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Yogeshwar Bachhav

Targeted Drug Delivery

Volume 82
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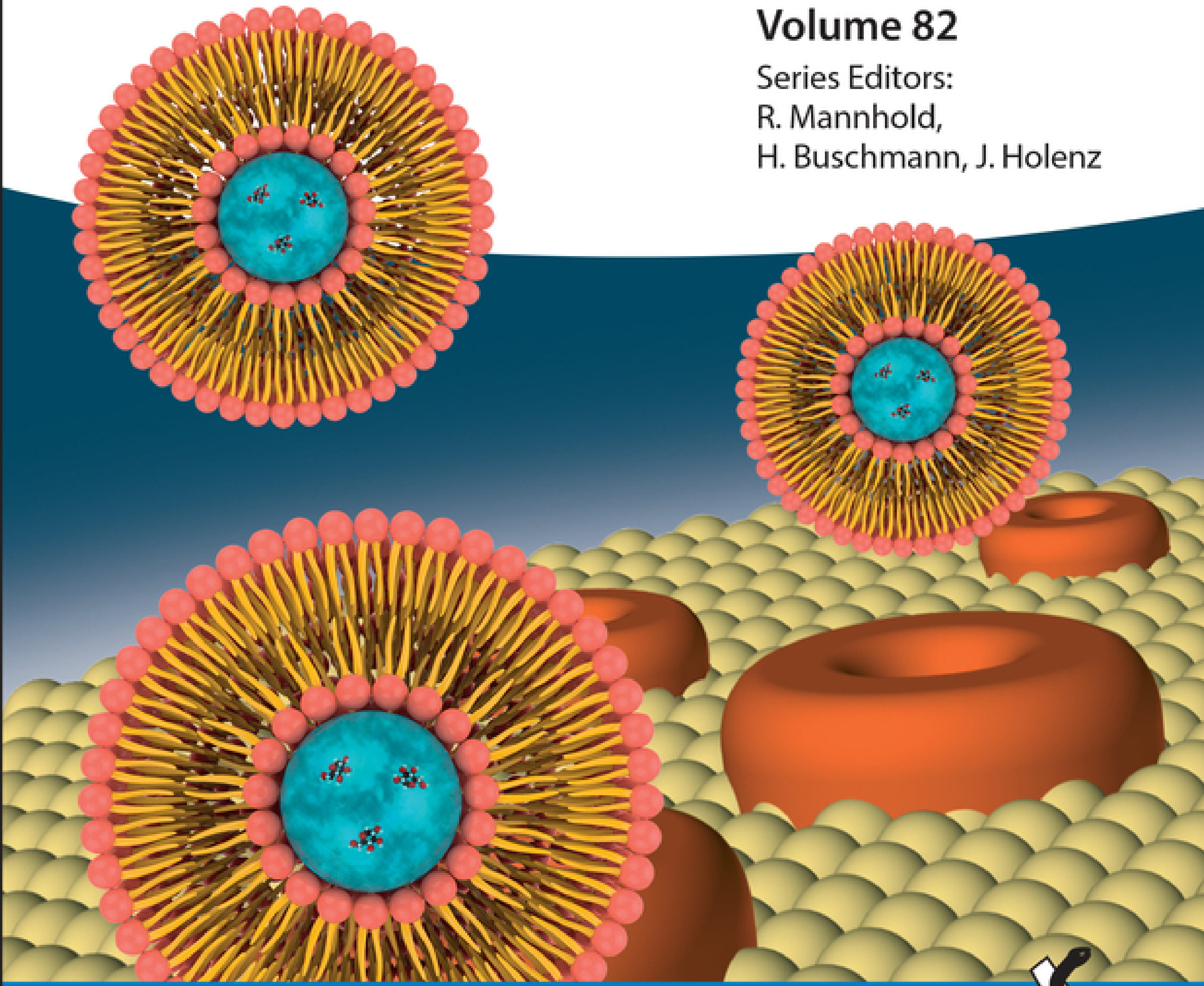
H. Buschmann, J. Holenz



Methods and Principles in Medicinal Chemistry

Targeted Drug Delivery

Methods and Principles in Medicinal Chemistry

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Targeted Drug Delivery

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Cover Image:
© SciWhaleDesign/Shutterstock

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-34781-0
ePDF ISBN: 978-3-527-82786-2
ePub ISBN: 978-3-527-82787-9
oBook ISBN: 978-3-527-82785-5

Cover Design: SCHULZ Grafik-Design
Typesetting Straive, Chennai, India

Contents

A Personal Foreword

Paul Ehrlich, the German scientist who was awarded Nobel Prize in Physiology or Medicine in the year 1908, formulated the "lock-and-key theory" of drug and receptor interaction. This was a significant milestone to understand the interaction of the drug molecules with the target receptor to induce any physiological activity, either desired or undesired. All the adverse events or side effects of any drug are linked to the undesired physiological activity induced by these therapeutic agents. And that's where the concept of the targeted drug delivery gains prime importance in the field of medicine. The overall and foremost objective of the drug-delivery scientist is to deliver the drug at the right site in a desired amount to achieve the cure without inducing any adverse effects.

