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A COMPREHENSIVE REVIEW ON CONTROLLED DRUG DELIVERY SYSTEMS: FUTURE DIRECTIONS

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ABSTRACT

The drug delivery system allows for the release of the active pharmaceutical ingredient to achieve the desired therapeutic outcome. Conventional drug delivery methods (tablets, capsules, syrups, ointments, etc.) do not achieve sustained release due to their poor bioavailability and variable plasma drug levels. Without a trustworthy delivery method, the entire therapeutic procedure may be unsuccessful. The medication must also be given at the intended location and at a precise controlled pace in order to achieve maximum efficacy and safety. By creating controlled medication delivery systems, the problems with conventional drug administration are solved. Systems for controlled drug delivery have significantly changed during the past 20 years, moving from large and nanoscale to intelligent focussed delivery. With an emphasis on the pharmacokinetics of the drug, the first section of this paper provides a basic overview of drug delivery techniques. The limitations of conventional drug delivery techniques are also discussed. Additionally, controlled drug delivery systems are thoroughly discussed, along with design elements, groups, and examples. Along with recent significant findings, the application of stimuli-responsive and intelligent biomaterials for targeted and smart medicine distribution is also presented. In the paper's conclusion, the challenges and potential opportunities for regulated medication distribution are examined.

KEYWORDS: Controlled release dosage forms, pharmacokinetics, nano-drug delivery, intelligent biomaterials.

1. INTRODUCTION

According to the FDA, an API is a substance that has been approved for use in the official pharmacopoeia and is intended for use in the diagnosis, treatment, mitigation, or prevention of disease. Drug delivery is a method of giving a patient their medication in a way that precisely raises the drug concentration in particular areas of the body over others.[1] Any delivery system's ultimate objective is to extend, contain, and target the medicine with a safe interaction in the sick tissue. Every dosage form consists of both a drug's active pharmaceutical ingredients (APIs) and excipients/additives, which are non-drugs. The actual chemical elements utilized to cure diseases are known as APIs.[2]

2. Need for a Dosage Form

Drug delivery systems (DDS) are typically favored because it is extremely rare to use active pharmaceutical ingredients (APIs) "as they are" in clinical settings. For particularly powerful medications (such as low mg and g dosages), API handling and precise dosing can be challenging or impossible.[3] Drugs can be degraded at the site of administration (for example, low pH in the stomach), and they may cause local irritations or injury when the drug concentration is high at the site of administration, making drug administration into the body cavities (rectal, vaginal) impractical and unfeasible.[3] Some APIs need to be chemically stabilized because of their intrinsic chemical instability, or they can benefit from having their exposure to environmental variables (light, moisture, temperature, and pH) reduced. Patients are less likely to comply with APIs because they typically have unpleasant organoleptic properties (taste, odor, and compliance).[2]

As a result, excipients and APIs are always combined during formulation. Excipients/additives are used to: give the formulation a specific structure and shape; increase stability; reduce bitterness and improve palatability; bulk up formulations that contain extremely potent active ingredients; enable convenient and accurate dosing; and facilitate the handling of the formulation and the manufacturing process.[4]

3. Excipients

Colorants, suspending agents, binding agents, solvents and lubricants, fragrances, sweetening agents, flavoring agents, solubilizing agents, and antioxidants are a few of the excipients that are typically included in formulations.[4] Since the "active ingredient" amount is frequently so small, the form of dosage would be too small to manage without filler, filler is added to the tablet

to increase its size (for example, lactose). After the tablet has been compressed, binders are added to keep it together and stop it from disintegrating into individual pieces (e.g., starch, HPMC, etc.).[5,6] Disintegrants aid in the dosage form's breakdown into manageable pieces after consumption, enabling the medication to dissolve and be absorbed by the body more quickly.[6] The glidants enhance the flowability of the tablet granules or powder and reduce friction between particles to prevent lump formation. Anti-adherents prevent the powder from adhering to the manufacturing equipment. By minimizing friction created during tablet ejection between the tablet's walls and the die cavity, lubricants ensure the smooth surface of the dosage form. Colorants are used to improve aesthetics and recognition, while flavoring compounds serve to cover up the disagreeable odor.[7]

