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The Evolution of Drug Delivery Systems: Historical Advances and Future Directions

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ABSTRACT

Drug delivery methods have evolved to improve therapeutic outcomes, patient compliance, and therapy outcomes. This review examines the historical progression of drug delivery strategies, current innovations, and emerging trends shaping the future of therapeutic approaches. Traditional methods of giving medications, like oral and injection routes, had many problems, such as low bioavailability and systemic side effects. This review looks at how drug delivery systems have changed throughout several drug development eras. It focuses on new developments such as nanotechnology-based delivery, biologics, and the creation of smart drug delivery systems. This review highlights breakthroughs in controlled-release systems, nanocarriers, transdermal patches, and implantable drug-delivery devices, comparing both conventional and modern strategies. Further, advances in microencapsulation technology, gene therapy delivery strategies, and AI-assisted drug formulation are examined in the context of precision and efficacy. These innovations reflect a paradigm shift toward precision medicine with personalized drug delivery strategies minimizing side effects while maximizing therapeutic outcomes. Importantly, nanomedicine and biological therapies have successfully addressed critical challenges of drug stability, bioavailability, and drug delivery mechanisms for controlled release devices.

Keywords: Smart drug delivery, Personalized medicine, Drug delivery system

INTRODUCTION

Drug administration has evolved significantly, improving treatment efficacy and enhancing patient compliance. The administration of medication in the past mainly entailed the intake of tablets and the administration of injection methods that, while effective, often had drawbacks such as poor absorption and unwanted side effects. Advancements in technology and scientific progress have allowed scientists to design more efficient ways of medication administration that enable the correct delivery within the body and prevent wasteful exposure. Despite the growing popularity of delivery platforms, there remains a lack of understanding of the real-world challenges, regulatory hurdles, and access issues surrounding these technologies. This review addresses these gaps by discussing key innovations and forecasting future directions.

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I. Understanding Drug Delivery Systems

Drug delivery systems include formulations or devices intended to deliver therapeutic agents to their intended site of action in the body, with optimal timing, suitable dosage, and minimal side effects. They use technologies that span nanoparticles, liposomes, and implant device technologies that maximize the medication and enable regulated drug discharge based on the needs of the patient. The evolution of the methods of drug delivery marks a giant leap in the field of medical sciences that has helped resolve issues that conventional drug-making methods struggled with. The findings reveal that the cutting-edge systems of drug delivery are particularly useful in areas with limited availability of vital medications [1]. Beyond improving patient outcomes, innovations in drug delivery also drive the development of the drug industry toward further horizons [2]. They are reshaping the future of medication in profound ways with each technology that advances.

A. The Importance of Drug Delivery in Modern Medicine

Drug delivery systems have undergone continuous evolution, shaped by innovations that responded to the limitations of traditional routes like oral and injectable methods. One of the key considerations includes the use of the Biopharmaceutics Classification System (BCS), categorizing medication based on solubility and the ability to pass through cellular layers. One such example includes the application of the use of Class III medication that dissolves quickly but fails to enter cellular layers and therefore yields minimal bioavailability. This calls for the application of superior drug delivery methods to make such medications effectively absorbed and capable of bringing the required therapeutic results [3]. The transition toward outpatient treatment also underscores the necessity of optimized medication delivery that ensures the patient's safety with the provision of good-quality treatment beyond the general hospital environment {4}. To comprehensively understand the significance of drug delivery systems in modern times, one has to explore their history and evolution along with key breakthroughs that have shaped their development.

B. The Historical Evolution of Drug Delivery Mechanisms

The progress in the evolution of drug delivery has progressed from primitive methods, such as injectable and oral delivery systems, to sophisticated systems characterized by targeted and controlled release. Such advancements have greatly enhanced therapeutic outcomes through increased bioavailability, reduced side effects, and optimized treatment regimens.

1. Preliminary Strategies for Pharmaceutical Administration

Historically, drug delivery was mostly via oral and topical routes, being convenient but also presenting issues like inconsistent absorption and systemic side effects. With time, injectable forms were developed that provided a faster onset of action; however, most required supervision by healthcare professionals.

2. Notable Pharmaceutical Delivery Breakthroughs (as shown in Table 1)

A variety of noteworthy milestones define drug delivery progress:

- 1950s – Delayed-release formulations: With the beginning of controlled-release drug formulation, drug action was prolonged, and drug frequency was reduced.
- During the 1960s, liposomes and niosomes greatly increased drug bioavailability and drug solubility, thus establishing foundational principles for modern nanocarriers.
- 1980s – Transdermal Patches: One of the breakthroughs in non-invasive drug delivery, enabling extended release via the skin.
- During the 1990s, PEGylation—drug modification with polyethylene glycol improved pharmacokinetic profiles by reducing immune clearance and extending drug half-life.
- 2000s – Nanotechnology-based delivery systems: Nanoparticle formation enabled precise delivery and targeting to specific locations.
- 2010s – Smart Drug Delivery Systems: Bio-responsive systems delivering pharmaceutical agents in response to biological stimuli to enhance the efficacy of precision medicine.
- During the 2020s, innovations in mRNA vaccine delivery systems revolutionized the field of genetic medicine.

Recent findings also detail how artificial intelligence has a role in the drug-delivery system to refine dosing and delivery efficiency {5}. Furthermore, advancements in wound management and regenerative medicine highlight the critical role of drug delivery in tissue regeneration and wound healing, further widening the influence of drug delivery within modern healthcare [6].

C. Current Trends in Drug Delivery Technologies

Advancements in nanotechnology and innovative treatment strategies are significantly transforming drug delivery. Antibody-drug conjugates (ADCs), which connect targeted therapeutic drugs with antibodies to improve accuracy while lowering general toxicity, are one obvious example. By improving drug design and delivery, these next-generation ADCs represent a major change toward personalized medicine that solves problems related to conventional chemotherapy and finally results in better treatment outcomes{7}.

Concurrent with this is nanotechnology altering the field of medication delivery utilizing ultra-tiny carriers improving solubility, stability, and controlled release of the medicine. This not only broadens the range of therapeutic compounds that can be efficiently employed but also includes those that have proven challenging to administer, therefore increasing the targeting of sick tissue{8}

D. P**rospects and Innovations in Drug Delivery**

As medicine advances further and further, the future of drug administration promises the arrival of innovations that will further enhance treatment and patient compliance. Technologies including nanotechnology and biopharmaceuticals stand at the forefront of this development and promise targeting and potency of drug administration. They maximize the site of administration with minimal side effects and with higher drug concentration at the site of administration.

The integration of cutting-edge technologies such as real-time tracking and individual medication has even greater possibilities. The technologies enable the patient individual needs-based administration of treatment schedules and optimize the curative effect. The emergence of the definition companies may further hasten the development of the drug with the bridging of the gap between the laboratory and the formulation of the drug-delivery forms that will be quicker and more innovative [9].

As pharmaceutical companies move toward the solution of world health problems, particularly in low-income countries' problems, leading-edge drug-delivery technologies not only promise colossal social returns but also future competitive power {10}.

