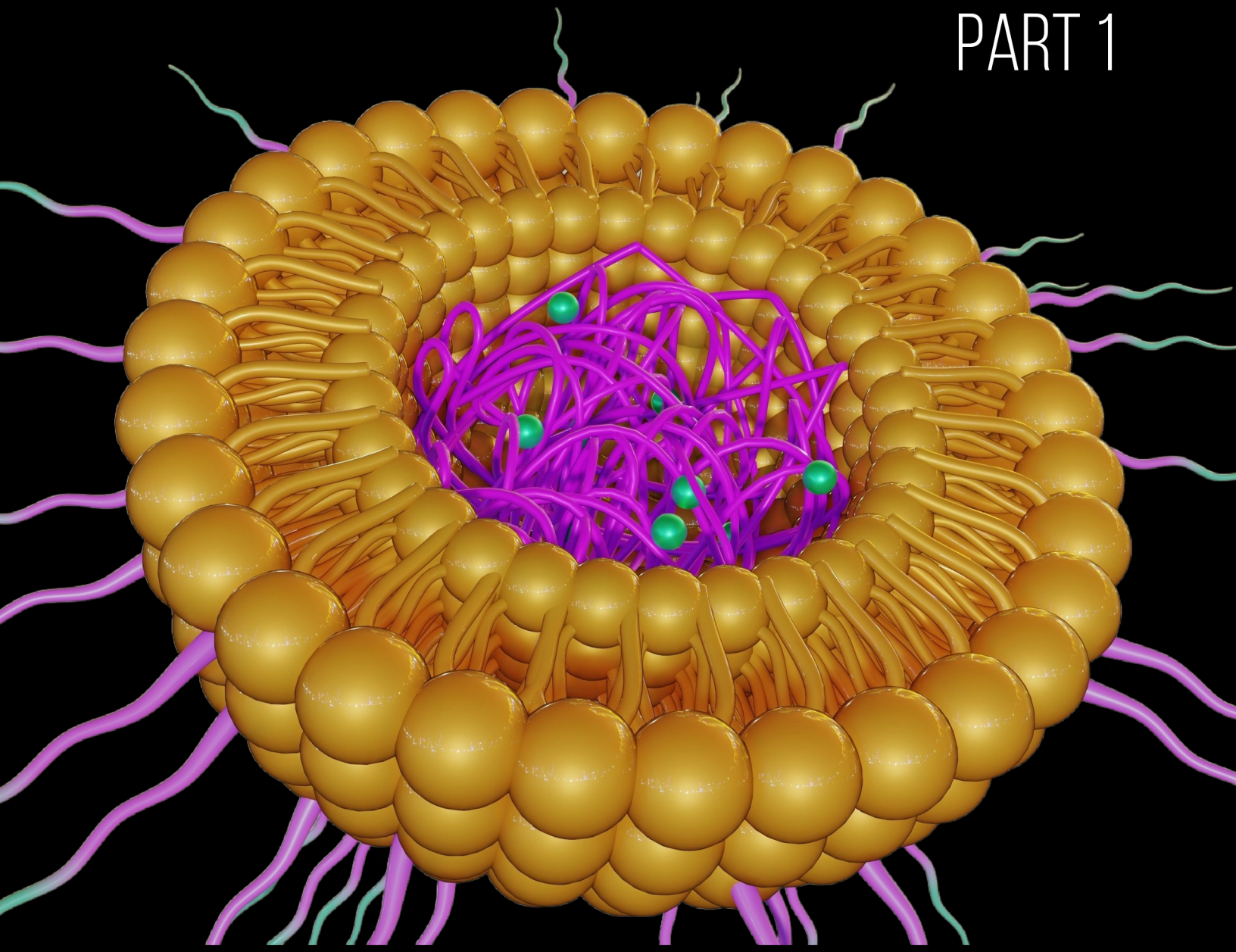
NOVEL DRUG DELIVERY SYSTEMS

PART 1



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Novel Drug Delivery Systems
(Part 1)

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FOREWORD I

I extend my heartful gratitude to all the authors who gave their valuable input in finalizing this book and to the editor for completing a monumental task. This book covers a detailed review of different drug delivery systems. The authors provide valuable insights into many delivery systems in a clear and concise manner. I found each and every article to be worth reading. The topics covered in this volume show elementary to current developments in drug delivery systems. This book contains more than enough references, to both primary and secondary sources, for those wanting to learn more about drug delivery systems. In my opinion, this book is a thought-provoking book that would be of interest to students, professors, and industry personnel. It can be used as supplementary material for teaching drug delivery systems at an undergraduate or postgraduate level and can be a great read for undergraduate and postgraduate students of pharmacy.

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FOREWORD II

The field of drug delivery systems has witnessed remarkable advancements over the past few decades, driven by the need for more effective, targeted, and patient-friendly therapeutic options. “Novel Drug Delivery Systems (NDDS)” is a comprehensive compilation of the latest innovations and research in this dynamic field, offering valuable insights into the development and application of advanced drug delivery technologies.

This book, meticulously curated by experts in the field, represents a comprehensive exploration of various controlled-release technologies that are reshaping the way medications are developed and delivered for patient compliance.

This book, meticulously curated by experts in the field, represents a comprehensive exploration of various controlled-release technologies that are reshaping the way medications are developed and delivered for patient compliance.

Microencapsulation is elucidated as a powerful tool augmenting controlled drug release mechanisms. Similarly, muco-adhesive, gastro-retentive, and naso-pulmonary drug delivery systems are meticulously explored, highlighting their specialized mechanisms and therapeutic advantages in treating diverse medical conditions.

