH, or temperature is one of the most important. As an example, poly(N-isopropylacrylamide) (PNIPAM), a thermosensitive polymer, is used in widespread CRDDS to release drugs at a particular temperature. This technology is particularly applicable to cancer treatment because the polymer can release chemotherapeutic agents only in tumor tissues that have elevated temperatures. In other applications, pH-sensitive polymers, such

as polyacrylic acid, are being used for targeted drug delivery in the gastrointestinal tract, where the material disintegrates,releasing drugs only in the presence of certain pH levels, e.g., the acidic stomach or neutral intestines.[117-120]

CRDDS is also being impacted by biodegradable polymers such as polylactic-co-glycolic acid (PLGA) and polycaprolactone (PCL). The byproducts of degradation of these polymers are non-toxic within the body, thereby eliminating the need for surgical removal once drug delivery is completed. A CRDDS example is the use of PLGA in Lupron Depot, a sustained hormone delivery product over several months. In this system, PLGA microparticles slowly degrade to release the hormone at a constant rate, resulting in long-term therapeutic effects. This is a very effective way to manage chronic conditions, including prostate cancer and endometriosis. Another emerging biomaterial of interest is hydrogels, with their unique properties such as high-water content, softness, and their ability to encapsulate both hydrophilic and hydrophobic drugs. CRDDS applications benefit from engineered hydrogels that can respond to stimuli, such as temperature, light, and electric fields. For example, hydrogels based on gelatine are being engineered to be used for wound healing applications where the hydrogel releases antimicrobial agents and growth factors in a controlled fashion, accelerating healing and dampening the risk of infection.[118-120]

One more promising innovation is the combination of nanomaterials, including graphene oxide, carbon nanotubes, and nanocellulose, in CRDDS. The mechanical strength, surface area, and drug loading capacity of these materials are exceptional. As an example, graphene oxide nanoparticles have been used to develop a hybrid delivery system for anticancer drugs where the graphene oxide nanoparticles act as a carrier to provide for targeted delivery and sustained release of the drug to the tumor site. Nanocellulose-based CRDDS is being developed for oral delivery of poorly soluble drugs where the nanocellulose increases the solubility and stability of the drug while providing sustained release. With these new biomaterials, CRDDS is being transformed by enhancing the control of drug release profiles, improving safety, and extending the range of drugs that can be delivered. However, the integration of these advanced materials with new technologies such as 3D printing and artificial intelligence is expected to carry this field forward and bring highly personalized and efficient drug delivery systems.[116-120]

7.2 Integration of AI and Machine Learning

Artificial intelligence (AI) and machine learning (ML) integration into controlled-release drug delivery systems (CRDDS) is transforming CRDDS design, optimization, and development of advanced therapeutic systems. Effective use of AI and ML algorithms allows researchers to work with complex datasets to predict the drug release profiles and optimize formulations much less time-consumingly than the traditional trial-and-error methods. These technologies are the best that CRDDS development has ever seen, providing unparalleled precision, efficiency, and cost effectiveness.[121,122]

Examples of implementation of AI in formulation design and optimization.

The use of AI and ML is being used to determine the ideal drug formulation by simultaneously taking into consideration variables such as drug property, excipients, and release mechanisms. Additionally, neural networks and genetic algorithms are used to predict the optimal polymer composition and drug-polymer interaction to achieve a desired release profile. AI algorithms are used in the development of extended-release tablets to determine if tablet size, polymer type, and coating thickness have the ability to maintain the drug release over a specific period. AI is used to optimize hydrogel-based CRDDS, where AI models are used to predict the swelling behaviour of hydrogels and their effect on drug release kinetics in a real-world example.[123-125]

In addition, AI is used to design nanoparticle-based delivery systems, such as liposomes or polymeric nanoparticles. For example, AI-driven models were used to tune the particle size, surface charge, and drug loading efficiency of nanoparticles in such a way as to deliver drugs targeted and to release them over extended times. The approach was employed to develop Doxil®, a liposomal formulation of doxorubicin, to improve therapeutic efficacy and reduce toxicity in the treatment of cancer.[126]

7.2.1 Predictive modelling and simulation

Predictive analytics is where ML models shine—the simulation of drug release kinetics and pharmacokinetics. Researchers train algorithms on experimental data, predicting the performance of a CRDDS under different physiological conditions. For example, AI-driven in silico models can be used to simulate drug release from osmotic-controlled systems like OROS technology, decreasing the need for extensive in vitro and in vivo testing. These simulations can then be used to predict the impact of changes to the formulation or to the manufacturing processes, and as such, they can enable rapid iteration and refinement.[127-129]

In addition, AI is being used to predict patient-specific responses to CRDDS. As ML algorithms can model such data, such as age, metabolism, and disease progression, the delivery of drugs can be optimized to match patient needs and increase therapeutic outcomes. AI-powered platforms have been used to

create personalized insulin pumps that can deliver insulin at a rate that changes in response to real-time glucose, enhancing diabetes management.[130-131]