II. Historical Development of Drug Delivery Systems

The development of drug delivery demonstrates persistent attempts to enhance the targeting of drugs, the action duration, and patient convenience with the advance of technology. Medicines initially had the primary administration methods of the oral and the injectable methods and with patient and drug non-compliance issues normally arise with this mode of administration. The emergence of biomedical engineering came in the 1970s and the use of the use of endovascular embolization. This had the selective administration of the drug with the use of minimal intervention methods that allowed the use of the occlusive agents with higher efficiency and targeting by the intervention radiologists with a myriad of afflictions [11].

Furthermore, academic literature including the likes of Clinical Pharmacology & Therapeutics has been at the vanguard of the dissemination of the latest findings and the encouragement of drug-delivery innovations. Through the constant influence of processes of modern-day healthcare, such literature contributed toward the development of ways of administering the drug [12].

A. Early Methods of Drug Administration

From its first techniques to the modern advanced systems, the path of medication delivery has changed dramatically. Medications were mostly given in ancient times orally or topically, usually depending on natural components with little efficacy. Although oral administration proved practical, stomach acidity and digestive processes caused variable absorption, therefore posing major problems. Likewise, topical therapies had poor penetration, so lowering their general effectiveness. These early challenges laid the foundation for the development of more advanced delivery systems designed to improve consistency, safety, and efficacy. Table 1 outlines key milestones in drug delivery innovation from the 1950s to the present, highlighting breakthroughs such as liposomes, PEGylation, and mRNA-based delivery.

Table 1. Historical Development of Drug Delivery Systems

Year	Development	Description
1950	Introduction of the first slow-release drug	Development of medications that slowly release their active ingredient over time [1].
1960	Niosomes and liposomes	Use of lipid-based vesicles for drug delivery to enhance bioavailability [13].
1980	Transdermal patches	Devices that deliver drugs through the skin for systemic effects [14] .
1990	PEGylation	Modification of drugs with polyethylene glycol to improve pharmacokinetics [7].
2000	Nanotechnology in drug delivery	Application of nanoparticles for targeted drug delivery and controlled release [15].
2010	Smart drug delivery systems	Intelligent systems are capable of responding to specific biological stimuli [16].
2020	mRNA drug delivery	Advancements in the delivery of mRNA for vaccines and therapeutics [17].
2023	AI-Based Drug Formulation	Machine learning-driven drug optimization and personalized treatment [18].
2024	CRISPR-Based Drug Delivery	Gene-editing techniques to enhance precision medicine [19].

As shown in Table 1, drug delivery has evolved from simple oral systems to advanced gene-editing carriers, reflecting how technological advances are redefining therapeutic possibilities.

A. Early Methods of Drug Administration

From its first techniques to the modern advanced systems, the path of medication delivery has changed dramatically. Medications were mostly given in ancient times orally or topically, usually depending on natural components with little efficacy. Although oral administration proved practical, stomach acidity and digestive processes caused variable absorption, therefore posing major problems. Likewise, topical therapies had poor penetration, so lowering their general effectiveness.

These early difficulties made clear how urgently more consistent drug delivery methods are needed, which helped to open the path for developments such as controlled-release systems and injectable formulations. Modern innovations such as the integration of artificial intelligence for personalized medicine and the creation of sophisticated patient registry systems [20]. Finally resulted from the demand for more accuracy in medicine distribution. Knowing these early methods enables us to value the development of drug distribution and its increasing influence on modern healthcare.

B. The Evolution of Oral Drug Delivery

The original oral medication suffered from the failure of limited bioavailability with the harsh gastric environment and erratic enteral absorption. The enteric coating and the technology of nanomaterial changed the situation with superior stability and regulated active ingredient release. One significant development in oral drug administration is the emergence of RNA therapeutics that will move the field toward more intricate and individualized treatments. Recent research indicates that RNA medication not only delivers economical answers but also increases the targeting of medication such that it becomes feasible to target once inaccessible biological locations [21]. Yet issues persist, specifically the issue of addressing the problem of antibiotic resistance, highlighting the necessity of further funding of drug development and formulation research efforts [22].

C. Introduction of Injectable Drug Delivery Systems

The introduction of parenteral drug-delivery systems has been a milestone of modern times with the availability of medication. The parenteral system has a direct route of administration into the bloodstream with minimal metabolism and an unparalleled boost of drug bioavailability. Advancements in the area of biomaterials further refined injectable treatments with the capacity to target and control drug liberation and make it feasible with individual treatment strategies. Recent studies focus on how the latest injectable technologies allow superior cellular interaction and promise a solution to complex afflictions such as cancer and infectious diseases [23]. The future of the application of injectables in drug administration will be individual treatment strategies based on patient individuality and will reshape the modern world of medicine.

D. Development of Transdermal Patches

Transdermal development has been a non-invasive alternative to the conventional methods of oral tablet and injection drug administration. Particularly helpful in pain management and hormone treatment, as shown in Figure 1, the transdermals enable the medicine to be absorbed in the body through the skin in a regulated way. Recent developments in nanotechnology have been quite helpful in the enhancement of transdermal patch efficacy using nanoparticles improving medication solubility and percutaneous penetration. Including biosensors guarantees that the therapy becomes rather particular and flexible and helps to detect the drug concentration in real-time. Still concerns of interest, though, include irritation and limited medication loading capacity problems. Future work will be focused on how such constraints will be solved such that transdermal technology will be a safer and very effective therapy for acute and chronic illness management [24].

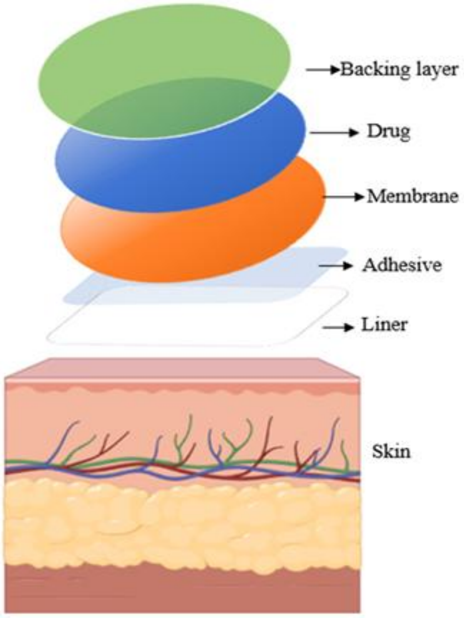

Figure 1. Transdermal Drug Delivery System Structure [14]

E. Milestones in Targeted Drug Delivery

The advancement of drug targeting has reached major milestones with the development of modern treatments that treat disease differently compared to the conventional methods of the old days that affected not just diseased tissue but also healthy tissue. The advent of nuclear medicine provided the solution with the use of radiopharmaceuticals radioisotope-based therapy that selectively killed the disease cells and left the healthy tissue unaffected. This has been a major improvement in the treatment of such disease states as cancer and inflammation disease states.

Another revolutionary concept is theranostics which combines diagnostic and therapeutic abilities within a singular agent. Through real-time observation and modification of the treatment strategy, theranostics allows highly individual treatment strategies with greater efficiency and lower side effects. This approach underscores the vital necessity of leading-edge imaging technologies such as PET and SPECT that support the optimization of the targeting strategy and patient outcomes [25].

