Chapter

1

Historical Development of Controlled and Novel Drug Delivery Systems

Riya Shivgotra, Jaanvi Khanna, Pushpinder Kaur, Suraj Jain, Subheet Kumar Jain

1.1 INTRODUCTION

The manner in which a drug is administered can greatly impact its effectiveness. Some medications have an ideal concentration range for achieving maximum benefits, with concentrations exceeding or falling below this range potentially leading to toxicity or no therapeutic advantages. Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dosage required, lower effectiveness, toxicity, and adverse side effects (Abu-Thabit & Makhlouf, 2018). Conversely, the slow progress in treating severe diseases has highlighted the need for a multidisciplinary approach to drug delivery to specific tissue targets. This has sparked innovative ideas for controlling drug kinetics, dynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy (Ma et al., 2022). These innovative approaches, often referred to as drug delivery systems (DDS), incorporate various disciplines, including polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. While DDSs have seen recent advancements, the concept itself is not new and has evolved over the centuries. The development of modern DDS appears to be paralleling that of humanity, having been modeled for ages. Current efforts are directed at developing drug delivery and targeting systems to minimize drug degradation, and side effects, and enhance bioavailability while increasing drug accumulation in the desired location (Uhrich et al., 1999). What was once merely a dream or a possibility, controlled and novel drug delivery has now become a reality. Over the past fifteen years, pharmaceutical and scientific researchers have undertaken extensive investigations in this realm of drug research.

The field of drug delivery is a highly active area of research, profoundly affecting millions of patients annually, within a substantial global pharmaceutical market valued at $980 billion (Tibbitt et al., 2016). With a compound annual growth rate (CAGR) of 5.9%, the pharmaceutical drug delivery industry is expected to reach

$2206.5 billion globally by 2026 (Gao et al., 2023). Notably, certain blockbuster drugs, such as Lipitor, Crestor, Nexium, Humira, Enbrel, Remicade, Seroquel, Cymbalta, Zyprexa, Advair, and Singular, have utilized sustained-release technology to enhance efficacy and manage product lifecycles effectively (Park et al., 2022). Various drug carriers have been developed to deliver medications to the intended location and protect them from degradation, ensuring optimal efficacy and minimal unwanted effects. However, the complex process of DDS development, including mass production, toxicity testing, chemical characterization, and clinical trials, hinders the swift transition from laboratory to clinical use.

The field has shifted from empirical methods to a more theoretical, mathematical, and materials science-based approach. However, there is no all-encompassing biopharmaceutical theory, and individual human subjects remain the ultimate test of performance (Vargason et al., 2021). The development of controlled release hinges on three critical elements: the drug, its formulation, and the route of administration, which are interrelated. The choice of the active substance and its matching with specific delivery systems and devices require more attention. While pinpointing the exact date of inventions or developments is challenging, the history of controlled release is closely linked to early attempts at drug administration *via* various routes and clinical outcomes. Early beliefs that subcutaneous and intramuscular drug administration had only local effects were later dispelled (Peppas, 2013).

The Spansule® sustained-release capsule technology, which can deliver the drug for 12 hr after oral administration with an initial instant dose followed by the remainder release gradually, marked the beginning of modern drug delivery technology in 1952 (Hillery & Park, 2016). Until the 1980s, oral and transdermal formulations dominated the field, offering up to 24)-hour therapeutic durations for small molecules (Park et al., 2022). In 1989, Lupron Depot® introduced long-acting injectables and implantables, extending drug delivery to months or years, even for peptide and protein drugs *via* parenteral administration. PEGylation technology, with the introduction of Adagen® in 1990, ushered in a new era, resulting in drugs like Doxil®, Movantik, and Onpattro®. Drug-polymer complexes, such as InFed® and Abraxane®, were introduced, as well as novel formulations like Mylotarg™ and Rapamune® in 2000 (Park et al., 2019). The National Nanotechnology Initiative in the same year spurred the global pursuit of nanomedicine. This, combined with PEGylation, led to the development of lipid nanoparticle formulations for COVID-19 vaccines in 2020 (Park et al., 2019; Hillery & Park, 2016).

Despite these advances, there are countless untapped technologies. With increasing life expectancy, the demand for long-term care for various diseases grows. Meeting these needs requires innovative drug delivery technologies, addressing challenges like water solubility, biological barriers, and long-acting depot formulations. Past lessons are crucial for future technology development, as seen in the rapid response to the COVID-19 crisis. Encouraging diverse research in drug delivery is essential in this ever-evolving landscape. In summary, understanding the historical development of controlled drug delivery is crucial for appreciating its evolution and the challenges that remain in achieving precise and effective drug release systems.

1.2 HISTORY OF DDS (EARLY FORMS OF DDS AND EMERGENCE OF CONTROLLED DDS)

The historical development of controlled and novel DDS represents a fascinating journey in the field of pharmaceutical sciences. Over the years, there has been a significant evolution in how medications are administered to patients, with the primary goal of enhancing therapeutic efficacy while minimizing side effects. The story begins with the early use of traditional drug formulations, such as powders and tinctures, which lacked precision in dosage and release. The mid-20th century marked a turning point with the advent of controlled DDS, including transdermal patches and sustained-release tablets. These innovations allowed for a more predictable release of drugs over time, improving patient compliance and reducing adverse effects. As science and technology advanced, researchers delved into novel approaches like nanoparticles (NPs), liposomes, and microspheres to further refine drug delivery. The 21st century continues to witness remarkable breakthroughs, including targeted DDS that can deliver medication to specific tissues or cells. This historical journey underscores the relentless pursuit of safer and more effective drug delivery methods, resulting in improved patient outcomes and quality of life. The historical development of control and novel DDS can be divided into three distinct eras: the macro, micro, and nano eras (Abu-Thabit & Makhlouf, 2018) (Fig. 1.1). Each era represents advancements in drug delivery technologies at different scales, offering unique approaches and capabilities.

