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SMART DRUG DELIVERY SYSTEMS

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ABSTRACT: Smart drug delivery systems are a key innovation in pharmaceutical technology that aims to enhance the efficacy and safety of therapeutic interventions. These systems integrate advanced materials, microelectronics, and responsive mechanisms to deliver drugs in a controlled, targeted, and adaptive manner. The development of smart drug delivery systems is driven by the need to improve patient compliance, minimize side effects, and optimize therapeutic outcomes. These cutting-edge delivery systems utilize various medication carriers, including nanoparticle systems such as inorganic nanoparticles (e.g., magnetic nanoparticles and quantum dots), monoclonal antibodies, microspheres, dendrimers, liposomes, and lipoproteins. The potential of smart drug delivery systems to revolutionize personalized medicine and improve treatment paradigms is critically analyzed. This paper reviews recent innovations in smart drug delivery, highlighting key technologies such as nanoparticle-based carriers, polymeric systems, and stimuli-responsive delivery platform. Emphasis is placed on the mechanisms of drug release, such as pH-sensitive, temperature-sensitive, and biologically triggered systems. Additionally, the integration of real-time monitoring and feedback mechanisms is explored, illustrating how these systems can adjust drug release rates in response to physiological changes. This review aims to provide a comprehensive overview of state-of-the-art technologies and their implications for advancing healthcare through intelligent and adaptable drug delivery solutions.

INTRODUCTION: An active pharmaceutical ingredient is a key player in medication and is responsible for the drug's desired health effects. Direct administration of an active pharmaceutical ingredient (API) into an organism can be challenging or impractical. Additionally, administering the drug into body cavities, such as the vaginal or rectal, is often unfeasible due to potential disintegration at the site of administration [1].

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To avoid the degradation of the active pharmaceutical ingredient (API), a drug delivery mechanism is preferred. A drug delivery system is a method of introducing an active pharmaceutical ingredient into an organism to achieve its therapeutic effects while minimizing adverse effects [2]. Furthermore, a well-designed drug delivery system can govern how a drug moves through an organism's biological system.

Conventional drug delivery systems are well-established and have been in use for an extensive period. Traditional approaches to administering medicine include tablets, capsules, pills, liquids, and semisolid preparations. They are also typically less expensive than modern, sophisticated drug delivery systems. However, they also have certain specific limitations. Conventionally, when a drug is

administered, during its course of travel in the system, it is likely to encounter the target site and non-target site to initiate drug action. The unnecessary exposure of the drug to the whole of the body is the major drawback of the conventional drug delivery method. This leads to an increased risk of toxicity and adverse drug reactions (ADRs). The most optimal method to overthrow this obstacle is to prepare magic bullets that act on specific target site. This will lead to reducing the amount of drug administered and bypassing unnecessary contact to the non-target site. His approach enhances safety and therapeutic benefits Traditional drug delivery methods, such as tablets, capsules, syrups, and ointments, often suffer from low bioavailability and inconsistent plasma drug levels, resulting in a lack of sustained release. Therefore, a reliable delivery method is necessary to achieve the intended therapeutic outcome.

To overcome the drawbacks of conventional drug delivery systems, an advanced approach has been laid down where drugs are directly delivered to the site of administration. Thereby enhancing the pharmacological effect of the drug and surpassing these adverse effects is achieved through a Smart Drug Delivery System (SDDS). A smart drug delivery system (SDDS) is a cutting-edge medical approach that employs carriers for transporting therapeutic medicines into specific sites within the body. These carriers are intended to deliver the medicine in a controlled manner, enhancing therapeutic efficacy while reducing adverse effects. The main challenge of an SDDS is ensuring the API remains inert during administration and transportation. Upon reaching the area near the objective, the API needs to be converted from a dormant state to an active state. Advancements in polymeric science have been made to create specialized drug delivery systems. The polymers are infused with characteristics such as responsiveness to different physical, chemical, and biological cues. Currently, SDDS methods involve innovative polymers that are highly responsive to various biological stimuli, as well as physical and chemical cues. SDDS involve directing drug towards specific targets *via* liposomes, drugs encapsulated within biodegradable microspheres, drug-polymer conjugates responsive to stimuli, intelligent hydrogels, polymer-based micelles particles, smart lipid carriers, and nano-carriers. For instance, an anti-inflammatory medication can be encapsulated in a polymer capsule that reacts to inflammation. Substances such as cytokines or leukotrienes act as mediators. These SDDS contain anti-inflammatory medication within microcapsules. When administered to an organism they distribute throughout the body. The SDDS has been designed in such a way that when inflammatory mediators are detected, the API is released for precise delivery with a low level of harmful or damaging consequences.