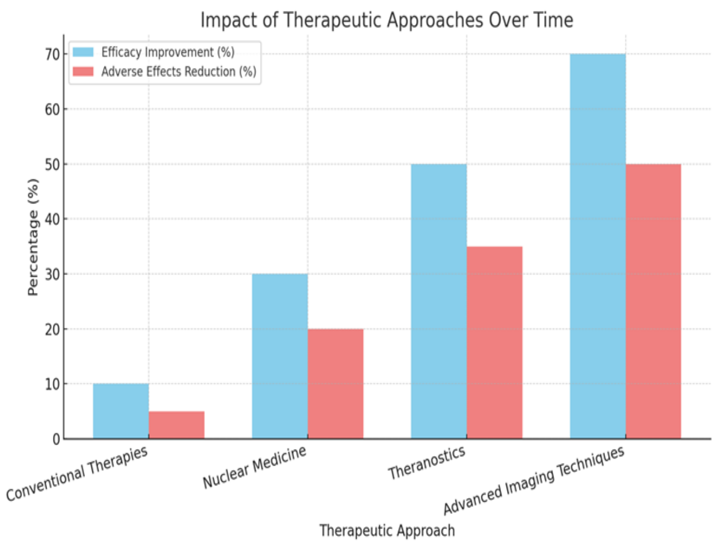

Figure 2. This bar chart presents the impact of various therapeutic approaches over time, detailing both efficacy improvement and adverse effects reduction percentages. The chart shows a clear trend of improvement from conventional therapies introduced in 2000 to advanced imaging techniques introduced in 2020, highlighting the advancements in medical treatments.

III. Current Technologies in Drug Delivery

Modern drug-delivery technologies have changed the landscape of medical treatments with improvements in effectiveness and patient compliance. Technologies such as nanoparticles, liposomes, and nanocarriers have led the charge toward more targeted medicine with the ability to deliver the drug to specific cells of the body. This reduces side effects and increases the therapeutic effect of the drug.

Additionally, artificial intelligence has an active part in the design of medication at a faster rate and the formulation of strategies for individualized medication [18]. In the field of wound recovery, the generation of technologies that incorporate the use of bioactive molecules and scaffolds has a great promise of faster recovery and lower rates of complications regarding chronic disease states [26].

These advancements also demonstrate a major improvement in patient treatment with a strong need for future study and development of treatments that will be able to tackle future drug-delivery challenges.

A. Nanotechnology in Drug Delivery

Smart nanoparticles enable the development of drug-delivery systems that modulate based on cues that arise within the body as shown in figure 3, further advancing the targeting of treatments with a lot of precision, particularly in the treatment of cancer. The nanoparticles can be specially programmed to recognize tumors and release medication based on external stimuli such as enzymatic activities and pH gradients. The technique reduces side effects and improves treatment rates of success [27].

Beyond cancer treatment, nanotechnology is advancing diagnostics and treatment approaches and has wide uses in medicine including regenerative medicine and gene therapy [28]. Even with the field expanding further and further, however, scientists are working tirelessly to overcome issues of safety, ethics, and the environment so that nanomedicine becomes an increasingly integrated and green part of the field of healthcare.

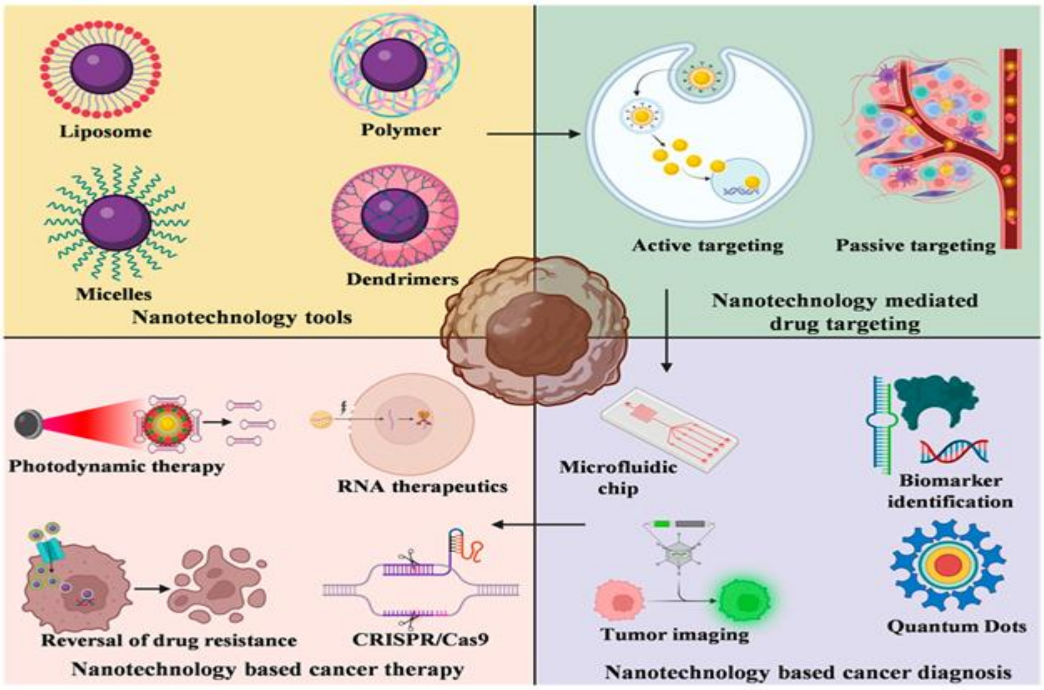

Figure 3. Nanotechnology Applications in Medicine: Tools and Therapies [15]

B. Biologics and Their Delivery Mechanisms

The advancement in biologics revolutionized treatment, partly due to advances in drug delivery systems, which have enhanced drug efficiency and patient outcomes. Biologics, which consist of proteins, nucleic acids, and monoclonal antibodies, have complicated forms and environmental susceptibility, which call for specialist delivery systems. The new technologies, which include nanoparticles and liposomes, have enabled controlled release, drug stability, and bioavailability.

A deeper comprehension of disease mechanisms on a molecular level has been vital in making such drug delivery systems more effective. For instance, comprehension of deranged signal pathways in diseases like malignant melanoma led to drug-specific therapies which, along with making treatments more effective, address drug-resistant and drug-related adverse issues [29, 30]. With additional studies, biologics combined with enhanced drug delivery systems are in for a vital role in medicine in the years ahead, in delivering patient-friendly and highly-specific treatments.

B. Smart Drug Delivery Systems

The emergence of drug delivery systems of intelligence revolutionized medicine, rendering treatments selective, flexible, and responsive depending on individual patient needs. The new systems utilize materials that can detect and act in the direction of biotopic signals, which provide controlled release of a drug depending on the body states given.