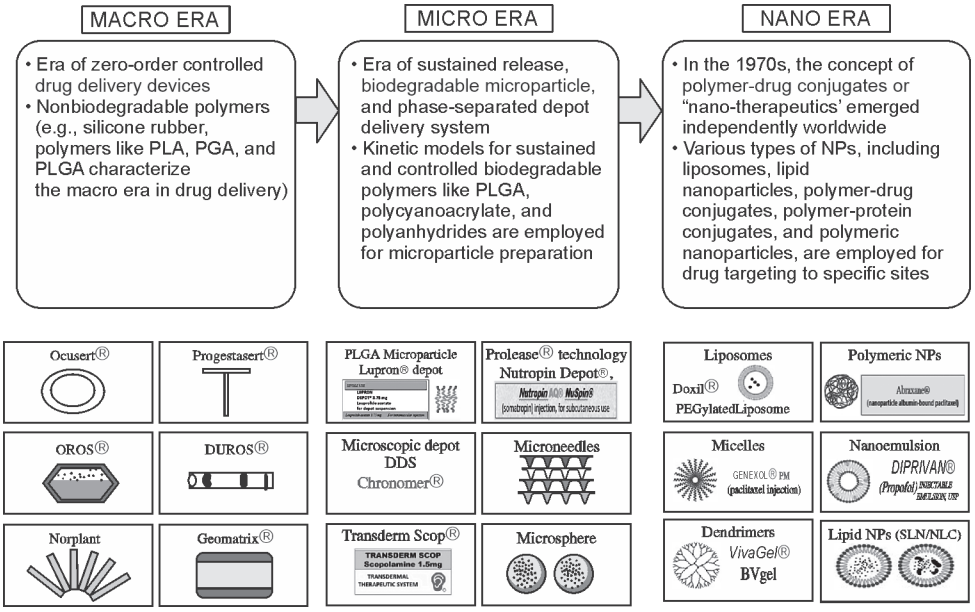

Fig. 1.1: Three eras representing the evolution of controlled and novel drug delivery systems with some selected FDA-approved drug products. *Abbreviation:* DDS: Drug delivery system; NPs: Nanoparticles; OROS: Osmotic-controlled release oral delivery system; PLGA: Polylactic-co-glycolic acid; PLA: Polylactic acid, PGA: Polyglycolic acid; PEVA: Poly (ethylene-co-vinyl acetate)

1.2.1 Macro Era (The Macro Era of Zero-order Controlled Drug Delivery Devices)

The use of non-biodegradable polymers like silicone rubber, polyurethane (PU), and poly (ethylene-co-vinyl acetate) (PEVA) in DDS is a characteristic of an earlier era in the field of drug delivery. These materials were commonly used in the past to develop various drug delivery devices and systems. These polymers function as drug reservoirs, allowing diffusion mechanisms to primarily regulate drug distribution. Table 1.1 provides a concise overview of formulations or products that received approval during the macro era.

- Norplant, which was licensed by the US Food and Drug Administration (FDA) in 1990 for use in contraception, is one of the first macroscale DDSs to be developed. This upper-arm implanted contraception comes in six 2.4 × 34 mm silicone tubes, each with 36 mg of progestin, levonorgestrel that are packaged in an insertion kit to make implantation easier. With a hormone release rate of 3.8 pg/cm length/day, the implant is functional for 5 years (Langer, 1983; Rowlands & Searle et al., 2014). Organon has recently brought a similar device to the clinic (Implanon®), using polyEVA as the rate controlling membrane (RCM). Implanon® was approved for clinical use by the FDA in 2006 (Hoffman et al., 2008).
- Many macro-scale commercial DDSs were developed as a result of the significant characteristics of ethylene-vinyl acetate (EVA) copolymers in early

Table 1.1: Overview of formulations or products that received approval during the macro era

Sl. no.	*Category*	*System Developed*	*Drug/Polymer*	*Year and company*
1.	Ophthalmic insert	Ocusert®	Anti-glaucoma drug, i.e. pilocarpine	1975 by Alza Corporation
2.	Vaginal insert	Contraceptive dough-nut-shaped device	Contraceptive steroid blended with silicone rubber	1970–1980
3.	Intrauterine device	Progestasert®	Drug-progesterone, and polymer - poly(ethylene-co-vinyl acetate) or polyEVA	1976
		Norplant®	Drug-levo-Norgestrel 6 silicone rubber tubes (cross-linked polydimethylsiloxane, PDMS)	1990
4.	Subcutaneous IDDSs	Testopel	Implantable testosterone pellet (for the treatment of testosterone deficiency syndrome)	1972
		Implanon	Etonogestrel	2006
5.	Ingestible capsules	OROS® and DUROS®	Osmotic capsule is cellulose acetate, sometimes blended with a small amount of a low MW PEG	By Alza cor. in 1970s and 80s
6.	Topical patches	Scopolamine	Scopolamine, (anti-motion sickness drug) with poly EVA or porous polypropylene (PP)	1979 Zaffaroni
7.	Hydrogels	Geomatrix®		Skye Pharma

research and development. Ocusert® is a controlled release method that was among the first to be developed for treating eye conditions, specifically glaucoma. With fewer side effects and better patient compliance than with daily eye drop administration, the device, a reservoir system inserted into the lower eyelid, delivers pilocarpine over a one-week period (Langer, 1983).

- Progestasert®, an intrauterine contraceptive device (IUD) shaped like a 'T,' is an alternative contraceptive method that uses PEVA for long-term contraception. The first progestin-releasing intrauterine system was approved and introduced to the market in 1976. Progestasert has a 38 mg progesterone medication reservoir that releases 65 μg of progesterone every day. ALZA Corporation manufactures Ocusert and Progestasert in the United States (Luukkainen et al., 2001). Transderm Scop, the first skin-patch DDS approved by the FDA in 1979, uses PEVA as the RCM to provide a consistent release rate of 0.50 mg of scopolamine over three days, equivalent to 1.5 mg. In 1971, Zaffaroni was issued one of the first patents on the patch, which he called a "Bandage for Administering Drugs" (Hoffman et al., 2008; Zaffaroni et al., 1971).
- Macroscale DDS kept developing in the 1970s and 80s, with an emphasis on oral drug delivery to the gastrointestinal (GI) tract. An innovative controlled-release oral DDS is the Osmotic Controlled Release Oral Delivery System (OROS®), which received its first patent issued in 1974. It has a single laser-drilled hole and is shaped like a rigid tablet containing a semipermeable outer membrane. Theeuwes and associates at ALZA Corporation developed the OROS platform, utilizing a water-permeable cellulose acetate hydrophilic polymer as the RCM (Theeuwes et al., 1983; Theeuwes et al., 1985).
- The ALZET implantable osmotic pump was developed for the preclinical study, and DUROS®, a matchstick-sized titanium implant operated by osmotic forces, was later developed for human usage. Therapeutic molecules can be continuously administered subcutaneously at predictable rates using sterile, non-biodegradable, single-use devices that are part of the DUROS delivery technology. Using a specially made semipermeable polyurethane (PU) membrane as the RCM, this method may deliver a broad variety of medicinal compounds for durations ranging from three to twelve months. In March 2000, the FDA authorized the Viadur implant, the first product based on DUROS technology. For the palliative treatment of prostate cancer, this implant releases a gonadotropin-releasing hormone (GnRH) analog leuprolide peptide drug. It is composed of a titanium cylinder with osmotically driven drug release that allows 12 months of maintaining the therapeutic concentration (Hoffman et al., 2008; Rohloff et al., 2008).
- Geomatrix® DDS of Skye Pharma system is a brand name for a different controlled DDS that uses the semisynthetic hydrophilic polymer, i.e. hydroxypropyl methylcellulose (HPMC) polymer. It is another zero-order DDS for oral delivery of drugs that is a cleverly designed swelling/gelling hydrogel system, conceived at the University of Padua in Italy by Paolo Colombo, Ubaldo Conti, and coworkers. Water-soluble pharmaceuticals are

