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A REVIEW ON SMART DRUG DELIVERY SYSTEM

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ABSTRACT

Getting medicinal substances to the right place is a big issue while treating various illnesses. The shortcomings of conventional chemotherapy include low selectivity and poor biodistribution. Lower dosages of medications are therefore needed in order to potentially overcome these restrictions by delivering pharmaceuticals to the site of action and preventing rapid drug breakdown or removal to improve drug concentration in target tissues. Active targeting, passive targeting and dual targeting are a few types of smart medication delivery systems. Drug delivery vehicles, therapeutic medicines, and targeting moieties are the three main parts of a smart drug delivery system that is intended to transport the drug to target tissue and facilitate simple biodistribution of a targeted drug. Drug delivery vehicles such as liposomes, dendrimers and viral vectors are utilized to successfully convey the loaded drug. A targeting moiety, such as an antibody, polyethylene glycol, or other proteins, helps release the medication into the intended organs, tissues, or cells by successfully and selectively recognizing the target cells. Even though a smart drug delivery system has the ability to treat a variety of ailments, its efficacy is influenced by a number of variables, including extracellular matrix, pH, glucose, low oxygen content, ions, enzymes, biological membranes and target site pH. Therefore, research should be done to appropriately choose, design and further alter drug delivery vehicles, therapeutic medicines and targeting moieties in order to overcome the constraints and improve the effectiveness and clinical applicability of smart drug delivery systems.

KEYWORDS

Smart drug delivery systems, Drug delivery vehicles and Targeting moiety.

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INTRODUCTION

Drug delivery, along with surgery, radiation, physical therapy, and psychotherapy, is one of the most significant medical treatment modalities. It is the process of delivering a pharmaceutical substance to achieve a therapeutic impact in the prevention of disease utilizing pharmaceuticals[1]. Severe side effects from such treatments include recurrent treatments, changes in drug

biodistribution, and cell acquisition of multidrug resistance (MDR)[2]. Drug delivery, along with surgery, radiation, physical therapy, and psychotherapy, is one of the most significant medical treatment modalities. It is the process of delivering a pharmaceutical molecule to achieve a therapeutic effect in the prevention of disease by pharmaceuticals[3]. The goal of targeted medicine delivery is the same. Targeted drug delivery, sometimes referred to as smart drug delivery, is a therapeutic approach in which a greater amount of medication is administered to one or a few body locations relative to others. As a result, it exclusively administers the drug to the body's targeted regions. This lowers negative effects while also improving therapy efficacy[4]. It is very hard to pinpoint the precise scope and effects of medication on health, but there is no denying that medication, when paired with improved food and hygiene practices, has raised life expectancy. Conventional chemotherapy involves the dispersion of medication via the bloodstream throughout the entire body, affecting both healthy and sick cells[5]. However, for all promising drug and vaccine candidates, it is necessary to develop appropriate drug delivery systems that are appealing ways to enable the efficient, safe, and dependable application of bioactive compounds to the patient in order to improve the efficacy and decrease side effects[6]. Drug delivery methods must be biocompatible-compatible with the body's processes and the drug to be delivered-ranging from implanted electronic devices to single polymer chains. DDS modify the drug's pharmacokinetics and biodistribution, which refer to the fraction of the administered dose that changes over time in each of the body's organs. Moreover, DDS may be able to overcome challenges brought on by low drug solubility, enzymatic or environmental degradation, quick clearance rates, non-specific toxicity, and the inability to pass through biological barriers, to name a few[1]. Administration systems (DS) are employed to localize, preserve the properties of the drug, guarantee a particular route taken for drug administration, target the targeted spot exclusively, lessen the side effects of the drugs and extend the duration of therapeutic contact with the diseased tissue[7]. Targeting cells, drug delivery methods, drug characteristics, organ-based targeted sites, illness, and drug-targeted vehicles are some of the strategies that this DT delivery system employs[8]. In order to achieve its intended therapeutic action within diseased body parts and prevent any unwanted side effects on normal body parts, an active pharmaceutical ingredient (API) must be transported from its dosage form to the target site in accordance with drug safety norms. This is known as a smart drug delivery system (SDDS), which refers to intelligent approaches in formulations technologies[9]. Thus, the purpose of this review is to examine the smart medication delivery system's applications and problems.

Smart Drug Delivery System

Utilising a smart drug delivery system (SDDS) for drug targeted (DT) distribution is an advanced method. Active drug molecules must selectively and highly controllably accumulate over time in the illness area in order to maximise their therapeutic effects and minimise related side effects. The phrase "drug delivery" refers to the combinations, structures, tools and processes that are utilised to safely and effectively distribute drugs throughout the body as needed to achieve the desired therapeutic effects[9]. The following conditions are met by the smart medication that this technology delivers: For absorption to occur, a biological membrane must be crossed, increasing the amount of the medicine administered to the intended bodypart of interest (tissue, cells, or organs), not be broken down by any physiological fluids, lessen adverse effects by making medication therapy more effective and be released to the body part of interest in the appropriate amounts[10]. Drug delivery systems (DDS) have to be biocompatible, meaning they can be anything from single polymer chains to implantable electronic devices, and they also have to be compatible with the drug to be supplied and biological processes[10]. DDS have an impact on the drug's pharmacokinetics, or the portion of the administered dose that varies with time in each organ of the body. In addition, problems caused by a drug's inability to cross biological barriers, quick clearance rates, enzymatic or environmental degradation, non-specific toxicity, and low solubility[7]. It is meant to improve drug biodistribution in specific body regions and cellular

component communication without disrupting normal tissue[11].