The chapters dedicated to transdermal and ocular drug delivery systems underscore the innovative strides made in enhancing patient compliance and therapeutic outcomes through non-invasive delivery routes. Nanotechnology, a rapidly advancing frontier, is explored for its potential to revolutionize drug delivery precision and efficacy

Furthermore, the development of implantable and controlled-release injectables is detailed, underscoring their role in sustained delivery and personalized medicine approaches. Each chapter is authored by leading experts, ensuring the content is not only authoritative but also at the forefront of current research and application.

"Novel Drug Delivery Systems (NDDS)" serves as an indispensable resource for researchers, academicians, and pharmaceutical professionals navigating the dynamic landscape of drug delivery. Each chapter is meticulously crafted to offer comprehensive coverage and depth, making this book an essential addition to the library of anyone involved in pharmaceutical sciences.

I commend the editors and contributors for their scholarly contributions and dedication, which have culminated in this authoritative reference. I trust this book will inspire further research and innovation in the field of drug delivery systems.

Warm regards,

Sandip Tiwari
Head of Technical Services
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PREFACE

We are delighted to present the first edition of our book, which focuses on Controlled Drug Delivery Systems (CDDS). In the rapidly advancing realm of pharmaceutical sciences, CDDS has emerged as a crucial innovation that enhances therapeutic efficacy and patient care. This book, crafted with the international readership in mind, seeks to provide a comprehensive understanding of the fundamental and practical aspects of controlled drug delivery systems.

This edition includes six carefully selected chapters, each authored by experts in the field. The book begins with Chapter 1, "Controlled Drug Delivery Systems: Concepts and Rationale," which lays the foundation for understanding the principles behind CDDS. It provides the necessary context and insight into why controlled release systems have become integral in modern therapy.

In Chapter 2, "Pharmacokinetic Considerations for Controlled Release Dosage Forms," the focus shifts to the essential pharmacokinetic aspects that influence the design and performance of controlled release systems. This chapter bridges the gap between theoretical knowledge and clinical application, ensuring readers grasp the critical factors affecting drug release and absorption.

Chapter 3, "Polymers: Backbone of Controlled Drug Delivery," delves into the world of polymers, emphasizing their indispensable role as the building blocks of many drug delivery systems. This chapter explores the design, development, and applications of various polymers in achieving desired drug release profiles.

Microencapsulation is the focus of Chapter 4, "Microencapsulation as a Tool for Controlled Drug Delivery." This chapter introduces readers to the concept and utility of microencapsulation technology in protecting drugs, controlling release rates, and improving stability, offering an in-depth look at a critical tool in the formulation of controlled release dosage forms.

Chapter 5, "Comprehensive Insights into Muco-Adhesive Drug Delivery Systems," addresses the specific niche of muco-adhesive systems, providing insight into their potential to enhance drug absorption and prolong residence time at the target site. The application of this technology offers promising solutions to various therapeutic challenges.

Finally, Chapter 6, "Gastroretentive Drug Delivery Systems," rounds off the book with a thorough exploration of gastroretentive technologies. This chapter presents innovative strategies to improve drug retention in the gastrointestinal tract, ensuring optimal drug delivery to the site of action.

Our goal with this book is to provide a robust resource for students, researchers, and professionals in the pharmaceutical sciences. By offering both theoretical foundations and practical insights, we hope to foster a deeper understanding of controlled drug delivery systems and inspire further innovation in this important field.

We extend our heartfelt thanks to the contributing authors, whose expertise and dedication have made this book possible. We are confident that the knowledge shared within these pages will serve as a valuable tool in the continued advancement of pharmaceutical sciences on a global scale.

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DEDICATION

I would like to dedicate this book
To
My Late Grandfather,
Whose love and Teachings have been guiding light throughout my life
To
My family Members

Atish S. Mundada

I would like to dedicate this book
To
My family and Friends

Alap Chaudhari

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CHAPTER 1

Controlled Drug Delivery Systems: Concepts and Rationale

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Abstract: Modern pharmaceutical research and development has evolved to rely heavily on controlled drug delivery systems because they provide creative ways to improve therapeutic results while reducing side effects. The underlying ideas and justification for controlled drug delivery systems are covered in detail in this chapter. Beginning with a discussion of the drawbacks of conventional drug delivery techniques and the benefits of controlled release, the chapter explains the need for controlled drug delivery systems in modern medicine. The requirements for the design and formulation of controlled drug delivery systems have also been discussed in the chapter. The concepts of controlled drug release, which cover a variety of mechanisms, including diffusion, erosion, and osmosis, take up a sizeable section of the chapter. Additionally, emphasis is put on the function that mathematical modeling plays in predicting and optimizing drug release characteristics. It examines the wide spectrum of therapeutic uses for controlled drug administration, such as the treatment of chronic pain, cancer, diabetes, and other chronic disorders. The chapter also illuminates the future trends of such drug delivery systems like nanotechnology, personalized medicines, and advancements in medical devices. It also explores regulatory aspects and challenges involved in the design and commercialization of these systems, placing emphasis on the necessity of stringent quality control and safety evaluations. In conclusion, this chapter is a useful resource for researchers, scientists, and medical experts who want to understand underlying ideas and justifications of controlled drug delivery systems.

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Atish S. Mundada & Alap Chaudhari (Eds.)

Keywords: Controlled drug delivery, Digital health, Drug release kinetics, Implantable devices, Nanoparticle-based delivery, Personalized medicine, Transdermal drug delivery.