the main target market for Geo-Matrix technology, and when dealing with drugs having low aqueous solubility, the release rate dramatically drops (Peppas & Colombo, 1997).

- The use of non-biodegradable polymers had certain limitations and drawbacks. For example, these materials could remain in the body for an extended period, potentially leading to long-term complications or the need for additional procedures to remove the delivery systems. Additionally, non-biodegradable materials might not be well-tolerated by the body's immune system, leading to adverse reactions. However, advancements in drug delivery technology have led to the development and utilization of more biocompatible and biodegradable materials in recent years. This approach helps to reduce potential complications and improve the overall safety and effectiveness of DDS. Biodegradable polymers like polylactic acid (PLA), polyglycolic acid (PGA), and polylactic-co-glycolic acid (PLGA) are now commonly used in DDS because they break down naturally in the body and are less likely to cause long-term issues. These advancements have contributed to the development of more precise and patient-friendly drug delivery methods (Abu-Thabit & Makhlouf, 2018).
- The discovery and development of the first synthetic biodegradable poly (hydroxy acids) for use in sutures was a noteworthy advancement in the 1960s and 1970s (Hoffman et al., 2008). Tissue hyperplasia, which mostly affects the areas where the stent struts contact the artery wall, is the main cause of in-stent restenosis. Polymeric coatings have been used to overcome this issue by allowing an embedded anti-restenosis drug to be released under controlled conditions. Over 2 million drug-eluting stents were implanted in 2004 when the TAXUS drug-eluting stent device received approval in both the US and Europe. The stent features a specialized coating called Translute, a proprietary polymer designed for TAXUS stents. Translute is a poly(styrene-b-isobutylene-b-styrene) (SIBS) block terpolymer, enabling the controlled release of paclitaxel drug to reduce tissue ingrowth (Park & Webster et al., 2005).

1.2.2 Micro Era

Prior to the 1970s, there was a misconception among polymer chemists and physicists that only drugs with low molecular weights (<600) could be delivered by polymers. The revolutionary work of Robert Langer and Judah Folkman in the 1970s led to the discovery of the controlled release of high molecular weight powdered molecules, including proteins, hormones, polysaccharides, and polynucleotides, from hydrophobic polymer matrices, and the development of microscale DDSs. Langer and his colleagues not only made these groundbreaking discoveries but also established kinetic models for the regulated and prolonged release of medications from different polymeric DDS (Hoffman et al., 2008; Abu-Thabit & Makhlouf, 2018).

The term "MICRO era" refers to a period in the history of drug delivery marked by the use of phase-separated depot delivery systems and biodegradable microparticles to create sustained-release systems. The micro era in DDS extended

from the late 20th century to the early 21st century and witnessed significant advancements in drug delivery technologies and devices. During this era, researchers and pharmaceutical corporations focused on developing innovative technologies to enable regulated and prolonged drug release within the body. These systems, with their long-term, progressive release of therapeutic compounds, enhanced the efficacy and convenience of medication therapies. Incorporating biodegradable components in microparticles and phase-separated depots is crucial because they allow the delivery system to gradually break down inside the body, reducing the need for device removal or extraction. These advancements have transformed the way medications are administered, improving precision, efficiency, and patient outcomes in drug delivery (Bae & Park et al., 2020).

The emergence of the micro era in the pharmaceutical industry, spanning from artificial intelligence-driven drug discovery to precision medicine and genomics, has accelerated the development of new drugs and improved patient outcomes (Johnson et al., 2021). During the micro era, various advanced delivery techniques, such as transdermal patches, microneedles, and implantable devices (offering less pain and ease of delivery) (Patra et al., 2018), as well as the use of biodegradable polymers (enhancing safety and reducing adverse effects) (Aldawood et al., 2021) and NPs like liposomes (improving bioavailability), were developed (Hakim et al., 2021). Table 1.2 provides a summary of formulations or products that were approved in the micro era.

- During the 1960s, Ed Schmitt and "Roco" Polestina, working at Davis & Geck, Cyanamid Co., undertook the synthesis and patented the utilization of PGA as a degradable suture. Ethicon enhanced this composition by incorporating lactic acid, resulting in degradable PLGA. They licensed the PGA technology from Davis and Geck and introduced the degradable PLGA suture known as Vicryl®. In parallel, Kureha Co. in Japan played a pivotal role by developing glycolidecyclic ester, which facilitated the polymerization of glycolic acid, ultimately leading to the efficient production of both PLA and PLGA (Emil & Albert, 1967; Hoffman et al., 2008).
- Peptide drugs were coupled with PLA in the late 1960s by DuPont researchers George Boswell and Richard Scribner to produce pellet depot DDS and microparticle DDS. For this invention, they were granted a patent in 1976, even though the patent application was submitted in 1969 (Wright & Hoffman, 2011). Simultaneously, in the 1970s, scientists at the University of Alabama in Birmingham and the Southern Research Institute (including Don Cowser and Danny Lewis) worked together to develop and test steroid-loaded PLGA microparticles for the delivery of contraceptive drugs in clinical settings (Hoffman et al., 2008).
- In the late 1970s, under a project sponsored by Syntex at Southern Research Institute, Tom Tice and Danny Lewis, along with Lynda Saunders and John Kent at Syntex, developed and patented long-acting (1-month) PLGA microparticles containing luteinizing hormone-releasing hormone (LHRH). These PLGA microspheres were utilized to encapsulate nafarelin, functioning as an analog for LHRH for contraceptive purposes. Subsequently, it became