Evolution of the drug dosage forms: The need of smartness

Pharmacological therapies aim to achieve the intended therapeutic effect by ensuring that the active component reaches the target and remains at a sufficiently high concentration for the required amount of time. Ideally, the medication should only be administered to the tissues that contain the pharmacological target in order to maximise the response and minimise side effects. Nevertheless, the conventional method of administering medication has been limited to putting the drug into the bloodstream, relying on tissue irrigation and drug affinity to arrive to the desired location. Actually, bioavailability is still determined by looking at the drug's levels in the bloodstream, not in the target environment. However, the drug by itself encounters numerous challenges, such as low tissue permeability, enzyme assaults and limited target access once the target enters the target cells, to mention a few. Because of this, the treatments usually involve administering huge doses of drug in the hopes that some will, albeit minute amounts, will get to the right tissues or cells. The complex structures and insufficient physicochemical and stability qualities of peptides, enzymes, and genes-new active substances generated by biotechnological processes-make them more problematic because they prevent them from entering or maintaining blood circulation. All things considered, the effectiveness of the therapy is mostly dependent on how quickly the active substances are able to reach the target site. Because of this, there are ever-increasing demands on therapy in terms of delivery location and rate. Most commercially available sustained-release drugs are designed to manage the drug's entry into the bloodstream and subsequent distribution to the body's tissues by releasing the drug at the absorption site at a predetermined rate. The basis of what is referred to as the "first generation" of controlled release systems is the idea that a rate-programmed drug release may ultimately prove to be the limiting factor in the absorption process[12,13]. The search for excipients, primarily polymers, that would enable dosage forms to control release through osmotic, diffusion, dissolution, or erosion mechanisms was greatly accelerated by its invention. By keeping drug levels within a therapeutically suitable range at a lower daily dose, it is possible to minimise side effects, improve the effectiveness of therapies utilising medicines with short half-lives, and greatly increase patient compliance[14]. Another phase in the creation of oral controlled release formulations is the use of components that can affect the location at which the release process should occur, i.e., the area of the gastrointestinal system most conducive to the stability or absorption of the medication. In the second generation of controlled release systems, activation-modulated drug release is accomplished by reacting excipients to specific physical, chemical, or biochemical processes that take place in the gastrointestinal tract, such as pH gradients or enzyme activity[15]. By using sophisticated dosage forms that can both deliver the drug to the intended location under ideal conditions (acting as a true courier) and feedback-regulate drug release according to the physiological and pathological conditions of the body, ideally in line with the progression of specific disease markers, the third generation of pharmaceuticals hopes to achieve feedback-regulated drug release[16-18]. Drug delivery systems (DDSs) are a term occasionally used to refer to pharmaceuticals of this latter generation, to differentiate them from dosage forms that just control drug release prior to absorption or distribution. A schematic representation of the three generations of mechanisms used in controlled release systems is presented in Figure No.1[19].

Finally, feed-back regulated release systems adjust the release rate based on the levels of a biomarker; the biomarker increases the release of medication, which in turn lowers the biomarker's level and eventually stops the release until the biomarker level rises again[19]. Both types of systems require components that can act as "sensors" of the surrounding environment and as "actuators," able to precisely change the rate in feedback-regulated systems or initiate the drug's release in activation-modulated systems. The development of such sensor/actuator (stimuli-responsive) excipients is a challenging task due to the intricacy of the biological environment and the largely microscopic

alterations caused by disease processes. In addition to the internal variables, focus has been given to the development of materials that can respond to external stimuli. As a result, two primary categories of responsive DDSs can be distinguished: a) closed-loop or self-regulated systems, which sense alterations in the biological medium (pH, temperature, or concentration of specific substances) and adjust the release rate accordingly; and b) open-circuit DDSs, which turn on or off drug release in reaction to specific external stimuli (e.g., light, an electric or magnetic field, or light). When triggered externally, these DDSs can provide pulsed drug release[20,21]. The search for improved excipients that can result in responsive formulations has involved an amazing effort to find suitable stimuli sensitive materials; this search is what's caused the exponential rise in publications on "smart" delivery systems. The terms "smart," "stimuli-responsive," and "environmentally responsive" are sometimes used interchangeably, despite some distinctions between them. To create bodily sensitivity to internal or external signals, semisynthetic or synthetic materials (mainly polymers) containing functional groups that vary their properties in response to signal strength and allow transduction into changes in material features are typically used[22-24]. These changes might range in complexity. Among the instances are:

Modifying the conformation of chemically crosslinked networks, which can lead to volume phase transitions and changes in affinity towards other chemical groups or molecular entities

Reversibly changing the shape, solubility, or state of aggregation of individual components (such as micelle unimer assembly or disassembly or sol-gel transition)

Reversibly stretching or shrinking surface-immobilized chains or networks on inert substrates (Figure No.2)[21,25-27] Only when these possible structural alterations are both reversible and commensurate to the stimulus intensity can the DDS be considered to operate in a "smart" manner.

It's important to note that several advanced DDSs go by the term SMART. The following three categories have lately been proposed[28]:

Type 1: Access, Retention and Therapy Maximisation Systems: Nanoparticles used in these systems have the ability to actively or passively target medications. These systems include monoclonal antibody-decorated nanoparticles, bioconjugates and magnetically guided particles. These systems are meant to improve targeting efficiency over DDSs, which only make use of the Enhanced Permeability and Retention (EPR) effect observed in some diseased tissues.