Compared to traditional methods, modern pharmaceutical delivery systems offer several significant advantages. These include minimizing pharmaceutical deterioration in the biological environment, facilitating site-specific administration, and circumventing the possibility of off target side effects [2]. Furthermore, it also reduces the overall dose of the drug, and the frequency of dosing needed to achieve the desired outcome. Thus, it results in improved patient compliance.

Smart Drug Delivery System: Smart drug delivery system (SDDS) refers to an intelligent approach in formulating medications, aimed at delivering an active pharmaceutical ingredient (API) from its dosage form to a specific target site in the body to enhance the therapeutic efficacy of the drug and reduce side effects. SDDS ensures that active drug molecules are released at their specific site and accumulated in the diseased area for a prolonged period in a controlled manner [1]. Smart drug delivery involves targeting and controlling the release of drug to a patient's treatment. SDDSs provide numerous opportunities to decrease variations in drug concentration, minimize drug toxicity, and improve therapeutic effectiveness [(2).] A potential method for delivering drugs precisely involves combining therapeutic molecules with nanoparticles and creating specific targeting pathways to transport a variety of molecules to precise locations within the body.

Numerous carriers, including liposomes, microspheres, serum proteins, immunoglobulins, erythrocytes, and niosomes, have been employed to target drugs [3]. The smart medicine offered by this technology must meet the following criteria. To deliver a drug to a specific body part, it must not be degraded by body fluids, minimize side effects,

cross a biological membrane for absorption, and be released in appropriate dosages [4].

SDDS has the following advantages over conventional delivery systems.

- It helps preserve optimal plasma drug levels.
- The potential to eradicate or minimize systemic administration side effects
- The possibility to enhance and facilitate medication delivery in regions with limited medical accessibility.
- The potential to mitigate the discomfort brought on by large dosages, thereby increasing patient compliance [5].

SDDS maintains plasma drug level, which releases a pre-determined dosage of the drug for a specific period. This results in patient compliance by minimizing the dosage and dosing frequency. Reduced drug toxicity and side effects are achieved by limiting drug exposure to the biological environment [6].

Strategies of Targeted Drug Delivery Systems: Targeted delivery improves therapeutic efficacy by managing the drug's side effects. Drug-targeted delivery systems can be achieved by two modes, namely active and passive targeting.

Active Targeting System: Active targeting refers to the specific interactions between the drug/drug carrier and the target cells often *via* interactions between ligands and receptors [1]. Interactions between ligands and receptors require proximity (<0.5 nm). After extravasation and blood circulation, ligands interact with receptors to localize intracellularly [4]. Active targeting enhances the dose delivery to the target cell, thereby enhancing its pharmacological efficiency. This is accomplished by decorating the nanocarrier surfaces with ligands that bind to overexpressed receptors on the target cell. This approach will boost the nanocarriers' affinities for the surface of targeted cells, thereby improving drug uptake [7]. Active targeting can easily be achieved once you know the nature of a receptor present on the cell against which the drug must act. The four primary categories of active targeting are aptamer-based targeting, small-molecule-based targeting, peptide-based targeting, and antibody-based targeting [8]. Through a bypass mechanism, the active targeting of nanoparticles in vivo first addresses the EPR effect before landing at the targeted site with surface transformations. By implementing active targeting systems, a drug loaded with nanoparticles has a significant advantage over a conventional delivery system.

Passive Targeting System: Passive targeting involves the buildup of a drug-carrier system or drug delivery to a particular location. The disease may be linked to various chemical, physical, pharmacological, and biological factors [1]. To optimize targeting and enhance circulation, the drug-targeted system's surface characteristics and nanoparticle size must be precisely regulated to avoid being absorbed by the reticulo-endothelial system. Fast-growing tumor tissue benefits from rapid vascularization, which also imparts a faulty or leaky architecture that increases the permeability of harmful chemotherapeutic agents [4].

Not all medications may be administered as prodrugs or inactive drugs; therefore, when they encounter malignant cells, they can change into extremely active forms. The passive targeting drugs delivery system comprises of liposomes, metal oxide nanoparticle, polymeric nanoparticles, etc. [8].