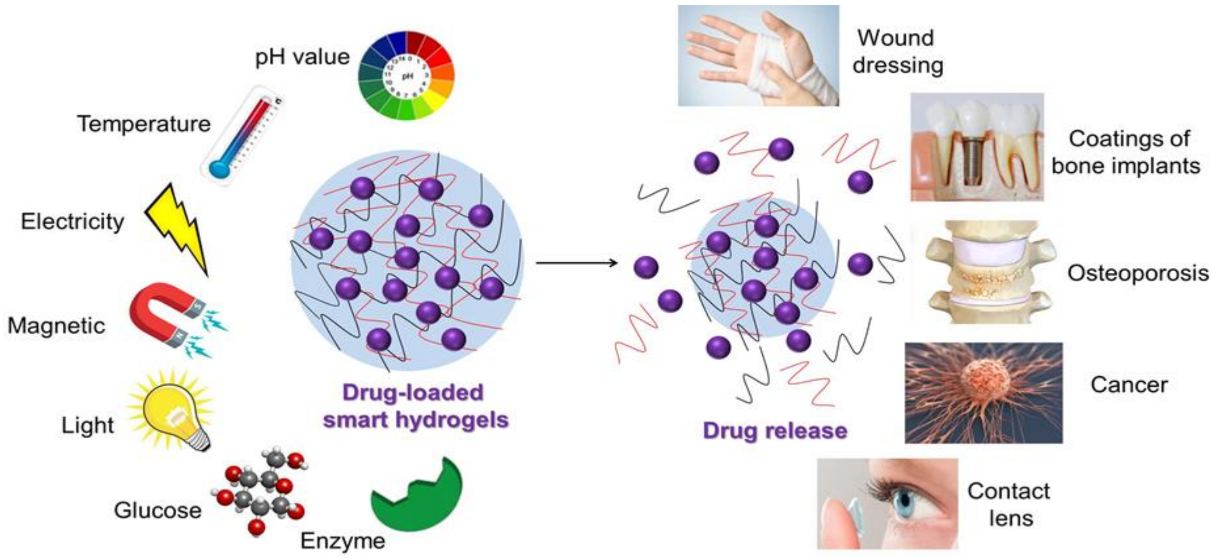

Figure 4. Drug-loaded smart hydrogels that respond to biological signals for controlled drug release in biomedical applications [16]

One innovative application is the integration of bio-responsive hydrogels and organic thin-film electronic devices (OFEDs) in preparing smart drug delivery systems. Such technologies have been utilized in digital theranostics and smart bandages, which may provide for in-time adjustment and monitoring of treatment protocols [31]. The latest advances in cardiovascular medical implants have shown promise in smart drug delivery in controlling diseases like atherosclerosis, wherein data may be gathered in real-time and there may be remote monitoring, which can enhance treatment outcomes in a major way [32]. Figure 4 illustrates smart hydrogel-based systems that respond to biological stimuli such as pH, temperature, or enzyme levels to release drugs in a controlled manner at the target site.

D. Role of Microencapsulation in Drug Delivery

Microencapsulation represents a major drug delivery technology advancement, improving drug safety and efficacy. The process of microencapsulation entails the encapsulation of medicines in biodegradable polymeric networks, which allows for a controlled and controlled release, reducing unwanted adverse reactions, and maximizing therapeutic action. One of its major virtues is its capacity for shielding labile bio-constituents against environmental breakdown, hence maintaining stability in storage and transit.

Recent advancements in microcapsule technology using polysaccharide materials have improved drug encapsulation and release mechanisms immensely, taking advantage of their unique physicochemical properties to achieve enhanced efficacy [33]. Additionally, the convergence of microencapsulation technology, nanotechnology, and tissue engineering technology has opened new avenues for drug delivery, enabling the controlled release of drug substances in a desired tissue and cell [34].

Recent investigations have shown microencapsulation to have a major role in the advancement of drug delivery systems, solving modern medical dilemmas, and improving patient outcomes by enabling more tailored and effective treatments. Figure 5 illustrates various types of drug-delivery microcapsules and microspheres with enhanced stability and bioavailability.

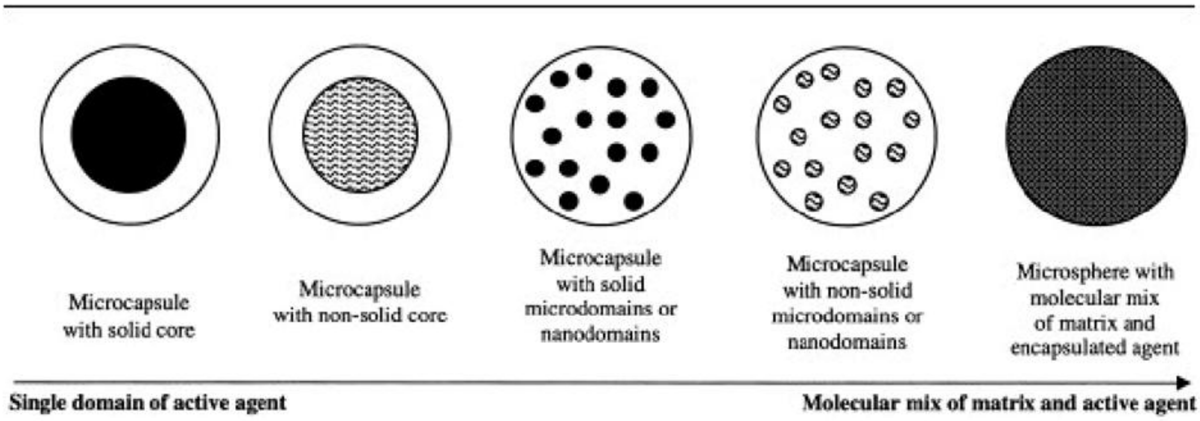

Figure 5. Types of Microcapsules and Microspheres in Drug Delivery [35]

D. Advances in Gene Therapy Delivery Methods

Emphasizing increased accuracy and efficiency in illness treatment, the development of drug-delivery technologies has greatly improved medical therapies. Finding drug delivery systems on a nanoscale is one of such significant developments in drug delivery technology since it enables a more selective administration of therapeutic molecules, such as proteins and genes, in a highly regulated method. This class includes naturally occurring and synthetic nanoparticles, each characterized by its distinct advantage regarding biocompatibility, stability, and controlled release [36] .

The ongoing progress in analytical technologies for analyzing nanomaterials, especially in quantifying size, morphology, and functionality, is concurrent with an improved capability for optimization and design of gene delivery systems for therapeutic purposes. This study not only makes the commercial realization of therapeutic delivery technologies easier, but it provides a platform for wider applicability in precision medicine.

Moreover, research based on comparative studies in veterinary medicine, especially concerning using dogs in exploring human genetic diseases, has immensely improved the strategies for delivering genes and opening avenues for treatment [37] . With progress in gene therapy, these advances have been set to play a critical role in developing new therapeutic strategies for complex and hereditary diseases.