The present edition focuses especially on the development of drug-delivery systems on the interface discovery and of clinical development of investigational drugs which covers both approved and marketed drugs, where targeting concept should allow precise delivery of a moiety at the site of action. Most importantly, the issue focuses on the targeted drug delivery of not only small molecules but also complex biologicals such as peptides, proteins, and antibodies.

I would like to thank all the authors for their contribution to this book; without their support, this compilation was not possible. You guys really went out of way to collect all the novel findings in the designated area which significantly increases the overall value of this edition.

My sincere thanks to Dr. Frank Weinreich for his timely guidance, fruitful discussion, and feedback to all the urgent queries. I would also thank to Ms. Stefanie Volk for all her help during the publication work.

Finally, I would like to thank Dr. Helmut Buschmann for all his encouragement; without that, it was simply not possible to edit two books for Wiley-VCH. Furthermore, I would like to dedicate this book to my Mother (a school drop-out from rural India) whose teachings always helped to fight against all the odds and to excel further.

Mumbai
June 2022

Dr. Yogeshwar Bachhav
Founder and Director
Adex Pharma Consultancy Services

Preface

The latest volume in our book series *Methods and Principles in Medicinal Chemistry* with the book title *Targeted Drug Delivery*, edited by Yogeshwar Bachhav, highlights the critical role of targeted drug delivery for unmet medical needs, by describing a wide range of different approaches for targeting small-molecule as well as peptide and macromolecular drugs. In the 15 chapters written by world-renowned experts in their field, a broad range of specific formulation aspects for different types of drug classes are provided. The art and science to craft good drugs require an ever-growing plethora of skills from a medicinal chemist. The overall process of drug discovery however requires significant changes to become a more sustainable endeavor. There are many aspects in the evolving role of medicinal chemistry to consider – from potentially encompassing different molecule types to moving closer to biological and pharmaceutical development to chemically navigate efficiently in biological and drug delivery space to better designing effective molecules and addressing the biological target within a living system. The best-designed molecule for a specific disease is successful only if it can be introduced to a patient safely and efficiently. Formulation is becoming a fast-growing success factor in drug development, and matrix interactions of drug-delivery systems are becoming a key role in early development stages.

The editor has intentionally included chapters which put an emphasis on the development on the interface of drug discovery and drug development and not just on approved or marketed drugs. Above all, the book covers the targeting options not only for small molecules but also for complex biologicals such as nucleic acids, peptides/proteins, and antibodies. Key aspects of this field are presented in the following chapters:

- Basics of targeted drug delivery
- Addressing Unmet Medical Needs using Targeted Drug-Delivery Systems: Emphasis on Nanomedicine-Based Applications
- Nanocarriers-Based Targeted Drug-Delivery Systems: Small and Macromolecules
- Liposomes as Targeted Drug-Delivery Systems
- Antibody–Drug Conjugates: Development and Applications
- Gene-Directed Enzyme Prodrug Therapy (GDEPT) as a Suicide Gene Therapy Modality for Cancer Treatment

- Targeted Prodrugs in Oral Drug Delivery
- Exosomes for Drug-Delivery Applications in Cancer and Cardiac Indications
- Delivery of Nucleic Acids such as siRNA and mRNA using Complex Formulations
- Application of PROTAC Technology in Drug Development
- Metal Complexes as the Means or the End of Targeted Delivery for Unmet Needs
- Formulation of peptides for targeted delivery
- Antibody-Based Targeted T-Cell Therapies
- Devices for Active Targeted Delivery: A Way to Control the Rate and Extent of Drug Administration
- Drug Delivery to the Brain: Targeting Technologies to Delivery Therapeutics to Brain Lesions

The present book provides exhaustive review of the advanced technologies evolving in the field of the targeted drug-delivery systems. The authors especially tried to cover the approaches used to develop fast-track vaccines in the covid pandemic. Also, there is particular emphasis on the different routes where the targeted delivery concept can be used.