Importance of Smart Drug Delivery System: Smart Drug Delivery Systems can be used to improve a drug's pharmacokinetic and pharmacodynamic properties [1]. Additionally, augments cell specificity and biocompatibility. Traditionally, the simplest way to explain systemic drug administration is to think of it as exposing a medicine to every part of the body to achieve its therapeutic response, a process known as "Random Walk" [1]. It is likely to encounter targets which pose a greater risk of toxicity to healthy cells as well as non-targets during its path. So, to reduce toxicity caused by conventional delivery system, SDDS is preferred. The three main reasons are as follows: - The first factor is pharmaceutical-related. Traditional medications tend to have lower solubility and greater instability compared to targeted drug delivery systems [9]. Secondly, they exhibit poor absorption, a shorter half-life, and require a larger distribution volume, which reflects

their pharmacokinetic characteristics [9]. Lastly, in terms of pharmacodynamics, traditional drugs show lower specificity and a reduced therapeutic index when compared to targeted drug delivery methods.

Components of Smart Drug Delivery System: A successful drug delivery system ensures that a drug is released at its desired site in a controlled manner, minimizing side effects and maximizing its therapeutic effect. The following components are required to form such an efficient delivery system: Drug delivery vehicle, Drug target, Targeting ligand, therapeutic drug payload [1].

Drug Delivery Vehicle: Drug delivery vehicles, also known as drug vectors, are the most crucial component needed for the loaded drug to be transported successfully. Replace "the medication administered within the target" with "the administered medication to the target" for clarity [2]. A drug vector is a special molecule, particle, composite, or system that can encapsulate or hold the medication with the help of a spacer [1]. Smart Drug Delivery Systems (SDDS) require different vectors depending on the type of targeting mechanism. An optimal drug delivery vehicle should possess several key attributes: it must be non-toxic, non-immunogenic, stable, biocompatible, biodegradable, easily eliminated from the body, and exhibit high specificity and selectivity. The mechanism of action for these delivery systems is characterized by; they typically undergo cleavage when exposed to specific stimuli, allowing for a sustained release of the drug over an extended duration. Commonly utilized drug delivery vectors include liposomes, dendrimers, hydrogels, microspheres, and nanoparticles.

Liposomes: Modify "size ranging from 20-100nm" to "with sizes ranging from 20 to 100 nm" for better readability [2]. They have been employed as drug vectors to stabilize medications and overcome barriers to their absorption by cells and tissues. Since the liposome's surface is composed of lipids, it is highly hydrophobic in nature. Thus, facilitating opsonization and uptake by mononuclear phagocytic cells. Encapsulating the drug in liposomes can be used for both active and passive targeting of drugs to achieve a safer and efficacious therapy [2, 4]. On systemic administration these liposomes recognize and bind to target cells with greater specificity [5]. The variation of liposomes for release of drug after uptake to tissue includes pH-sensitive liposomes (destabilized upon encountering the low pH environment of endosomes), heat-sensitive, enzyme sensitive, and photosensitive liposomes [6]. When exposed to 42°C, the thermosensitive liposomes release medication. With this technology, the medication can accumulate to its full capacity in the tissues to exhibit targeted action, and at the threshold temperature, its quick release can be initiated [2].

Targeting Moiety: In SDDSs, the pharmacological target is an essential component. Commonly explored targets are:

Receptors on Cell Membranes: They enable drug carriers to selectively interact with cells and enhance absorption *via* receptor-mediated endocytosis, are frequently studied pharmacological targets. For instance, folate receptors (FRs), which are often overexpressed in epithelial cancer cells, are used for targeted drug delivery in breast, ovarian, brain, and lung cancers.

Additionally, receptors such as G protein-coupled receptors (GPCRs), integrins, sigma receptors, and epidermal growth factor receptors are commonly leveraged in preclinical cancer studies for selective drug delivery through receptor-ligand interactions. Targeting ligands are attached to drug-loaded nanocarriers, which then bind to their respective targets on the surface of diseased cells that exhibit overexpression. A variety of natural and synthetic compounds from different chemical classes have been employed to enhance the targeting of nanocarriers. Frequently used targeting agents include antibodies, proteins like transferrin, aptamers, small molecules such as folic acid, and peptides. Selecting ideal targets is justified by identifying receptors that are expressed at higher levels on target diseased cells than on normal cells [8].

The Lipid Components of Cell Membranes: Synthetic phospholipid analogs alter the lipid composition, fluidity, and permeability of biological membranes through interaction. Consequently, apoptosis is brought on by the disruption of signal transduction pathways [9].