INTRODUCTION

Historical Overview

For more than sixty years, controlled drug delivery systems (CDDSs) have been available on the market [1]. The term-controlled drug delivery describes the release of a medicine gradually and in a controlled manner. Spansule® was the first CDDS that had 12 hours of release time and was developed by Smith, Klein, and French laboratories. Spansule laboratory used this mechanism to control the dissolution of the drug core by forming a barrier around it, *i.e.*, a polymer coat, to prevent the degradation of the drug by gastrointestinal (GI) fluids. After this, various formulations were developed based on this mechanism. Other mechanisms are also coming into the picture after the rapid success of dissolution-controlled systems, namely diffusion-controlled, osmotic-controlled, and ion-exchange-controlled systems [2]. The evolution of CDDS is classified based on generations; the first generation of CDDSs was developed between 1950-1980, when most oral and transdermal dosage forms were formulated. First generation of drug delivery usually dealt with overcoming physicochemical barriers, and the most commonly used mechanisms were dissolution and diffusion-controlled systems for the delivery of drugs [3]. The 2nd generation of CDDSs was difficult as compared to the first generation and was focused more on physicochemical barriers. Most of the 2nd generation drug delivery was focused on the formulation of parenteral. The 1st generation was more successful as the manipulation of the drug's physicochemical properties was easy, whereas 2nd generation also focused on the body's response to the drug rather than the drug's profile. The 3rd generation was more advanced in terms of drug delivery. It focused mainly on formulation barriers and biological barriers. Formulation barriers include poor solubility of drugs and initial burst release (*i.e.*, the drug is initially released in a significant quantity before the release rate stabilizes.) [4]. Today, drug delivery systems continue to evolve, with emerging nano-scale delivery systems being developed for the management of different illnesses. Fig. (**1**) highlights the evolution of drug delivery systems.

Rationale Behind CDDS

To solve problems with conventional drug delivery techniques, CDDSs were developed. Modifying the pharmacokinetics and pharmacodynamics of pharmacologically active drugs by changes in physiological factors, molecular

structures, or new drug delivery methods is the main objective of controlled drug delivery [5, 6]. The following are some of the reasons why CDDSs are important:

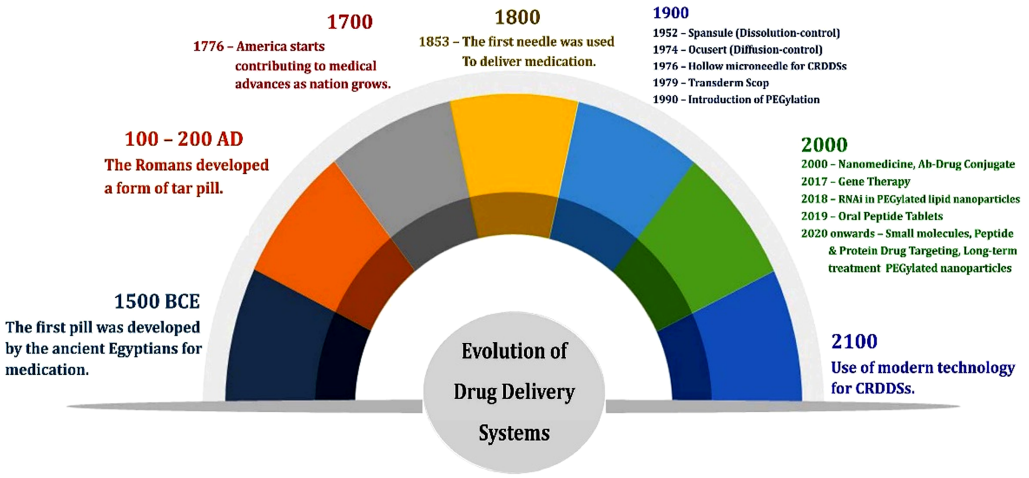

Fig. (1). Evolution of drug delivery systems.

- For traditional dosage forms, the only flexible factors for each medication are the dosage (D) and the frequency of administration (C). Each drug possesses a specific therapeutic range. When the concentration of a drug falls below the Minimum Effective Concentration (MEC), it fails to produce its desired therapeutic effect, and when it exceeds the Maximum Safe Concentration (MSC), it can lead to harmful side effects. The therapeutic index is a measure calculated as the ratio between LD_{50} (median lethal dose) and ED_{50} (median effective dose). Whereas in the case of controlled drug delivery, it offers the constant release of drugs between the range of MEC and MSC, as shown in Fig. (**2**).
- Patients typically find drugs with short half-lives administered through frequent daily injections or tablets less appealing than the same compounds released gradually through a once-daily oral dose, a semi-annual implant, or a three-day skin patch. The inconvenience of complex dosing schedules can lead to reduced effectiveness, as many patients tend to skip doses when required to adhere to such regimens. Hence, CDDS lowers the medication level, therefore increasing safety and minimizing adverse effects.
- To ensure that a drug is used to its maximum potential with minimal side effects and in the shortest possible time, drug developers can optimize its biopharmaceutics, pharmacokinetics, and pharmacodynamics properties. This can be achieved by employing several strategies, such as lead optimization, half-life optimization, potency and specificity optimization, molecular property design, and choosing the most suitable route of administration. By doing so,

