Smart Drug Delivery

Smart Drug Delivery:

Innovations in Reactive Oxygen Species and Glucose-Triggered Systems

By

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PREFACE

Drug delivery science has taken a spectacular turn in the past two decades from straightforward traditional strategies to newer smart, stimuli-responding systems for targeted therapeutics. **Smart Drug Delivery: Innovations in ROS and Glucose-Triggered Systems** is a culmination of a growing need to summarize and put together recent advances in reactive oxygen species (ROS) and glucose-sensitive drug delivery technology. The technologies hold immense promise for therapeutics for complex diseases such as cancer, diabetes, and inflammatory disease because they hold promise for on-demand delivery of drugs to the desired locus of action.

The book was envisioned as a definitive text for scientists engaged in research, pharmacy scientists, graduate students, and industry experts who all share a passion for considering a future for targeted delivery therapies that become personalized. It begins with a primer on introductory material on drug delivery systems that increasingly converges on controls for release mechanisms, polymer science, along with a focus on the pivotal role for nanocarriers. The latter portions of the book address advanced ROS systems and glucose-sensitive systems with an exploration of their designs of principle, mechanism of action, and potential therapeutic uses.

Each chapter has been structured with equal care to seamlessly combine theory with practice so that while the reader grasps its science effectively, he also appreciates its translational potential. All subjects from thioether-containing polymers to boronic ester-mediated systems to glucose oxidase-conjugated delivery systems are discussed with due consideration to recent literature and correlative illustrations.

I am particularly in debt to the contributors, reviewers, and mentors whose expertise and remarks shaped this endeavor. I also extend special thanks to many of the original researchers whose seminal papers continue to

develop the science of drug delivery. I hope that this book inspires further innovation and collaboration in the field for more effectively translating laboratory science into practical therapeutic utility. As a seasoned expert or newcomer to the field, I hope that you find this volume both enlightening and practical.

Dr. Prakash Rajak, Mr. Deepjyoti Debnath and Dr. Biman Bhuyan, July, 2025

CHAPTER 1

INTRODUCTION

Introduction

Drugs, as defined by the U.S. Food and Drug Administration (FDA), are substances used to diagnose, treat, cure, or prevent diseases and include compounds that can alter the body's structure or function. Ideally, a drug should reach the exact site of disease, interact with target cells, and deliver its therapeutic effect at the right concentration. However, in reality, most drugs face challenges such as poor stability, uncontrolled release, and a lack of precision in targeting specific tissues or cells. Once administered, they often disperse throughout the body, affecting both healthy and diseased cells, which can lead to reduced efficacy and unwanted side effects. Traditional drug delivery systems struggle to control how and where a drug is released, making treatments less effective and sometimes even harmful. This has driven the need for advanced drug delivery systems, designed to enhance drug stability, control release rates, and ensure site-specific action. These innovations aim to improve therapeutic outcomes while minimizing side effects, ultimately making treatments safer and more efficient (Tibbitt, Dahlman, and Langer 2016, 704–717). Medicine has long depended on pharmacologically active agents, or drugs, to help manage, treat, or even reverse the course of diseases. The global pharmaceutical market is massive, valued at around $980 billion every year, reflecting the vital role that medicines play in modern healthcare. In the U.S., nearly half of the population has used at least one prescription medication in the past month, showing just how common it is for people to rely on drugs for various health conditions. However, even with all these medications, traditional drug delivery methods still face challenges, such as poor stability, lack of targeted delivery, and inefficient release, which can affect how well treatments work and how safe they are for patients. This highlights the need for innovative drug delivery systems that can make treatments more effective and safer for everyone (IMS Institute for Healthcare Information 2014) (CDC/National Center for Health Statistics 2012). A drug delivery system refers to the formulation and method by which a drug is administered to ensure effective therapeutic action. This includes common dosage forms such as tablets, capsules, ointments, and solutions. However, traditional formulations often release the drug rapidly and without control, which can lead to fluctuations in drug concentration and variable therapeutic effects. To address this, controlled release drug delivery systems have been developed, incorporating specialized technologies that regulate the release of the drug over an extended period, improving both efficacy and patient compliance. Unlike immediate release (IR) formulations, which deliver the drug all at once, controlled release systems aim to maintain a stable drug concentration in the bloodstream for a prolonged duration. Despite their advantages, achieving precise and sustained drug release particularly in oral controlled release formulations remains a challenge due to physiological factors such as drug metabolism, absorption variability, and individual patient responses (Park, Otte, and Park 2022, 53–65). Every dosage form is made up of two essential components: the active pharmaceutical ingredient (API), which is the actual drug responsible for treating the disease, and excipients or additives, which help ensure stability, effectiveness, and ease of administration. In most cases, using APIs in their pure form is not practical due to several challenges (Arab, Kassai, Kilo, and Cornu et al. 2022, 445–452). Many drugs are extremely potent, requiring precise dosing in very small amounts, which can be difficult to measure and handle accurately. Some routes of administration, like rectal or vaginal delivery, are often impractical because drugs can break down at the site of administration such as in the acidic environment of the stomach or cause irritation if present in high concentrations. Additionally, many APIs are sensitive to environmental factors like light, moisture, temperature, and pH, which can lead to instability and reduced effectiveness. Another common issue is that many drugs have an unpleasant taste or odour, making them difficult for patients to tolerate, which can affect treatment adherence (Langer 1990, 1527-1533). To overcome these challenges, drug delivery systems (DDS) play a crucial role, not only in delivering the drug effectively but also in improving stability, safety, and patient compliance, ensuring better treatment outcomes. Drugs can be administered through various routes, depending on factors like the target site, treatment duration, and the drug's physical and chemical properties. The most commonly used dosage forms include tablets, capsules, pills, ointments, syrups, and injections, each tailored for a specific route of administration. Table 1 provides an overview of different administration routes, highlighting their advantages and limitations. The choice of route largely depends on three key factors: the area of the body being treated, how the drug behaves within the body, and its solubility and permeability. For instance, some drugs degrade in stomach acid when taken orally, reducing their effectiveness. To avoid this, alternative routes such as parenteral administration are preferred, ensuring the drug reaches the bloodstream without being broken down. Among these, intravenous (IV) administration is the most efficient, as it delivers the drug directly into the bloodstream, providing 100% bioavailability meaning the entire dose is available for therapeutic action without any loss (Verma and Verma 2022).