Cell Surface Antigens or Proteins: the diseased cells either overexpress or under express proteins that are expressed differently in healthy cells, or they create new proteins. It is used to use monoclonal antibodies against such proteins. One tumor-specific antigen expressed solely and consistently by all tumor cells can be used to target medications [10].

Targeting Ligand: Sugars, folic acid, peptides, monoclonal antibodies, and specially engineered antibodies serve as ligands that interact with specific receptors present on certain cell types, ensuring specific binding. Cellular targeting components have also been identified as carbohydrates like galactose, mannose, and other sugars, microbes like vitamins, and nucleic acids like aptamers [10].

Therapeutic Drug Payload: Smart drug delivery systems (SDDSs) for targeted therapy typically comprise a carrier, a linker, and a therapeutic agent. The therapeutic agent is selected to remain inactive when conjugated, transforming the SDDS into a pro-drug that is activated specifically within diseased tissues [7]. Drug delivery methods that target specific moieties can be administered locally or systemically. It is possible to deliver the drug payload inside or outside of the target cells [1].

While smaller drug-delivery systems can be directly endocytosed, larger drug-delivery systems can produce valuable local drug concentrations. In systemic administration, drug payloads can be given to specific tissues owing to the precise construction of the SDDSs. The main goal of SDDS's platform is to release the medication where drug carriers are concentrated by active or passive targeting and to observe that the drug does not diffuse throughout blood circulation [11].

Methodologies of Smart Drug Delivery System: The methodologies of smart drug delivery systems revolve around the ability to control and target the release of drug in response to specific stimuli or conditions. Following are the key methodologies:

Stimuli-Responsive Mechanisms: In the following system, therapeutic agents are released in response to specific external or internal stimuli. At present, stimuli-responsive delivery is considered one of the most appealing approaches in drug delivery. This strategy is being actively researched to enable tumor-specific delivery and controlled release of therapeutic agents, utilizing either endogenous or exogenous triggers.

pH-Responsive Systems: The pH changes within the body can be used to induce a response since each organ or tissue in the body has a unique pH [2]. Nanoparticles made of pH-responsive biomaterials can serve as DDSs as when subjected to externally acidic or alkaline environments, they might deform or disintegrate [3]. Also, the pH values of healthy tissues, diseased tissues differ from one other, nanogels have been engineered to be sensitive to the specific pH range of interest, enabling drug release solely in the targeted tissue [4]. In acidic settings, pH-responsive nano systems experience physical or chemical changes such as swelling, dissociation, and disintegration. This allows the loaded medicines to be released effectively [5]. For instance, in the acidic environment of a tumor of stomach, these materials can release the drug.

Temperature-Responsive Systems: Employ materials that change their properties with temperature variations. The idea of having a device able to recognize this deviation and release a therapeutic agent is particularly interesting [2]. To release the cargoes at higher temperatures (such as >40 °C) through considerable physico-chemical changes in response to a limited temperature rise, the DDSs must be stable and able to hold the cargoes at normal body temperature (up to 37 °C) [5, 6]. For example, a thermoresponsive hydrogel might release a drug when the body temperature exceeds a certain threshold.

Enzyme-Responsive Systems: Incorporate enzymatically degradable linkers or polymers that release drugs when exposed to specific enzymes present in the target tissue or environment. The following enzymes are constantly used are elastase, horseradish peroxidase, trans-glutaminase and tyrosinase [7]. For instance, human neutrophil elastase (HNE) anovel enzyme-responsive DDS was designed by Aimetti and coworkers to treat local inflammation [3].

Magnetic and Light-Responsive Systems: Utilization of external magnetic fields or light to trigger drug release. Magnetic nanoparticles can be

heated by an external magnetic field, causing drug release, while light-sensitive materials can release drugs upon exposure to certain wavelengths of light. Because of their deep penetration into biological tissues, magnetic fields can be used for both controlled drug release in conjunction with Alternating Magnetic Fields (AMF) and the visualization of magnetic materials through Magnetic Resonance Imaging (MRI) with a static magnetic field [8].

Light responsive system is effective since it's non-invasive and is easy to handle. In this way, heat-responsive polymers have been used to create infrared-sensitive medication delivery devices. By opening and shutting their structure in response to a single or periodic light irradiation, they may cause an ON/OFF release of the drug cargo [8].

Targeted Delivery: By accurately delivering medications to the intended location, smart drug delivery systems can minimize side effects and increase efficacy.