The book editor Yogeshwar Bachhav is a pharmacist by training and has a PhD in advanced drug-delivery systems from ICT, Mumbai (India). He has around 16 years of post-PhD experience in Europe in the field of pharmaceutical development of investigational drugs. He has contributed to the success of the clinical candidates ranging from preclinical to phase 1, 2, and 3 trials followed by commercial launch.

Yogesh has worked as a Research Scientist for around four years on a collaborative project between Pantec Biosolutions AG (Lichtenstein) and University of Geneva, Switzerland. After this, he has worked as a Formulation Manager at Debiopharm Group, Lausanne, Switzerland, for around four years in the capacity of a lab head, where he successfully developed preclinical and clinical formulations for oncology indication.

Currently Yogesh is working as a Senior Director at AiCuris Anti-infective Cures AG Germany and responsible for pharmaceutical development of investigational drugs in the domain of innovative anti-viral and anti-bacterial drugs.

Yogesh has also started a consultancy firm called Adex Pharma which deals with solving complex issues in the pharmaceutical development of new and approved drugs since 2016.

Yogesh's expertise in the field of advanced drug-delivery system comprises pre-formulation, formulation development of small molecules and/or peptides for oral, dermal, and parenteral applications. Also, he has exposure to in-house development and outsourcing these novel dosage forms.

Besides several publications in the targeted formulation field, Yogesh is a well-known expert with over 30 conference proceedings and has been named as inventor in several patent applications. He has already edited a book for Wiley-VCH in the same book series titled *Innovative Dosage Forms: Design and Development at Early Stage*.

In summary, the present book will be a very good source of the advanced knowledge in the field of targeted drug-delivery systems for many medicinal chemists facing the interdisciplinary drug discovery and development interfaces.

With this, we – the series editors – sincerely believe that readers would be highly benefited from the contents of this book.

We, as series editors, would like to thank Yogesh for putting together the brilliant contributions of the authors, all authors for their brilliant contributions, and Frank Weinreich, Stefanie Volk, and their co-workers for their great support to make this book possible.

May 2022
Aachen, Porto, and Frankfurt

Helmut Buschmann
Jörg Holenz
Raimund Mannhold

1

Basics of Targeted Drug Delivery

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1.1 Introduction

Biological effects conferred by drugs are associated with drug mechanism of action, and drug pharmacological and physicochemical properties. To elicit pharmacological response, drugs are commonly designed to bind to a target and activate or inhibit them, for example, chemotherapy drug belonging to the class of topoisomerase-2 inhibitors binds to and stabilizes enzyme topoisomerase-2 in cells to induce cell death, antidiabetic medication exenatide binds to and activates good lab practices (GLP)-1 to increase insulin secretion. Further, depending upon the route of drug administration, drugs undergo four main processes – absorption (absorption of drug from site of administration into blood), distribution (distribution of drug to different tissues from bloodstream), metabolism (breakdown of drug), and excretion (elimination out of the body) which are predominantly affected by the physicochemical properties of the drug. These factors largely account for the rate and extent of drug efficacy and overall potency.

In addition to the above-mentioned processes, pharmacological response and efficacy induced by the drug are also governed by its delivery to the site of action, the selective delivery to the target, and associated safety. To facilitate safe and effective drug transport, various drug-delivery systems (formulations, dosage forms, drug-device combinations, etc.) have been developed thus far. During the last several decades, multiple technologies and formulations, including controlled-release drug-delivery technology, oral and transdermal drug-delivery systems, nanotechnology-based products, have significantly improved patient outcomes [1]. While significant improvements have been made in multiple disease indications, there continue to remain areas that require attention to fulfill the unmet need in terms of increasing drug efficacy by improving patient compliance, reducing side effects, and reducing dosing frequency. Targeted drug-delivery systems have gained wide attention in recent years to selectively target the drug at the site of action and thereby facilitate site-specific delivery to ensure high safety, efficacy, and patient compliance. This chapter introduces some basic concepts

Targeted Drug Delivery, First Edition. Edited by Yogeshwar Bachhav.