Table 1.2: Notable drug delivery products approved during the micro era

Product name	*Use*	*Approval year*	*Inventor/ discoverer*	*Company name*	*Reference*
Liposomal doxorubicin	Improved cancer therapy	1995	Alberto Gabizon	Ortho Biotech, Janssen	Gabizon et al., 1996
Insulin pump	Diabetes management	1963	Dean Kamen	Medtronic, Insulet	Kesavadev et al., 2020
Transdermal patch	Controlled drug release through the skin	1979	Alejandro Zaffaroni	Various manufacturers	Alkilani et al., 2015
Nanoparticle-based drugs	Enhanced drug solubility and targeting	2000s	Various scientists	Various manufacturers	Severino et al., 2019
Microneedle patches	Pain-free and minimally invasive drug delivery	2000s	Mark Prausnitz	Various manufacturers	Prausnitz et al., 2004
Smart inhalers	Inhalable medications with connectivity	2010s	Various scientists	Various manufacturers	Zabczyk and Blakey, 2021
Biodegradable implants	Prolonged and targeted drug release	2000s	Robert Langer	Various manufacturers	Langer, 1998
Targeted antibody-drug conjugates	Precision cancer therapy	2000s	Researchers in academia	Various manufacturers	Beck et al., 2017

apparent that controlled-release LHRH, aimed at suppressing testosterone, held the potential for applications in the treatment of prostate cancer (Sanders et al., 1984; Tice, 2017).

- In the early 1980s, Debiopharm collaborated with the Southern Research Institute to develop triptorelin microparticles using PLGA, resulting in Decapeptyl®SR, the first FDA-approved injectable PLGA microparticle for prostate cancer treatment in 1986. This product provided extended-release duration due to the gradual degradation of PLGA microspheres (Abu-Thabit & Makhlouf, 2018). Three years later, the Syntex patent developed in collaboration with Southern and assigned to Syntex was licensed to the Takeda-Abbott Pharmaceutical Co. (TAP) and marketed as the Lupron Depot® (Sennello et al., 1986).
- During the late 1980s, Richard Dunn and a team of researchers at the Southern Research Institute devised degradable drug depot DDS using PLA or PLGA, which entailed administering subcutaneous or intramuscular injections of drug/polymer/solvent combinations to produce phase-separated, substantial "depots." The utilization of these depot systems in clinical applications expanded when Dunn transitioned to Atrix, Inc (Hoffman et al., 2008).
- A primary challenge in the development of biodegradable polymer microspheres for controlled drug release applications has been achieving consistent microsphere size, which is crucial for precise control of release rates.

In the early 1990s, Wayne Gombotz and his team at Enzytech developed the ProLease process, which employed a low-temperature ultrasonic spraying technique and a bath of liquid nitrogen and frozen ethanol to freeze uniformly sized particles and remove the solvent (Kamaly et al., 2016). This innovation effectively addressed the issue of size variation and preserved the integrity of proteins, resulting in high protein encapsulation efficiency. However, Nutropin Depot®, produced using the ProLease technology, was FDA-approved in 1999 but withdrawn from the market in 2004 due to elevated production and manufacturing costs (Kim & Pack, 2006).

- Jan Feijen at Twente University in The Netherlands introduced an additional biodegradable polyester in the 1990s, created from a copolymer of poly(ethylene glycol terephthalate) (PEG-T) and poly(butylene terephthalate) (PBT). This polymer, known as "Locteron®," is currently undergoing clinical trials conducted by the Dutch company OctoPlus for the delivery of α interferon using microparticle depot formulations (De Leede et al., 2008).
- There were other degradable depot solutions developed as well. For instance, employing di-block and tri-block copolymers of PLGA-PEG, Sung Wan Kim and YoungroByun of Utah University developed thermally responsive, aqueous solutions. Furthermore, Alza developed a macroscopic depot DDS utilizing "Chronomer®," a degradable polyorthoester (POE) that was invented at Alza by Nam Choi and Jorge Heller. In the meantime, a variety of polyanhydrides were developed by Langer and his colleagues and used in clinical settings as depot systems in the form of discs to treat glioblastomas (Hoffman et al., 2008). Both Kim and Langer developed businesses that made clinical applications possible and provided major contributions to the field of controlled drug delivery (Hoffman et al., 2008).
- Microscopic drug particles have gained approval for clinical applications in inhalation therapy. Key figures in this domain encompass John Patton, a co-founder of Inhale (later renamed Nektar), and, more recently, David Edwards from MIT and Bob Langer, who innovated "flakey" leaf-like drug-loaded particles for inhalation therapy. They founded AIR, which is currently a part of Alkermes (Hoffman et al., 2008).

1.2.2.1 Microneedles

Microneedles, as the name indicates, are small needles ranging in length from hundreds of micrometers to a few millimeters. Various types of microneedles are developed including solid, hollow, coated, dissolving, hydrogel, biodegradable, and microneedle arrays (Kim et al., 2012). Microneedles are designed to puncture the skin's outermost layer, the stratum corneum, for drug administration, while minimizing damage to nerve cells and blood vessels, resulting in a less painful alternative to traditional methods. They initially originated in the late twentieth century, whereas they acquired major acceptance during the micro era as a result of medical improvements (Aldawood et al., 2021). Microneedles represent a transformative technology that is reshaping drug delivery in the micro era. Their potential to improve patient compliance, enhance drug bioavailability, and expand

the scope of drug delivery applications make them a promising innovation in pharmaceuticals and healthcare.

Prof Prausnitz is the father of "microneedle technology," a technology that he invented for painless drug delivery through the skin. Prof Prausnitz's publication in 1998 in collaboration with Prof Mark Allen, a Professor of Electrical and Computer Engineering at Georgia Tech at that time, was the first demonstration of microneedles for drug delivery of insulin (Gill et al., 2019). The "MicronJet600," a patch used for administering vaccines, was the first microneedle-based device to get FDA approval. This was a crucial turning point in the use of microneedles in the medical field (Levin et al., 2015).

1.2.2.1.1 Applications in Drug Delivery

Microneedles have various applications in drug delivery such as:

- **Vaccine delivery:** Microneedle patches have shown potential for painless, self-administered vaccination administration, obviating the need for needles and healthcare personnel (Donnelly et al., 2023).
- **For diabetes management:** Insulin microneedle patches are a painless and simple substitute for regular injections for diabetics (Zhao et al., 2022).
- **In pain management:** With the help of microneedle-based patches, painkillers can be administered locally to increase the concentration of the drug and reduce systemic adverse effects (Priya & Singhvi, 2022).