Type 2: Real-time Monitoring, Analysis and Response Systems. These DDSs adjust drug release by feed-back using mechanically driven mechanisms or cell-based structures. First, the integrated system consists of a biosensor that monitors the concentration of particular biomarkers, therapy management software and a pump system that administers the medication at the appropriate pace. In the second scenario, a missing part of the body is replaced by stem cells or xenotransplants of non-human cells.

Type 3: Until a remote trigger activates them, systems are silent. Previous research has examined remote triggering release of oral capsules and parenteral nanocarriers using near infrared (NIR) light, magnetic fields, or ultrasound as trigger agents. Research and clinical trials for most of these SMART technologies are still in their early phases. Two Type 1 nanomedicines that have been commercialised thus far and are beyond a doubt proven to control adverse reactions and toxicity in systems are Abraxane® and Doxil®. As for "smart" (stimulus-responsive) materials, in this context it should be noted that although they lack the artificial or natural intelligence of living cells or computer software, they do have the advantage of being simpler, less expensive and for the most part, more akin to the natural mechanisms of substance delivery and transport found in living bodies, where a variety of biochemical processes are controlled by variations in the concentrations of physical or chemical factors[29]. Therefore, they could be pertinent elements of advanced DDSs Type 2 and 3 and possibly Type 1, as recently reviewed in the large book Smart Materials for Drug Delivery[30]. In addition, several stimuli-responsive products, such as ThermoDox® and OpaxioTM, are being evaluated in clinical settings[31,32] A few of these itemsCertain products-like NanoTherm®-have already been approved for clinical use and other

products-like commercialisation for use solely in research—have already reached the market[33-35] More smart nanomedicines should be developed and approved more easily with the help of the knowledge gathered from the evaluation and design of these innovative products. From this moment on, in the context of this review, "smart" will refer to stimuli responsiveness for drug delivery. More in-depth analyses of the particle requirements for targeting, along with examples of ingenious changes to surface properties like size, shape, and alignment, can be found elsewhere[36]. The current review aims to provide an overview of the state of the art by using recent examples of formulations undergoing clinical trials or that are currently on the market of the art in terms of delivery site and release rate for smart DDS.

Mechanism of drug delivery system

A new class of responsive, intelligent delivery systems known as "intelligent therapeutics" is meant to perform a variety of functions, including locating, isolating, and/or releasing therapeutic agents to treat diseases[37]. The majority of intelligent drug delivery systems work with stimuli-responsive polymers, which are able to recognise alterations in a specific variable and initiate a reversible delivery method[38]. This review examines the advancement of stimuli-responsive polymer-based open-loop and closed-loop control systems and their uses as pulsatile, self-regulating pharmaceutical delivery devices[39].

Single Unit Capsular System

The majority of one-unit systems are designed as capsules. During the lag time, which is extended by a plug that is pushed away by swelling or erosion, the medication is released as a pulse from the insoluble capsule body. Plugged (insoluble but permeable and swellable) at the open end of the Pulsincap® system, a water-insoluble body containing the drug formulation is sealed with a swellable hydrogel. Following a lag period, the plug expands and forces itself through the capsule when it comes into contact with the dissolving media or gastrointestinal fluid. Drugs that are insoluble in water are given effervescent or disintegrating chemicals to aid in their rapid release.

Pulsatile Delivery by Osmosis

This system consists of a capsule with a semi-permeable membrane covering it. Within the capsule is an insoluble plug composed of an osmotically active ingredient and the medication formulation. This method demonstrates good *in vivo* and *in vitro* correlations in humans. One such system is the Port®System, which consists of a gelatin capsule with the drug formulation, an osmotically active ingredient and an insoluble plug (like lipidic) coated in a semi-permeable membrane (like cellulose acetate). Delivery of Pulsatile through Membrane Erosion Solubilisation These systems are based on a drug reservoir that is surrounded by a soluble or erodable barrier layer that dissolves with time, enabling the drug to release immediately after the lag time.The Time Clock® system, which combines surfactants like polyoxyethylene sorbitan monooleate with lipid barriers like beeswax and carnauba wax to coat a solid dosage form, is an example of this type of delivery. The system emulsifies or erodes after the lag-time, regardless of the pH, enzyme level, gastric residence, or gastrointestinal motility. This is dependent on the thickness of the coat.

Pulsatile Delivery by Rupture of Membrane

These systems are based on a reservoir system with a ruptureable membrane covering it. The outer membrane bursts due to pressure produced by swelling or effervescent substances. Citric acid and sodium bicarbonate are combined to create an effervescent mixture within the ethyl cellulose-covered tablet core. When the system comes into contact with water, carbon dioxide gas is released. After a lag time, the pressure from this gas causes the membrane to rupture, quickly delivering the medication. Specifically for drugs with high first pass effect, a reservoir system with a semi-permeable coating is proposed to achieve an in vivo drug pattern similar to the administration of multiple immediate release doses. When sodium starch glycolate, low substituted hydroxyl propyl cellulose, or cross carmellose sodium are utilised as swelling agents, the whole film ruptures and the drug is released quickly. The lag time is controlled by the composition of the outer polymeric membrane.