1.1 Evolution of Drug Delivery Systems

The evolution of drug delivery systems has progressed through five distinct generations, each bringing innovations that enhance therapeutic efficacy and patient outcomes. The first generation (1G) includes conventional dosage forms like tablets, capsules, emulsions, and suspensions, relying on passive drug release. The second generation (2G) introduced modified-release systems, such as enteric coatings and prolonged-action formulations, to improve drug stability and controlled absorption. The third generation (3G) marked a shift towards controlled delivery mechanisms, utilizing osmotic pressure, swelling, and diffusion-based systems to regulate drug release more precisely. The fourth generation (4G) focused on targeted and self-regulated delivery systems, ensuring site-specific drug action while minimizing systemic side effects. The most advanced stage, the fifth generation (5G), incorporates cutting-edge technologies like nanorobots, gene therapy, and biologics, enabling long-term drug delivery over six to twelve months. These advancements have significantly improved drug bioavailability, therapeutic precision, and

Table 1-1: Routes of drug administration (Adepu and Ramakrishna 2021, 5905).

Route of administration	Description	Advantage	Disadvantage
Buccal	The medication is placed inside the cheek, where it dissolves and gets absorbed directly into the bloodstream.	Bypasses the digestive system, allowing for faster absorption and avoiding breakdown by stomach acids.	Limited to small doses, and prolonged use may cause irritation or discomfort.
Sublingual	The drug is placed under the tongue for rapid absorption through the mucosal membrane.	Provides a quick onset of action and avoids first-pass metabolism by the liver	Not all drugs are suitable for this route, and some may have an unpleasant taste.
Oral (Enteral)	The most common route, where medications are swallowed and absorbed through the digestive tract.	Convenient, non-invasive, and widely accepted by patients.	Absorption can be slow and inconsistent, with some drugs being broken down by stomach acids before they take effect.
Inhalation	Delivered through an inhaler or nebulizer to reach the lungs directly.	Rapid action, especially for respiratory conditions, with minimal systemic side effects.	Requires proper technique for effective delivery and not all drugs can be administered this way.
Nasal	Medication is administered as a spray or drops into the nasal passages.	Provides quick absorption and is a good alternative for patients who have difficulty swallowing.	Can cause nasal irritation or discomfort with frequent use.
Ophthalmic (Eye Drops/Gels)	Applied directly to the eye for local treatment.	Targets eye conditions directly, reducing systemic side effects.	Can be difficult to administer properly, with a risk of contamination if not handled carefully.