1.2.2.1.2 Chronological Development of Microneedle

- The First Microneedle Concept was introduced in 1987 for the delivery of macromolecules (like insulin *via* skin) by Norman Weldon and Stephen Davis who own the patent also.
- Solid microneedles were first developed in 1998 using silicon to achieve improved and painless drug administration. This groundbreaking technology was pioneered at the Georgia Institute of Technology by Mark R. Prausnitz, Vladimir Zarnitsyn, and Mark G. Allen.
- Scientists developed hollow microneedles during the first years of the 2000s to deliver drugs in liquid form and expand the usage of microneedle technologies.
- Mark Prausnitz and his team in 2004 at Georgia Tech developed dissolving microneedles made of sugar-based materials. These microneedles could be used to painlessly deliver vaccines and drugs and then dissolve within the skin.
- In 2009, Microneedles for Influenza Vaccination Researchers conducted successful clinical trials using microneedles for influenza vaccination. The study demonstrated the safety and effectiveness of microneedles in delivering vaccines.
- In 2010, organizations such as 3M and Corium started offering solutions based on microneedle innovations for a variety of uses, such as administering medications and beauty treatments.

- FluMist is a microneedle-based flu vaccination approved by the US Food and Drug Administration (FDA) in 2014 for microneedles employed for intradermal, painless skin delivery.
- In 2019, research proceeded to work on microneedle-based insulin delivery systems, with the goal of providing a painless and cost-efficient substitute to regular needles for people with diabetic complications.
- Microneedles came to light as an exciting option for the administration of vaccines in the COVID-19 pandemic 2020. The scientists investigated the possibilities for painless and practical COVID-19 vaccination administration.
- The microneedle technology is still evolving during the 2020s, as scientists looking at novel parts, uses, and production processes in an effort to make microneedles more widely available and functional.

1.2.2.2 Microspheres

Microspheres are small, spherical particles typically ranging in size from a few micrometers to a few hundred micrometers. They are engineered materials with a wide range of applications in various fields, including pharmaceuticals, medicine, and materials science. During the micro era, which spans from the late 20th century to the early 21st century, microspheres underwent significant development and innovation (Galande et al., 2022). The precise control over their properties and versatility in design make microspheres valuable tools for researchers and engineers working on cutting-edge technologies and applications (Li and Zhang et al., 2019). Microspheres are typically made from a variety of materials, including polymers, ceramics, glass, and metals. They are characterized by their uniform size, spherical shape, and precisely controlled properties (Lengyel et al., 2019).

1.2.3 Nano Era

The "nano era" of DDS is a relatively recent development in the field of pharmaceuticals and medicine. It involves the use of nanotechnology to design and develop DDS that can target specific cells or tissues in the body, enhance drug solubility, improve bioavailability, and reduce side effects. This approach has the potential to revolutionize the way drugs are administered and improve patient outcomes. The term "nano-therapeutics," or polymer-drug conjugates, became popular in different regions of the world in the middle to late 1970s. The enormous activity and clinical success of nanotherapeutics from the late 1980s to the present was mostly driven by three technologies (Peppas et al., 2013). First, emerged the concept of "PEGylation," which describes drugs or drug carriers that are coupled with polyethylene glycol (Howard et al., 2008; Butcher et al., 2016). The second is the idea of "active targeting" of the drug conjugate, which involves attaching small molecule cell ligands, peptides, or antibodies that bind to cell membrane receptors to the polymer carrier. The third was Hiroshi Maeda's discovery in Kumamoto, Japan of the "enhanced permeation and retention effect" (EPR), which describes how the fast-growing tumor's leaky vasculature traps nano-scale carriers inside solid tumors. In contrast to active targeting, this is commonly referred to as "passive" targeting (Hoffman et al., 2008).

Nanocarriers are sub-micron-sized particles having a significant surface area, which enables them to provide more loading or dosing per unit volume. They provide better bioavailability where and when it is required (Deng et al., 2020). The new drug delivery approaches include the distribution of poorly water-soluble medications, long-term and non-invasive protein/nucleic acid/peptide delivery, targeted drug delivery by utilizing NPs, and drug delivery *via* self-regulation (Park et al., 2014).

The advancement that enabled nanomedicine delivery involved coating NPs with hydrophilic PEG, a process known as PEGylation, creating the "stealth effect." This coating offered benefits like increased NP stability, longer circulation time, and reduced macrophage recognition due to PEG's properties. PEGylation prevents opsonin protein adsorption on NP surfaces and can be achieved through adsorption or covalent attachment of PEG. Passive targeting of PEG-coated NPs was made possible by the discovery of NPs accumulating in tumors *via* the EPR effect. Clinical trials for passive targeting using nanocarriers began in the mid-1980s, with liposomes and polymer protein conjugates emerging as the first products in the mid-1990s (Peppas et al., 2013).

In a related field, the Nobel Prize in Medicine in 1972 recognized Gerald M. Edelman and Rodney R. Porter for their antibody structure discoveries (Abu-Thabit & Makhlouf, 2018). Antibody technology took a major leap in the late 1980s with the development of efficient antibody gene cloning and expression systems in bacteria. This led to the emergence of active targeting nanocarriers, enabling the creation of NPs designed for specific disease antigens (Peer et al., 2020; Maynard & Georgiou, 2000).

Paul Ehrlich, an enormity, is credited with being the predecessor of NP. Being the 'Father of NPs', he pioneered the notion of NP after witnessing Karl Maria von Weber's opera, to enhance medication therapy by targeting drugs or physiologically active substances (Kreuter, 1995). Gerd Birrenbach pioneered the "Micelle polymerization" process to manufacture NPs in 1969, and the resulting NPs were utilized to evaluate antibody reactions. Following that, Helmet Kopf used a similar "micelle polymerization" principle to create the first NPs for sustained delivery of drugs *via* intravenous administration (Birrenbach & Speiser, 1976; Kopf et al., 1976). Patrick Couvreur developed the first fast biodegradable acrylic-based NPs made of poly(methyl cyanoacrylate) and poly(ethyl cyanoacrylate) (Couvreur et al., 1979).