Electrically Regulated Systems

Because the electric field acts directly on the solute or on the rate-limiting membrane, controlling the solute's passage over the membrane, these systems exhibit drug release in response to an applied electric field. Electric field-sensitive polyelectrolyte hydrogels have been developed for artificial muscles, actuators and solute penetration control because of their swelling-deswelling properties.

Photoresponsive Systems

When exposed to photoradiation, photoresponsive gels undergo reversible changes in their chemical or physical properties. A photoresponsive polymer consists of a photoreceptor-typically a photochromic chromophore and a functional element. After the photochromic molecules capture the optical signal, the chromophores are isomerised in the photoreceptors to transform it into a chemical signal. The mechanism proposed was direct heading to the network polymer reaction to the light, which causes a phase shift in polymer gels when visible light is present.

Ultrasonically Modulated Systems

The feasibility of polymeric delivery systems with ultrasonic control, which allow for constant modification of chemical external release rates. Both bioerodible and non-erodible polymers can be used to create drug carrier matrices. Poly(bis(p-carboxyphenoxy)alkane anhydrides) and polyglycolide, polylactide, and their copolymers with sebacic acid are examples of bioerodible polymers. Insulin, p-nitroaniline, p-aminohippurate and bovine serum albumin were the bioactives that were used. Ultrasound exposure increases the breakdown of polymers and the release of medications. Within two minutes, the technology reacts to ultrasonic triggering in a reversible manner.

Magnetically Modulated Systems

This technique makes use of elastic polymers that have been mixed with magnetic beads. Applying an oscillating magnetic field has been shown to increase the amount of medication released. Insulin and other macromolecular bioactives can be continuously delivered by encapsulating them in a carrier, such as ethylene vinyl acetate copolymer (EVAc). Another system that makes use of EVAc-protein matrices incorporating magnetic beads shows higher release rates when subjected to an oscillating magnetic field.

Design rationale of smart drug delivery nanoplatforms

It is common knowledge that in order to maximise therapeutic efficacy and minimise side effects, medications should ideally be released gradually at the target sites. The loaded drugs possess "smart" properties, which they inherit from the controlled release nanoplatforms. Research on the phase transition of polymeric gels has increased significantly since Tanaka's observation of the phase transition of polyacrylamide gels in 1978[40]. Thermally sensitive liposomes for drug delivery were first reported almost simultaneously[41]. Biomaterials that respond to stimuli have been developed gradually and are now widely used for regulated drug delivery. Pharmaceuticals can now be conjugated with various nanoparticles thanks to advancements in nanotechnology and nanomaterials. The nanomaterials are functioning as one of the most promising smart DDSs by taking advantage of their superior size and surface characteristics. According to this review, "Smart DDSs" refers to the method wherein the drugs are only released at the appropriate rates at the sites of action, not before reaching the target tissues or organs (or at a very slow rate). While drug molecules themselves can occasionally function as smart components, the focus of this discussion is on smart drug delivery systems (DDSs) that use nanotechnology to transport drug molecules. The release of payloads at targeted tissues during systemic administration is made possible by the smart nanoplatform's delicate design.Currently, the drug-loaded nanoplatform makes sure that the medication won't extravasate freely throughout blood circulation, but will only release at the locations where active or passive targeting strategies have accumulated nanocarriers. As illustrated in Figure No.4, these intricately constructed smart or stimuli-responsive nanoplatforms are capable of reacting to either endogenous or exogenous stimuli. Endogenous triggers that are linked to the pathological features of the disease include pH changes, hormone levels, enzyme concentrations, small biomolecules, glucose, and redox gradients[42,43]. However,

exogenous triggers such as temperature, magnetic fields, light, ultrasound (US), electric pulses, and high-energy radiation can also be utilised to enhance or initiate drug release at diseased areas.

RECENT ADVANCES

INSULIN PUMP

The ultimate objective of insulin therapy for diabetes mellitus is blood glucose regulation and the avoidance or stabilisation of long-term diabetic complications. Nowadays, the main treatment for diabetes is the subcutaneous injection of insulin. To keep the blood glucose level within normal range, two or three injections must be administered daily. The patient would not have a good quality of life because this procedure is taxing and invasive to living things. Thus, research has been done on an insulin pump made of polymer materials. Wang created an insulin reservoir made of silicone rubber that compresses to create a pressure gradient that releases insulin that has been stored inside. One elastic material that can be used to prepare the insulin reservoir is segmented polyurethane (SPU).A novel copolymer consisting of 2-methacryloyloxyethyl phosphorylcholine (MPC) and 2-ethylhexyl methacrylate (EHMA) can be designed to improve insulin permeability and biocompatibility. The biocompatibility of the original polymer is improved when the MPC polymer is added to other polymers. Under delivery events are typically caused by two main mechanisms: catheter occlusions and insulin aggregation in the pump insulin pathway. Furthermore, in many patients receiving treatment with implantable pumps, these aggregates-which are probably the result of hydrophobic interactions with the pump circuits-seem to encourage an increased production of anti-insulin antibodies. Under delivery was decreased in part due to concurrent advancements in catheter design. Implantable pumps currently offer the most efficient and physiological insulin delivery despite these issues.

GLUCO WATCH

The non-invasive, watch-like Gluco Watch TM biographer measures glucose. a plastic biographer component that snaps into the watch and adheres to the skin. It takes an automatic reading every 10 minutes to 13 hours. Right now, Gluco Watch is the most popular approach for monitoring blood sugar levels that is easy to use. The reverse iontophoresis principle is the foundation of this system. Glucose is drawn through the skin by a mild electric current. The auto sensor collects glucose in two gel collection discs. The auto sensor has an additional electrode for measuring glucose. Thus, it is possible to generate a signal proportional to the interstitial glucose level.