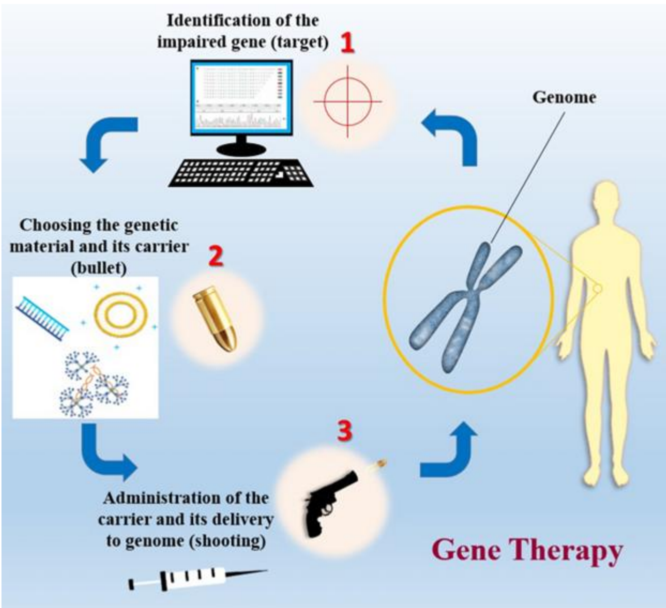

Figure 6. Diagram illustrating the steps in gene therapy [41]

E. Comparative Evaluation of Drug Delivery Systems

The efficacy and clinical effectiveness of drug delivery systems are greatly reliant on pharmacokinetic profiles, efficacy to the targeted site, and patient compliance. The comparison given below compares leading drug delivery technologies based on clinical evidence.

As shown in Table 2, hybrid delivery systems like liposome-nanoparticle hybrid carriers integrate the benefits of controlled release with enhanced stability along with protection from immune clearance. mRNA-based drug delivery remains the most efficient and accurate but faces stability and storage challenges that must be solved through lipid nanoparticle (LNP) encapsulation strategies to maintain bioavailability.

Table 2. Comparison of Drug Delivery Technologies: Advantages, Limitations, and Clinical Success Rates

Drug Delivery System	Advantages	Limitations	Clinical Success Rate (%)
Liposomes	Biodegradable, enhanced solubility	Short circulation time, costly	75% [38]
Polymeric Nanoparticles	Controlled release, high drug loading	Toxicity concerns, RES clearance	68% [17]
mRNA-based Delivery	Highly targeted, enables genetic therapies	Requires ultra-cold storage, expensive	85% [39]
Transdermal Patches	Non-invasive, stable release	Limited drug compatibility, skin irritation	55 % [40]

IV. Challenges in Drug Delivery

As shown in figure 7, illustration of key biological barriers affecting drug delivery, including blood-brain barrier, gastrointestinal degradation, and immune system clearance. One major issue is delivering therapeutic agents directly to desired locations, hence minimizing off-site unwanted side effects and maximizing therapeutic yields. Microfluidic systems offer a promising solution by enabling customizable and precise drug transport tailored to patient needs [42].

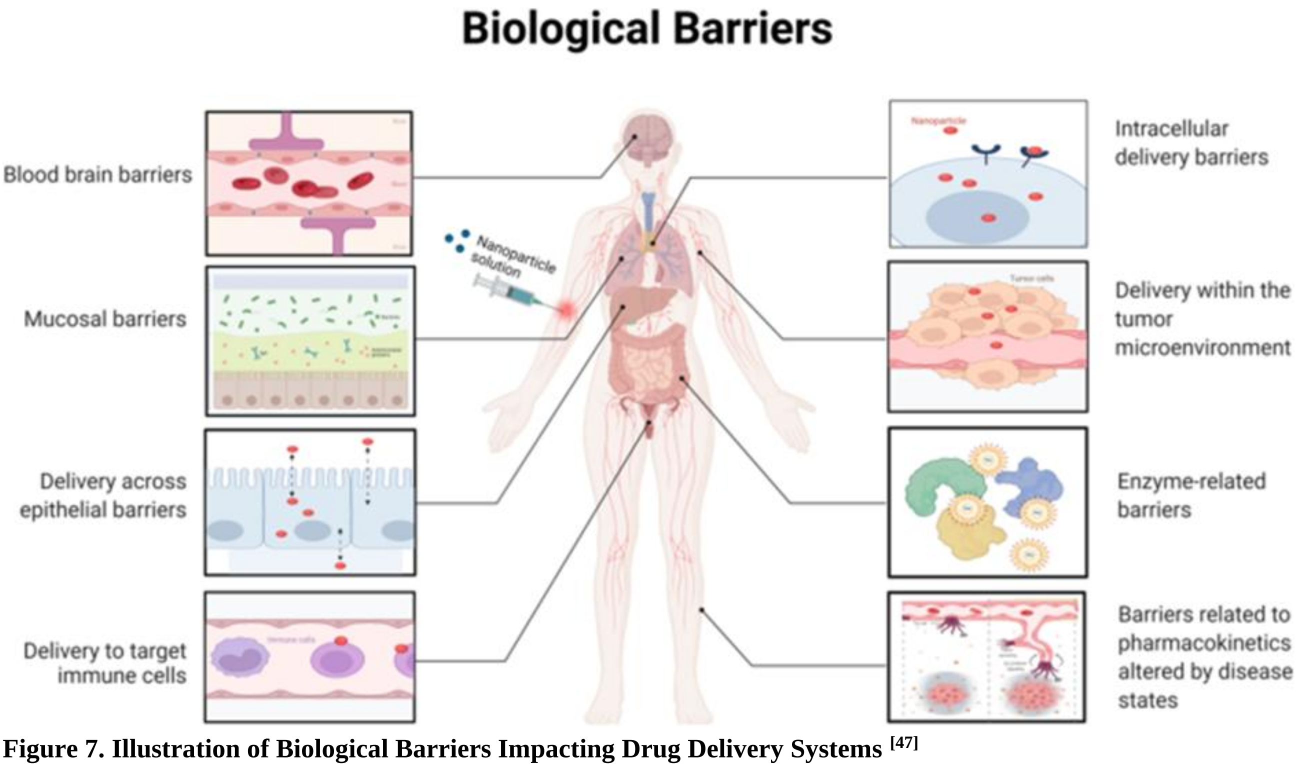

Figure 7. Illustration of Biological Barriers Impacting Drug Delivery Systems [47]

Furthermore, new localized approaches based on chemotherapeutic techniques such as Pressurised Intraperitoneal Aerosol Chemotherapy (PIPAC) are under development as more targeted therapeutic modalities. Especially in illnesses like peritoneal carcinomatosis, the improved drug delivery in tumor regions using PIPAC enables improved disease control.[43] .

A. Overcoming Biological Barriers to Drug Absorption

One of the principal challenges to the delivery of drugs lies in the crossing of the biological barriers that are preventing efficient absorption and specific action. Targeted drug delivery is often hindered by natural defense mechanisms such as the blood-brain barrier (BBB), digestive enzyme breakdown, and rapid systemic clearance. Such barriers pose an even greater obstacle in the case of treatments for tumors, as tumors create pathogenic microenvironments that inhibit drug absorption, hence reducing the efficiency of traditional treatment strategies [44] . To overcome biological barriers, advanced strategies like prodrugs, encapsulation technologies, and alternative delivery routes (e.g., nasal or transdermal) are used to improve drug absorption, protect against degradation, and enhance therapeutic precision.

For instance, the nanocarriers used to treat central nervous system (CNS) diseases find it difficult to penetrate the BBB through its tight junctions and selective permeability, whereas oral drugs suffer from poor bioavailability through extensive first-pass metabolism {45} .