Ligand-Receptor Binding: Nanoparticles or carriers are modified with ligands that specifically bind to receptors overexpressed on target cells (e.g., cancer cells). This ensures selective delivery of the drug to the desired location. The advancement of targeted drug delivery systems (DDS) involves both local administration and ligandbased active targeting methods. Hydrogel-based local delivery and ligand-mediated interactions facilitate the precise localization of drugs, including biomacromolecules (like growth factors or genes) and small molecules, at their intended target sites [9].

Antibody-Drug Conjugates: Drugs are conjugated to antibodies that specifically target antigens on the surface of disease cells, allowing for targeted delivery. Antibodies, also known as immune-globulins (Ig), are glycoproteins found on the surface of B cells, serving as antigen receptors. When a specific antigen binds to these receptors, it triggers a signaling cascade that activates and differentiates B cells into plasma cells, which then secrete antibodies into the bloodstream or other body fluids. Antibody-drug conjugates (ADCs) refer to antibodies that are linked to other molecules *via* a chemical linker. One example of ADC application is the targeting of osteoclasts using an anti-RANK receptor monoclonal antibody combined with the peptide calcitonin, which has been shown to reduce osteoclast development.

Controlled Release System: The controlled release system is formulated for maintaining the concentration of the drug within the therapeutically effective range. A controlled release system regulates the concentration of the target chemical by adjusting its release rate [1]. This new system resolves many issues, including low solubility, poor absorption in the body, poor bioavailability, and *in-vivo* instability [2, 3]. It can also be used to enhance gene delivery [4] promotes better ocular delivery [5] *etc*. Controlled Release system has played an extensively progressed role in past decade. It has successfully been used in effective disease management [6].

Matrix System: To create a matrix system, the medication is combined with a slowly dissolving carrier and compacted [7]. In this type of controlled release system, a drug molecule is dispersed in a polymeric membrane. These systems deliver medication continuously *via* both diffusion- and dissolution-controlled mechanisms [8].

Matrix technologies have frequently been shown to be attractive because of their ease of use, simplicity in manufacturing, high degree of reproducibility, stability of the dosage form and raw ingredients, and ease of process validation and scaling up [9]. Few marketed preparations of such type of systems are Glucotrol XL, Procan SR.

Reservoir System: In the Reservoir system, the drug core is encapsulated within a polymeric membrane [10]. In the drug reservoir compartment, the drug can be present in various forms, such as a solid polymer matrix, gel, suspension, or solution.

The polymeric membrane is composed of non-biodegradable polymers. In this system, the rate of drug release is regulated by the characteristics of the polymer, including its composition, molecular weight, and film thickness, along with the physicochemical properties of the drug being contained, such as solubility, particle size, and molecular weight [12, 13]. Few marketed preparation of reservoir systems are Nico-400, Nitrospan.

Reservoir-Type and Matrix-Type Drug Delivery System:

Various Routes of Smart Drug Delivery System: The human body can absorb drugs through a variety of anatomical pathways. They might target specific organs and illnesses, or they might be designed to have systemic effects. Depending on the disorder, the intended outcome, and the available product, the route of administration must be selected. Medications can be supplied systemically and specifically to the diseased organ, or they can be given directly to the affected organ.

Classification of Anatomical Route:

- Oral delivery systems
- Transdermal delivery
- Inhalation systems
- Intravenous delivery
- Ocular delivery
- Vaginal and rectal delivery

Oral Delivery Systems: Since, oral delivery is easy to use, inexpensive, non-invasive, and has a high rate of patient compliance, it has grown into one of the most widely utilized methods for drug administration in the body [1, 2]. The successful targeting of medications to a GI region of interest and the release of drugs from the GI into the bloodstream for systemic circulation are the two main objectives when creating materials for oral drug administration [3].

Transdermal Delivery: Transdermal drug delivery systems provide a stable, efficient, and safe strategy for disease therapy [4]. The medicine is administered topically in accordance with the diffusion mechanism. To create a microneedle device, hundreds of microneedles are arranged in arrays on a small patch, like a typical transdermal patch found in the market, with the goal of delivering enough medication to produce the necessary therapeutic response [5, 6]. It avoids the barrier layer by penetrating the stratum corneum. When the medication reaches the site of action, it immediately penetrates the upper dermis or epidermis, enters the systemic circulation, and exhibits a therapeutic reaction [7].