Otic (Ear Drops)	Instilled into the ear canal for localized treatment.	Effective for treating ear infections and inflammation with minimal systemic absorption.	Application can be tricky, and some patients may experience temporary discomfort or dizziness.
Rectal	Medication is inserted into the rectum, where it is absorbed into the bloodstream.	Useful for patients unable to take oral medications, such as those experiencing nausea or unconsciousness.	Can be uncomfortable and unpredictable in terms of drug absorption.
Vaginal	Administered as a suppository, cream, or gel for local or systemic effects.	Ideal for targeted treatment of vaginal infections and hormone therapies, bypassing first-pass metabolism.	Some patients may find it inconvenient or experience local irritation.
Topical	Applied directly to the skin for localized effects.	Minimizes systemic side effects and provides direct treatment at the site of application.	Drug penetration may be limited, requiring frequent reapplication.
Transdermal (Patches)	A medicated patch is placed on the skin to deliver the drug gradually over time.	Offers a sustained drug release and avoids gastrointestinal degradation.	Slow onset of action, with potential for skin irritation or allergic reactions.
Intravenous (IV Drip/Injection)	Administered directly into the bloodstream through a vein.	Ensures 100% bioavailability with immediate therapeutic effects.	Requires medical supervision, and improper administration can lead to complications like infection or thrombosis.
Intramuscular (IM Injection)	Injected into muscle tissue for systemic absorption.	Faster absorption compared to oral routes and suitable for larger drug volumes.	Can be painful, with a risk of muscle damage or infection.
Subcutaneous (SC Injection)	Injected just beneath the skin for slow, sustained absorption.	Allows for self-administration, making it convenient for long-term treatments like insulin therapy.	Limited drug volume per dose, with a possibility of local irritation or swelling.

patient adherence. The transition from traditional dosage forms to sophisticated, technology-driven drug delivery highlights the continuous push toward personalized medicine and more effective treatments. With each generation, the field has moved closer to optimizing drug administration, ultimately improving the quality of care and treatment success (Tewabe, Abate, Tamrie, and Seyfu et al. 2021, 1711–1724). Advancements in drug delivery technologies continue to evolve, with several formulations receiving approval from the U.S. Food and Drug Administration (FDA). The success of any drug delivery system is ultimately determined by its safety and therapeutic efficacy, as validated through FDA approval. Early developments in this field primarily focused on oral and transdermal formulations, utilizing four core drug release mechanisms: diffusion-controlled, dissolution-controlled, osmosis-controlled, and ion exchange-controlled systems. Among these, diffusion- and dissolution-controlled release methods have been the most widely implemented in pharmaceutical applications. Significant research efforts have also been directed toward modulated or self-regulated drug delivery, particularly for the controlled administration of insulin. Despite ongoing advancements, a fully developed system capable of precisely regulating insulin release based on physiological needs has yet to be realized. The advancement of drug delivery technologies can be understood through different perspectives, such as the classification of therapeutic agents and the strategies used for their delivery. The evolution of drug delivery technologies is driven by advancements in therapeutic approaches, which can be grouped into five main categories: small molecules, proteins and peptides, antibodies, nucleic acids, and live cell therapies. Each group presents its own set of challenges that require specific modifications at the molecular level, adjustments to the surrounding environment, or the use of specialized delivery systems to improve overall efficacy. For example, small molecules often struggle with issues like poor solubility, low permeability, and the need for tight pharmacokinetic control, which makes it essential to enhance target specificity while minimizing off-target effects. In contrast, proteins and peptides demand improved stability and methods for non-invasive administration, along with strategies to overcome biological barriers and reduce immune reactions. Antibodies face hurdles related to achieving high therapeutic doses, maintaining stability, and mitigating immune responses, while nucleic acids require innovative solutions for effective intracellular targeting, avoiding immune activation, and ensuring precise gene editing. Live cell therapies add further complexity with concerns about cell viability, unpredictable pharmacokinetics, and the challenge of directing cells to specific sites, not to mention the difficulties in scaling up production. To address these diverse challenges, researchers have developed a range of modification strategies such as altering functional groups, PEGylation, conjugating targeting ligands, and employing genetic modifications along with environmental adjustments like pH modulation, permeability enhancements, and the use of dispersion enhancers and endosomal escape techniques. These innovations have given rise to a variety of drug delivery systems tailored to each therapeutic class. Examples include microneedle patches, microparticle depots, transdermal systems, polymer films, and controlled-release implants for small molecules; injectable devices, wound dressings, and pH-responsive capsules for proteins and peptides; antibody-drug conjugates and coated microparticles for antibodies; lipid nanoparticles for nucleic acids; and drug-loaded contact lenses or swellable hydrogels for live cell therapies. Collectively, these advancements optimize drug delivery by ensuring controlled release, targeted action, and improved therapeutic outcomes (Vargason, Anselmo, and Mitragotri 2021, 951–967).