As of December 2021, nine vaccines had been licensed for full usage (Corum et al., 2020), with the first two FDA-approved vaccines, Pfizer/BioNTech and Moderna vaccines, employing mRNA. Because mRNAs are exceedingly fragile, they must be well protected. To be successful, protection must be followed by efficient distribution into cells and further release from the endosome. This is a fantastic feat for formulation scientists by any standard. This rapid development of PEGylated-based lipid nanoparticles (LPNs) was rapidly developed for mRNA delivery lipid due to the accumulation of decades of advancement in complex delivery systems for genetic therapeutics like as siRNA, mRNA, and plasmids DNA (Cullis & Hope, 2017).

PEGylation of NPs creates a steric barrier to opsonin protein adsorption due to the neutrality, hydrophilicity, flexibility, and hydration capacity of the PEG moiety.

PEGylation of particle surfaces can be accomplished through simple adsorption (i.e. coating) or by covalent attachment of PEG to activated functional groups on the particle surface (Howard et al., 2008). After identifying the accumulation of NPs in tumors through the EPR effect, great research endeavors for passive targeting utilizing PEG-coated NPs were recognized as a feasible technique (Matsumura & Maeda, 1986; Maeda, 2010).

There can be two ways by which the drug can be targeted through NPs, namely, active and passive targeting. In passive targeting, the polymer size determines the building up of the biocompatible polymer at the specific site of diseased cells. Extrusion of polymers can occur as a result of defective or leaking vascular junctions, allowing the polymer to reach the diseased site (Shah et al., 2021). Passive targeting nanocarriers' initial clinical trials started in the mid-1980s, with the first drugs based on liposomes and polymer protein conjugates reaching the market in the mid-1990s. However, passive targeting has some drawbacks such as the diffusion problem of some medications to the specified tumor cells and in addition to this, an unpredictable characteristic of this strategy makes it challenging to control the process. This lack of control may result in multiple-drug resistance, a circumstance in which chemotherapy treatments fail patients due to cancer cells' resistance to one or more medications (Peer et al., 2020). This passive technique is further constrained since some tumors fail to demonstrate the EPR effect, and vascular permeability may vary throughout a tumor (Peer et al., 2020; Jain, 1994). Numerous research attempts have recently been made to address the aforementioned drawbacks by applying active targeting of antineoplastic medications to a specific cancer tissue or a cell as a result of a specific ligand-receptor interaction (Peer et al., 2020; Allen, 2002; Nicolas et al., 2013). ONTAK, an active targeting NP, was authorized by the FDA in 1999. ONTAK (Denileukin Diftitox) is an authorized complex protein that comprises cytotoxic chemicals and targeting proteins (Bobo et al., 2016).

There are various types of NPs used for drug targeting to a specific site: Liposomes, Lipid nanoparticles, Polymer-drug conjugates, Polymer-protein conjugates and Polymeric nanoparticles. Numerous drug products that were marketed after being approved are given in Table 1.3 along with their specific uses and type of nanocarriers used for targeting.

1.2.3.1 Liposomes

With a hydrophilic "head" and hydrophobic fatty acid "tails," liposomes are spherical lipid vesicles composed of at least one lipid bilayer. "Lipos" means fat, and "soma" means body in Greek, which is how they got their names. After Alec Bangham discovered multilamellar lipid structures in 1964 (Bangham & Home 1964), liposomes were originally referred to as Bangosomes or smectic mesophase (Park et al., 2022). The name was eventually modified to liposomes because the lipid-based vesicles were made with phospholipids (Makwana et al., 2021). Gregoriadis and Gregory were the first to propose the concept of liposomes as a means of drug delivery (Gregoriadis et al., 1971; Gregoriadis 2016). Liposomes were later employed for the delivery of DNA to cells (Smith et al., 1993). Liposomes are commonly

Table 1.3: Some nanotechnology-based approved marketed drug products and their specific uses

Sl. no.	*Types of nanocarrier*	*Product name*	*Company*	*Approval year*	*Uses*
1.	Liposomes	Doxil®	Sun Pharma Global FZE	1995	Cancer treatment
		Marqibo	Talon Therapeutics Inc.	2012	
2.	Lipid nanoparticles	Onpattro® (siRNA in lipid nanoparticles)	Alnylam Pharmaceuticals	2018, 2021 and 2022	Polyneuropathies vaccines against COVID-19 (Lin et al., 2023)
		Comiranty® and Spikevax® (mRNA in lipid nanoparticles)	BioNTech Manufacturing GmbH and Moderna		
3.	Polymer-protein conjugate	Adagen	Enzon	1990	SCID syndrome (Levy et al., 1988)
4.	Polymeric nanoparticles	Livatag Abraxane	Onexeo (BioAlliance-pharma)	2023	Cancer treatment (Alphandéry et al., 2015; Heidel & Davos, 2011)
5.	Micelles	Generol-PM	Samyang biopharm	2007	Breast cancer and NSCLC (Yi et al., 2018; Svenson, 2012)
6.	Polymeric drug conjugate	PEG-adenosine deaminase ADAGEN®	Enzon	1990	SCID syndrome
		PEG-adenosine ONCASPAR®	Enzon	1994	Acute lymphoblastic leukemia (Schütz et al., 2013)
7.	Dendrimers	VivaGel®	Starpharma	2017	Topical microbicide
		Starburst®	Starpharma	2021	Targeted diagnostic, therapeutic delivery for cancer cells (Mignani et al., 2021)

prepared using either natural or synthetic phospholipids, and some synthetic phospholipids are derived from their natural counterparts. Because of their purity and the potential to be altered with particular characteristics, like PEGylation; semisynthetic phospholipids are favored for the production of stealth liposomes (SSL), which have prolonged bloodstream circulation durations.1,2-dioleoyl-phosphatidylethanolamine (DOPE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), and the DSPE-PEG conjugate, known as DSPE-mPEG-2000 with a molecular weight of 2000, represent some of the synthetic phospholipids employed in the creation of liposomes. Egg phosphatidylethanolamine.

More than a dozen lipid formulations have been clinically tested since the first approval of a PEGylated liposome formulation, Doxil® in 1995 (Bulbake et al., 2017). Doxil® (Caelyx; Alza Pharmaceuticals, San Bruno, California) incorporates the type of anticancer drug doxorubicin that is administered by SSL technology. When compared to free doxorubicin, Doxil has a considerably longer half-life (55 hr) in

humans, which results in a lower profile of adverse effects. Cardiomyopathy, a side effect that is frequently linked to long-term doxorubicin treatment, is rarely experienced by patients receiving Doxil therapy.