Inhalation Systems: Inhalation system is a modern approach to the combating lung diseases. The system administers drugs directly to the lungs and respiratory tract. Some key technologies used in inhalation delivery systems include metered-dose inhalers and dry powder inhalers. Since, they are all non-directional, their particle deposition rates in the targeted nose or lung regions are generally low [8]. Propeller-free delivery devices are easy to use, portable, and offer deep lung deposition with greater physicochemical stability [9, 10]. Additionally, it is increasingly being chosen for the delivery of insulin, pain relief, cancer treatment, and nanotherapeutics.

Intravenous Delivery: Cation Intravenous (IV) delivery is a method of administering drugs directly into the bloodstream through a vein. This route is preferred for its rapid onset of action, precise control overdosing, and suitability for medications that require immediate or controlled delivery. Few innovations in intravenous drug delivery system are infusion pumps, implantable infusion devices, injectable hydrogels, etc. For instance, drugs are injected into the hydrogel, either directly into or near the tumor [11]. Drugs can be confined within a 3D network of hydrophilic polymer chains. In this method, medication toxicity is restricted to a specific area containing tumor cells [12, 13]. Localized hydrogels enable efficient drug administration at the tumor location.

Ocular Delivery: Ocular drug delivery involves administering medications directly to the eye to treat various ocular conditions like glaucoma, macular degeneration, and dry eye. One solution with tremendous potential is the contact lens used as a medication delivery vehicle to bypass this constraint [14] Thanks to its substantially increased drug penetration, high bioavailability, minimally invasive or non-invasive properties, and on-demand drug delivery, smart contact lens systems are currently garnering a lot of attention for ocular drug delivery and therapy [15]. In situ gels consisting of two or more polymers are also utilized for ocular medication delivery. These systems, like regular eye drops, are easily given into the eye due to their stimuliresponsive phase transition features. They have specific qualities like extended retention at the site of administration and sustained drug release because of their distinctive gelling capabilities [16].

Vaginal and Rectal Delivery: If taking medications by mouth is not possible, other routes like the vaginal or rectal routes can be utilized for drug delivery. Each path possesses unique features and uses. In cases such as convulsions, in highly behaviourally challenged and cognitively impaired patients, prior to GI or other surgeries where NPO is needed, enduring nausea and vomiting, complex oral aversion episodes, medication allergies; and when IV access is not possible or delayed, rectal medication delivery could be a fascinating option. These pathways may be uncomfortable, yet they prevent and offer more effective specific treatment and overall effects by bypassing First Pass Metabolism. Delivering drugs through the vagina is beneficial as it allows for smaller doses, keeps drug levels stable, and reduces the need for frequent dosing compared to taking drugs orally.

Smart Drug Delivery Systemin Treatment of Cancer: Cancer is a condition marked by uncontrollable cell growth and division, which can invade nearby tissues and travel to other areas of the body to create tumors (metastasis). It is marked as the second highest cause of death worldwide. Even with years of study and findings, cancer is still a serious and unsolvable issue for global health [6]. Resistance in cancer cells to chemotherapy, hindered drug transport within the cells, inactivation of treatment drugs, and considerable harm to the body and organs are the primary challenges to successful cancer therapy. Hydrogels and nanogels have been used as drug transporters as a remedy. Their ability to offer reduced toxicity, targeted drug release in tumor regions, and sensitivity to specific stimuli makes them more suitable for cancer therapy compared to alternative carriers. These smart nanogels can respond to various cues in the tumor environment like changes in pH, temperature, light, redox, and more, enabling accurate drug delivery in cancer treatment. Tumor cells often exhibit imbalanced enzyme levels that deviate greatly from those of normal cells, disrupting cellular homeostasis in the process. Tumor cells release MMPs and proteolytic enzymes into the extracellular matrix, leading to its degradation and enabling tumor growth. MMP-sensitive hydrogels utilize peptide-bound amino acid fragments to create a matrix responsive to MMP activity, like the MMP-2 responsive hydrogel developed by Li et al using hyaluronic acid and an MMP-2-sensitive peptide. In laboratory conditions, this hydrogel exhibited a reactive trend in releasing medication [16, 110, 111]. Faster hydrogel disintegration at the tumor location was shown in vivo tests, which led to increased medication release and tumor growth suppression without endangering the organs.