4. Biopharmaceutics Classification System (BCS) Classification of Drugs

Based on their intestinal permeability and solubility, medicines are divided into four kinds according to the Biopharmaceutics Classification System.[8] Drugs in class I are well absorbed, have high solubility and permeability, and their rate of absorption exceeds that of excretion (e.g., metoprolol, paracetamol, etc.). Class II medicines have high permeability but low solubility, and their rate of solvation limits their bioavailability (e.g., glibenclamide, aceclofenac, etc.) Drugs in class III have low permeability but high solubility, meaning they dissolve quickly; yet, absorption is still constrained by the rate of permeation. Class I criteria can be used if the formulation has no effect on the permeability or duration of the gastro-intestinal tract (e.g., cimetidine). Class IV medicines are poorly absorbed by the colon because they have low permeability, low solubility, and they have poor bioavailability with high variability (e.g., Bifonazole).[8]

5. Several Routes of Drug Administration

Different dose forms and delivery methods are possible depending on the target site, length of therapy, and physicochemical properties of the drug.[9] The majority of dosage forms include tablets, capsules, pills, ointments, syrups, and injections. The three main factors that determine the optimum route of drug administration are the body part being treated, the drug's activity inside the body, and the drug's solubility and permeability. For instance, some drugs may have poor bioavailability when taken orally because stomach acids might break them down. They must therefore be given intravenously. If medication is given intravenously, 100% bioavailability is reached.[9]

6. Conventional vs. Controlled Drug Delivery Systems

The therapeutic window is poorly maintained for typical DDS doses (tablets, capsules, syrups, etc.), and these doses are swiftly excreted from the body. After a single conventional dose, the medication metabolizes very quickly, first raising the drug level and then sharply lowering it exponentially. There might not be enough time to have a significant therapeutic effect, which would cause a subtherapeutic reaction. In order to keep the plasma medication concentration above the minimal effective concentration (MEC) and below the dangerous value, various procedures have been investigated. Even though administering many doses at regular intervals may appear preferable to administering a single dose all at once, the former generates fluctuations in plasma drug levels that frequently cause them to fluctuate between dangerous and effective levels. When medications are administered in various doses throughout the day, patient compliance diminishes. Giving a single dose that is greater than what is required is another tactic, although doing so results in unintended side effects. Controlled release DDS are so required to maintain plasma drug levels constant within the therapeutic window and give the desired therapeutic impact for a longer time.[10,11]

7. Controlled Drug Delivery System

This is a technique for administering medication that maintains a drug's level in the blood and tissue for an extended period of time. For both conventional and controlled delivery methods, pharmacokinetics (PK) curves display a drug's plasma concentration vs. time. In a conventional delivery system, a typical bolus PK for multiple dosing with oral tablets or injections happens when the drug level fluctuates over and below the minimal effective concentration. On the other hand, the controlled delivery system displays zero-order PK following a single dose of controlled drug delivery from a specific formulation or device. For drug levels, the therapeutic window is continuously maintained.[12]

Controlled DDS delivers the precise dose of the medicine for the predetermined amount of time at each time point to continually sustain drug plasma levels. In addition to improving patient compliance, this enables dose and dosing frequency decrease. Less exposure to the biological environment reduces drug toxicity and unwanted consequences. The overall efficacy of the dosage form is elevated.[11] Figure 1 depicts schematically the medical justification for controlled DDS.