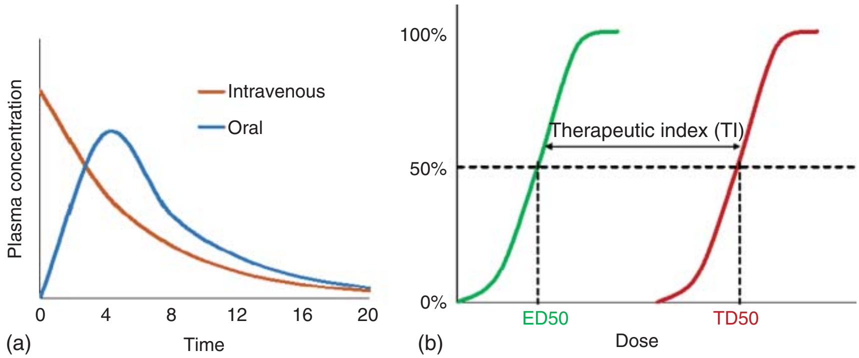

Figure 1.1 (a) Bioavailability of an agent administered intravenously (in red) and orally (in blue). (b). Therapeutic index (TI) of an agent as defined by the ratio of ED50 to TD50. ED50: Effective dose for 50% response points, TD50: Toxic dose for 50% response points.

followed by the rationale for development of targeted drug-delivery approaches, different approaches to achieve this, commercial success to date, and challenges associated with this approach.

1.1.1 Concept of Bioavailability and Therapeutic Index

Bioavailability (BA) is the rate and extent to which the drug is absorbed from the drug product and becomes available at the site of action [2]. BA of an agent administered intravenously is high as compared to oral administration. This is a result of instant entry of the agent in the systemic blood circulation following intravenous dosing as compared to absorption from the Gastrointestinal (GI) tract followed by entry into systemic circulation with oral dosing (Figure 1.1a). Therapeutic index (TI) is an indicator of relative safety of a drug. TI is defined as the ratio of maximally tolerated toxic dose to minimum effective dose. A common method used to calculate TI of an agent is to calculate ratio of dose that induces toxic effects in 50% response points (TD50) to the dose that induces therapeutic effects in 50% response points (ED50) (Figure 1.1b).

1.2 Targeted Drug Delivery

The terms “targeted drug delivery” and “targeted drug therapy” are frequently used in drug discovery research; however, both these terms are distinct from one another and cannot be used interchangeably. Targeted drug therapy refers to specific interaction between drug and a certain protein or moiety on target/disease cells [3]. Targeted drug delivery, on the other hand, refers to predominant accumulation of the drug/drug formulation in the target/disease zone [4]. Effective drug-delivery system design, for all kinds of formulation, requires four key requirements – retain, evade, target, and release.

Retain: The delivery system should remain intact in its original form throughout the course of formulation development, processing, and administration.

Evade: Upon administration, it should be retained in the form such that it evades body defense mechanisms, stays protected from the body's immune system attacks, and reaches desired target zone in an optimal time frame.

Target: Drug-delivery system should be designed to result in exclusive drug accumulation at the intended site of action, i.e. disease area, while avoiding healthy tissues and drug-associated toxicity.

Release: Once at the desired site of action, the system should be capable of releasing drug from the formulation for the agent to confer its therapeutic effect.

The goal of targeted drug-delivery system is to increase TI of a drug over a nonspecific drug-delivery system. A delivery system that results in preferential accumulation of drug at the disease site while sparing nondisease sites in the body and limiting overall toxicity is considered to have a higher TI as compared to a system that results in equal accumulation of the drug in both disease and nondisease sites [5]. A general rule is delivery system that confers higher drug TI is clinically safer as compared to lower TI.

1.3 Strategies for Drug Targeting

Over the last few decades, multiple ideas have evolved ranging from identification of different materials to invention of novel concepts to potentiate and improve delivery of drugs to intended target region. Strategies for drug targeting are often classified into three main categories – passive targeting, active targeting, and physical targeting (Figure 1.2).

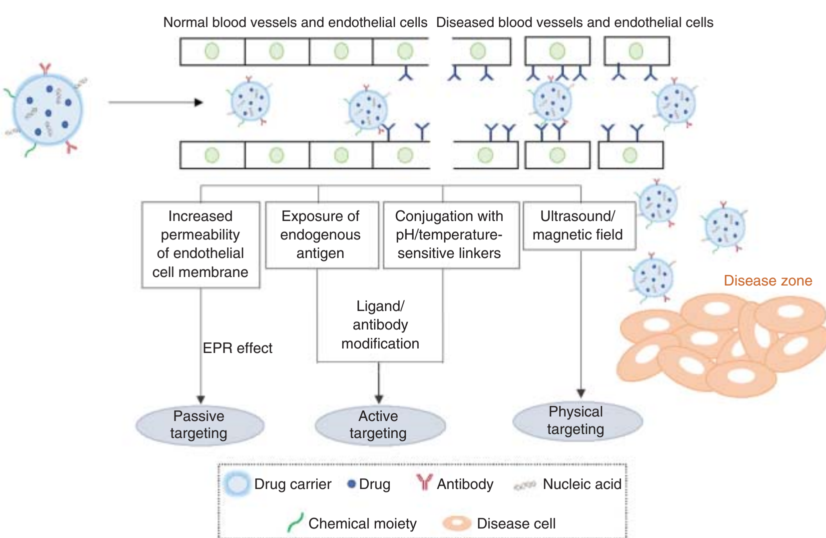

Figure 1.2 Schematic representing different directed drug-delivery-targeting techniques.