CHAPTER 2

Pharmacokinetic Considerations for Controlled-release Dosage Forms

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Abstract: The pharmaceutical industry has shown significant interest in controlled-release dosage forms due to their ability to improve pharmacological therapy by providing prolonged and regulated drug administration. The pharmacokinetic properties of a medicine are essential in establishing its efficacy and safety in a therapeutic setting. Controlled-release dosage forms offer significant advantages, such as reduced dosing frequency, improved patient compliance, and fewer adverse effects. To maximize the use of these benefits, it is critical to understand the complex interplay between formulation design, pharmacological properties, and controlled release systems pharmacokinetics. This chapter examines the pharmacokinetic aspects of controlled-release formulations, providing insight into their drug-release methods, absorption, distribution, metabolism, and excretion. The chapter also delves into the various elements that influence the rate of drug release from controlled-release dosage forms. These aspects include mechanisms such as diffusion, dissolution, and erosion. This study also investigates the impact of these mechanisms on medication absorption in the gastrointestinal tract and their influence on the drug's pharmacokinetic characteristics. Furthermore, the chapter emphasizes the importance of employing modeling and simulation approaches to predict the behavior of pharmaceuticals released from controlled-release formulations. Furthermore, the chapter undertakes an endeavor to examine the impact of pharmacokinetic parameters on the dosing schedule, therapeutic monitoring, and methods to enhance bioavailability. The chapter also discusses the importance of tailored drug delivery methods for specific patients, as well as the potential of personalized medicine. Understanding the pharmacokinetic parameters of controlled-release formulations is critical for optimizing pharmaceutical treatment. Gained knowledge can guide the development of innovative drug delivery methods, enhance patient outcomes, and accelerate pharmaceutical sector advancements.

Keywords: Absorption, Distribution, Drug action, Excretion, Metabolism, Pharmacokinetic, Plasma drug concentration, Pharmacokinetic, Steady state.

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Atish S. Mundada & Alap Chaudhari (Eds.)

INTRODUCTION

Pharmaceutical research has made great progress in the field of controlled drug delivery systems (CDDSs). CDDSs provide tailored solutions to improve drug therapy by ensuring the maintenance of therapeutic levels of medicine over an extended or desired period of time. These formulations minimize side effects, reduce the frequency of administration, improve patient adherence, and ultimately increase therapeutic outcomes. A thorough understanding of pharmacokinetic principles is a must to ensure and achieve efficacy, safety, and reliable drug delivery patterns from CDDS. Pharmacokinetics is the scientific study of medication absorption, distribution, metabolism, and excretion (ADME) in the body. The knowledge of pharmacokinetics is vital for the rational conception and evaluation of formulations for controlled release. The study of pharmacokinetics aids in our understanding of how drugs enter the body and interact with biological processes. It also provides crucial details on the release of medications from various dosage forms, including liposomes, transdermal patches, sustained-release tablets, and microspheres [1-3].

The pharmacokinetic parameters that are essential for the creation and enhancement of CDDS are attempted to be thoroughly examined in this investigation. The book explores the intricate relationship that exists between a medication's characteristics, physiological factors, and formulation-specific properties. The combined effect of these factors dictates how controlled-release formulations behave pharmacokinetically. This research offers a thorough analysis of the processes involved in medication absorption, distribution, metabolism, and excretion. It tries to make clear the primary variables that affect how quickly medications are released from the body and how well they are absorbed by the body [4, 5].

Gaining therapeutic goals and reducing the likelihood of giving too little or too much medicine depends on an understanding of the complex processes involved in the body's processing of controlled-release pharmaceuticals. Several parameters, including drug solubility, permeability, dissolution rate, particle size, and formulation excipients, have a substantial impact on medication absorption and distribution. Moreover, physiological factors that affect medication release and distribution throughout the body include enzyme activity, pH fluctuations, and gastrointestinal motility [6].

To ensure a consistent and dependable medicine distribution, it is also essential to carefully adjust the delicate balance between the efficacy of therapy and the kinetics of drug release. Sometimes, the release rate and duration of the formulation need to be carefully adjusted to match the drug's pharmacodynamic

properties and therapeutic window in order to get the optimal plasma concentration-time profile. Moreover, problems like dosage proportionality, dose dumping, and food-drug interactions necessitate a thorough pharmacokinetic review when developing a formulation [7].

In the end, successfully developing and implementing controlled-release drug forms require a thorough grasp of pharmacokinetic principles and how to apply them to formulation optimization. Researchers and pharmaceutical scientists may completely utilize controlled release technologies to increase patient adherence, boost drug therapy efficacy, and foster pharmaceutical innovation by including pharmacokinetic considerations in the formulation design process. In order to facilitate the development of controlled-release pharmaceutical forms, this chapter aims to offer comprehensive and in-depth guidance for comprehending the intricate topic of pharmacokinetics. The ultimate objective is to assist in converting scientific advancement into meaningful and efficient therapeutic interventions [8].

EXAMPLES OF CDDS

Transdermal Patches

Transdermal patches are commonly used for drugs requiring constant blood levels, such as pain relievers and hormone therapies. They provide controlled and continuous drug release through the skin [9].

Microspheres and Nanoparticles

These small drug carriers release drugs gradually as they degrade or dissolve. They can be administered through various routes, including injection, inhalation, and oral ingestion [10].

Implants

Implantable devices can release drugs over an extended period, often ranging from months to years. They are particularly useful for conditions requiring long-term therapy, such as contraception or hormone replacement [11].

Osmotic Pumps

Osmotic pumps release drugs based on osmotic pressure gradients, enabling controlled and predictable drug delivery [12].

CHAPTER 3

Polymers: Backbone of Controlled Drug Delivery

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Abstract: The concept of a drug-delivery system (DDS) is not entirely new. Recent years have undoubtedly seen notable advancements in the identification and management of several illnesses. Medication administration to affected areas is an important part of DDS. A sufficient number of drug carriers are required to deliver an adequate amount of drug to the lesion. Polymers that expand and condense in reaction to pH levels outside of the body are being studied by researchers. The investigation is being carried out at a breakneck pace all over the world. Not only are advances in traditional technologies being made but innovations are also being developed and tested. The purpose of this chapter is to discuss a few of the polymer compounds that are utilized in controlled medication delivery systems. Both newcomers and scientists working in this fascinating field of applied polymer research will find the paper to be a valuable resource.