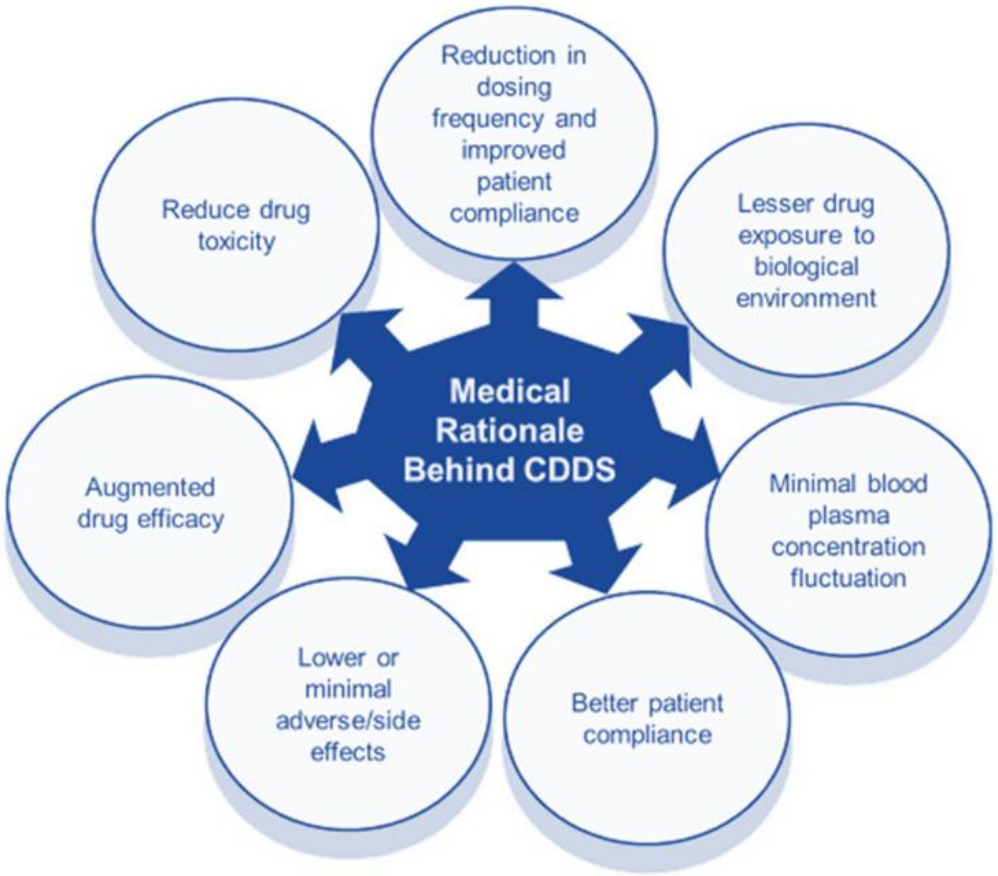

Fig. 1: Controlled release drug delivery systems (CRDDS).[11]

7.1. Classification of Controlled Release Drug Delivery Systems

- Dissolution Controlled Drug Delivery Systems

In dissolution-controlled release systems, drugs are either coated with or enclosed within slowly dissolving polymeric membranes (reservoir systems) or matrices (monolithic systems). Drugs with low solubility are protected by polymeric barriers in reservoir systems. Most typical immediate-release tablets, pills, and effervescent tablets have dissolution as the rate-limiting phase.[13]

- **Diffusion-Controlled Drug Delivery Systems**

Diffusion-controlled release systems use polymeric matrix or inert, water-insoluble polymeric membranes to trap and release drugs via diffusion (monolithic systems). These are separated into membrane control reservoir systems and monolithic matrix systems. The drug release is decided by the Fick diffusion laws. In diffusion-controlled systems, drug diffusion is the rate-limiting step.[14,15]

Osmotic Controlled Drug Delivery Systems

Osmotic drug delivery makes use of osmogens and osmotic pressure to administer medications in a regulated way. Osmosis is the process of moving a solvent from a solute with a lower concentration to one with a greater concentration. The force created when water crosses a semipermeable barrier separating two solutions with various solute concentrations is known as osmotic pressure. Both injectable and oral medications may be administered with these devices.[16]

It is essential to use a semipermeable membrane that is biocompatible, has sufficient wet strength and water permeability, and is rigid enough to support the pressure inside the device. Additionally, a substance that is solvent-resistant but permeable to water can be used for the exterior coating. Polymers including cellulose acetate, cellulose triacetate, and ethyl celluloses are frequently used in osmotic drug delivery systems. Osmotic-controlled delivery systems include advantages such as increased drug efficacy, controlled drug distribution, and reduced dose frequency.[17] A pump with two compartments split by a movable wall serves as a simple osmotic delivery method. Over the contents of Compartment 1, a semi-permeable membrane containing an osmotic agent is inserted. Compartment 2 is protected by a robust, rigid shell with a delivery aperture.[17]

- **Chemically Controlled Drug Delivery Systems**

Chemically regulated delivery systems modify their chemical make-up when exposed to a biological environment. These are made of biodegradable polymers that disintegrate in the body as a result of regular biological processes, reducing the need to remove the delivery system when the active medicine has been consumed by the system. These can be divided into two

groups: polymer-drug conjugate systems and polymer-drug dispersion systems. In polymer-drug dispersion systems, a biodegradable polymer is utilized to dissolve or distribute the drug uniformly. As the polymer degrades under physiological conditions, the drug is subsequently released. Only a few of the factors that can affect deterioration (bioerosion and bulk erosion) include chemical composition, structure, configuration, molecular weight, and the presence of unexpected units or chain defects.[18]