Recent drug delivery systems and applications

The successful development of drug delivery systems based on organic, inorganic, and hybrid nanoparticles as drug carriers for active targeting, especially in chemotherapy, has advanced significantly in recent years. Newer drug delivery systems (DDS) are designed with better qualities like stability, toxicity, sustained delivery, specific site targeting, increased permeability, increased solubility, and smaller particle sizes. Compared to traditional dosage forms, they can greatly enhance the performance of therapeutic agents[44,45]. Recent drug delivery systems are acknowledged as the most recent advancements and creative understanding of the pharmacokinetic and pharmacodynamic behaviour of pharmaceuticals in the development of an ideal drug delivery system. These DDS can deliver material to the site of action and maintain drug concentrations in the therapeutic range for extended periods of time because they are transporters. The innovation's commercial and therapeutic success is closely linked to the delivery mechanism's adoption. This would mean identifying any issues, including involving patients early in the development process and making sure they get the most out of the device. enhancing delivery methods that boost effectiveness while lowering toxicit. Figure No.5 shows the various kinds of drug delivery systems.

Challenges associated with current drug delivery systems

The quest to deliver drugs from various plant sources to their target sites for treatment in the body has advanced greatly in recent years, with many delivery systems being used successfully. Nevertheless, there are many restrictions and difficulties with what these systems can accomplish in terms of treatment, some of which are covered

below. A significant obstacle impeding the progress of drug delivery systems is the scarcity and heterogeneity of existing literature. The advancement of any research, including in this case, nanomedicine treatment approaches, depends on the availability of vital information in literature. One of the main obstacles to the advancement of nanotechnology application in medicine is the disparity in published studies concerning the documented characterisation of reported experimental details[46].

Future advances in nanomedicines may be hampered by the incomplete and inconsistent data that ought to serve as a guide for industry, delaying the transition from laboratory and research to clinical application[47]. It is widely acknowledged by researchers that nanoparticles can have positive or negative effects. However, there is a lack of information regarding the safety of these particles, their degree of interaction with non-target proteins, and how they move and interact with other organs outside of their intended target organs[48]. The use of much smaller particles for delivery to the human biological system is a solution that addresses the problems that come with using much larger particles. Some of these delivery systems use large particles as carriers, which are not particularly favourable for treatment because they can constitute challenges such as poor absorption and solubility, in vivo instability, poor bioavailability, target-specific delivery complications, and several adverse side effects upon administration[49]. A problem that all delivery systems encounter is target-specific delivery complexity. Target-specific delivery has been shown to demonstrate more effective treatment and reduce toxicity, but its effectiveness cannot be guaranteed until it is able to reach the targeted site in a sufficient amount. This is observed when siRNA is given systemically; they are rarely absorbed by the body because they are quickly broken down by body enzymes and, when given in large quantities, their negative charge prevents the cells from absorbing them[50], which means that the body absorbs very little or none of them. Lipid nanoparticles called liposomes and miceelles are being researched for target drug delivery; however, the drawback of this approach is that the body's reactions to the nanoparticles, such as phagocytic absorption and hepatic filtration, can reduce their effectiveness and cause toxicity[51]. Targeted delivery faces several challenges, including the inability to administer a dose to an unconscious patient, low solubility and permeability at the target site, potential for food interactions, and potential degradation by the stomach flora[52]. Another major issue facing drug delivery systems generally is the toxicity of the particles used in delivery; certain nanomaterials can be hazardous to both human health and the environment[53]. Research conducted both in vivo and in vitro has demonstrated the deleterious impact of using silver, gold, silica and titanium as drug-delivering and coupling nanoparticles[49]. Drug delivery, bioimaging and gene therapy are three fields in which carbon nanotubes (CNTs) are now widely employed[54]. Because it has been discovered that carbon nanotubes can cross cell membranes even when they are used as biomolecule carriers[55]. However, due to experiments showing that carbon nanotubes can harm genes, embryos, the liver, heart, neurones and the immune system[49], researchers are concerned about the properties of carbon nanotubes, particularly when it comes to their use in drug delivery. Even though carbon nanotubes have demonstrated promising results in their application, critical toxicity testing must be conducted to guarantee their safety prior to a broad implementation in treatment[54]. Their side effects have made it difficult to use them as a cancer treatment[56]. Drug delivery systems face several challenges, including acceptability (the ability to be absorbed by the body without inciting the immune system) and biocompatibility (the ability to work with the body in specific situations), which arise from the body's differing reactions to biological and synthetic materials[53]. Scientists have successfully produced drugs that can act as carriers in addition to drugs. The blood brain barrier (BBB) has a selectively permeable feature that makes it difficult to achieve therapeutic drug concentration in the brain tissues. The BBB also prevents carrier particles from entering the brain and entire central nervous system, which results in the ineffectiveness of therapeutic agents in the treatment of cerebral diseases due to the inability to efficiently deliver and sustain intended drugs within the brain[57].

Furthermore, due to the complex structure of the human system, there may be natural barriers to the functions of these delivery systems. Additionally, monoclonal antibodies (mAb) are among the body's most prevalent carriers because they bind to liposome surfaces to form immunoliposomes. However, because these liposomes can elicit an immune response and have low levels of absorption, distribution, metabolism and elimination by the body, their uses are limited, which makes it difficult to use liposomes effectively as site-specific drug carriers[58].