Keywords: Biodegradable polymers, Controlled drug delivery, Drug release method, Polymers.

INTRODUCTION

A polymer is a class of natural or synthetic substances composed of very large molecules called macromolecules, which are multiples of simpler chemical units called monomers. Polymers make up many materials in living organisms and are the basis of many minerals and man-made materials.

Poly indicates “many” in Greek, and meros indicates “units or parts”. Low-molecular-weight particles lack the distinct collaborative properties that make polymers so successful. The polymer formation is shown in Fig. (**1**).

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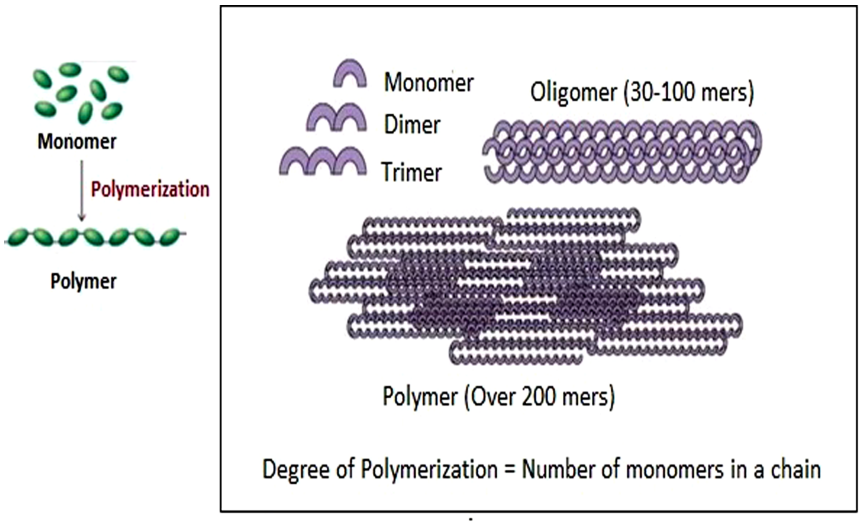

Fig. (1). Polymer anatomy.

Polymers that are commonly found in nature include:

- Amino acids, disaccharides, and polysaccharides that include maltose, sucrose, and glycogen make up every type of protein.
- A nucleotide is a building block for nucleic acids that include DNA and RNA.

Polymers are utilized in medical devices due to their long-lasting and self-renewal potential. Polymers have long been employed as flow enhancers in liquids, suspensions, and emulsions. They also act as an excipients in capsule creation. Polymers are now entering the parenteral market as blood circulation enhancers, treatment stability boosters, and pharmaceutical property adjusters. To disguise a drug's bad flavor, they are additionally offered as a film coating product [1, 2].

They can now provide pharmaceuticals with complex features such as drug targeting. By simply lengthening their chains through cross-linking or by enhancing their hydrophobic or hydrophilic properties through copolymers and other groups, polymers can readily change their ability to dissolve in water, resulting in a varied spectrum of materials with multiple applications [3, 4].

TYPES OF POLYMERS

The following list illustrates how several criteria are used to classify polymers into various categories.

Classifications Based on Source of Origin

Natural Polymers

Natural polymers are derived from natural sources, such as plants or animals. Some examples include cellulose, jute, leather, silk, wool, and rubber from plants [5].

Semi-synthetic Polymers

Semi-synthetic fibers such as viscous rayon, cupra ammonium silk, and acetate rayon are produced through simple chemical treatments designed to enhance the chemical and mechanical properties of natural fibers such as reliability and tensile strength.

Synthetic Fibres

Synthetic fibers are created in a laboratory by polymerizing basic chemical elements. Polyethene and polystyrene, nylon, PVC, backlite, teflon, synthetic rubber, and synthetic materials are examples [6, 7].

Classifications Based on the Structure

Linear Polymers

These polymers are composed of long, slender chains of monomers linked together. There are no side chains on these chains. They have molecules that are tightly packed and have high melting points, tensile strengths, and densities. Examples include polyester, nylon, polyethene, and PVC.

Branching Polymers

They have long, straight chains with numerous side chains. Due to the disorganized organization of its particles, they have poor density, tensile strength, and melting temperature. Polypropylene (side chain — CH_3), glycogen, and amylopectin are a few examples.

Network or Cross-Linked Polymers

A three-dimensional network is formed by joining these monomeric components together. Cross-links are the type of connections involved. Because of their network framework, they are rigid and fragile.

CHAPTER 4

Microencapsulation as a Tool for Controlled Drug Delivery

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Abstract: Controlled drug delivery systems, which release drug/s in a predetermined manner, offer numerous advantages over conventional drug delivery systems. These advantages include improved bioavailability, reduced dose frequency, minimized fluctuations in plasma drug concentration, and sustained drug release. The major drawback of the unit dosage form is dose dumping, which can be effectively overcome by multiple unit dosage forms like microcapsules. The microencapsulation technique involves enclosing drug/s by a thin coating shell, and the resultant product is referred to as microcapsules. This technique has potential applications, especially in delivering enclosed drug/s in a controlled manner, protecting them from harsh environments, masking unpleasant tastes, and many more. Several techniques, such as mechanical processes, chemical processes, and physicochemical processes, are used to encapsulate drug/s. Drug release from microcapsules is predominantly facilitated by diffusion, whereas swelling and dissolution, erosion and degradation, and osmosis are minor mechanisms. The polymers, which can be natural or synthetic, play a stellar role in the controlled release of drug/s from microcapsules. Prepared microcapsules are characterized and evaluated by various techniques for shape, size, surface characteristics, drug release and release kinetics, rheological behavior, *etc.* Despite the significant promise, various constraints and restrictions hinder the use of microencapsulation technology, creating a gap between real-life clinical practice and its therapeutic applications. The current chapter provides a comprehensive analysis of the most recent techniques, characterization and evaluation techniques, challenges, and commercially available microencapsulated pharmaceutical products.