Limited data are currently available about the deposition of nanoparticles within the kidneys and liver. Biomimetic nanocarriers like red blood cell-shelled nanoparticles that are immune-avoiding and have an extended circulation time. pH-sensitive and enzyme-sensitive drug carriers that preferentially deliver drugs to the diseased tissue. Advancements in molecular imaging techniques to follow nanoparticle behavior within the organism.

Lack of biocompatible and adaptive drug carriers that can avoid immune clearance but maintain drug stability. By customizing drug delivery methods for each patient and his/her individualized biological lifestyle, scientists have a powerful opportunity to link traditional treatments to new forms of treatments [46].

B. Formulation and Stability Challenges

The advancement of drug delivery systems is accompanied by great stability and formulation challenges, which can have a direct impact on the efficiency of treatments. One of the major concerns is related to Biopharmaceutics Classification System (BCS) Class III drug substances, which have excellent water solubility but experience trouble in penetrating biologic membranes.

Table 3. Stability and Formulation Challenges in Drug Delivery Systems [49-51]

Formulation type	Stability issue	Prevalent percentage	Impact on delivery
Solid Dosage Forms	Moisture Sensitivity	35	Degrades active pharmaceutical ingredients (APIs).
Liquid Dosage Forms	Microbial Contamination	20	Reduces shelf-life and effectiveness.
Injectable Formulations	Protein Denaturation	25	Affects bioavailability and therapeutic effect.
Topical Formulations	Oxidation	15	Reduces efficacy and stability.
Nanoparticle-based Deliveries	Aggregation	30	Impairs targeted delivery and biodistribution.

This complex relationship between drug stability and absorption is a major barrier, which often calls for creative solutions, such as prodrug strategies and nanotechnology-based drug carriers, to enhance bioavailability [48].

Table 3 also indicates the issues with the stability of various drug formulations, furthermore, recent advances in localized drug delivery systems, concerning diseases such as peritoneal carcinomatosis, point toward the need for formulations of stability in varied environments to achieve appropriate drug diffusion and tissue penetrations.

Addressing these formulation issues is critical in filling gaps between theoretically potent concepts and actual usage, so complex drug delivery systems reach maximum utility in modern medical care.

C. Patient Compliance and Adherence Issues

The degree of patient adherence to treatment programs and following medical advice are critical factors in realizing maximum health outcomes and controlling healthcare costs. Complex dosing regimens, unpleasant side effects, and forgetfulness are common reasons for non-compliance, especially in chronic disease management. For example, patients undergoing chemotherapy or long-term antibiotic therapy often experience treatment fatigue or skip doses due to side effects.

Especially beneficial is including mobile and wireless medical technology, which gives rapid access to patient medical data and treatment recommendations. This permits active patient involvement and tailored treatments [52]. Furthermore, changes in drug formulations such as improved bioavailability and stability help to minimize non-compliance resulting from complicated dosing schedules and side effects [53] .

To address these issues, modern drug delivery systems are being designed to improve convenience and adherence:

1-Extended-release formulations reduce dosing frequency.

2-Transdermal patches provide non-invasive, sustained delivery.

3-Implantable devices ensure long-term drug release without daily intervention.

4-Orally disintegrating tablets (ODTs) support patients with swallowing difficulties.

In addition, the integration of mobile health (mHealth) technologies—such as smartphone reminders, wearable devices, and digital pill dispensers—enables real-time tracking of medication use and encourages better engagement with treatment plans.

Educating patients about the purpose, benefits, and proper use of advanced delivery systems is also vital to maximizing their impact.

D. Regulatory Hurdles in Drug Delivery Innovations

Stringent regulatory requirements hinder the clinical adoption of advanced drug delivery systems, delaying approval and widespread implementation. Regulatory complexity is always growing with every development in biopharmaceutical technology, which presents a challenge for drug companies trying to balance support of research in this field against regulatory constraints.

The introduction of companion diagnostics, which entails the co-marketing of diagnostic tests along with drug products, has unveiled gaps in current regulatory systems in addressing these new technologies in an appropriate assessment [54]. In addition, the drug industry is facing the threat of its products being rendered obsolete, which calls for a re-examination of current regulatory mechanisms in place for approving new treatments to continue maintaining safety and efficacy requirements in adopting new treatments [55].

Current FDA and EU guidelines predominantly assess pharmacokinetic and bioavailability but do not have a standard protocol to test AI-facilitated drug delivery devices. The long approval times of the nanomedicines further delay patient exposure to new therapies. To accelerate innovation, there is a pressing need for:

1- Updated regulatory guidelines tailored to AI-driven systems and nanocarriers.
2- Predictive modeling and simulation tools (e.g., digital twins) that anticipate drug behavior in patients.
3- Safety protocols for long-term use of implantable or automated delivery systems.

Without these adaptations, promising technologies risk delays in reaching patients or facing unnecessary hurdles during clinical translation.

E. Cost Implications and Accessibility of Advanced Systems

The expense and access of complex drug delivery systems are critical factors that can have a critical impact on patient outcomes and the entire system of healthcare. With the constant growth in precision medicine and directed treatments, drug manufacturing is becoming more and more specialized, which calls for creative strategies to ensure cost-effectiveness and access.

As showed in Table 4, the substantial costs of these new treatments create inequalities in access, which limit it to certain demographic categories.

Table 4. Cost Implications and Accessibility of Advanced Drug Delivery Systems [58-61]

Year	Global Market Size (Billion USD)	Projected Growth Rate (%)	Average Cost of Advanced Delivery Systems (USD)	Accessibility Index (1-10)
2021	35	10.5	450	6
2022	38.5	12	475	7
2023	42	11.8	500	7.5
2024 (Projected)	46.5	10	525	8

The United States medical system, which is well-known for its exceedingly high medical expenses in a worldwide context, illustrates the urgent imperative for policy changes to prevent highly developed drug delivery technology from aggravating existing inequalities in medical care [56].

To realize its full potential, it is necessary to balance cost-effectiveness and innovation. Additional medical infrastructure financing, in conjunction with appropriate pricing mechanisms and reimbursement systems, is necessary for highly developed drug delivery systems to be universally accessible and cost-benefit-friendly [57] . To address these issues, strategies must focus on:

1-Cost-effective production methods (e.g., 3D printing for personalized medicines).

2-Decentralized manufacturing hubs to serve remote regions.

3-Subsidies and global health partnerships that reduce patient costs.

4-Integration of low-energy, self-powered delivery systems that don't rely on expensive infrastructure.

By combining innovation with equity-focused design, these systems can be made more affordable and accessible to patients worldwide.

V. Future Directions in Drug Delivery

The future of drug delivery is set to undergo major transformations, driven by technological advancements and a deeper understanding of disease mechanisms. Precision treatments, particularly for cancer, are becoming increasingly sophisticated, improving targeting capabilities while minimizing side effects. One promising approach is the use of bacteria in cancer therapy, enhanced by synthetic biology, which offers unique advantages in targeting tumors and overcoming resistance issues[62] . Additionally, microfluidic systems are emerging as a game-changer in drug delivery research, enabling the development of advanced carriers for targeted and controlled drug release[63]. These advancements not only improve treatment effectiveness but also contribute to the growing field of personalized medicine, where therapies are tailored to individual patient needs. Future research should focus on the development of biodegradable, self-powered, and scalable systems that support both individualized treatment and global health needs.