An extended-release formulation can be just as effective as an immediate-release version when the drug's concentration in the bloodstream remains within a defined therapeutic window that is, below the maximum safe concentration (C_{max}) and above the minimum effective concentration (C_{min}). This balance, often expressed as the ratio C_{max}/C_{min}, is known as the therapeutic index and ensures that minor fluctuations in drug levels do not compromise overall efficacy. Controlled release drug delivery systems are carefully engineered to minimize the peaks and troughs in plasma concentration, thereby reducing side effects and avoiding periods when the drug is either subtherapeutic or potentially toxic. Because maintaining an absolutely constant drug concentration is not required for safety and effectiveness, various formulations have been developed to provide a sustained or extended release of the active ingredient (FDA/SUPAC-MR

1997). Over the years, terms such as “sustained release,” “extended release,” “therapeutic system,” and “modified system” have been used interchangeably to describe these approaches, which ideally deliver the drug at a steady zero- or first-order rate. According to the U.S. Food and Drug Administration, modified-release solid oral dosage forms include both extended-release and delayed/enteric-coated formulations, and the United States Pharmacopeia details the specific release requirements in monographs USP <724> and USP <1088> (USP 2021). This strategy not only enhances therapeutic outcomes by keeping drug levels within the optimal range but also improves patient compliance by reducing dosing frequency and minimizing the risks associated with fluctuating plasma concentrations.

Controlled-release drug delivery systems began with the introduction of Spansule® 12-hour release technology by Smith, Kline & French Laboratories. This innovative method was initially used to formulate Dexedrine® for dextroamphetamine sulfate and later adapted for Contac® 600, which delivers phenylpropanolamine hydrochloride and chlorpheniramine maleate (Ullyot, Ullyot, and Slater 2000, 17) (Sharma and Varghese 2016, 75–76). The technology operates by controlling the dissolution of the drug core through a specialized coating that restricts the access of gastrointestinal fluids, thereby achieving a dissolution-controlled release mechanism. This breakthrough paved the way for a range of oral formulations that employ distinct release strategies. For example, diffusion-controlled systems, such as Ocusert® for pilocarpine, became widely adopted, while osmotic pressure-controlled approaches illustrated by Oral Osmotic (OROS®) systems in products like Acutrim® for phenylpropanolamine and Concerta for methylphenidate also emerged as effective alternatives. Ion-exchange-controlled systems were investigated as well, with Delsym® serving as a notable example for dextromethorphan delivery. Over time, however, dissolution- and diffusion-controlled systems have come to dominate the market, with only about 20 products based on osmosis and a single product utilizing ion-exchange methods. Since the ion-exchange approach is less suitable for sustained release in high-salt environments, resin particles are typically coated with diffusion-limiting polymers. Additionally, diffusion-controlled mechanisms have been successfully applied to transdermal delivery systems, such as Transderm Scop®. Although other controlled-release methods were explored during the 1950s to 1980s, most commercial products now rely on either dissolution- or diffusion-controlled systems or a combination of both to achieve consistent and effective drug release. Many researchers have been drawn to the concept of zero-order drug release, a method in which the drug is dispensed at a steady rate over time with the aim of maintaining constant blood levels. Developing oral formulations that achieve this consistency is challenging due to several physiological constraints. For instance, as an oral dosage form transits from the stomach into the intestine, the efficiency of drug absorption tends to decline because the lower regions of the intestine have reduced capacity for uptake. This decrease in absorption is further compounded by a gradual reduction in the drug release rate from the formulation itself over time. A notable example is the phenylpropanolamine HCl formulation found in Acutrim®, an Oral Osmotic (OROS) system that maintains a stable plasma concentration for approximately 16 hours (Liu, Farber, and Chien 1984, 1639–1661) (Keraliya, Patel, Patel, and Keraliya et al. 2012, 528079). In addition to these efforts, significant research has focused on developing modulated, or self-regulated, delivery systems. Such systems are particularly critical for drugs like insulin, which require precise dosing due to fluctuations in blood glucose levels (Volpatti, Matranga, Cortinas, and Delcassian et al. 2019, 488–497). Ideally, an insulin delivery system would integrate a glucose sensor, an actuator, and a feedback mechanism to adjust the release rate in real time. To date, most controlled release technologies offer only a continuous, fixed-rate release rather than true modulation. This approach ensures a more predictable pharmacokinetic profile, thereby enhancing both safety and efficacy. Furthermore, minimizing the peaks and troughs seen in immediate-release formulations reduces the risk of adverse side effects and improves patient compliance. Researchers continue to face challenges in designing fully implantable modulated systems, which remain one of the most complex technical hurdles in the field. There is optimism that ongoing innovations will eventually lead to the successful development and commercialization of such systems, ultimately providing more reliable and patient-friendly therapeutic outcomes (Verma and Garg 2001, 1–14).

