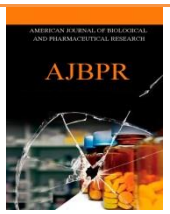
e- ISSN - 2348-2184
Print ISSN - 2348-2176

AMERICAN JOURNAL OF BIOLOGICAL AND PHARMACEUTICAL RESEARCH

Journal homepage: www.mcmed.us/journal/ajbpr



ADVANCES IN DRUG DELIVERY SYSTEMS: A REVIEW OF NOVEL APPROACHES

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Article Info

Received 06/01/2026
Revised 27/01/2026
Accepted 14/02/2026

Key words: -
Drug Delivery Systems, Nanotechnology, Controlled Release, Targeted Therapy, Liposomes, Polymeric Nanoparticles.

ABSTRACT

The delivery system (DDS) has evolved more than ever before, gradually leaving behind the traditional formulation in the form of tablets, capsules and injections to the innovative system that has the capacity of controlled, targeted and responsive drug delivery. The use of traditional delivery systems is usually associated with shortcomings such as low bioavailability, systemic toxicity, non-specificity to the site, and non-compliance with the patients. Conversely, novel drug delivery systems (NDDS) utilize the emerging technologies in nanotechnology, biomaterials and intelligent polymers to improve the efficacy and safety of therapeutic delivery systems. Nanocarriers like liposomes, polymeric nanoparticles and solid lipid nanoparticles have resulted in revolution in pharmacotherapy by enhancing solubility, stability and targeting efficiency. Physiological triggers such as pH, temperature or enzyme reactions are monitored by stimuli-responsive systems allowing drugs to be released in the desired location and quantity thereby reducing the side effects. Also, recent developments like microneedle patches, 3D printed dosage forms and transdermal systems have also enhanced patient ease and compliance. The combination of specific and controlled-release technologies has specifically been of benefit to cancer therapy, central nervous system conditions, diabetes management, vaccination and gene therapy. With these developments, there is an implication of a paradigm shift in personalized and precision medicine where drug delivery is best tailored to the needs of each patient. The current merging of nanotechnology with biotechnology and materials science is still reshaping the future of drug delivery with more efficient, safer, and patient-centered therapeutic results in the future.

INTRODUCTION

Background of Drug Delivery Systems

One of the most important aspects within the sphere of pharmaceutical science and the contemporary medicine is the development of drug delivery systems (DDS) [1–3]. Drug delivery concept is not just a process that involves introduction of therapeutic agents into the body, but it is a meticulous planning of systems that will ensure maximum release, absorption, and distribution of

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the active pharmaceutical ingredient (API) to produce the desired therapeutic action.

Drug delivery has evolved over the decades to include less sophisticated forms of administering medications like pills, capsules, and injections, to more intelligent and sophisticated methods which can regulate the rate, time and location of drug release in the body. History of drug delivery can be traced back to the time of ancient civilization, in which natural medicines in the form of herbs and extracts were used as a basic compound to deliver the effective remedy in the format of an ointment, tea or poultices. Nevertheless, the 20 th century is the time when drug delivery started to be a scientific field. It was also revolutionized by the creation of synthetic polymers, nanotechnology and biomaterials which offered research a chance to deliver directly and selectively. The conventional drug delivery systems, though effective in a good number of instances, are usually limited by poor bioavailability, fast clearance, systemic toxicity and lack of specificity. Indicatively, oral medications tend to experience a large amount of first-pass liver metabolism, which lowers their effectiveness, whereas parenteral drugs can cause changes in plasma drug levels and side effects [4–7].

In the case of a drug delivery system, the primary aim is to deliver the active compound to the target site within the body in a safe, effective and controlled way. That are able to circumvent biological barriers, which include gastrointestinal tract, blood-brain barrier (BBB), and cell membranes. Controlled drug delivery systems (CDDS) have been made to discharge the drug on a controlled rate, to keep therapeutic concentrations during long intervals with minimal toxicity. Some examples are sustained-release pills, osmotic pumps, transdermal patches and implantable devices. The entry of nanotechnology in the recent years has significantly increased the potential of the drug delivery systems [8–10]. Liposomes, polymeric nanoparticles, micelles, dendrimers and solid lipid nanoparticles (SLNs) belong to the category of nanoparticles as nanocarriers which have been given a lot of attention due to their properties of enhancing the solubility, stability and bioavailability of drugs. Such systems have the ability to host hydrophobic or hydrophilic drugs, shield them against degradation, and accurately delivery of such drugs to particular tissues or cells, either passively or actively, using targeting systems. Passive targeting involves taking advantage of physiological events like the enhanced permeability and retention (EPR) effect in tumor cells, whereas active targeting relies on the use of ligands, antibodies, or peptides which connect to special receptors on target cells [11,12].