7.2. Evolution of the Controlled Release Dosage Forms

First-generation: Dosage types of controlled release medication were offered between 1950 and 1980. Four various types of drug release mechanisms speed up the release of the drug from the oral and transdermal formulations of this class of dosage forms. The four different types of processes are ion exchange, osmosis, diffusion, and dissolution. The most common pharmaceutical administration strategies use diffusion and dissolution-controlled processes. The success of the first generation of drugs was largely due to the development of the oral and transdermal routes. For this generation of drugs, there were no biological barriers discovered, and the connection between in-vitro and in-vivo formulation was well known.[19]

Second-generation: These are less efficient, but unlike the first, they can transport proteins and peptides using formulations for extended release that use biodegradable polymers. During this time, systems for administering insulin to the lungs were developed. It must be supplied at doses that are many times higher than those required for parenteral injection because of its poor bioavailability, which has detrimental effects. During the latter decade of the second generation, researchers studied nanoparticles that target the gene and the tumor.[20]

Third generation: Self-regulating pharmaceuticals, long-term and non-invasive protein/nucleic acid/peptide administration, drug delivery to the targeted region using nanoparticles, and delivery of medications that are poorly water-soluble are some of the novel drug delivery technologies.[20]

7.3. Nanocarriers in Controlled Drug Delivery

Liposomes

These are the colloidal particles produced when lipid bilayers and amphiphilic phospholipids combine to enclose an aqueous compartment.[21] A closed bilayered structure is produced by the hydrophobic effect, which facilitates the arrangement of the amphiphilic molecules and reduces unfavorable interactions between hydrophobic chains and the surrounding aqueous environment.[22] Depending on the polar head group, phospholipids can either be phosphatidylcholine or phosphatidylserine. Phosphatidylcholine is frequently used in the production of liposomes. The size spans from 25 nm to 200 nm.[23] Sizes greater than 200 nm are removed by the reticuloendothelial system and briefly circulate in the circulation. Liposomes are mostly used to target tumor cells because of their increased permeability and retention (EPR).[24]

- **Dendrimers**

The word "dendrimer," which means "tree," is taken from Greek and refers to something that resembles a tree's branches. Dendrimers are symmetrical around a core and have a sphere-like three-dimensional structure.[25] Monomers, which can be either natural or synthetic, are the building blocks for them.[26] In biological applications, dendrimers of two different types—polyamidoamines (PAMAM) and polypropyleneimines (PPI)—are used.[27]

- **Exosomes**

Exosomes are nanosized, membrane-bound vesicles with a size range of 30 to 100 nm that are produced by cells. Both exogenous and endogenous substances are transported between cells using them. Small proteins, mRNA, and nucleic acids are just a few examples of the therapeutic compounds that exosomes can carry. These molecules can then be sent to certain cell or tissue types for targeted drug delivery. They have been employed widely and developed swiftly in recent years because they have such a high potential for internalization with cells. Exosomes, both natural and synthetic, are employed for the transfer of peptides and genes.[29]

- **Nanoparticles**

In order to provide physical stability of the drug and controlled release property, these are initially solid colloidal particles of less than 100 nm made up of macromolecules in which pharmaceuticals can be entrapped or chemically bound (covalent bond). Examples include solid-lipid nanoparticles, metallic, polymeric, and inorganic-clay particles. The drug's therapeutic impact is increased by the use of nanoparticles, which can be administered through a variety of methods. The ability of the nanoparticle to deliver the medication to a hard-to-reach place is crucial. It effectively executes the drug's controlled release while minimizing side effects.[31,32]

- **Solid-Lipid Nanoparticles**

Alternatives to traditional colloidal nanocarriers have evolved in the form of solid-lipid nanoparticles (SLNs), which combine the advantages of polymeric nanoparticles and liposomes without the toxicity. Spherical SLNs are made of API, emulsifiers, and lipids that are solid at room temperature and have a size range of 50 to 1000 nm.[33,34] The SLN safety profile's base is made up of biocompatible lipids that the body and lungs can tolerate quite well. The potential of SLNs to carry hydrophilic and lipophilic drugs, in addition to proteins and nucleic acids, creates new opportunities for drug and gene delivery.[35] Phospholipid fatty molecules used in SLNs are thinner, more flexible, and biologically compatible, which allows them to pass through tiny arterioles and fenestrations without clotting.[35]