Long-acting injectable formulations have made significant strides over the years, beginning with the approval of Lupron Depot® by the FDA, which delivers leuprolide acetate over a one-month period. Since its debut in 1989, advancements in PLGA microparticle technology through careful adjustments of the lactide:glycolide ratios and polymer molecular weights have extended the duration of drug release up to six months. This progress has opened the door for a variety of systems capable of delivering a range of therapeutic agents, from small molecules to peptides and proteins (Park, Skidmore, Hadar, and Garner et al. 2019, 125–134). Achieving controlled drug release over such prolonged periods presents a fundamentally different challenge compared to managing release over a single day. Long-acting formulations, especially those intended to last up to six months, necessitate higher doses and require that the release of the drug remains precisely controlled throughout the entire period. Presently, three primary formulation approaches are used to achieve this extended release: microparticles, in situ forming implants, and solid implants. Among these, microparticle formulations have become the most prevalent because they can encapsulate a significant amount of drug up to approximately 35% of the total solids content while providing reliable and controlled release profiles through intramuscular or subcutaneous injections. Despite over three decades of research and development in PLGA-based formulations, no generic long-acting injectable products have yet received FDA approval. A key challenge in this area is the insufficient thorough characterization of PLGA polymers. For a generic product to gain approval, the FDA mandates that it must be qualitatively (Q1) and quantitatively (Q2) equivalent to the reference listed drug (RLD) regarding its inactive ingredients, ensuring that the product maintains consistent safety and efficacy (FDA/CDER 2020). Nanocrystal suspensions are a unique form of long-acting injectable formulations that primarily consist of hydrophobic drugs, using very few excipients or surfactants, which enables them to achieve remarkably high drug loadings. These formulations are typically produced using high-energy milling techniques. In some cases, the active drug is chemically modified into a prodrug often by attaching a long-chain fatty acid to further reduce its solubility in water and slow its dissolution. This modification means the drug must be converted back into its active form by enzymes or through hydrolysis once administered (Compri, Felli, Lourenço, and Takatsuka et al. 2019, 1848–1856). For example, paliperidone palmitate (Invega Sustenna®) is formulated as a nanocrystal suspension of the palmitate ester of paliperidone, with its active metabolite originating from risperidone. Another approach involves formulating the drug as a salt or co-crystal with a hydrophobic counterion; an example of this is olanzapine pamoate (Zyprexa Relprevv®), where olanzapine is combined with pamoic acid. Although these nanocrystal formulations offer the benefit of exceptionally high drug loading, they also present challenges. Potential issues include changes in the crystal structure (polymorphism), the aggregation of particles within the suspension, and the possibility of tissue irritation upon administration (Jarvis, Krishnan, and Mitragotri 2019, 5–16). The first injectable PEGylated protein formulation, Adagen® (pegademase bovine injection), received FDA approval in 1990, shortly after the debut of the first long-acting injectable PLGA formulation, Lupron Depot®. Over the past 30 years, approximately 20 PEGylated protein formulations have been developed, and today, PEGylated interferon α2b is even used in treating COVID-19. PEGylation, which involves attaching poly(ethylene glycol) (PEG) to protein molecules, is designed to extend the time these proteins remain in circulation and to reduce their immunogenicity (Davis and Portland 1995) (Davis 2002, 457–458). Subsequent research, however, revealed that the body can produce antibodies against PEG, leading to accelerated blood clearance, a phenomenon known as ABC (anti-PEG antibodies) (Park 2018, 257). The hydrophilic nature of PEG causes its molecules to exhibit dynamic movement on the protein surface, which helps reduce uptake by the reticuloendothelial system, decreases proteolytic degradation, and lowers immune activation, ultimately enhancing therapeutic efficacy. While PEGylation can sometimes reduce a protein drug's bioactivity by diminishing its binding affinity to target sites, the overall benefit of prolonged circulation generally outweighs this drawback. The concept of PEGylation was pioneered in the late 1970s by Professor Frank Davis at Rutgers University (Hoffman and Lai 2020, 2–3). Beyond protein formulations, PEGylated lipids have been successfully incorporated into liposomes and lipid nanoparticles for oligonucleotide delivery, as exemplified by Onpattro® (approved in 2018 for siRNA delivery). Moreover, one of the most notable applications of PEGylation technology has been in the rapid development of mRNA-based COVID-19 vaccines, which utilize PEGylated lipid nanoparticles to ensure effective and targeted delivery. This innovative approach has not only improved drug performance but also broadened the scope of therapeutic applications across various fields of medicine (Khurana, Allawadhi, Khurana, and Allwadhi et al. 2021, 101142) (Brader, Williams, Banks, and Hui et al. 2021, 2766–2770) (Park, Sun, Aikins, and Moon 2021, 137–151).