The creation of the stimuli-responsive or smart delivery systems is another step in the history of drugs delivery. These systems are able to discharge drugs based on definite physiological or external conditions like pH level, temperature changes, enzymes, light or magnetic fields. These innovations are especially important in cancer treatment, where local drug delivery reduces the toxicity to the system and enhances treatment results. As an example, acid-specific nanoparticles can be used to deliver chemotherapeutic medications to the tumor microenvironment (and not to the normal tissues) because of the acidic pH. The biodegradable polymers including polylactic acid (PLA), polyglycolic acid (PGA) and their copolymers have significantly contributed to the development of the contemporary drug delivery systems. These substances are biocompatible, naturally degradable in the human body, and do not have to be removed through surgery, as drugs have been released. When combined with biodegradable material and nanotechnology, implantable and injectable drug carriers have been developed with the capability of sustained release of weeks or months to enhance patient adherence and decrease the number of administration times [13–15].

Importance of Innovative Drug Delivery

Drug delivery systems innovation is part and parcel of dealing with constraints of traditional therapies and supporting the rising concerns of personalized medicine. The conventional drug formulations are associated with poor pharmacokinetic characteristics, low patient adherence, and unwanted side effects, undermining the therapeutic activity. Innovative drug delivery systems are supposed to surmount these challenges by providing precision, control and enhanced safety in drug delivery. Targeted delivery is one of the best benefits of innovative drug delivery systems. Targeted delivery decreases drug exposure to healthy tissues and minimizes systemic toxicity by directing its therapeutic agents to diseased tissues or cells which is achieved by directing therapeutic agents to the site of disease [16–18]. This becomes of utmost importance during the treatment of cancer since in most cases, when using conventional chemotherapy the drug destroys the cancer as well as normal cells resulting in severe side effects. Using nanoparticle-based carriers and ligand-mediated systems, it has become possible to specifically target the tumor cells and avoid normal tissues so that the index of therapeutic of the treatment can be enhanced.

The other important advantage of innovative drug delivery is the controlled and sustained release. Controlled-release systems are able to provide constant plasma concentrations with a long duration of time as opposed to using a drug in multiple doses and over the course of the day. This does not only increase the efficacy of the therapy but increases the compliance of the patient with the therapy which is essential in chronic illness like diabetes, high blood pressure and schizophrenia. As an example, injectable antipsychotic medications in long-acting

formulations have drastically enhanced the compliance of patients who cannot manage to take medications daily. Other innovative systems of drug delivery also result in enhanced bioavailability of poorly soluble or unstable drugs in the gastrointestinal tract. Numerous current therapeutic molecules, particularly those based upon biotechnology are susceptible to enzyme destruction or lack of permeability through biological membranes. Complex structures such as liposomes, polymeric nanoparticles and nanoemulsions are used to protect these molecules and to carry them to their specific pathways of absorption [19–21].

Moreover, innovations in drug delivery have seen the use of non-invasive drug delivery methods in the administration of drugs which were formerly administered as injections. Parenteral routes are substituted by more convenient routes such as transdermal patches, nasal sprays, pulmonary inhalers, and oral thin films. These systems have not only improved the comfort of the patients but also increased the range of treatment of different medical conditions. As an example, insulin administration via the transdermal or inhalation route has been investigated to substitute the conventional subcutaneous injection and has also enhanced the quality of life of diabetic patients. Innovative drug delivery systems in addition to enhancing efficacy and patient compliance are important in helping in the reduction of health care costs. Sustained-release and targeted delivery will decrease the number of visits to the hospital and frequent dosage schedule, and thus result in a reduction in the overall cost of treatment. This is also because the ability to administer drugs in a more efficient and lower dose will decrease wastage and possible adverse effects, providing cost-effective healthcare solutions [22–25].

The development of drug delivery has also improved the emerging technologies like gene therapy, RNA delivery, and immunotherapy. The protective carriers that protect fragile genetic materials such as mRNA or siRNA and help achieve successful delivery of these materials are necessary. One example of how novel drug delivery vehicles can transform the healthcare system of the world is the use of lipid nanoparticles (LNPs) in mRNA vaccines, including those designed to combat COVID-19. In addition, new methods of drug delivery are opening up new horizons of personalized medicine in which therapies are customized to the unique genetic, physiological, and environmental needs of the individual patient. Biosensors or responsive materials in smart drug delivery platforms can regulate drug delivery in real-time changes in physiological conditions. This method guarantees maximum treatment and reduction of side effects [26].

Conventional vs. Novel Drug Delivery Systems

Over the past several decades, drug delivery methods have radically changed because of the necessity to enhance the effectiveness of treatment, minimise the side effects, and the patient adherence. The pharmaceutical therapy was based on the use of conventional drug delivery methods which include tablets, capsules, syrup, injections, and topical creams. Nonetheless, there usually exist considerable drawbacks to these systems associated with drug stability, absorption, targeting and dosing frequency. As a solution to these problems, scientists have come up with new drug delivery systems (NDDS), which involves use of modern materials, nanotechnology and new mechanisms to maximize the release, bioavailability as well as therapeutic outcome of drugs. This section presents weaknesses of the traditional drug delivery systems and explains why the technologies should be advanced and be the basis of the modern drug delivery science [27–30].