1.3.1 Passive Targeting

Often referred to as "no targeting," passive targeting utilizes the principle to accumulate drugs into specific regions of the body due to inherent features and characteristics of the said tissue. Passive targeting makes use of differences in anatomical features between target tissue and nontarget tissue to ensure preferential accumulation of drug. Common examples of passive targeting include accumulation of drugs via the reticuloendothelial system (RES), increased accumulation of drugs due to enhanced permeability and retention (EPR) effect, and localized delivery.

1.3.1.1 Reticuloendothelial System (RES) System

RES is an essential part of the immune system that lines organs, including liver and spleen. RES consists of phagocytic immune cells, including monocytes and macrophages, that can recognize and uptake foreign moieties. Biological function of monocytes and macrophages includes opsonization or capturing foreign substances that reach the systemic circulation. Thus, the RES system enables preferential uptake of nanoparticles by organs, including liver and spleen. For example, nanoparticles with strong hydrophobic surfaces are preferentially taken up by the liver followed by spleen and lungs.

1.3.1.2 Enhanced Permeability and Retention (EPR) Effect

Tumor vasculature is highly leaky and discontinuous as compared to normal tissue vasculature. Unlike normal vasculature, which is lined with endothelial cells tightly held together, tumor vasculature is more heterogeneous in size and permeability. Depending on the stage of tumor progression and anatomical location, gaps between endothelium range in size from 100 to 780 nm [6, 7]. Additionally, elevated expression of proteins, including vascular epithelial growth factor (VEGF), epithelial growth factor (EGF), and basic fibroblast growth factor (bFGF), enhances vasodilation and extravasation of drugs from the leaky vasculature in tumors [8]. These characteristics of tumor vasculature enable enhanced delivery and retention of high-molecular-weight drugs in the target region. Augmented therapeutic effect achieved as a result of this phenomenon is associated with EPR effect. EPR effect is commonly used for passive targeting of agents >40 kDa in molecular weight. Additionally, low-molecular-weight agents that are administered in drug carriers, including conjugates, nanoparticles, and liposomes, can also be delivered preferentially to the tumor by leveraging the EPR effect.

Examples of commercially available formulations that target drug to tumor region leveraging the EPR effect include Daunosome™ and Doxil™, clinically used anticancer agents. Both Daunsosome and Doxil are liposomal formulations that efficiently accumulate in the tumor cells minimizing the frequency of drug-induced adverse effects [9].

1.3.1.3 Localized Delivery

As the name suggests, localized delivery emphasizes direct delivery of the drug to the disease site or organ, thus limiting systemic exposure of drug to blood circulation and minimizing adverse drug toxicities. Localized delivery is often amenable to certain tumor types, including some forms of prostate and breast cancer, but not all tumor types or all diseases, thus limiting its use. Preclinical work has shown intratumoral delivery of paclitaxel nanoparticles conjugated to transferring ligand was effective in inducing tumor regression in mice models of prostate cancer. This treatment was significantly more effective as compared to systemic administration of paclitaxel [10]. Corticosteroids, a class of drug commonly used in asthma maintenance, are administered locally by using metered-dose inhalers. Other examples of drugs administered via local delivery systems include corticosteroids, used in metered-dose inhalers for asthma management and metronidazole, an antibiotic used in a gel formulation for treatment of periodontal diseases.

1.3.2 Active Targeting

Active targeting is by far the most well-recognized and implemented form of targeted drug delivery. This approach confers targeting properties to the drug that enables accumulation and consecutively pharmacological action toward specific molecule or region. Commonly used strategy to enable active targeting includes techniques that impose targeting properties on the drug, i.e. combining drug with other components that possess targeting features. This can be done in one of two ways. Firstly, by coupling drug with components that do not display affinity or binding toward a specific target but enable release of drug under a unique environment, e.g. sensitive to diseased (impacted) tissue pH, temperature, or enzymes. Many pharmaceutical and biotechnology companies are undertaking development of prodrugs – where drugs are conjugated and masked by enzyme-sensitive linkers to maintain them in an inactive state. On reaching the target site, these linkers are cleaved by enzymes specifically known to be upregulated in tumor microenvironment, thus making the active drug moiety selectively available for tumor region and limiting off-target adverse events.