In 2000, the U.S. government introduced the National Nanotechnology Initiative (NNI), marking a turning point in drug discovery and delivery through nanomedicine. From the outset, nanomedicine has mainly focused on tumor-targeted drug delivery (Wang, Li, and Nie 2021, 766–783), with formulations such as Mylotarg®, Doxil®, and Abraxane® the albumin-paclitaxel complex approved in 2005 becoming defining examples of this approach. FDA approvals for Doxil® and Abraxane® were driven largely by their ability to reduce side effects, rather than by superior efficacy compared to conventional therapies, underscoring the importance of minimizing adverse reactions. Although the enhanced permeability and retention (EPR) effect was initially seen as the primary mechanism behind these improved outcomes, practical experience shows that benefits extend beyond EPR alone. A major advancement in this field has been the engineering of lipid molecular structures that facilitate the escape of nanoparticles from endosomes, ensuring that the drug reaches its intracellular target. Since nanoparticles confined within endosomes have limited access to other cellular compartments, enabling their release is critical for enhancing drug efficacy (Wei, Sun, Yang, and Xiao et al. 2020, 81–94) (Tang, Svirskis, Leung, and Kanamala et al. 2019, 89–100). This design principle is well demonstrated by the lipid formulations used in Onpattro®, an siRNA delivery system that received FDA approval in 2018, and illustrates how thoughtful molecular engineering can overcome biological barriers to improve targeted drug delivery (Akinc, Maier, Manoharan, and Fitzgerald et al. 2019, 1084–1087). Although progress in developing tumor-targeted drug delivery systems within nanomedicine has been gradual, the evolution of this technology has played a crucial role in the rapid emergence of mRNA vaccines against COVID-19. Remarkably, it took only two months from the announcement of the SARS-CoV-2 genetic sequence for clinical trials to begin for these vaccines (Rappuoli, De Gregorio, Del Giudice, and Phogat et al. 2021, 1-7). By December 2021, nine vaccines had received full approval, with Pfizer/BioNTech and Moderna leading the way using mRNA technology. Given the inherent instability of mRNA, it is essential that it be effectively protected, delivered into cells, and released from endosomes to exert its therapeutic effect. PEGylated lipid nanoparticles have proven highly effective in meeting these challenges, performing as designed to shield the mRNA and promote its cellular uptake. This impressive achievement is the culmination of decades of progress in advanced delivery systems developed for genetic therapies, including those used for siRNA, mRNA, and plasmid DNA. The collective experience and technological improvements in these sophisticated platforms have not only enabled the swift development of effective mRNA vaccines but also laid the groundwork for future breakthroughs in gene-based therapeutics. These innovations promise to expand the scope of precision medicine, offering new opportunities for targeted, effective treatments in a variety of clinical applications (Cullis and Hope 2017, 1467–1475).