- **Nanofibers**

Solid fibers known as nanofibers have a diameter ranging from a few nanometers to 1000 nm and a higher surface to volume ratio, which makes them perfect for use as a drug delivery system. Nano-fibres' diameter, shape, and porosity can be altered to provide different drug release kinetics.[36] High loading efficiency and consistent medicine distribution are made possible by nanofibrous delivery systems.[37] Nanofibers can be made using the electrospinning technique, and drug release can be managed using patterning.[38] Since they are produced naturally from a type of bacterium called bacterial cellulose, silk fibroin nanofibers are an excellent alternative to synthetic nanofibers in the administration of drugs.[39–42] The polymer used to create the nanofibrous mesh has a large specific surface area, an interconnected porous design, and high porosity to provide quick drug release. The nanofibers' drug release can be adjusted to be extended, stimulus-responsive, and dual-mode/biphasic.[43]

- **Polymersomes**

Liquid drugs are stored in tiny polymersomes, which are made of synthetic materials. These are typically created using diblock copolymers and polymer-lipid composites because they have higher membrane properties, encapsulation effectiveness, colloidal stability, etc. Polymersomes have been shown to be more stable and less harmful to the body than liposomes. Both hydrophobic and hydrophilic drugs can be encapsulated using them.[44]

- **Polymeric Micelles that self-assemble**

Self-assembled micelles are formed by spontaneous self-assembly of amphiphilic polymers. The hydrophobic segment acts as the core, and the hydrophilic segment as the shell. Micelles can range in size from 10 nm to 100 nm.[45] The core protects the medicinal drugs from early degradation. These have increased permeability and retention due to their are helpful for targeting tumor cells (EPR).[46]

- **Carbon Nanotubes**

Carbon nanotubes (CNTs), which are cylindrical large molecules comprised of a hexagonal arrangement of graphene sheets, can be produced by rolling and coating with spherical fullerene (hybridized carbon atoms). Single wall CNTs (SWCNTs) are built from a single graphene sheet, whereas multiwalled CNTs (MWCNTs) are layers of rolled graphene sheets.[47] Carbon nanotubes have lately gained importance due to their huge surface area and capacity to interact with drugs (both molecules and cells).[48] Additionally, they show increased selectivity and efficiency. The only application of carbon nanotubes up to this time has been the delivery of anti-cancer drugs.[49] In a larger sense, carbon nanotubes can be engineered to transport medicines, proteins, peptides, and nucleic acids to different cells and organs. Compared to unfunctionalized carbon nanotubes are less immunogenic and impart minimal toxicity.[50,51]

- **Nanoemulsions**

A nanoemulsion is a heterogeneous mixture of oil and water (two immiscible liquids) that has been stabilized by surfactants or emulsifiers. They are used to carry drugs that are hydrophobic and are administered in a number of ways. They are more resistant to flocculation, creaming, and sedimentation than conventional emulsions. Due to its enhanced surface area and other characteristics, nanoemulsion can deliver a drug to a particular region efficiently.[52]

- **Hydrogels**

Hydrogels are made from cross-linked networking of water-soluble/insoluble polymers. When it comes in contact with water, a glassy polymer called a hydrogel expands and releases the drug that is placed inside of it. The release regulates swelling and water absorption.[53] When hydrogels are stretched past a certain point, they swell several times more than their actual volume, which helps with drug delivery and polymer chain relaxation.[54] Hydrogels can offer spatio-temporal control over the release of various therapeutic agents, such as macromolecules, small compounds, and cells. Temperature, pH, and ionic strength must all be taken into account in order to make use of the hydrogel's swelling.[55,56]

Supramolecular hydrogels, which are three-dimensional cross-linked networks with both intra- and inter-molecular bonding, exhibit greater water retention, drug loading efficiency, and biocompatibility than conventional hydrogels. These hydrogels work best in applications that require injection and self-healing.[57] Bacterial nanocellulose is one such instance of a supramolecular hydrogel that has lately received extensive research in drug delivery. Interpenetrating network (IPN) hydrogels are composed of two or more polymeric networks that are at least partially interlocked on a polymer scale.[58-60]

8. Challenges and Future Directions

In the preceding 20 years, regulated medicine administration systems have undergone a significant advance. To overcome the limitations and expand potential futures, development is still needed.