7.2.2 Quality control and automation

CRDDS is being automated using AI-driven automation in manufacturing and quality control. Real-time production parameters are monitored, and defects are detected by use of machine learning algorithms. For example, in the drug delivery microsphere production, such as in the production of microsphere-based drug delivery systems, AI systems use images and data generated from manufacturing lines to verify the uniformity of particle size and drug encapsulation efficiency. It ensures high-quality products and low production costs, as well as low waste.[132-134]

Additionally, CRDDS acts as a critical role in ensuring regulatory compliance by analyzing and validating data associated with the safety, efficacy, and consistency of CRDDS using AI. Predictive models are used to predict potential stability issue formulations, which manufacturers can act on before regulatory submission.[135]

7.2.3 Future prospects and emerging applications

AI has a promising future in CRDDS as a part of other emerging technologies, including 3D printing and smart drug delivery systems. Through the use of AI algorithms, 3D printing is being used to design patient-specific CRDDS to optimize drug release profiles for individual therapeutic needs. AI is, for example, used by researchers to generate 3D-printed oral tablets with customizable release rates, thereby offering a personalized route of drug delivery.[136-140]

These smart drug delivery systems use AI-driven sensors and controllers to monitor and adjust the real-time release of drugs. For example, such AI-integrated transdermal patches are currently being developed to release drugs according to physiological signals like temperature or pH for precise and on-time drug delivery.[142-143]

Example: AI in COVID-19 Drug Delivery

The CRDDS for the antiviral drugs and vaccines developed during the COVID-19 pandemic relied heavily on AI's ability to rapidly develop CRDDS. Lipid nanoparticles were designed for mRNA vaccine delivery, designed using AI-driven models such as those from Pfizer-BioNTech and Moderna. AI is now accelerating CRDDS innovation because these nanoparticles protect the mRNA and ensure controlled release upon administration.[142-143]

7.3 Research and Patents

The Controlled-Release Drug Delivery Systems (CRDDS) field is developing thanks to innovative research and patent filings. Advancements in materials science, nanotechnology, and engineering, however, have led to the development of new CRDDS platforms, and these platforms have been shown to provide better therapeutic outcomes, reduce side effects, and improve patient adherence. This section presents ongoing research and recently filed epithelial CRDDS patents and shows how these CRDDS contributions are moving us forward to address the current challenges and forge future trends.

7.3.1 Recent research

7.3.1.1 Advanced polymers for CRDDS

Advanced biodegradable polymers such as (polylactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and natural polymers including chitosan or alginate have been investigated by researchers as potential matrix for subcutaneous microencapsulation. In 2023, a Journal of Pharmaceutical Sciences study showed the use of PLGA nanoparticles for controlled drug release, which sustained release for several weeks with therapeutic efficacy.[144,145]

7.3.1.2 Stimuli-responsive systems

Research on stimuli-responsive CRDDS is underway, including pH-responsive and enzyme-triggered systems. In a 2024 paper on pH-sensitive hydrogels for colon-targeted drug delivery, polymers swell and release the drug only in the alkaline environment of the colon; the result is site-specific drug delivery.[25-30]

7.3.1.3 Lipid-based nanocarriers

Research into CRDDS has been largely focused on liposomal and lipid nanoparticle-based systems. For example, researchers have improved the stability and release profile of liposomal formulations of anticancer drugs, as shown in more recent work on Doxil®, a liposomal formulation of doxorubicin.[146,147] Recent Patents on CRDDS mentioned in Table 7

7.3.2 Recent patents

Patent activity in CRDDS reflects the growing interest in innovative drug delivery technologies. Below are some key patents filed in recent years:

8 IMPACT ON FUTURE DEVELOPMENT

The continuous research and patenting of CRDDS technologies is a clear sign of the huge potential of innovation in this field. These advances enable the design of more efficient, patient-centric, and environmentally friendly drug delivery systems for unmet medical needs and therapeutic innovations. As the CRDDS technologies mature, we can expect further integration with recent trends such as AI-driven formulation design and smart drug delivery systems.

9 CONCLUSION

Controlled release drug delivery systems (CRDDS) are a major milestone in the pharmaceutical science because they can provide targeted, sustained, and efficient drug release to minimize side effects and maximize therapeutic efficacy. Several strategies, including diffusion-controlled, osmotic, and stimuli-responsive systems, and the materials and formulation used to optimize the various strategies are reviewed. Although CRDDS are a promising solution, they suffer from challenges of scalability, stability of formulation, and regulatory hurdles. But new technologies such as 3D printing, nanotechnology, and smart drug delivery systems have strong potential to overcome these barriers. The dynamic nature of that field in ongoing research and recent patents in CRDDS further illustrates the signalling the level of innovation has to resolve unmet medical needs. As we continue to advance, CRDDS will have a major role to play in personalized medicine and chronic condition treatment. Future investigations should aim at reducing the cost and increasing the scalability and process for regulatory approval, as well as exploring new materials and technologies that will enable the development of more sustainable, patient-centred drug delivery systems.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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