Limitations of Conventional Drug Delivery Systems

The conventional drug delivery systems are meant mainly to carry a drug to the systemic circulation by some of the most common routes of administration like oral, parenteral or topical administration. Although these methods are well established, they are not usually very precise in the release of drugs or in targeting specific sites in the body. This may cause inefficiencies and unwanted side effects that jeopardize the outcomes of treatment. Overall limitations of traditional systems are low bioavailability, systemic side effects, inability to target, and requirement to be frequently administered.

1. Poor Bioavailability

Bioavailability is the proportion of a drug that is administered that gets into the systemic circulation and is made available to produce its pharmacological action. There are a large number of drugs that have poor solubility, low permeability, or high first-pass metabolism which have limited bioavailability when administered by traditional routes [31].

A. Challenges in Oral Drug Delivery

The most preferred route is the oral administration as it is convenient and well taken by the patient. Nevertheless, it has a lot of challenges that inhibit the absorption of drugs. Orally administered drugs have to cross different physiological barriers to enter the bloodstream, such as the acidic stomach, enzyme destruction in the gastrointestinal system, and hepatic metabolism (first-pass effect). As an illustration, insulin and other therapeutic proteins like peptides are digested by enzymes and therefore cannot be absorbed across the intestine. They therefore do not get to the therapeutic levels of the systemic circulation upon oral administration. Also,

the dissolution of drugs is a significant factor in their bioavailability. Drugs that are not soluble in water can only dissolve poorly in the gastrointestinal fluids limiting their absorption. Examples would include some of the modern drugs that are produced using sophisticated chemical methods and which are lipophilic, and thus, non-soluble in water, resulting in unpredictable pharmacokinetic patterns. This is further complicated by the variable gastrointestinal transit time, variation in pH and the presence of food that further complicate drug absorption and consequently, the attainment of consistent therapeutic effects [32–35].

Table 1: Conventional and Novel Drug Delivery Systems

Parameter	Conventional Drug Delivery Systems	Novel Drug Delivery Systems (NDDS)
Bioavailability	Often poor due to enzymatic degradation, poor solubility, and first-pass metabolism	Enhanced through nanocarriers, liposomes, and controlled-release systems improving solubility and absorption
Systemic Side Effects	High, as drugs distribute non-specifically throughout the body	Reduced, due to targeted and site-specific delivery minimizing exposure to healthy tissues
Targeting Capability	Lacks specificity; drugs affect both diseased and healthy tissues	High specificity through active (ligand-mediated) and passive (EPR effect) targeting mechanisms
Drug Release Control	Immediate or uncontrolled release leading to fluctuating plasma levels	Controlled or sustained release maintaining steady therapeutic levels
Patient Compliance	Low due to frequent dosing and side effects	Improved with long-acting, non-invasive, and patient-friendly formulations (e.g., patches, implants)
Technological Approach	Simple formulations like tablets, capsules, injections	Advanced systems utilizing nanotechnology, polymers, biomaterials, and 3D printing
Therapeutic Efficacy	Variable and often limited by pharmacokinetic constraints	Optimized through precise delivery, enhanced stability, and smart release mechanisms

B. Challenges in Parenteral Drug Delivery

Parenteral routes (e.g., intravenous, intramuscular and subcutaneous) avoid the gastrointestinal tract offering fast and full bioavailability. They, however, have their own disadvantages. In cases where injectable formulations are used, numerous doses to sustain therapeutic concentrations may be inconvenient and painful to the patient and may result in low compliance to chronic treatment. In addition, the high rate of drug elimination of drugs in the circulation may lead to the occurrence of intermittent plasma levels, which may lead to toxicity or treatment failure [36–38].

C. Stability and Degradation Issues

The other major limitation of standard systems is that the drug may become unstable when stored or on administration. Peptides, proteins, and nucleic acids, among other bioactive molecules, are susceptible to degradation by temperature, pH, and enzymes. The normal formulations do not have the capacity to stop the degradation of these molecules before they reach their target, which diminishes their therapeutic potential to a considerable extent [39,40].

2. Systemic Side Effects

One of the most urgent issues in the traditional drug delivery is systemic side effects. By not using targeted routes of administration, a drug that is administered at non-targeted routes spreads all over the body instead of just the area of action. The result of this extensive distribution may be harm to healthful tissues and organs [41].

A. Lack of Selectivity in Drug Distribution

The traditional drug delivery systems are unable to tell diseased and healthy tissues apart. An example is the case of chemotherapy where anticancer drugs are spread throughout the body, killing malignant and normal quickly dividing cells with serious side effects of losing hair, nausea and bone marrow transplantation. This nondiscriminatory measure restricts the dose limit that can be taken, which reduces the treatment effect on tumors. On the same note, orally administered non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of pain may destroy the gastric mucosa resulting in ulcers and gastrointestinal bleeding. It takes place since the drug interacts alike with inflamed and noninflamed tissues [42].