The other technique, and which is often used, includes coupling drugs to components that display potent affinity and binding to a particular receptor expressed in the pathological tissues. This form of active targeting is also called ligand-mediated targeting. Ligand-based active targeting is commonly used in the development of many therapeutic and diagnostic modalities. Active cellular-targeting strategies involve use of affinity ligands on the surface of nanocarriers or developing antibodies against a certain ligand that can induce specific homing along with increased retention and uptake by the target cells. Antibody–drug conjugates (ADCs) utilize the principle of conjugating a drug to an antibody directed against antigens with increased expression on disease cells using cleavable linkers, thus ensuring selective binding of the ADC to the target cell over other tissues to minimize adverse drug reaction (ADR).

1.3.3 Physical Targeting

Physical targeting refers to a technique that utilizes external stimuli to induce release of the drug at a specific target site in the body. Common indications that utilize physical targeting to achieve targeted drug delivery include cancer treatment, chronic lung diseases, including chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). Commonly used techniques for physical targeting of drug to pathological area include using ultrasound and magnetic field to target the pathological tissue.

1.3.3.1 Ultrasound for Targeting

Research focused on utilizing ultrasound waves to target tissue to release drug from polymeric micelles and enable uptake by disease cells is underway for over a decade now. Ultrasound waves can induce delivery of anticancer agents by either degradation of micelles to release drug at target site or partition of drug out of the micelles at the target tissue [11]. One of the main advantages of this technique is its noninvasive nature, leading to increased patient compliance. This technique also offers the unique advantage of deep penetration into the body along with extensive control to cater the waves to specific target sites. Despite the advantages, there are concerns associated with use of ultrasound radiations, including their effect on cell plasma membrane. Preclinical studies addressing the effect of lower-energy ultrasound radiations on the efficacy of drug release from micelles and damage to cellular membranes are underway [11].

1.3.3.2 Magnetic Field for Targeting

Magnetic targeting utilizes an external magnetic field to induce preferential localization of an intravenously injected therapeutic agent bound to or encapsulated in a magnetic drug carrier. Such drug carriers include magnetic liposomes, nanospheres, and magnetic ferrofluids and incorporate materials, such as iron, nickel, and magnetite [12]. Preclinical investigation for many magnetic drug carriers or various anticancer agents, including mitoxantrone, etoposide, and epirubicin, is currently underway [13, 14].

1.4 Therapeutic Applications of Targeted Drug Delivery

Nanocarriers are the most commonly used drug carrier system to mediate targeted drug delivery. These employ nanosized materials, including nanoparticles, liposomes, micelles, and dendrimers for targeted and controlled drug-delivery systems [15]. These delivery systems are commonly used for a wide range of purposes, ranging from disease diagnosis to management. Different disease indications that can be detected and treated with targeted drug-delivery systems are discussed below.

1.4.1 Diabetes Management

Diabetes mellitus (DM) is a chronic metabolic disorder that has significantly impacted lifestyle due to increased frequency of occurrence over the last decade. DM can be classified into Type 1 (T1DM) and Type 2 (T2DM), where T1DM results due to absolute deficiency of insulin and T2DM is a result of insulin resistance, increased glucose production, or impaired insulin secretion. Liposomes, composed of phospholipids and cholesterol, can entrap and deliver both hydrophobic and hydrophilic agents to site-specific regions. Many reports have used liposome-based delivery systems to improve site-specific delivery of insulin. Zhang et al. have shown liposomes composed of 3 : 1 ratio of lipid – cholesterol show increased entrapping of insulin, optimal membrane fluidity along with minimal insulin leakage [16]. Additional reports have shown enhanced target-specific delivery when the liposomes are coated with folic acid [17]. Nanoparticle-based targeted therapy has also been developed and tested for targeted delivery of insulin in DM management. Nanoparticles encapsulating DNA-encoding interleukins, including IL-10 and IL-14, have been designed and tested in prediabetic animal models. Results from these studies showed nanoparticles encapsulating these interleukins were potent in inhibiting response of T-cells against native islet cells and significantly inhibited development of DM [18]. Overall, treatment with nanoparticle and liposomal-based approaches has significantly improved DM management as compared to conventional treatment.