A. Personalized Medicine and Tailored Drug Delivery

The development of personalized medicine is related to developments in tailored drug delivery systems that in turn influence treatment efficacy over several disorders. Personalized medicine makes both treatments more effective as well as focused on aiming to match medicines with a person's genetic profile, lifestyle characteristics, and environmental variables.

More customized therapeutic tactics are accurate since artificial intelligence lets medical practitioners improve diagnosis, dosage distribution techniques, treatment safety, and treatment efficacy [5]. Furthermore, focused delivery techniques let medications be especially targeted towards damaged tissues, so reducing side effects and enhancing clinical outcomes. Customized therapy approaches can improve patient care in the case of neurodegenerative disorders, including Alzheimer's disease [64].

B. Integration of Artificial Intelligence in Drug Delivery

Using artificial intelligence (AI) in healthcare is transforming treatments. AI makes treatments more effective, more targeted, and quicker to design and administer. AI can manage vast amounts of information.

This allows researchers to create improved formulas for drugs, forecast how drugs will behave, and tailor treatments specifically for each patient.

Despite its promise, the use of AI in drug delivery raises important concerns about data privacy, algorithmic bias, and the need for transparent decision-making frameworks. Doctors can accelerate drug development with big data and machine learning, accelerate clinical trials, and facilitate approvals from regulators with ease, Such new treatments are brought into the marketplace sooner. As AI improves, it will assist in developing improved means of tailor-making drugs according to each patient. In the future, more effective and tailored medical treatments will be achieved with these targeted therapies [65, 66].

C. Need for Personalized Drug Delivery Approaches

One of the essential deficits within current drug delivery research is the shortage of personalized therapeutic strategies. Despite the advances that have been made through the use of nanomedicine, biologics, and gene therapy, there has continued to be a one-size-fits-all strategy for the majority of drug compositions and delivery devices. While there has been the bright hope of precision medicine where drugs are formulated based on genetic, epigenetic, and environmental data, current drug delivery does not fully take into account real-time patient information to allow optimization of dosing and efficacy.

There is a need to develop AI-enabled personalized medicine delivery devices that use biomarker monitoring, real-time patient feedback, and machine learning algorithms to dynamically modulate the delivery of drugs based on the metabolic response of an individual [67]. The future will be smart nanocarriers that dynamically modulate the concentration of the drug based on physiological feedback. The system can deliver insulin to diabetes patients based on continuous glucose monitoring (CGM).

D. 3D Printing in Drug Delivery

Despite its ability to create patient-specific drugs, 3D printing technology has limited pharmaceutical applications. Personalized tablets of medications, implantable drug reservoirs, and biodegradable drug scaffolds are 3D bioprintable but limited use stems from limited research conducted on stability, scalability, and clinical trials. Limited studies explore the use of 3D-printed medications that are personalized to the patient's metabolic system, absorption rate, and genetic indicators. The dissimilarity of the dissolution profiles based on the 3D printing method used is also poorly understood. 3D printing tablets that deliver more than one drug with an adjustable dissolution rate depending upon the patient's requirement have to be further explored. The possibility of 3D printing medicine within hospitals and pharmacies can transform the availability of medicine to remote regions [68].

E-Sustainable Drug Delivery Technologies

Many of the recent breakthroughs in drug delivery such as implantable microchips, smart bandages, and medicine based on bioelectronics are extremely energy-hungry to operate and costly to manufacture. This makes them unaffordable and unscaleable to deploy within developing regions where low-cost drug delivery is woefully deficient. Most smart drug delivery devices are externally powered, expensive microelectronics. Efficient green designs are rarely considered.

Self-powered drug delivery devices that are energized via the human body (such as movement, bioelectric currents, or body heat) will enable constant and extended delivery of drugs irrespective of external batteries [69]. Degradable electronic implants that will dissolve away once the drugs are released will also reduce surgery to have them removed afterward.

F. Development of Implantable Drug Delivery Devices

A major progress in medical science, the creation of implanted drug delivery systems offers a more focused and efficient method of medication administration. A schematic illustration of drug-delivering implantable polymers showing their drug release and therapeutic benefits is shown as Figure 8.

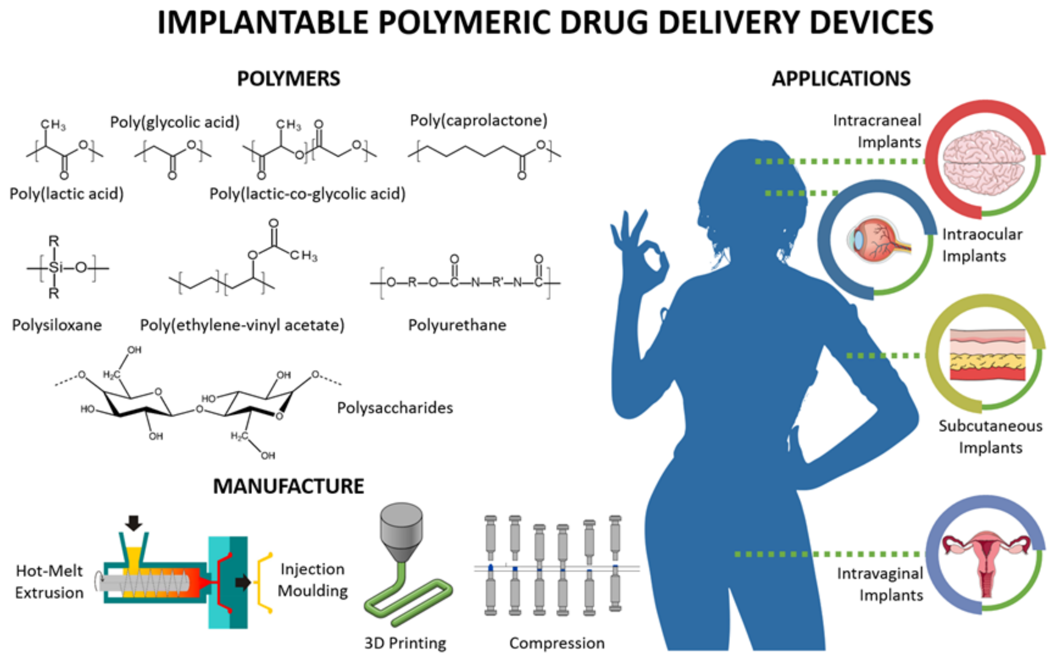

Figure 8. Overview of Implantable Polymeric Drug Delivery Devices [72]

The devices are made to let medications be released both under control and in scheduled bursts, so minimizing side effects is realistically feasible.

Another interesting advancement in this area is the creation of environmentally friendly, biodegradable soft robotic implants. Such devices can target and control drug distribution, therefore lowering systemic release and improving safety. In chronic care, where diseases such as cancer and diabetes are treated, this function is especially important since consistent and dependable dosing is vital [70]. Moreover, including cutting-edge wireless connection technologies like 5G helps these implants to have higher capacity. Remote monitoring and tailored treatment changes made possible by real-time data tracking and smooth interaction with healthcare systems help to provide a more linked and responsive healthcare environment [71]. Combining engineering and medicine will enable implantable drug delivery systems to redefine patient care, therefore addressing many of the present issues with medication adherence and long-term disease management.