The body's natural detoxification processes include the kidney and liver, which can handle nanoparticles as possible waste products. Their actions may obstruct 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 amount of nanomaterials. Once nanomaterials enter the renal system, their destiny is determined by the kidney's size, charge and shape[59].

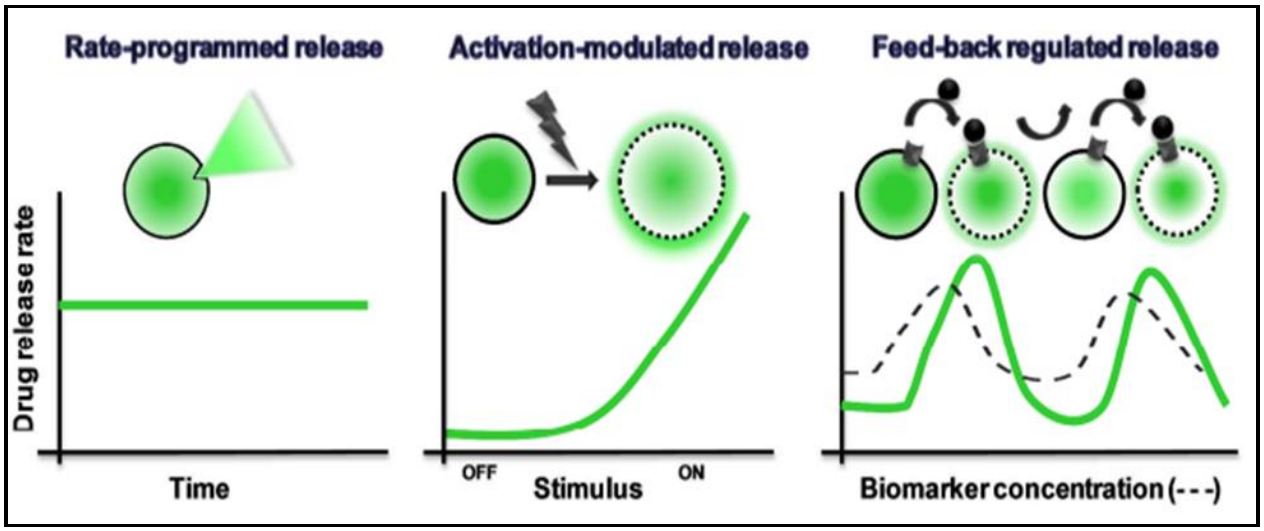

Figure No.1: Displays drug release patterns from a dosage form. Rate-programmed systems release based on a preset pattern, independent of physiological states, Activation-modulated systems release a response to certain internal or external stimuli

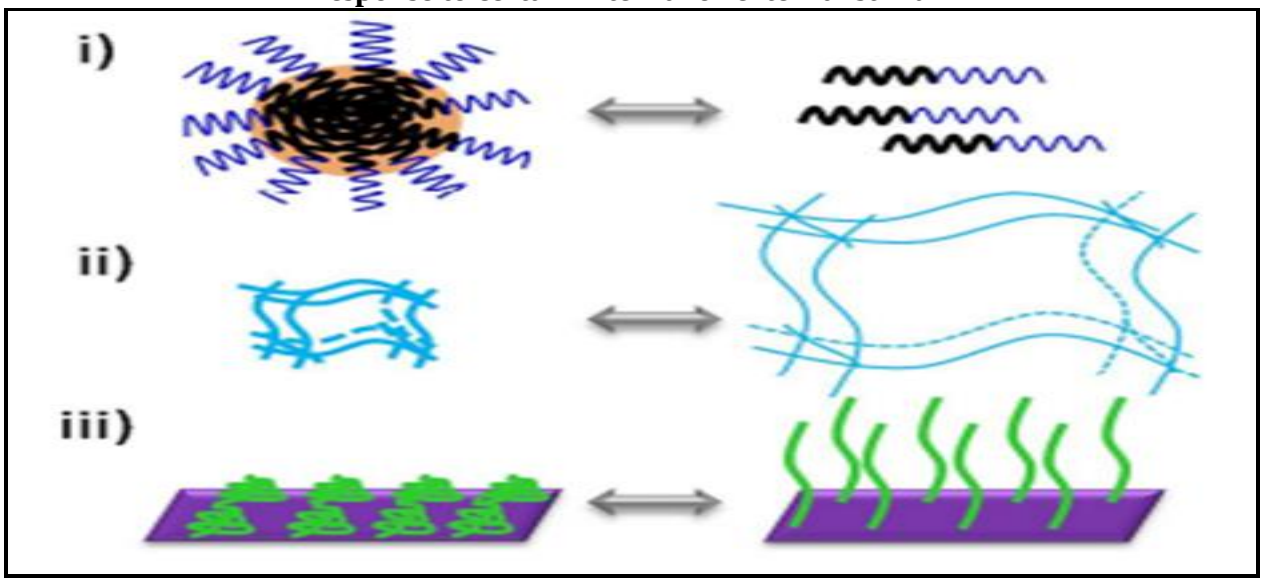

Figure No.2: Some transitions associated to the responsiveness to a stimulus: i) deaggregation of amphiphilic polymers; ii) volume phase transition and iii) helix to random coil