B. Uncontrolled Drug Release

The customary formulations usually cause a quick release and absorption of the drugs which causes the plasma concentrations to increase soon after administration only to fall quickly below therapeutic levels. These variations are capable of causing inefficiency as well as toxicity. As an example, when

using antibiotics, sub-therapeutic concentration of the drug could lead to microbial resistance, and overdose can result in the toxicity of some essential organs like the liver and kidneys [43,44].

C. Immunogenicity and Allergic Reactions

Some traditional medicines, especially the ones that are based on proteins, may cause the immune response or allergy. This is a condition that arises when the body perceives the foreign substance as harmful. These immune responses can be severe without regulated or directed delivery and this further restricts the safety and usefulness of most drugs [45–47].

3. Lack of Targeting Capability

One of the most basic disadvantages of conventional delivery systems is the inability to target a drug specifically to where it will be used. Drugs that are administered via common pathways are disseminated via the systemic circulation, targeting as well as non-target tissues. This non-targeting decreases the effectiveness of the therapeutic action and it exposes to side effects [48,49].

A. Biological Barriers

The human body has a number of physiological barriers that do not allow effective targeting of drugs. These are blood-brain barrier (BBB), blood-retinal barrier and mucosal barriers. An example is that the BBB is very selective and it blocks the entry of most drugs to the central nervous system; therefore, it is very difficult to cure brain disorders like Alzheimer disease or glioblastoma by using the conventional method of delivery.

B. Poor Tumor Targeting

The classical mode of drug delivery does not reach enough drug concentration in the tumor site because of the complicated tumor microenvironment and low vascularization in certain regions in cancer treatment. Consequently, a large fraction of the drug gets lost in the systemic circulation, which causes poor therapeutic effects and high toxicity of healthy tissues.

C. Inability to Respond to Physiological Changes

Conventional systems deliver drugs at a constant rate, irrespective of the dynamics of the physiology of the body. They are not able to adjust to change that can occur in pH, temperature, and enzyme concentration during a disease progression or treatment. This restricts their offering of individualized or on-call treatment [50–55].

4. Frequent Dosing and Patient Non-Compliance

Most traditional medicines have to be taken several times a day to take care of the therapeutic level which sometimes can be cumbersome to the patient who has chronic illness. Regular dosing predisposes the chances of missed dosage, resulting to poor compliance and treatment failure. An example is that hypertensive patients or diabetic patients will have a problem with taking numerous drugs many times per day. Moreover, injections and infusions are frequently accompanied by pain and discomfort which prevent long-term compliance [56].

5. Inconsistent Therapeutic Outcomes

Traditional methods of drug delivery usually result in inconsistency in drug absorption and metabolism because of individual factors affecting patients, which include age, gender, genetics, diet, and disease condition. Such inter-individual variability may lead to unpredictable therapeutic effects and it is difficult to optimize a dose. Also, narrow therapeutic index drugs need accurate dosage, which is hard to obtain by conventional preparations.

Need for Advanced Drug Delivery Technologies

The shortcomings of the traditional drug delivery systems have prompted the need to develop new drug delivery systems (NDDS) that could address therapeutic efficacy, safety and patient compliance. These high-tech technologies are meant to administer the drugs at the right location, at the right time, and the right quantity, abating the failure of the old formulations.

A. Enhanced Bioavailability and Controlled Release

New forms of drug delivery systems have been developed, including nanoparticles, liposomes and nanoemulsions to enhance the solubility and stability of poorly soluble drugs. The drugs are secluded, shielded, and improved to be absorbed between biological membranes by these carriers. The controlled-release formulations, including transdermal patches, osmotic Pumps and polymeric implants, deliver the same plasma concentration, without peaks and troughs of traditional dosing.

B. Targeted and Site-Specific Delivery

The ability to target a particular tissue or cell is one of the greatest benefits of NDDS. Passive targeting involves the exploitation of the physiological processes (including the enhanced permeability and retention, EPR, effect) in tumors to deliver drugs to the disease sites. Active targeting is the functionalization of the drug carriers using ligand, antibody or peptide that binds on a receptor denoted on the target cells. As an illustration, liposomes that have been conjugated with anticancer drugs and monoclonal antibodies can be used to target tumor cells systemically with minimum exposure.

C. Reduction of Systemic Toxicity

NDDS maximize the target site drug action by minimizing systemic exposure and adverse effects. It comes in quite handy in the field of oncology, where localized delivery of the drugs into the tumors spares the healthy tissues. Likewise, inhalable and intranasal delivery systems provide the ability to deliver drugs to lungs or the brain bypassing the systemic circulation and minimizing toxicity.

D. Overcoming Biological Barriers

Drug delivery technologies have been developed to overcome physiological barriers that reduce the effectiveness of drugs. Nanocarriers have the potential of bypassing the blood-brain barrier creating new opportunities in the treatment of the diseases of the nervous system. Likewise, the mucoadhesive and transdermal systems increase the absorption across the skin and mucosal layer and make drug delivery more efficient.