1.2.3.2 Lipid Nanoparticles (LNPs)

Unlike liposomes, LNPs create micellar structures within the core that can be altered based on formulation and synthesis conditions, presenting a unique colloidal system (Figueroa-Espada et al., 2020). A solid lipid core, consisting of triglycerides or any other mixture of glycerides, makes up the structure of lipoprotein candidates. A standard LNP comprises four components: (i) The lipid portion that is ionizable, facilitating self-assembly, increasing the rate of mRNA encapsulation, and therefore aids in endosomal escape; (ii) The phospholipid that stabilizes the bilayer and encapsulates the lipid structure (Guevara et al., 2020), (iii) The stabilizing agent for membrane fusion and stability purposes, and (iv) Lipid-based stabilizing agent such as polyethylene glycol (PEG) decreases nonspecific binding to proteins and lengthens the half-life. Because of their kinetic stability and firm morphology, LNPs are preferred as carriers over liposomes. LNPs also increase circulation time by facilitating evasion of the reticuloendothelial system (RES) or bypassing first-pass metabolism. They are a desirable drug delivery method due to their capacity to transfer a wide range of therapeutic substances, including therapeutic medicines and nucleic acids (mRNA, siRNA, and DNA) (Etheridge et al., 2013; Immordino et al., 2006; Kong et al., 2019). mRNA is translated into an immunogenic protein against particular antigens after it leaves the endosome and reaches the cytoplasm (Kauffman et al., 2015; Xue et al., 2015).

Aside from liposomes, LPNs incorporating PEGylated lipids have demonstrated efficacy in delivering oligonucleotides, such as Onpattro® (siRNA in PEGylated LPNs), which was approved in 2018. PEGylation technology proved crucial in the rapid fabrication of mRNA-based COVID-19 vaccines in PEGylated LPNs (Xue et al., 2015; Khurana et al., 2021; Park et al., 2021; Schoenmaker et al., 2021; Brader et al., 2021). The FDA granted complete approval for Comiranty® (Pfizer/BioNTech formulated mRNA COVID-19 vaccine) in August 2021.

1.2.3.3 Micelles

Amphiphilic polymers combine themselves into nanoscale structures called self-assembled polymer micelles. When polymer chains, or unimers, dissolve in water above a specific concentration (called the critical micelle concentration) and temperature (called the critical micelle temperature); micelles are formed. It is also possible to dissolve amphiphilic polymers with limited water solubility in organic solvents and dialyze them against an aqueous buffer. There are several ways to integrate insoluble drugs into micelles (Batrakova et al., 2006).

A low molecular mass and biodegradability prevent toxicity in the most widely used block copolymers that are employed in the production of these micelles. Typically, these micelles feature a hydrophilic shell that inhibits protein binding and aggregation during delivery and a hydrophobic core for loading drugs (Jones & Leroux, 1999). A few micelles are made to resemble targeted NPs by joining ligands

to the polyethylene glycol (PEG) polymers' distal ends. Genexol-PM®, encapsulating paclitaxel in poly(lactic acid)-b poly(ethylene glycol) (PLA-PEG) micelles, was the first micelle-based nanomedicine for drug cancer treatment. It received approval in Korea in 2007 and was subsequently commercialized by Samyang Biopharm (Svenson, 2012). Other micelle-based nanomedicines, such as NK105, NK012, and NK911 have been developed for the treatment of cancer. Clinical experiments have demonstrated the potential of these micelles.

Poloxamers, which were previously known as "Cremophor" and are also marketed under trade names like Pluronics, Synperonics, and Kolliphor, are copolymers with a tripartite structure comprising both hydrophobic and hydrophilic components. These copolymers have demonstrated the capacity to improve drug transport across biological barriers and sensitize multidrug-resistant tumors to anticancer treatments. They are utilized in the synthesis of micelles. Interestingly, Pluronic L61 and F127 were used to develop the 22–27 nm SP1049C doxorubicin-loaded micellar formulation, which is now undergoing phase III clinical trials (Schmolka, 1994; Adeli & Mortazavi, 2014).

1.2.3.4 Polymer-protein Conjugate

Numerous barriers exist in the way of using proteins directly as targeted therapeutic agents, such as immunogenicity, short half-lives, limited stability *in vivo*, and quick excretion from the body (Jung & Theato, 2013). The first commercially available polymer-based DDSs were developed as a result of the conjugation of proteins to polymers, which helped to overcome the aforementioned challenges. Because polymer-drug conjugates have a huge hydrodynamic volume greater than the glomerular filtration barrier, it is possible to lower the renal excretion rate (Pasut & Veronese, 2007). All FDA-approved protein conjugates are PEG that have been covalently bonded (PEGylated), and because of their extended circulatory half-lives, patients can benefit greatly from less frequent treatment (Pelegri-O'Day et al., 2014).

In order to prevent the occurrence of neutropenia due to cancer chemotherapy, FDA approved Pegfilgrastim in January 2002 (Kinstler et al., 2002). Pegfilgrastim is a conjugated product of filgrastim, human granulocyte colony-stimulating factor (GCSF), a recombinant methionyl and monoethoxypolyethylene glycol (Ho & Gibaldi, 2013).

1.2.3.5 Polymeric Nanoparticles (PNPs)

PNPs are the colloidal polymeric particles ranging in size from 100 to 1000 nm. Natural or synthetic polymers can be used while manufacturing PNPs by two methods:

a. Monomer polymerization *via* emulsion and dispersion polymerization.
b. Polymer dispersion (nanoprecipitation and emulsification diffusion method).

Drugs can be physically or chemically integrated, adsorbed, or absorbed. One of the key advantages of PNPs over colloidal systems is their increased stability in blood fluids after they are delivered (Cagel et al., 2017). One of the marketed PNP formulations is Abraxane, a paclitaxel containing albumin-bound NP by Abraxis BioScience (Svenson, 2012). Treatment of metastatic breast cancer using Abraxane

was approved by the FDA in January 2005 and by the European Medical Agency in January 2008. In 2012, the FDA expanded the usage of Abraxane's approved use for the treatment of non-small cell lung cancer (NSCLC). A less toxic substitute for FOLFIRINOX, Abraxane was also approved by the FDA in 2013 for the treatment of advanced pancreatic cancer (Damascelli et al., 2001).