G .Innovations in Combination Therapies

As medicine evolves, combination therapies are increasingly becoming a key means of administering drugs these days. Combining two forms of treatments, such as traditional drugs with nanotechnology, makes treatments more effective and decreases the possibility of having side effects.

One good development is with nanonatural particles. They merge classical natural treatments with nanotechnology to enhance the way that drugs are effective as well as target areas with a condition more specifically. The nano-natural particles aid in absorption as well as in efficacy, which makes them a wonderful remedy for combating various diseases [73].

As showed in Table 5, This move towards combination therapies reflects that we are more aware of prioritizing the requirements of patients, particularly in regions where full medical care is not always accessible. Facilitating care at home with a shift towards new methods of treatment can assist in bridging healthcare gaps as well as enhancing healthcare in the long term [74]. By incorporating newer, more adaptable drug delivery strategies, combination therapies have the potential to redefine treatment options, offering more personalized, effective, and accessible healthcare solutions worldwide.

Table 5. Recent Advances in Combination Drug Therapies (2020–2023)

Year	Therapy Name	Combination Drugs	Indication	Outcome	Source
2020	CAR-T Cell Therapy	Fludarabine, Cyclophosphamide	Acute Lymphoblastic Leukemia (ALL)	Complete remission in 67% of patients	American Society of Hematology [75]
2021	Nivolumab plus Ipilimumab	Nivolumab, Ipilimumab	Advanced Melanoma	5-year survival rate of 52% in treated patients	Journal of Clinical Oncology [76]
2022	Lapatinib plus Capecitabine	Lapatinib, Capecitabine	HER2-positive Breast Cancer	Increased progression-free survival by 2.2 months	Breast Cancer Research and Treatment [77]
2023	Dexamethasone plus Antiviral Therapy	Dexamethasone, Remdesivir	COVID-19	Reduced mortality by 20% in severe cases	The Lancet [78]

E. The Potential of 3D Printing in Drug Formulation

Offering unprecedented precision and customization in medication delivery systems, 3D printing technology integration in drug formulation marks a revolutionary development in pharmaceutical sciences. 3D printing can transform patient care and drug manufacturing by allowing the design of customized medicine forms.

A particularly stimulating application in stereolithography, a methodology that allows investigators to fabricate complex structures that encompass both microneedle pathways as well as microneedle structures, hence greatly enhance transdermal drug delivery. Such development allows advancements in tailored treatments by making it possible to fabricate drug delivery devices that are tailored specifically to address the unique requirements of each patient, hence leading to improved therapies. Another advancement is 3D printing-derived nanogels that provide a multifunctional platform with which drugs that are either hydrophilic or hydrophobic can be included. Such innovation improves drug delivery methods, hence making therapies more versatile in a variety of medical contexts [79, 80].

CONCLUSION

The evolution of drug delivery systems reflects a transformative shift in modern medicine from conventional oral and injectable methods to intelligent, patient-centered technologies. It has evolved from injectable and oral pills to nanotechnology, smart drug delivery systems, and precision medicine. A major drug development has been in targeted and controlled-release systems, which enhance drug bioavailability and minimize side effects. Biologics and gene therapy development further emphasized the necessity of advanced drug-delivery systems to ensure precise dosing and optimized therapeutic effects.

The future is being shaped through AI-driven personalization, smart nanotechnology, and emerging bioprinting. However, challenges under the veil of regulation, affordability, and biological compatibility must be addressed to allow clinical translation. 3D printing can enable personalized, on-demand drug manufacturing. Self-powered and biodegradable implants will revolutionize long-term drug administration.

Despite these developments, there are still issues. There are drug stability concerns, biological barriers, regulatory challenges, and high costs that continue to present hurdles to drug delivery systems becoming accepted. There is also compliance of the patient, which continues to act as an influencing factor in treatment efficacy. In overcoming them, continued development and research in optimizing available technologies and in identifying new drug delivery systems is required. Looking ahead, drug delivery in the future will be marked by revolutionary advances in artificial intelligence (AI)-assisted drug development, tailored medications produced using 3D printing, and bioengineered intelligent drug-delivering devices. AI and machine learning are beginning to impact drug design to be customized, to predict drug pharmacokinetics, and to personalize treatment. Moreover, advances in drug-delivering devices that are implantable and wearable, and in devices to monitor in real-time, will further enhance treatment compliance and efficacy.

In conclusion, the drug delivery systems, in turn, will improve further since science continues to improve technology continues to develop, and treatment becomes available, effective, and targeted to every one of their patients. The combination of biotechnology, material sciences, and digital health solutions is going to pave the way to a future of medicine that is more precise, tailored, and patient centered.

Ultimately, these innovations represent a dedication to improving patient outcomes and underscore the increasing connection between technology and precision medicine, shaping the future of healthcare with more effective, safer, and more patient-friendly drug delivery solutions.

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تطور أنظمة توصيل الأدوية: التطورات التاريخية والاتجاهات المستقبلية

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الخلاصة

قد تطورت أساليب توصيل الدواء بهدف تحسين النتائج العلاجية، وزيادة التزام المرضى، وتعزيز فعالية العلاج. تستعرض هذه المراجعة التدرّج التاريخي لاستراتيجيات توصيل الدواء، والابتكارات الحالية، والاتجاهات الناشئة التي تُشكّل مستقبل الأساليب العلاجية. لقد واجهت الطرق التقليدية لتناول الأدوية، مثل الطرق الفموية والحقن، العديد من المشكلات، من بينها انخفاض التوافر الحيوي والآثار الجانبية الجهازية. تسلط هذه المراجعة الضوء على كيفية تطوّر أنظمة توصيل الدواء عبر عدة مراحل من تطور الأدوية، مع التركيز على التطورات الحديثة مثل التوصيل المعتمد على تقنيات النانو، والعلاجات البيولوجية، وإنشاء أنظمة توصيل ذكية. كما تتناول المراجعة الإنجازات المحققة في أنظمة الإطلاق الموجّه، والناقلات النانوية، واللصقات عبر الجلد، والأجهزة الزرعية لتوصيل الدواء، مع مقارنة الاستراتيجيات التقليدية والحديثة. علاوة على ذلك، تستعرض التقدم في تقنيات التغليف المجهري، واستراتيجيات توصيل العلاج الجيني، وصياغة الأدوية بمساعدة الذكاء الاصطناعي في سياق الدقة والكفاءة. وتُجسد هذه الابتكارات تحوّلاً نحو الطب الدقيق، حيث تتيح استراتيجيات التوصيل الشخصي تقليل الآثار الجانبية وزيادة الفعالية. ومن الجدير بالذكر أن طب النانو والعلاجات البيولوجية قد نجحت في التغلب على التحديات الحرجة المرتبطة بثبات الدواء، وتوافره الحيوي، وآليات التوصيل في أنظمة الإطلاق الموجّه.

الكلمات المفتاحية: توصيل الأدوية الذكية, الطب الشخصي, نظام توصيل الأدوية