1.4.2 Neurological Diseases

Incidence of neurological diseases, including Alzheimer's and Parkinson's, has significantly risen over the last few years. While Alzheimer's is associated with extracellular deposition of amyloid beta-peptide and tau proteins, Parkinson's is associated with degeneration of dopaminergic neurons in the brain. Effective targeting of neurological disorders is often complex due to the inability or limited ability of treatment modalities to cross the blood–brain barrier (BBB). However, nanomedicines have evolved with positive outcomes in overcoming the BBB and increasing BA of therapeutic agents in neurological disorders. Acetylcholinesterase inhibitors (AChEs) inhibitors, including donepezil, rivastigmine, and galantamine, are commonly used therapeutic agents for Alzheimer's management [19]. Preclinical studies with rivastigmine-loaded poly(lactide-*co*-glycolide) (PLGA) and polysorbate 80 (PBCA-80)-coated poly(*n*-butylcyanoacrylate) nanoparticle formulation have demonstrated improved memory in mice behavioral studies as compared to rivastigmine-in solution [20]. Furthermore, nanoformulations for donepezil encapsulated in PLGA particles demonstrated higher penetration and accumulation in the brain compared to drug in solution formulation [21]. Nerve growth factor (NGF), an essential protein in survival of neurons, is currently being investigated for its therapeutic potential for neurological diseases. While NGF has limited ability to penetrate the BBB, NGF adsorbed on PBCA-80-coated poly(*n*-butylcyanoacrylate) nanoparticles have shown beneficial effects in slowing neurodegeneration and reversing amnesia in rat models [22]. Furthermore, encapsulation of curcumin and NGF in nanoformulation induced synergy and enhanced therapeutic effect in preclinical studies [23].

Treatment with dopaminergic agents, including levodopa and carbidopa, is the first-line therapy for management of patients with Parkinson's. However limited permeability across the BBB and BA of dopamine agonists necessitates increased dosing frequency of these agents. This has, however, resulted in lower patient compliance given the systemic side effects induced by increased dosing frequency. Nanodrug-delivery strategy has shown promising outcomes in management of Parkinson's. Dopamine-loaded chitosan nanoparticles demonstrated dose-dependent increase in dopamine levels and increased BA in preclinical settings [24]. Continuous stimulation of dopaminergic neurons is beneficial in the treatment of Parkinsons disease. While dopamine receptor agonist rotigotine is a potent stimulator of dopaminergic neurons in in vitro systems, its utility is limited due to poor penetration across the BBB in animal models. However, chronic administration of rotigotine loaded in PLGA-MS demonstrated sustained exposure of drug in the brain over an extended period along with improved safety and tolerability in monkeys and rats [25, 26]. In addition to nanoformulations, ADCs administered subcutaneously or systemically are being studied for management of neurological diseases. SER-241 is an investigational once-a-week ADC from Serina Therapeutics that utilizes apomorphine conjugated to an antibody for treatment of Parkinson's. SER-214 is currently in Phase 2 clinical testing in patients with advanced Parkinson's disease.

1.4.3 Cardiovascular Diseases

Cardiovascular diseases (CVDs) are the leading cause of death in the United States. Targeted drug delivery offers the potential of fulfilling unmet needs in treatment of CVDs by minimizing renal excretion of the drug, which in turn elongates residence time of the drug in systemic circulation.

Atherosclerosis is a CVD characterized by hardening and narrowing of arteries due to excessive plaque formation that eventually decreases blood flow to the heart and brain ultimately leading to conditions, such as stroke and coronary heart disease. Targeted drug delivery not only offers therapeutic options in treatment of CVD, but has also shown significant improvement in diagnosis and imaging of plaques. N1177, an iodinated aroyloxy ester, has successfully been used to identify macrophage accumulation in arterial walls in animal models of atherosclerosis [27]. This approach has shown promising results and is currently undergoing clinical testing in human patients. Targeted therapy combining physical and active targeting showed increased internalization of nanoparticles in atherosclerotic macrophages when super-paramagnetic iron oxide nanoparticles were used [28].

Myocardial ischemia–reperfusion (IR) injury is a cardiovascular condition characterized by apoptosis of cardiomyocytes due to mitochondrial disturbances and generation of reactive oxygen species. Multiple promising therapeutic agents tested for treatment of myocardial IR have failed clinical testing due to inefficient delivery of drug within a critical time frame. Nanodrug-delivery vehicles, including PLGA nanoparticles as well as PEGylated liposomes, have shown significant promise in targeting inflammatory cells due to increased inflammation-induced permeability of myocardium [29]. ONO-1301, a synthetic prostacyclin IP receptor agonist, is currently under development for myocardial IR. Preclinical work has demonstrated selective accumulation of the drug in the ischemic myocardial tissue when administered intravenously as a nanoparticle formulation as compared to ONO-1301 solution. Furthermore, ONO-1301 NPs also led to increased secretion of cytokines and tumor necrosis factor-alpha in turn increasing myocardial blood flow and reduction in infarct size [30].