1.2.3.6 Dendrimers

At first, the focus of polymer technology was primarily on linear polymers. However, it was later discovered that the characteristics of extensively branched polymers can vary from those of typical polymers. These highly branched molecules, known as dendrimers, are now recognized as the fourth primary architectural category of polymers, alongside the three well-known types: linear, branched, and cross-linked polymers. Over the past two decades, dendrimers have gained significant attention due to their applications in a wide range of fields, including electronics, catalysis, and biomedical uses. Dendrimers are characterized by their highly branched, spherical, multivalent, uniformly sized macromolecules with precisely defined symmetric three-dimensional structures. Dendritic structures are commonly employed natural patterns, particularly when a specific function needs to be enhanced or highlighted. The structure of a dendrimer consists of a central core molecule, branching structures, internal cavities, and numerous terminal groups (Nikzamir et al., 2021).

Since their discovery in the early 1980s, dendrimers have exemplified controlled hierarchical synthesis, enabling the creation of intricate systems. Notably, dendrimer synthesis offers precise control over size, composition, and chemical reactivity, resembling a finely tuned machine. Almost any polymer can be employed to produce a dendrimer. The first extensively characterized type is the polyamidoamine or PAMAM dendrimers, which are constructed through a repetitive sequence of steps, yielding dendrimers up to generation 10. Over the past decade, numerous diverse dendrimer variations have emerged and been explored, demonstrating their suitability for various applications (Mainardes & Silva, 2004; Nikzamir et al., 2021).

1.3 FUTURE OF DRUG DELIVERY SYSTEMS

The primary objective in drug delivery research is to develop formulations capable of accurately targeting specific sites and releasing drugs with precise kinetics and duration. Although basic research holds significance, it does not always directly translate into products used by patients. Transforming new technologies into clinical products is a lengthy process, akin to the extensive research and development involved in the creation of penicillin (Cullis & Hope, 2017).

The future is marked by high unpredictability, exemplified by unexpected events like the COVID-19 pandemic and the pivotal role played by LPNs in addressing it. Adapting and expanding drug delivery technologies become essential to navigate such uncertainties. Creative thinking and diversified approaches are urged to better confront unforeseen challenges, recognizing that there is no one-size-fits-all solution for every disease, and flexibility is vital in addressing new problems. Learning from mistakes in the field is crucial for progress, especially considering that scientific

advancements in drug delivery progress slower compared to industries like computing. The extended development process, driven by rigorous safety and efficacy testing for clinical products, necessitates a shift towards prioritizing clinical applications over minor technological improvements to expedite progress. To accelerate the translation of basic research into clinical products, a change in funding priorities is necessary, moving away from favoring popular topics to support the development of crucial clinical applications. Scientists are encouraged to approach each disease with the urgency seen with COVID-19 to enhance research focus and progress in drug delivery, transitioning from theoretical knowledge to practical, life-saving applications (Park et al., 2022).

The convergence of artificial intelligence (AI), functionalization, carbon nanotubes (CNTs), quantum dots (QDs), and nanotechnology has opened up exciting possibilities in the field of drug delivery. These innovations collectively propel the future prospects of drug delivery towards personalized and highly efficient therapeutic interventions, marking a paradigm shift in healthcare towards precision medicine in the nano era.

- **Artificial intelligence:** AI facilitates the identification of potential drug candidates by analyzing vast datasets and predicting molecular interactions. It expedites the drug discovery process by narrowing down the search space and suggesting novel compounds. AI enables the development of personalized drug delivery systems by analyzing patient-specific data, optimizing treatment plans, and predicting individual responses to medications (Paul et al., 2021).
- **Functionalization:** Functionalization of nanoparticles, such as CNTs and QDs, involves modifying their surfaces with specific functional groups to enhance biocompatibility, stability, and targeting capabilities. Functionalization allows for the attachment of ligands that can selectively target specific cells or tissues, enabling a more precise and efficient drug delivery (Amina & Guo, 2020).
- **Carbon nanotubes:** CNTs can encapsulate drug molecules, protecting them from degradation and facilitating controlled release. The unique physical and chemical properties of CNTs make them suitable for targeted drug delivery, reaching specific cells or tissues (Srivastava et al., 2023).
- **Quantum dots:** Imaging and tracking: QDs possess excellent optical properties, making them useful for imaging and tracking drug delivery in real-time. This aids in monitoring the distribution and effectiveness of the drug. QDs can be integrated into theranostic systems, combining therapeutic and diagnostic functions for a more comprehensive approach to treatment (Ajith et al., 2023).

The potential of DDS in the future is vast, propelled by progress in nanotechnology, biotechnology, and materials science. While nanoparticle-based drug delivery systems have seen extensive development, predominantly focused on targeting tumors, there is a need to think beyond current paradigms and explore different ideas and approaches for various medical conditions. The development of smart DDS, responsive to physiological cues or controlled remotely, represents a new frontier for personalized medicine. However, these prospects are accompanied

by notable challenges, including ensuring the safety and biocompatibility of novel materials, addressing regulatory concerns, and optimizing manufacturing processes for scalability. Additionally, integrating digital technologies into DDS, while holding potential for improved monitoring and patient adherence, demands solutions to cybersecurity and privacy issues. Navigating these challenges in the evolving landscape of DDS requires a collaborative effort from researchers, clinicians, and regulatory bodies to unlock the full potential of transformative therapeutic approaches.

1.4 CHALLENGES AND FUTURE PERSPECTIVES

Challenges include regulatory hurdles, biocompatibility issues, and the need for personalized medicine. The pharmaceutical and medical device industries face significant challenges in navigating rigorous regulatory frameworks to ensure patient safety and efficacy. Compliance with standards demands extensive testing and documentation, making development and approval processes complex and resource-intensive. Biocompatibility issues, such as inflammation and immune responses, can arise from the introduction of foreign substances in drug delivery. Overcoming these challenges necessitates thorough testing and refinement of delivery materials. Achieving personalized drug delivery requires advancements in precision medicine, diagnostics, and therapeutic strategies to tailor treatments to individual patient needs.

Future prospects involve integrating artificial intelligence for personalized drug delivery and exploring new materials. The future of drug delivery incorporates artificial intelligence (AI) for personalized treatments, utilizing vast datasets to analyze genetic information and patient history. Machine learning predicts patient responses, enabling adaptive drug delivery systems. Advances in materials science enhance delivery with biocompatible, controlled-release, and targeted materials, including nanotechnology. Future systems may feature innovative mechanisms like implantable devices and smart materials, responding to physiological signals for real-time adjustments in drug release.

CONCLUSION

The historical development of DDS reflects a progression from simple methods to sophisticated, targeted approaches. Ongoing research and technological innovations continue to shape the future of controlled and novel DDS.

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