The ultimate aim of drug delivery research is to create formulations that deliver medications precisely to their target sites with predetermined release rates and durations. While basic research forms the foundation for these innovations, not every laboratory discovery ultimately becomes a product that benefits patients. There is a clear distinction between showing the potential of a new drug delivery technology and developing a clinically viable product. In many instances, it takes decades to transform innovative ideas into market-ready therapies because ensuring safety, efficacy, and scalable manufacturing requires extensive research and development. For example, the discovery of penicillin's antibacterial activity alone would not have saved lives without overcoming the challenges of large-scale production a breakthrough recognized by the joint Nobel Prize awarded to Ernst B. Chain, Sir Howard W. Florey, and Sir Alexander Fleming. A comparison with the computer industry illustrates the slow pace of progress in drug delivery. In 1964, when liposomes were first discovered, the UNIVAC 1108 computer boasting only 1 MB of memory and priced at $566,460 was introduced (Dietrich 1986, 159–169) (Walker 1996, 1968).

By 2021, technological advances had increased computer memory 30,000-fold, reduced costs by 200 times, and significantly shrunk device sizes. In contrast, it took over 30 years for liposomes to evolve into Doxil®, a PEGylated liposome formulation, and more than 50 years to develop PEGylated lipid nanoparticles for siRNA and mRNA delivery. This comparison underscores the gradual yet steady progress in drug delivery research, where long development timelines are essential to ensure that new therapies are both safe and effective for clinical use.

Table 1-2: Evolution of drug delivery systems – key developments and notable innovations by decade (Park, Otte, and Park 2022, 53–65).

Decade	Key Advancements	Notable Technologies
1950s	Introduction of dissolution-controlled release	Spansule® (1952)
1960s	Development of liposomal drug delivery	Liposome (Bangosome, 1964)
1970s	Advancements in controlled-release mechanisms	Ocusert® (1974, diffusion-controlled), OROS® (1975, osmosis), InFeD® (1974, iron-dextran complex)
1980s	Introduction of ion-exchange systems and transdermal patches	Delsym® (1982, ion-exchange), Transderm Scop® (1979, transdermal system)
1990s	Adoption of injectable depot formulations and PEGylation technology	Lupron Depot® (1989, PLGA microparticle), Norplant® (1990, implant), Adagen® (1990, PEGylated protein), Taxol® (1994, paclitaxel in PEGylated castor oil), Doxil® (1995, PEGylated liposome)

2000s	Emergence of nanomedicine, nanocrystals, and antibody-drug conjugates	Mylotarg™ (2000, antibody-drug conjugate), Rapamune® (2000, nanocrystal), Abraxane® (2005, paclitaxel-albumin complex)
2010s	Innovations in RNA-based therapies and peptide drug delivery	Movantik® (2014, PEGylated naloxol), Onpattro® (2018, siRNA in PEGylated lipid nanoparticle), Rybelsus® (2019, oral peptide tablet)
2020s	Advances in gene therapy and lipid nanoparticle formulations for vaccines	Kymriah® (2017, CAR-T gene therapy), Comirnaty® (2021, PEGylated lipid nanoparticle)
2030s (Future)	Focus on small molecules, peptides, and long-term drug delivery	Targeted and sustained-release systems

1.2 Conventional Vs Controlled Drug Delivery System

Traditional drug delivery systems (DDS), such as tablets, capsules, and syrups, have been the cornerstone of pharmaceutical treatments for decades. However, one of their primary limitations is the inability to maintain drug concentrations within the therapeutic window for an extended period. After administration, the drug is rapidly metabolized, leading to an initial spike in plasma concentration, followed by a sharp decline. This fluctuation can result in sub-therapeutic effects, where the drug concentration falls below the minimum effective concentration (MEC), or in some cases, toxicity if the drug accumulates beyond safe levels. To counteract this, patients are often required to take multiple doses at regular intervals. While this approach helps sustain therapeutic levels, it introduces inconsistencies in plasma drug concentration, increasing the likelihood of therapeutic failure or adverse effects. Additionally, frequent dosing can lead to poor patient adherence, reducing overall treatment effectiveness (Hardenia, Maheshwari, Hardenia, and Dwivedi et al. 2019, 1–28).

Controlled drug delivery systems, in contrast, are designed to overcome these challenges by ensuring a steady, predictable release of the drug over an extended period. Unlike conventional DDS, which exhibit peaks and troughs in plasma drug levels, controlled release formulations follow a zero-order pharmacokinetic profile, maintaining a stable drug concentration within the therapeutic range. This precision not only enhances therapeutic efficacy but also reduces the risk of toxicity and minimizes the frequency of administration, significantly improving patient compliance. Furthermore, by optimizing drug release, controlled DDS reduce unnecessary drug exposure to biological systems, thereby limiting side effects and improving overall safety. This shift from conventional to controlled drug delivery represents a significant advancement in pharmacotherapy, offering patients a more effective, safer, and convenient treatment experience (Park 2014, 3–8).