E. Personalized and Smart Drug Delivery

Smart drug delivery systems have developed as a result of nanotechnology combined with both biotechnology and materials science and can react to environmental or physiological conditions (e.g. pH, temperature, enzyme concentration, etc.). On-demand drug delivery can be controlled by these systems giving specific control of dosing and timing. Moreover, the progress in the field of biosensors and wearable technologies allows real-time checks of the therapeutic levels, and this leads to personalized medicine.

F. Improved Patient Compliance

New design like long-acting injectables, implantable depots and transdermal patches lower the number of administration intervals which improves patient compliance. Other non-invasive methods such as inhalation, buccal, and transdermal routes are also more comfortable and convenient to the patient [57–60].

Recent Advances in Drug Delivery Systems

The past decades experienced unprecedented changes in the drug delivery system, which was motivated by the need to have a precision medicine, improved bioavailability, and patient-centered therapy. Traditionally prepared drug formulations despite their efficacy in most instances are characterized with serious shortcomings in the form of systemic toxicity, lack of solubility and unselective distribution. Researchers have created novel platforms of drug delivery to counter these shortcomings; these novel platforms combine emerging technologies, such as nanotechnology, smart materials, targeted carriers, and new fabrication methods such as 3D printing. The latest developments are expected not only to enhance the therapeutic efficacy, but also to guarantee safety, convenience and personalization of drug therapy. The subsequent sections dwell on the main developments in the current drug delivery systems, including nanotechnology-based carriers, stimuli-responsive delivery systems, targeted delivery systems, transdermal developments, and 3D-printed customized formulations [61–63].

1. Nanotechnology-Based Delivery Systems

The science of nanotechnology has completely changed the nature of pharmaceutical science with the ability to handle materials accurately by manipulating them at a molecular and nanometer level (100 nm 1). Nanocarriers have the ability of encapsulating hydrophobic drug and hydrophilic drugs, shield them against degradation and deliver them effectively to the targeted regions of the body. Nanoparticles have high drug-loading capacity due to high surface area-volume ratio, and they can be modified to be targeted by diverse surface modifications. Some of the most notable nanocarriers include liposomes, polymeric nanoparticles and solid lipid nanoparticles (SLNs) [64–66].

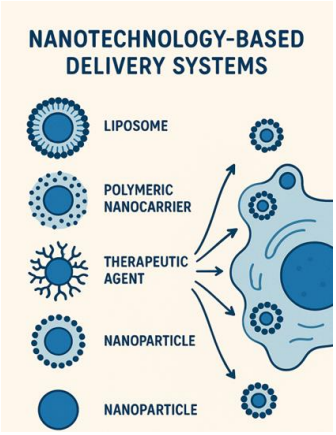

Figure 1: Nanotechnology-Based Delivery Systems

Liposomes

Liposomes are spherical bubbles that are made of a single or a multiplicity of phospholipid bilayers and an aqueous core. This structure allows them to entrap hydrophilic drugs in the core and lipophilic drugs in the lipid bi-layer. Liposomes resemble the natural cell membranes and therefore are biocompatible and biodegradable [67, 68].

Polymeric Nanoparticles

Polymeric nanoparticles are biodegradable polymeric colloidal particles, including polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), and their copolymers (PLGA). Such systems may be able to imprison drugs in their polymeric framework

(nanospheres) or at a core in the midst of a polymer shell (nanocapsules) [69].

Solid Lipid Nanoparticles (SLNs)

SLNs are a hybrid system, which incorporates the benefits of liposomes and polymeric nanoparticles. They are made of solid lipid center stabilized by surfactants and have the capacity to entrap hydrophilic and lipophilic drugs. Examples of poorly water-soluble drugs that can be delivered using SLNs include anticancer agents, peptide, and anti-inflammatory drugs. Topical formulations have also been tested on them to increase their skin penetration [70].

Stimuli-Responsive Drug Delivery Systems

Smart drug delivery systems, or stimuli-responsive, can be seen as an important development in the field of controlled drug delivery. They can react to a certain internal or external stimulus, i.e., pH, temperature, enzymes, magnetic fields, etc. to release the drug at the right place and right time. The technique guarantees great treatment efficacy and reduction of systemic toxicity.

pH-Sensitive Systems

pH-sensitive delivery systems of drugs are based on the variation of pH in different body parts or healthy and diseased tissues. As an example, tumor microenvironment is a bit acidic (pH 6.5-6.8) as opposed to normal tissues (pH 7.4). On the same note, the value of pH inside the cells is even lower (pH 4.564.5) in endosomes and lysosomes. Carriers that are designed using pH-sensitive polymers e.g. poly (methacrylic acid) and chitosan derivatives are created to be stable at physiological pH but release their cargo in acidic conditions. This concept has proven useful in cancer treatment and oral drug delivery whereby carriers discharge drugs in the stomach or colon [71].