Keywords: Air suspension, Coacervation phase separation, Interfacial polymerization, Ionotropic gelation, Microencapsulation, Microcapsules, Vibrational jet extrusion.

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INTRODUCTION

Microencapsulation is a process in which active agents or core materials present in solids, liquids, or even gases are enclosed by a thin coating or shell. The approach originated in the late 1930s as an environment-friendly alternative to carbon ribbons and carbon paper, which were developed by the business machine industry. The finding of carbon paper and ribbons that emitted dyes upon impact by a typewriter key or pen pressure in the 1950s inspired the creation of various microencapsulated materials, such as pharmaceuticals. The initial study that prompted the advancement of pharmaceutical microencapsulation technology was published in 1931. This study primarily focused on the formulation of gelatin spheres using a gelatin coacervation method [1]. At this time, classifying microcapsules based on their size is not available. They can be classified according to their size as nanocapsules (size less than 1 nm), macrocapsules (size more than 1000 μm), and microcapsules (size range between 3 to 800 μm) [2].

Despite their comprehensible differences, the terms microparticles, microcapsules, and microspheres are often used interchangeably, creating confusion among readers. Microparticles are particles of size between 1 and 1000 μm, regardless of their internal or external structure. In the category of microparticles, microspheres are spherical microparticles, while microcapsules are microparticles with a core contained by a substance that is apparently distinct from the core. The core material might exist in solid, liquid, or gas states. A typical microsphere formulation is thought to be composed of a fairly uniform blend of drug and polymer, whereas microcapsules have at least one separate compartment of drug along with additional components [3].

Reasons for Microencapsulation

• To sustain or prolong the release of the drug from dosage form.

• To mask the unpleasant taste and undesirable odor of drugs.

• To modify the physical states of liquid drugs into solid powder as solids can be handled conveniently.

• To protect medications from environmental factors, for instance, light, humidity, oxygen, and heat. Microencapsulation cannot create a complete barrier against environmental influences but can offer a high level of protection from them.

• To separate incompatible substances *e.g.*, eutectic mixture.

• To reduce the volatility of substances that are volatile at room temperature *e.g.*, aspirin.

• To reduce gastric irritation.

• To reduce the hygroscopic tendency of substances.

• It can be employed for selective absorption of drugs from the gastrointestinal tract (GIT) *e.g.*, enteric-coated dosage form.

• Intrauterine contraceptive devices made using the microencapsulation technique have been suggested [3, 4].

FORMULATION CONSIDERATION

For effective implementation of the microencapsulation process, an in-depth knowledge of the core and coating materials, stability, drug release kinetics, and the microencapsulation technique to be employed is required. One should appreciate that the possibility of different microcapsule compositions, qualities, and applications depends on the manufacturing process used. The composition of microcapsules is shown in Fig. (**1**).

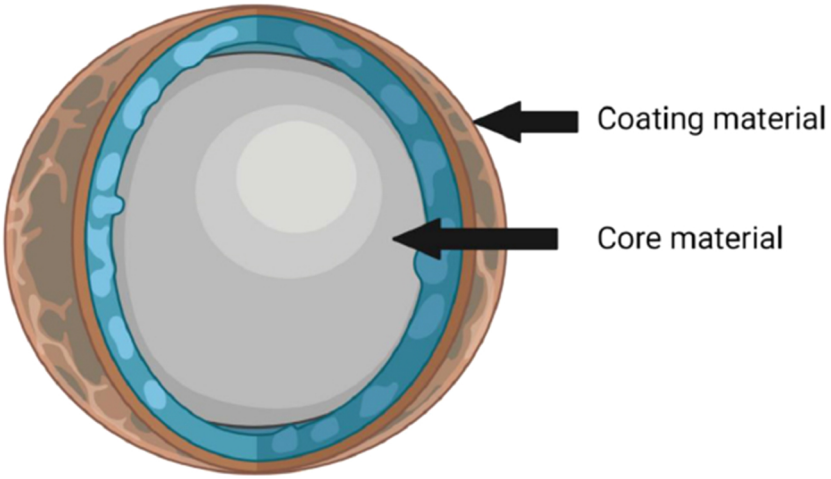

Fig. (1). Composition of microcapsules.

Core Material

The core material refers to a particular substance that can exist in solid, liquid, or gaseous form and is intended to be coated. The solid core of a drug may consist of a blend of drug/s, diluents, stabilizers, excipients, and release rate modifiers. On the contrary, the liquid core may comprise components that are dispersed or dissolved. The ability to modify the composition of the core materials provides system flexibility, and utilizing these properties frequently results in the successful design and fabrication of microcapsules with desired features.