Additionally, tumor tissues generally have a lower pH compared to normal tissues [15, 107, 108, 109]. pH sensitive hydrogels can be produced by utilizing the pH discrepancy to precisely deliver and disperse anti-tumor drugs at tumor sites. To enhance the effectiveness against tumors and prevent resistance to drugs, Liu developed a pH-responsive peptide nanogel that can deliver both gemcitabine and paclitaxel to the tumor site simultaneously. The nanogel's ability to reach the tumor site was proven in *in-vivo* experiments, allowing the two drugs to release slowly and steadily into the tumor microenvironment.

Challenges Associated with SDDS: In recent years, significant progress has been made in the development of various successful drug delivery systems aimed at effectively reaching target treatment sites in the body. However, there are numerous restrictions and hurdles in terms of what these systems can achieve in treatment, some of which are discussed below. Even though they offer benefits, SDDS encounter obstacles like requiring consistent manufacturing procedures, toxicity evaluations, and regulatory authorizations. The shortage and diversity of available literature poses a major challenge for advancing medication delivery systems. Developing research, such as nanomedicine treatment strategies, relies on essential information in literature. One major challenge hindering the progress of nanotechnology in medicine is the inconsistency in research publications regarding the thorough documentation of experimental findings.

Incomplete and inconsistent data for the pharmaceutical industry could impede the advancement of nanomedicines and delay moving from research to clinical use. Many researchers agree that nanoparticles can have positive or negative effects, despite the limited knowledge on their safety, interaction with non-target proteins, and behavior in organs besides their target ones.

Using much tiny particles for transport into the human body is a resolution that tackles the issues associated with utilizing significantly larger particles. Several delivery systems utilize big particles as carriers, which are not ideal for treatment due to issues like low absorption and solubility, instability in living organisms, limited bioavailability, difficulties with specific targeting, and various negative side effects when administered [79, 104, 105, 106].

All delivery systems face challenges when it comes to delivering to specific targets. Targeted delivery has proven to be a more efficient treatment option that reduces toxicity, although its success depends on reaching the intended area with an adequate amount, as seen with siRNA administration. When administered systemically, they have low absorption as they are rapidly metabolized by body enzymes and, in high amounts, their negative charge hinders cellular uptake, resulting in minimal or no absorption by the body. Research is being done on lipid nanoparticles known as liposomes and micellar particles for targeted drug delivery, but the challenge lies in the body's responses to these nanoparticles, which can decrease their efficiency and lead to toxicity. Administering medication to a specific location is challenging because unconscious patients cannot ingest it, the target site may have limited permeability and solubility, and there is a risk of interaction with food and breakdown by gastrointestinal flora [39, 101, 102, 103].

Another important concern for medication delivery systems in general is the potential toxicity of the particles used for distribution; some nanomaterials could pose risks to human health and the environment. Studies done in both living organisms and controlled laboratory settings have shown the harmful effects of utilizing silver, gold, silica, and titanium as nanoparticles for delivering and connecting drugs. The medical delivery uses of carbon nanotubes (CNTs), gene therapy, and bioimaging have grown significantly [98, 99, 100]. because it has been discovered that carbon nanotubes can pass through cell membranes even when they are utilized as biomolecule carriers [(42),] yet these characteristics have caused researchers to become concerned particularly when used in drug delivery, as studies have shown that they can affect genes, the immune system, liver, heart, neurons, and embryos [36]. Even if carbon nanotubes have demonstrated promising outcomes in their application, critical toxicity testing must be conducted to guarantee their safety prior to a broad implementation in treatment [80, 95, 96, 97]. Their side effects have made it difficult to employ them as a cancer treatment [43].

Researchers have successfully created medications that can act as both carriers and pharmaceuticals. However, biocompatibility the ability of a drug to work with the body in particular circumstances and acceptability, the ability of a drug to enter the body without inciting the immune system are two major issues facing drug delivery systems The way the body responds to synthetic materials differs greatly from that of biological materials [81, 92, 93, 94].

For instance, the blood brain barrier (BBB) has a selectively permeable quality that hinders the attainment of therapeutic drug levels in brain tissues. The BBB stops carrier particles from reaching the brain and central nervous system, making it difficult to effectively treat cerebral diseases by delivering and maintaining drugs in the brain. Furthermore, the intricate organization of the human body can create inherent obstacles to the functioning of these delivery systems. Moreover, monoclonal antibodies (mAb) are commonly found within the body as they form immunoliposomes by attaching to liposome exteriors. However, due to potential immune reactions and poor absorption, distribution, metabolism, and excretion rates, the functionality of these immunoliposomes is restricted [145].