Temperature-Responsive Carriers

Drug delivery systems are temperature-sensitive, and the release is triggered by alterations in local or system temperatures. Poly(N-isopropylacrylamide) (PNIPAAm) is a polymer with a sharp phase change that occurs at certain temperatures referred to as the lower critical solution temperature (LCST). When the solution is below LCST, the polymer is soluble, whereas when it is above LCST, it becomes hydrophobic, and collapses releasing the drug.

Enzyme-Triggered Systems

Enzyme-responsive drug delivery systems are based on enzymes which are overexpressed in a particular disease (ex: cancer, inflammation, infections) to release the drug. The carrier contains enzyme-sensitive linkages which are broken after interacting with the target enzyme.

Tumor therapy: Matrix metalloproteinase (MMPs) expressed in tumors have the ability to cleave peptide linkers which release the drug at the site of the tumor.

Inflammatory disorders: Enzyme sensitive systems such as elastase or lipase come in handy when treating arthritis or colitis.

Infection control: Bacterial enzyme-based systems can discharge antibiotics selectively at the sites of infection [72,73].

3. Targeted Drug Delivery

Targeted drug delivery systems is to deliver therapeutic agents to diseased cells or tissues with a high degree of efficacy and a reduced level of adverse effects. Their strategies of targeting are ligand-receptor interactions, antibody-drug conjugates and cell-specific carriers.

Ligand–Receptor Interactions

Ligand-based targeting is the process of attaching molecules to the surface of drug carriers that have the capability of binding to receptors that are over expressed on the target cells. Usual ligands are folic acid, transferrin, peptides, aptamers, and carbohydrates.

Antibody–Drug Conjugates (ADCs)

ADCs are a fusion of monoclonal antibody specificity targeting and the cytotoxic agent potency. The antibody component attaches itself to certain antigens present on the cancer cells and once it has been internalized, the drug is discharged intracellularly.

Cell-Specific Carriers

Cell-specific carriers are modified to take advantage of cellular markers that are specific to a tissue or a cell type. Such carriers may be made of lipids, polymers or biomimetic materials (exosomes or cell membranes).

Neural targeting: Nanoparticles conjugated to transferrin or lactoferrin are able to permeate the blood-brain barrier.

Cardiac delivery: Post-infarction repair Cardiomyocyte-targeted Peptide-functionalized carriers are used to repair the heart.

Immune modulation: Vehicles that target macrophage or dendritic cells to administer a vaccine or treat an autoimmune disease.

4. Transdermal and Microneedle Delivery Systems

The use of transdermal drug delivery has been popular because it is non-invasive, first-pass metabolism

avoidance, and may result in sustained release. Innovations in the recent past like microneedle patches have contributed greatly to increasing drug permeability through the skin.

Passive vs. Active Transdermal Systems

Passive systems are based on the diffusion process through the stratum corneum of the skin, which is appropriate to small, lipophilic, drugs. Their application to large or hydrophilic molecules is however restricted by the barrier properties of the skin. Physical or chemical modalities used in active transdermal systems include iontophoresis, sonophoresis, or microneedles to increase the permeability of the skin. Through these systems it is possible to deliver peptides, vaccines, and other poorly absorbed macromolecules.

Table 2: Passive vs. Active Transdermal Drug Delivery Systems

Feature	Passive Transdermal Systems	Active Transdermal Systems
Mechanism of Drug Transport	Relies on passive diffusion through the stratum corneum	Uses external energy or physical enhancement techniques to facilitate drug permeation
Driving Force	Concentration gradient	Electrical, mechanical, or thermal energy (e.g., iontophoresis, sonophoresis, microneedles)
Suitable Drug Type	Small, lipophilic, and potent drugs	Large, hydrophilic molecules, peptides, and proteins
Control Over Drug Release	Limited control; dependent on skin permeability	Enhanced control through modulation of applied energy or device parameters
Drug Absorption Rate	Slow and variable	Faster and more consistent
Examples	Nicotine patch, estradiol patch	Iontophoretic fentanyl patch, microneedle insulin patch
Advantages	Simple design, non-invasive, cost-effective	Allows delivery of macromolecules, improved penetration efficiency
Limitations	Limited to certain drugs; low permeability	Requires specialized equipment and higher cost

Microneedle Patches

Microneedles are microscopic extensions (50-900 μm) which penetrate painlessly stratum corneum forming temporary microchannels of drug diffusion. They may be solid, coated, dissolving or hollow, depending on the drug and use. Microneedle patches have been successfully implemented in influenza and COVID-19 vaccines, insulin delivery in diabetes and hormone therapy. They have a potential to replace injections because they are easy to use and versatile [74].

3D Printed Drug Delivery Systems

The advent of the 3D printing technology has unleashed new possibilities in individualized medicine. The 3D printing technology can be used to obtain individual patient-based drug delivery systems by precisely controlling the geometry, composition, and distribution of a dosage form [75].