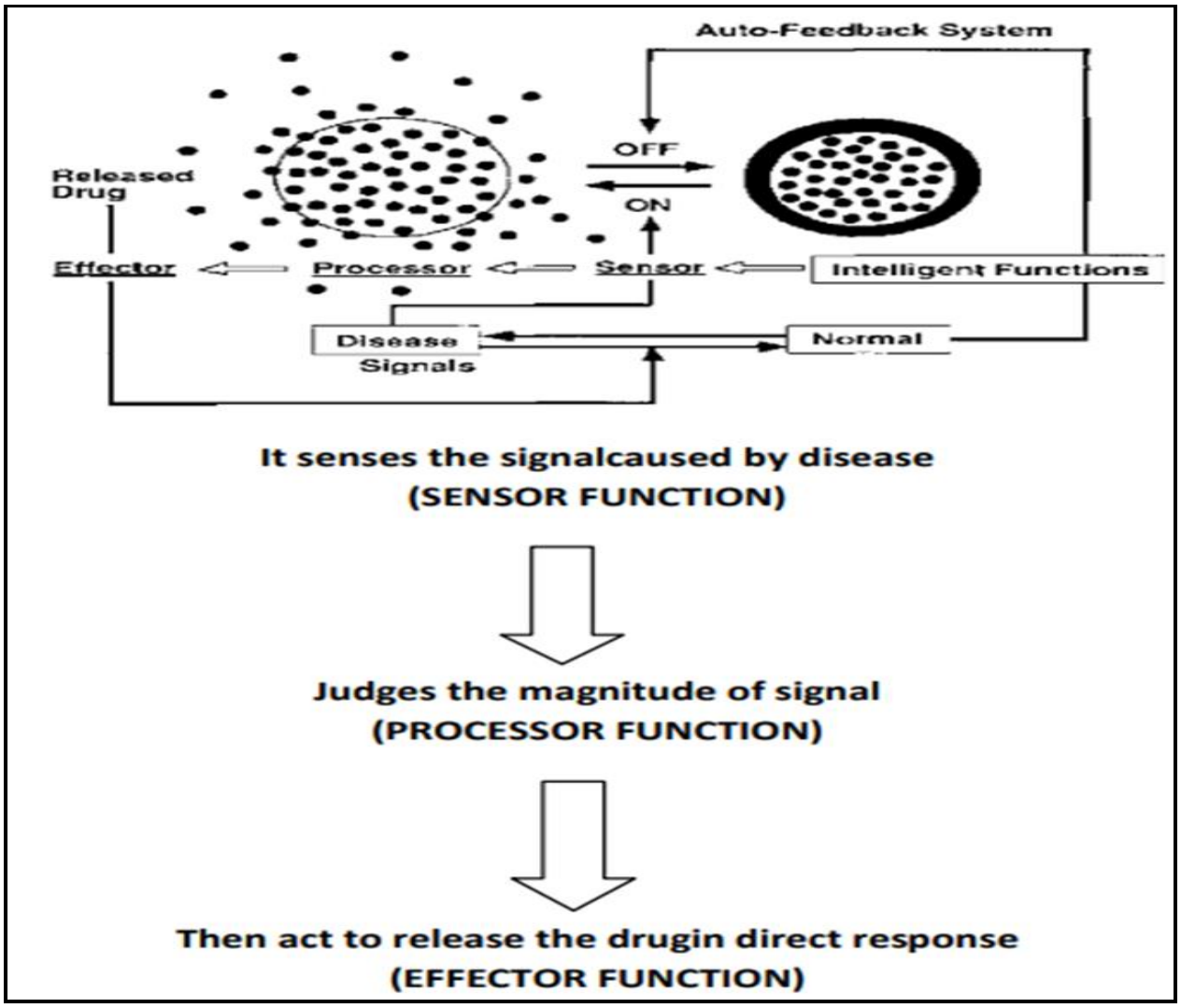

Figure No.3: Mechanism of drug delivery system

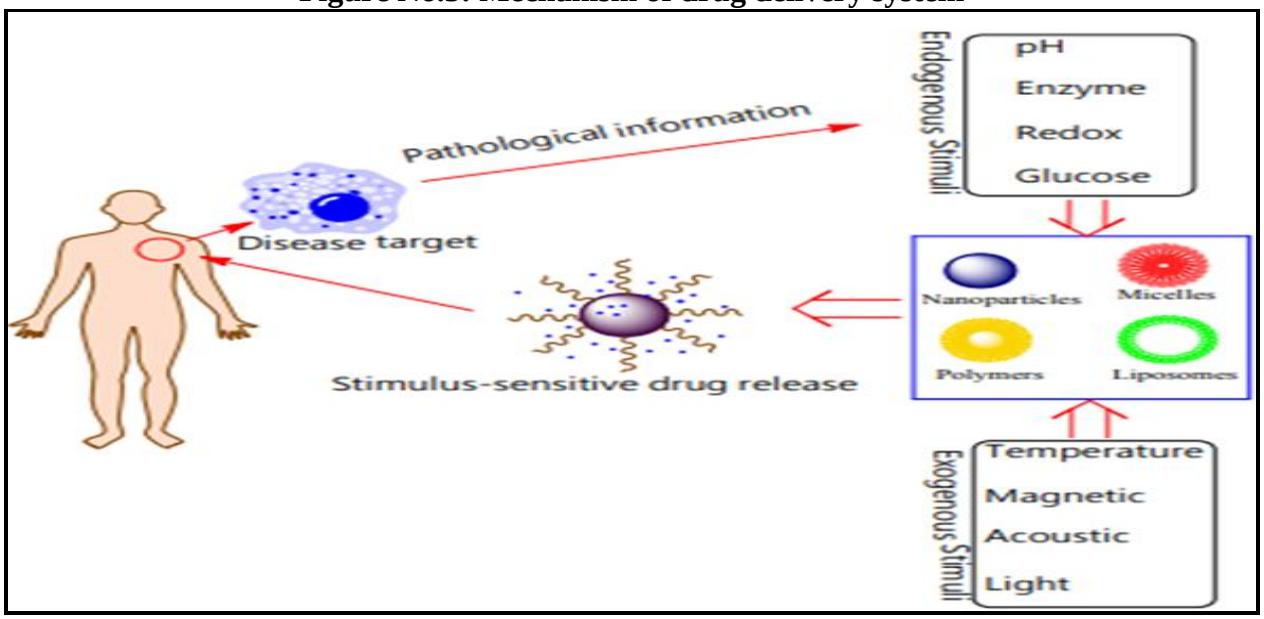

Figure No.4: Schematic illustration for stimuli-responsive DDS

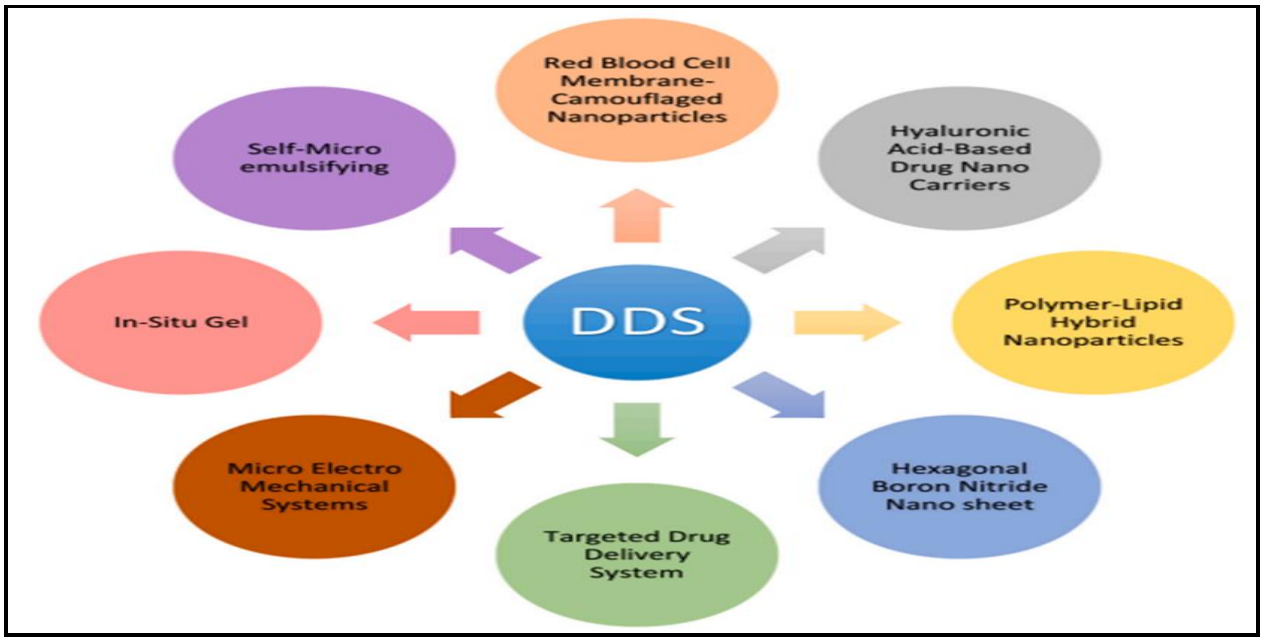

Figure No.5: Several types of recent drug delivery systems for different therapeutic purposes

FUTURE DIRECTIONS AND CONCLUSION

Drug delivery and nanomedicine have emerged as two of the most exciting areas of modern science research; in recent years, they have attracted a lot of interest in terms of study, testing, and clinical trials[60]. The recent drug delivery system has a lot of potential despite the obstacles that have prevented it from being used clinically. To help achieve this efficiency, we need to collaborate across academic theory, laboratory experimentation, medical knowledge, pharmaceutical knowledge and excellent research[61]. According to Khalid *et al*[50] a way to According to Vargason *et al*[62], the application of cell therapies can significantly address the bio-acceptability problems that drug delivery systems encounter. They also believe that it will result in an effective single dose that prevents a high buildup of drugs in the system. In actuality, cell therapies promise to dismantle innate biological barriers, produce responses that seem natural within the system and provide a seemingly sustained source of complex biologics. Adepu[63] has proposed the use of molecular imprinting polymers, micro fluids and inorganic mesoporous nanoparticles as strategies to address some of the problems associated with drug delivery. By using priming agents that can alter the biological environment in which they are administered-particularly those that can alter tissue form and function so that the administered drug is advantageous without endangering the patient-it is possible to increase the efficacy of drug delivery. Additionally, since cells are a natural part of the human body, cell-based drug systems-which combine the use of cells with nanomaterials-should be taken into consideration in the field of biomaterials. This is a novel approach that is still in theory but looks to be very creative, encouraging drug delivery methods in an effort to achieve the maximum drug delivery pattern. More studies and clinical trials are required to improve the effectiveness of these contemporary drug delivery systems and the challenges that face their usage.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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