Using liposomes effectively as carriers for drugs at specific sites is challenging due to this issue. The body's natural detoxification processes include the kidney and liver, which may handle nanoparticles as possible waste products. Their actions may hinder the delivery of drugs and cause nanoparticles to accumulate in these organs. Nanomaterials mostly gather in the liver's Kupffer cells, hepatic stellate cells, sinusoidal endothelial cells, and macrophages. Hepatocytes also contain a small number of nanomaterials. In the meantime, the kidney's dimensions, charge, and form determine the nanomaterials' destiny after they enter the renal system [82].

Future Prospect of Smart Drug Delivery System: Smart drug delivery systems (SDDSs) are revolutionizing the healthcare landscape by offering targeted, controlled, and personalized treatment options. As technology advances, the potential of SDDSs to improve patient outcomes and address unmet medical needs is immense [83]. Here are some key future prospects of SDDSs:

Personalized Medicine:
Tailored Treatment Plans: SDDSs can be designed to deliver specific dosages of medication at precise times, based on individual patient needs and genetic makeup.

Enhanced Efficacy: By targeting drugs directly to the affected area, SDDSs can minimize side effects and improve therapeutic efficacy [84].

Advancements in Nanotechnology:
Nanoparticles: The use of nanoparticles as carriers for drugs can enhance their solubility, bioavailability, and tissue penetration.

Targeted Delivery: Nanoparticles can be engineered to recognize specific cells or tissues, allowing for highly targeted drug delivery [85].

Integration with IoT and Wearables:
Real-time Monitoring: IoT-enabled SDDSs can track patient data, such as vital signs and medication adherence, providing valuable insights for healthcare providers.

Remote Monitoring: Wearable devices can be integrated with SDDSs to enable remote monitoring and adjustments to treatment plans [86].

Stimuli-Responsive Systems:
Controlled Release: SDDSs can be engineered to release medications when triggered by certain stimuli, like alterations in pH, temperature, or enzymes.

On-Demand Delivery: This approach can ensure that drugs are released only when needed, reducing side effects and improving patient outcomes [87].

Combination Therapies:
Synergistic Effects: SDDSs can be used to deliver multiple drugs simultaneously, potentially enhancing therapeutic effects and reducing the need for multiple administrations.

Personalized Treatment: By combining different drugs in a controlled manner, SDDSs can offer more personalized treatment options [88].

Overcoming Drug Resistance:
Novel Delivery Methods: SDDSs can help overcome drug resistance by delivering drugs in a way that bypasses resistance mechanisms.

Enhanced Drug Penetration: By improving drug penetration into resistant cells, SDDSs can increase the effectiveness of existing treatments [89].

Regenerative Medicine:
Stem Cell Delivery: SDDSs can be used to deliver stem cells to damaged tissues, promoting regeneration and repair.

Tissue Engineering: SDDSs can also be employed to deliver growth factors and other molecules to support tissue engineering and regeneration [90].

With the ongoing advancement of research and development in SDDSs, we anticipate witnessing further innovative and efficient applications in the coming years. These systems have the potential to revolutionize healthcare by providing personalized, targeted, and efficient treatment options for a wide range of diseases and conditions [91-95].

CONCLUSION: In conclusion, smart drug delivery systems represent an exciting frontier in medicine that has the potential to vastly improve patient outcomes across many diseases. Smart drug delivery systems hold great potential to revolutionize how medications are administered, particularly in the treatment of complex diseases such as cancer. It embodies a transformative approach to medication administration by integrating advanced technologies such as nanotechnology, biomaterials, and real-time monitoring. These systems are designed to enhance therapeutic efficacy, improve patient compliance, and reduce side effects through targeted, controlled, and responsive delivery of drugs. By intelligently responding to physiological conditions and patient needs, smart drug delivery systems not only optimize therapeutic outcomes but also pave the way for personalized medicine. Their ability to dynamically adapt to the body's needs and environmental cues represents a leap forward from traditional drug delivery methods. These systems

can significantly improve patient adherence and quality of life. By providing controlled release and reducing the frequency of administration, smart drug delivery systems make managing treatment regimens easier and more convenient for patients. Real-time monitoring and feedback mechanisms further empower both patients and healthcare providers to make informed decisions, leading to more personalized and responsive care. Utilizing these treatments could effectively tackle bio-acceptability challenges faced by drug delivery systems, leading to a potent single dose that can prevent excessive drug accumulation. However, ongoing research, development, and collaboration across various fields are crucial to overcoming the existing challenges and bringing these innovative systems into widespread clinical use.

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