Personalized Dosage Forms

3D printing enables drugs dosage, release profiles and combinations of various drugs within one tablet (polypills), to be customized. The personalization is especially important in the treatment of chronic illnesses, pediatric dose treatment and in the care of the elderly as the dosage requirement differs widely.

Layer-by-Layer Drug Release Design

Multilayered structures allowing regulated or timed drug delivery can be produced by advanced methods of 3D printing. The various layers may include a drug or polymer with distinct dissolution properties, to be able to control the release time accurately [76].

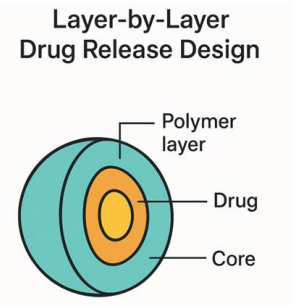

Figure 2: Layer-by-Layer Drug Release Design

Applications of Advanced Drug Delivery Systems

This is because with the ever-changing nature of the developed drug delivery system (ADDS) therapeutic approaches in many medical disciplines have changed. Some of the newest technologies being used by these systems are nanocarriers, controlled-release, targeted delivery and biomaterials to enhance the effectiveness, safety, and accuracy of treatment. The uses of their applications include oncology, neurology, endocrinology, and immunology. In this section, the most important clinical uses of ADDIS in cancer therapy, central nervous system (CNS) disorders, diabetes and hormone regulation, and in vaccination and gene therapy will be discussed, and how the innovations are transforming the handling of different diseases and patient outcomes.

1. Cancer Therapy

Cancer is also among the major causes of mortality in the world, and conventional chemotherapy can be characterized by inadequate selectivity, systemic toxicity and multidrug resistance. These constraints have been overcome by the use of sophisticated drug delivery systems that allow the use of targeted, controlled and combination-based therapies that allow an increase in the amount of drug localization in tumor-affected areas with a decrease in the destruction of normal tissue.

Nanocarrier-Based Drug Delivery in Cancer

Some of the nanocarriers that have been extensively utilized in the oncology field include liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles. They take advantage of the enhanced permeability and retention (EPR) effect, which enables tumor tissues to accumulate preferentially the nanoparticles because the vasculature is leaky. Such as Doxil (liposomal doxorubicin) and DaunoXome, (liposomal daunorubicin) liposomal doxorubicin and daunorubicin, respectively, have demonstrated increased therapeutic index (reduced cardiotoxicity) and increased concentration of the drug in the tumor.

Active Targeting Approaches

Along with passive accumulation, active targeting makes use of such ligands like antibodies, peptides, and folic acid to connect with cellular receptors of tumor cells in particular. This increases the uptake of the drug by receptor endocytosis. Antibody-drug conjugates (ADCs) are another important development, including Trastuzumab emtansine (Kadcyla 1) which is a cytotoxin targeting the cancer cells of the HER2/neu-positive and normal tissues sparing.

Stimuli-Responsive Cancer Therapy

On-demand release of drugs is achieved by smart drug delivery systems responsive to internal or external stimuli, such as pH, redox potential or enzymes or heat, light or magnetic fields respectively. As an example, pH-sensitive nanoparticles can be used to deliver their cargo into the acidic tumor microenvironment, enhancing therapeutic specificity. Thermosensitive liposomes are a combination of localized hyperthermia and drugs that are released upon heating of the tumor areas. New designs involve the co-delivery of chemotherapeutic agents, siRNA or gene therapies to circumvent drug resistance and silence oncogenes. These versatile systems are able to control tumor biology on the genetic level and pharmacologically assault the cancer cells, enhancing the overall treatment results.

2. Central Nervous System (CNS) Disorders

The neurological diseases that require treatment include Alzheimer disease, Parkinson disease, epilepsy, and brain tumors, and it is a very challenging task because of the blood-brain barrier (BBB) an exclusive membrane that does not allow most drugs to penetrate into the brain. Developments have been made on advanced drug delivery systems that circumvent or penetrate the BBB so as to deliver therapeutics to the CNS.

Nanoparticle-Mediated BBB Transport

The development of nanocarriers, which then cross the BBB, includes polymeric nanoparticles, liposomes, and solid lipid nanoparticles. Ligand modification of the surface, like transferrin, lactoferrin or apolipoproteins, helps the surface to bind to the endothelial receptors, increasing uptake by the brain. Examples of this include the use of PLGA nanoparticles in transferrin-functionalized nanoparticles to deliver dopamine in cases of Parkinson diseases and neuroprotective therapy in case of the Alzheimer disease.

Intranasal Drug Delivery

The intranasal route is a non-invasive route of administering drugs to the brain via the olfactory and trigeminal nerve pathways, through the endogenous route bypassing the systemic circulation and the BBB. Intranasal delivery of neuroactive drugs like insulin (to enhance cognitive in Alzheimer) and levodopa (to treat Parkinson) have been delivered by nanostructured lipid carriers and mucoadhesive polymeric nanoparticles.