CHAPTER 5

Comprehensive Insights into Mucoadhesive Drug Delivery Systems

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Abstract: Mucoadhesive drug delivery systems have gained significant attention in the field of pharmaceutical research due to their ability to enhance drug bioavailability, prolong residence time, and improve therapeutic outcomes. This chapter provides a comprehensive overview of mucoadhesive drug delivery systems, highlighting their importance in overcoming various challenges associated with conventional drug delivery. The chapter commences by elucidating the physiological and biochemical aspects of mucosal surfaces, emphasizing the significance of mucoadhesion in optimizing drug absorption and distribution. It explores the diverse applications of mucoadhesive systems across different mucosal sites, including the buccal, nasal, ocular, vaginal, and gastrointestinal mucosa. Additionally, the mechanisms underlying mucoadhesion, such as hydrogen bonding, electrostatic interactions, and covalent bonding, are thoroughly examined. The chapter delves into the various classes of mucoadhesive polymers, such as natural, synthetic, and semi-synthetic polymers, highlighting their distinct properties, applications, and evaluations. The chapter addresses key considerations such as biocompatibility, safety, and regulatory aspects associated with the development of mucoadhesive formulations. In conclusion, this chapter serves as a valuable resource for researchers, scientists, and practitioners in the field of drug delivery, offering a comprehensive understanding of mucoadhesive drug delivery systems and their potential to revolutionize the delivery of therapeutic agents across mucosal membranes.

Keywords: Mucoadhesive DDS, Mucus membranes, Mucoadhesion mechanism, Mucoadhesion theory, Mucoadhesive polymers, Patient compliance.

INTRODUCTION

Mucoadhesion, which is the capacity of a formulation to stick to mucous membranes, holds a distinguished place among the different strategies for changing various pharmaceutical delivery systems to increase bioavailability. The

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key advantages of mucoadhesive drug delivery formulations are their enhanced bioavailability and decreased total dose of active medication, whether it is administered locally or systemically. Understanding the mechanism of interaction between the mucosal layer and the mucoadhesive formulation is the main obstacle to the successful formulation of the mucoadhesive drug delivery system [1]. According to the American Society of Testing and Materials, in the adhesion of polymeric material to the mucosal surface, interfacial or intermolecular forces may be developed. Bioadhesion is a process that occurs when one of the biological materials forms strong interfacial forces with another polymeric material over a sustained period. It is the capacity of a substance, either biological or synthetic, to remain adhered to mucosal tissue for an extended period. In terms of novel drug delivery systems, bioadhesion is the adhesion of a drug carrier system to a particular surface of a tissue or epithelial tissue. Mucoadhesion is the term used to describe the process when an adhesive attaches to a mucous membrane [2].

Three distinct forms of bioadhesion exist within biological systems:

Category I

This form of bioadhesion emerges when two biological systems adhere to each other. Illustratively, instances include blood platelet aggregation and the natural wound healing process.

Category II

This type involves the adherence of a biological phase onto a man-made base material. For instance, the formation of biofilms on implants and inserts, as well as the growth of cells in such environments, represents examples of this phenomenon.

Example: Development of biofilm on implants and inserts as well as cell growth.

Category III

It involves the attachment of a synthetic component to biological tissue, for example, the adhesion of sealants to tooth enamel and synthetic hydrophilic polymers to epithelial cells [3].

Advantages of Mucoadhesive Drug Delivery System

Comparing mucoadhesive delivery systems to other oral controlled-release drug delivery systems reveals various benefits, such as:

1. The residential time of drugs in the gastrointestinal (GI) tract is prolonged.

2. Increased residence time of dosage form at the site of administration results in high drug flux at the absorbing tissue and increased bioavailability of the drug.

3. Drug localization and targeting at an area of interest [4].

Mucus Membrane

The moist linings on the walls of various body cavities, such as the gastrointestinal and respiratory tracts, are referred to as mucous membranes. Comprising a layer of connective tissue termed the lamina propria, these membranes are succeeded by an epithelial layer. This surface is commonly maintained in a moist state through the presence of a mucus layer (Fig. **1**). Instances of multilayered or stratified epithelia encompass the esophagus, vagina, and cornea. Conversely, single-layered epithelia can be observed in the stomach, small and large intestines, and bronchi. The latter are adjacent to tissues housing specialized glands, like salivary glands, responsible for producing mucus onto the epithelial surface. Goblet cells, a member of the first category, immediately secrete mucus onto the epithelium's surfaces. This mucus may be present as a solution or suspended condition within the luminal fluid, or it may be seen as a layer that resembles gel that is adhered to the mucosal surface [4].

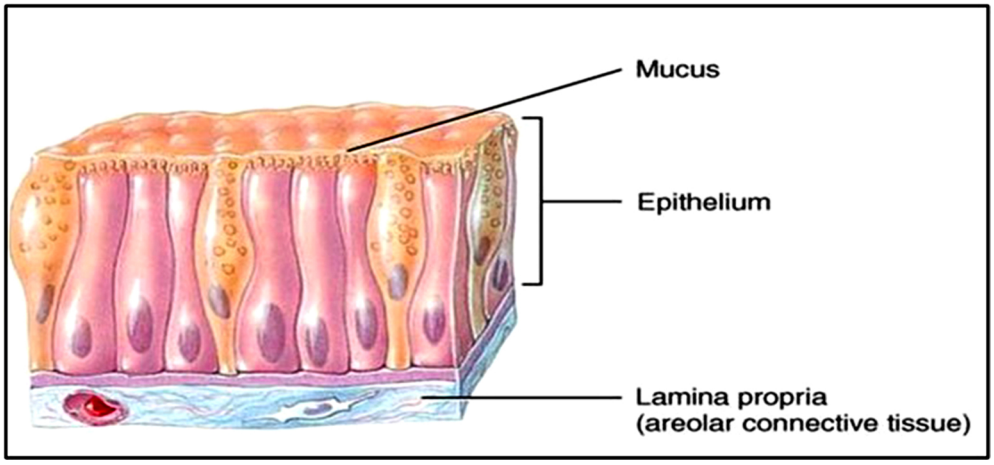

Fig. (1). Mucus membrane.