8.1. Nanomedicine Improvements and Challenges

One of the many advantages of adopting nano-drug delivery systems instead of more conventional ones is targeted drug administration with greater effectiveness. Toxicology and safety traits for nanoparticulate systems must be established, though. Numerous studies have suggested that nanoparticles cause the reticuloendothelial system to absorb them, which leads to inflammation of the liver, lungs, and brain.[61] The capacity of nanocarriers to cross the blood-brain barrier is advantageous in brain diseases, but also results in neurotoxicity when the intended site of action is other than the brain. Nanoparticles can occasionally have immunomodulatory effects as well. Using this immunomodulatory effect of nanoparticles, inflammatory monocytes can be targeted across the blood-brain barrier to inhibit the progression of auto-immune illnesses such autoimmune encephalomyelitis.[62] Inorganic mesoporous nanoparticles have gained interest in regulated drug administration due to their structured mesopores (2–6 nm), variable size (50–200 nm), and ease of surface modification. They are therefore perfect for endosomal release and improved medication targeting. In order to provide spatio-temporal control during the release of a specific medication into the target cell's cytoplasm and avoid the premature release of pharmaceuticals through them, mesopores can be lined with stimuli-responsive polymers.[63]

8.2. Microfluidics in Controlled Drug Delivery

It appears hopeful that future research will focus on implantable and controlled microfluidic delivery systems. Since it makes use of tiny microdevices with chambers and channels, it is frequently referred to as lab-on-a-chip (LOC) technology.[64] To more effectively administer the medication to the desired location, these small devices control fluid flow behavior.[65] Recent research has suggested the creation of synthetic polypeptides by polymerizing -amino acid N-carboxy anhydrides (NCAs), which can be structured into nanostructures and precisely deliver the medication at a particular area. The release of therapeutic substances can also be regulated by modifying the physical and chemical properties of the polypeptide structure.[66] Cell transport and antibody identification are two additional crucial applications of microfluidics.[67,68]

8.3. Molecularly Imprinted Polymers (MIPs)

Molecular imprinting polymers are cross-linked polymers with binding sites specific to the target molecule. These are the cross-linked polymers with specialized binding sites for the target molecules. The five elements required to produce molecularly imprinted polymers are the template, cross-linker, porogen, monomer, and initiator.[69] The template helps in choosing the appropriate functional monomer. It functions as an artificial receptor for target molecules, mimicking the behavior of biological antibody-antigen systems. The lock and key illustration clarifies how MIPs function to bind molecules that served as their synthesis templates in a targeted manner. MIPs are good and promising options in the development of vaccines and biologic drug delivery because the drug-target specificity may be properly defined.[70]

8.4. Intelligent Biomaterials

Intelligent biomaterials that can sense their surroundings, autonomously adjust to them, and control the release of medications have a lot of potential. In order to detect the blood sugar levels in its immediate environment, an intelligent hydrogel may, for instance, sense the pH or temperature of its surroundings. It would then give the exact quantity of insulin required to maintain those levels. Building smaller hydrogels is important, but doing so is currently challenging since smaller biosensor hydrogels are more delicate and can't be given the mechanical strength to perform the intended function.[66]

8.5. CRISPR CAS9 Based Systems

Clustered Regularly Interspaced Short Palindromic Repeats, or CRISPR, is a group of DNA sequences that is mostly present in prokaryotes and serves as an effector of the adaptive immune system. In recent years, it has drawn increased attention. This has resulted in significant advancements in the field of tissue-specific gene editing.[176] The single guided RNA (sgRNA) and Cas9 endonuclease make up this recently developed CRISPR-based delivery mechanism. When coupled with sgRNA, Cas9 is directed to a specific target site on RNA and DNA. The specific target is recognized by the crRNA or CRISPR RNA sequences. However, efforts are being made to lessen the off-target effects of the Cas9 protein and sgRNA combination. The entire system is quite applicable while delivering any protein drug substance instead of Cas9.[70]

9. CONCLUSION

In the dosage form, drugs and excipients are mixed. Excipients are added to products to improve stability, give them structure, and mask flavors. Due to changes in plasma drug levels, traditional dosage forms like solid, semisolid, and liquid demand high doses and frequent administration with poor patient compliance. Any dosage form must contain a bioavailable medication in order to achieve the desired outcome. In order to keep drug plasma levels within the therapeutic range, increase bioavailability, prolong drug release, and reduce side effects, controlled drug delivery systems have emerged as a viable alternative to conventional approaches. Controlled drug delivery increases the drug's solubility and stability while delivering targeted drug administration with a predictable pace and mechanism to specific organs, tissues, and cells. Diffusion, water

penetration, dissolution, and chemically controlled drug delivery systems are among the various types of controlled drug delivery systems. Targeting and controlling the release of substances in a range of disease scenarios, such as cancer and infections, is possible with delivery mechanisms that react to stimuli. Nanocarriers with intelligent biomaterials and additive manufacturing techniques can be developed to further achieve controlled targeted distribution. The key objectives of drug delivery in the future include patient-specific therapy using microfluidic-based, 3D-printed devices, and CRISPR cas9-based delivery systems connected with quantum sensing.

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