Choosing the right drug delivery system (DDS) is crucial for achieving the best therapeutic results, ensuring patients stay on track with their treatment, and reducing any unwanted side effects. Both conventional and controlled DDS have their own unique strengths and challenges that can influence how well they work in real-world settings.

Advantages of Conventional Drug Delivery Systems

Conventional drug delivery methods, like tablets, capsules, and syrups, are still the most commonly used formulations because they are simple to use and widely accepted by patients. These forms are non-invasive, and their effects are usually predictable, meaning doctors can rely on them to deliver the right amount of medicine when needed. One of the biggest benefits of conventional DDS is their accuracy in dosing, making it easier for healthcare providers to ensure patients get the right amount of medication. They also have long shelf lives and can be adapted for different patient groups. For doctors, it’s convenient to adjust dosages based on each patient's specific needs, and since these systems are cheaper to produce, they remain accessible to a broader population.

Limitations of Conventional Drug Delivery Systems

Despite their popularity, conventional DDS often come with some limitations. For one, these systems can struggle with delivering the drug efficiently to the right place in the body, leading to poor absorption. Without targeting specific areas, drugs are often spread throughout the body, which can increase the chances of unwanted side effects. Drugs in conventional forms are also quickly broken down or eliminated from the body, reducing their effectiveness and requiring more frequent doses. This can be a major hurdle for patients with chronic conditions who need long-term treatment, as it can decrease their adherence to the prescribed regimen.

Advantages of Controlled Drug Delivery Systems

Controlled drug delivery systems were created to overcome these challenges. They offer sustained or targeted drug release, ensuring that the drug stays at effective levels in the bloodstream for longer periods, minimizing the need for frequent dosing. This can lead to better patient compliance, especially for those with long-term illnesses. Since controlled DDS can target the drug directly to where it's needed, they reduce the chances of unwanted side effects and make treatment more effective. Additionally, these systems help protect the drug from being broken down too soon, increasing its bioavailability and prolonging its action. Overall, controlled DDS are designed to make drug administration more precise and less invasive, leading to better health outcomes for patients.

Limitations of Controlled Drug Delivery Systems

While controlled DDS offer significant benefits, they’re not without their own set of challenges. One concern is that the materials used in these systems may have potential toxicity issues. Another risk is "dose dumping," where the drug is released too quickly, which could cause toxicity and other adverse effects. Additionally, some controlled DDS require surgical implantation or removal, which can be uncomfortable or not acceptable to some patients. There are also concerns about how the body’s immune system might clear the drug too quickly, reducing its effectiveness. Compared to conventional systems, controlled DDS can sometimes be less predictable in terms of how they behave in the body, making it harder for doctors to anticipate how the treatment will work. Finally, these systems tend to be more expensive to develop and produce, which can make them less accessible for widespread use.

1.3 Classification of Controlled Released Drug Delivery Systems

Controlled release drug delivery systems are designed to regulate the rate and duration of drug release, ensuring sustained therapeutic effects while minimizing side effects. These systems are classified based on their release mechanisms, each offering unique advantages in optimizing drug delivery. Dissolution-controlled systems rely on the gradual solubility of the formulation to release the drug over time, while diffusion-controlled systems allow the drug to pass through a polymer matrix or membrane at a controlled rate. Water penetration-controlled systems, including osmotic pressure-controlled and swelling-controlled mechanisms, regulate drug release based on fluid absorption, ensuring consistent delivery. Additionally, chemically controlled systems use biodegradable polymers or chemical reactions to trigger drug release in a predictable manner. Nanoparticle-based systems, on the other hand, offer advanced capabilities such as targeted delivery, improved bioavailability, and enhanced drug stability. By tailoring the release profile of medications, these systems improve therapeutic efficacy, reduce dosing frequency, and enhance patient adherence, making them a valuable innovation in modern medicine (Gupta, Thakur, Jain, and Banweer et al. 2010, 571).

1.3.1 Dissolution Controlled Systems

The process of drug dissolution occurs in two key stages: first, drug molecules separate from the solid structure and move into the surrounding liquid, and second, they diffuse further into the bulk liquid medium. By carefully modifying these steps, scientists can develop controlled drug delivery systems that regulate both the rate and timing of drug release, optimizing therapeutic effectiveness. There are two primary methods used to achieve controlled release: matrix-based systems and barrier (or membrane-based) systems. In matrix-based systems, the drug is uniformly