1.4.4 Respiratory Diseases

Targeted drug-delivery systems administered intranasally are known to be highly effective in management of respiratory diseases, including asthma and chronic obstructive pulmonary disorder. Advantage of intranasal formulation includes minimizing drug resistance, increasing lung deposition of the drug, and minimizing toxic effects to nonpulmonary tissue. Targeted drug delivery in the form of nanoformulations, including liposomes and nanoparticles, is the new paradigm for the treatment of respiratory diseases.

Asthma is a common chronic condition characterized by shortness of breath, coughing, and wheezing. Corticosteroids and bronchodilators are commonly used in management of asthma. Preclinical studies showed nanoparticles containing salbutamol resulted in long-term relief due to sustained accumulation in the lungs as compared to solution formulation. Liposomal formulation of salbutamol sulfate also resulted in extended retention of the drug in lungs, ~10 hours, thus prolonging therapeutic effect [31]. *Mycobacterium tuberculosis* (MTB), commonly known to cause tuberculosis (TB), is one of the leading causes of fatalities worldwide. MTB reaches lung alveoli and resists macrophage-mediated destruction by preventing formation of phagolysosome. Standard-of-care drugs for the treatment of TB include rifampicin, isoniazid, and ethambutol used either alone or in combination with injectable agents (streptomycin and viomycin), fluoroquinolones, or few oral agents (ethionamide and para-aminosalicylic acid). Targeted drug delivery using the platform of mesoporous silica nanoparticles (MSNPs) has shown promising outcomes for the delivery of anti-TB drugs. Surface functionalization with poly(ethylene imine) (PEI) yielded higher loading and controlled drug delivery of rifampicin MSNPs. Furthermore, MSNPs-containing pH-sensitive pores have been shown to release isoniazid directly to MTB-infected macrophages following endocytosis [32].

1.4.5 Cancer Indications

Cancer, also referred to as malignant tumors, is characterized by a condition where genetic or acquired mutation in DNA leads to uncontrolled proliferation of cells that also has the potential of migrating from primary site of origin and invading into a secondary site. Heterogeneous nature of tumors along with dense tumor microenvironment makes treatment of cancers much more complex. Multiple technologies, including nanoformulations, radiation therapy, immunotherapy, and chemotherapy, have shown improvement in cancer management; however, toxicities associated with systemic delivery, poor drug accumulation at tumor site, and nonspecific drug effects limit the benefits offered by current drug-delivery technologies.

Antibody-mediated target engagement, a commonly used form of active targeting, has shown promising success in oncology treatment. Antibodies are commonly raised against tumor-associated antigens (TAA) that provide critical downstream signaling for cancer cell survival, thus providing therapeutic option for targeting them. Many such antigens show increased expression on cancer cells as compared to nonmalignant tissue, thus making this a targeted therapy approach. Examples include Trastuzumab developed by Genentech against Her-2 receptor and is upregulated in breast cancer cells. Another FDA-approved monoclonal antibody is bevacizumab which targets VEGF and inhibits angiogenesis in tumors. Both Trastuzumab and bevacizumab have shown improved patient survival in cancer management [33]. Drugs conjugated to TAA antibody using cleavable linkers, i.e. antibody–drug conjugates, are extensively being evaluated in preclinical and clinical studies to achieve tumor-specific targeted delivery of cytotoxic drugs. Liposomal formulations of anticancer agents have demonstrated a promising strategy for many chemotherapeutic agents, including doxorubicin and paclitaxel. PEGylated liposomal doxorubicin (Doxil) showed potent anticancer activity and reduced cardiotoxicity for first-line treatment of metastatic breast cancer [34]. DaunoXome (daunorubicin liposomes) has shown significant improvement in therapeutic efficacy and survival in patients with Kaposi's sarcoma [35]. In addition to antibodies and nanoparticles, dendrimers have also shown promise in delivering anticancer agents to specific targets. Doxorubicin-conjugated dendrimers using polyamidoamine significantly reduced tumor burden through enhanced drug accumulation in B16F10 melanoma tumors in mice [36]. Another group also showed pH-sensitive dendrimers increased tumor penetration and release of drugs into tumor microenvironment [37].

1.5 Targeted Dug-Delivery Products

Over the past few decades, multiple targeted drug-delivery products have received Food and Drug Administration (FDA) approval. Currently, the market has more than 50 products based on this technology (Table 1.1) [38, 39]. Notably, targeted delivery systems are extensively developed for drugs, which have low aqueous solubility and high toxicity, such that when administered as nanoformulations, these drugs show enhanced BA, better accumulation, pharmacokinetic properties, and reduced toxicity.