Hydrogel and Implantable Systems

The implants are hydrogel-based with effects of a localized sustained release of drugs in the brain especially when the tumors have been surgically removed. One such method is the FDA-approved Gliadel, a wafer of polymer that releases carmustine, which is an

implantable disc, to be used in the brain, but with minimal exposure at the systemic level.

Gene and RNA-Based Neurotherapeutics

There is also the development of advanced carriers such as lipid nanoparticles (LNPs) to deliver RNA-based therapies against neurodegenerative diseases. These nanocarriers shield RNA molecules against degradation and improve cellular absorption, and it is a new direction in the treatment of diseases such as Huntington and ALS.

3. Diabetes and Hormonal Treatments

The chronic endocrine diseases like diabetes would need the sustained or intermittent use of hormones such as insulin, thus becoming very vulnerable to compliance, stability, and efficiency of delivery. Drug delivery systems are advanced in order to make the drug delivery system simpler, less often, and attain physiological release profiles.

Smart Insulin Delivery Systems

The normal insulin injections do not usually replicate the glucose-regulated insulin secretion. Nanoparticles and hydrogels smart systems such as glucose-responsive nanoparticles and hydrogels are in a position to detect the level of glucose in the blood and can release insulin to the body. They involve glucose oxidase or phenylboronic acid moieties as the sensing element to activate the release of insulin when glucose increases, which has the effect of an artificial pancreas.

Transdermal and Microneedle Delivery

A micro level needle patch has also become a minimally invasive method of delivering insulin. The nanoparticles or polymeric microneedles containing insulin dissolve as soon as they are administered and enter the skin through these painless injections, rapid absorption of the nanoparticles or polymeric nanoparticles is achieved. These patches stabilize insulin levels and remove the necessity to have frequent injections.

Oral Insulin Nanocarriers

The oral insulin development is still a problem because of enzyme degradation in the gastrointestinal tract. But still, lipid-based nanoparticles, chitosan-coated system, and mucoadhesive nanocarriers are under development to ensure that insulin is not digested and to improve absorption at the intestinal mucosa.

Hormone Replacement and Controlled Delivery

Hormone replacement therapy (HRT) has also undergone advanced drug delivery. The use of transdermal patches, vaginal rings and biodegradable implants offers controlled delivery of hormones such as estrogen, progesterone and testosterone over a long-term period. This provides stable hormone levels, reduces side effects and enhances patient adherence.

4. Vaccination and Gene Therapy

The most promising fields of advanced delivery systems have also demonstrated great success in vaccination and gene therapy, with the mRNA vaccines being the most rapid developed ones and gaining significant focus due to the COVID-19 pandemic. The success of these therapies is highly dependent on the capability of the delivery vehicle to preserve sensitive biological molecules and deliver them to specific cells.

Nanoparticle-Based Vaccine Delivery

The conventional vaccines typically need adjuvant to stimulate immunity and repeated doses in order to sustain immunity. Nanoparticles serve as vaccine carriers (liposomes, polymeric nanoparticles, and lipid nanoparticles (LNPs) protect the antigens against degradation, enhance antigens uptake in antigen-presenting cells (APCs), and ensure long-term release of antigens to induce sustained immunity. The transformation of nanotechnology in vaccination was demonstrated with Pfizer-BioNTech and Moderna mRNA, both of which are developed using LNPs.

DNA and RNA Vaccine Delivery

The development of sophisticated systems allows the transport of genetic material with viral or tumor antigens. These vaccines which are based on genes induce the endogenous generation of antigens in host cells, which lead to potent cellular and humoral immunity. LNPs, cationic polymers and dendrimers have been demonstrated to be effective in the efficacious delivery of mRNA and plasmid DNA.

Viral Vector and Non-Viral Gene Delivery

Gene therapy is used to treat genetic diseases by suppression or replacing defective genes with functional ones. Popular viral vectors are adeno-associated viruses (AAVs) which are used in the treatment of diseases such as spinal muscular atrophy. Alternatives to these viral systems include the use of non-viral systems, including polymeric nanoparticles, exosomes, and lipid-based carriers, which are safer and less immunogenic and can be much easier to scale up.

Targeted Immunotherapy

Nanoparticles have the ability to deliver immune modulators (e.g., cytokines or checkpoint inhibitors) to immune cells in order to augment immune response to cancerous or infectious diseases. This is a more focused

mode of action lowering the systemic toxicity and increasing the therapeutic efficacy [77].

CONCLUSION

The advancement in drug delivery systems has transformed the modern therapeutics with the incorporation of the concepts of nanotechnology, smart biomaterials, and personalized medicine. These inventions have brought a lot of improvements to bioavailability, precision of targeting and patient compliance with minimum side effects. New delivery platforms guarantee safer, more efficient and patient specific treatment in cancer therapy and neurological disorders, the management of diabetes, and gene-based vaccination. In the end, such technologies will provide a paradigm shift towards smarter, more controlled, and personalized healthcare systems to achieve better therapeutic outcomes in the world.

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