Mucus Structure, Composition, and Function

The complex, thick, adherent secretion known as mucus is produced by specialized cells called goblet cells. It has been discovered that mucus performs a variety of functions in these areas, including lubrication for the passage of objects, maintainence of the moist epithelium layer, protection against pathogens and

CHAPTER 6

Gastroretentive Drug Delivery Systems

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Abstract: Administration through the oral route is the most accessible and preferred due to its many advantages. Most of the drugs administered orally show poor bio-availability due to less residing time at the gastric absorption site. To boost the bioavailability of such drugs, it is important to extend the residing time of the drug in the upper GIT, which can be achieved by using gastroretentive drug delivery systems (GRDDS). There are multiple conventional and advanced gastroretentive systems based on various mechanisms, namely high-density systems, floating systems, magnetic systems, mucoadhesive systems, expandable systems, raft-forming systems, and many more. Novel techniques like 3D printing technology are also an emerging approach in the fabrication of GRDDS. Various *in vitro* and *in vivo* techniques are used for the analysis of GRDDS, like buoyancy time, gastroscopy, scintigraphy, ultrasonography, *etc*. This chapter is the comprehensive literature exploring GRDDS, including various principles in the fabrication of GRDDS, techniques of preparation of GRDDS, polymers used in the fabrication of GRDDS, evaluation of GRDDS, application of 3D printing in GRDDS, and patent scenario.

Keywords: Gastroretentive drug delivery, Mucoadhesive, Floating, Swellable systems, Effervescent system, Non-effervescent system.

INTRODUCTION

The oral route is the most preferred route of drug delivery due to a wide variety of advantages that include the ease of drug administration, high patient compliance [1], and easy formulation, storage, and transport of these dosage forms. It also offers a large surface area for the passive absorption of the medicament [2]. This route is the most dominant way to deliver active ingredients to treat local gastrointestinal (GI) diseases with systemic diseases. The mouth, esophagus,

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stomach, small intestine, and colon are the components of the GI tract that play a role in food digestion and medication absorption.

Despite the obvious advantages, oral drug delivery also faces some challenges, such as the harsh environment of the gastric system, enzymatic activity, and regional pH [3]. Conventional systems of drug delivery fail to overcome these issues, which leads to the ineffectiveness of the drug and an increase in the dose administration frequency. To overcome these obstacles that emerged due to the harsh environment in the GI tract and other physiological barriers, significant attempts have recently been made, which are dependent on a better awareness of the healthy and pathological characteristics of the GI tract. The therapeutic range is the total serum abundance of a drug needed to achieve the therapeutic effect of a particular drug. To get the continuous impact of a drug, it is necessary to sustain the drug concentration in the therapeutic range with the help of frequent administration, which is responsible for fluctuation in drug plasma concentration [4]. This has led to the formulation of a controlled drug delivery system.

Controlled drug delivery systems (CDDS) are primarily considered for the prolonged release of drugs and to achieve stable plasma concentration for a longer period. The primary goals of controlled drug delivery are to increase drug efficacy by modifying the pharmacokinetics and pharmacodynamics of the pharmaceuticals, maintain drug concentration in the desired tissue, and decrease the number of administrations. However, it is less helpful for drugs with an absorption window in the upper GI tract due to the gastric transit time. Although the duodenum and jejunum show rapid absorption, the movement through this part is swift, which limits the scale of absorption [5]. To enhance the bioavailability of such drugs, it is vital to extend the residence time of the drug in the upper GI tract, which can be obtained by the use of a gastroretentive drug delivery system (GRDDS), which can endure the rough environment, grinding, crushing, and peristaltic movements, and which can also release the drug at a controlled rate in the GI tract. The created system should not impair gastric movability or ruin the mucosa lining of the stomach. GRDDS is important to achieve better drug efficacy and targeted drug delivery.

PHYSIOLOGY

The digestive system travels from the mouth to the anus *via* the midsection of the body. The pharynx, esophagus, stomach, and small (which includes the duodenum, jejunum, and ileum) and large (which includes the cecum, appendix, colon, and rectum) intestines are the main components of the GI tract. The GI tract is a 9 meters long tube that appears from the esophagus to the anus, with some adjacent variations.

The oral cavity is protected by the oral mucosa and possesses favorable permeability, a moderate microenvironment, easy access to circulation, and good drug absorption. However, the greatest obstacles to drug delivery in the mouth are the smaller surface area of the oral cavity, saliva, and enzyme makeup of saliva [6].

The esophagus has a short residence time and low permeability, and it is not a target for drug delivery. The stomach is a muscular hollow organ located in the left upper portion of the abdominal cavity, beneath the diaphragm and liver. The three major functions of the stomach are digestion, churning, and limited absorption. Structurally, the stomach is divided into 4 sections: the cardia, fundus, corpus (body), and pylorus (Fig. **1**). Its prime responsibility is to briefly store and crush food before releasing it gradually into the duodenum. Fundus and corpus are the reservoirs of undigested food, and at the same time, the antrum serves as a pump to help with gastric emptying *via* a pushing mechanism [7]. The pyloric area is an essential area for the mixing of food, and it also connects the stomach with the duodenum. It has a very acidic pH of about 1-2.5, and it helps to crumble food, deteriorate microbes [8], and degrade acid-unstable drugs [9].

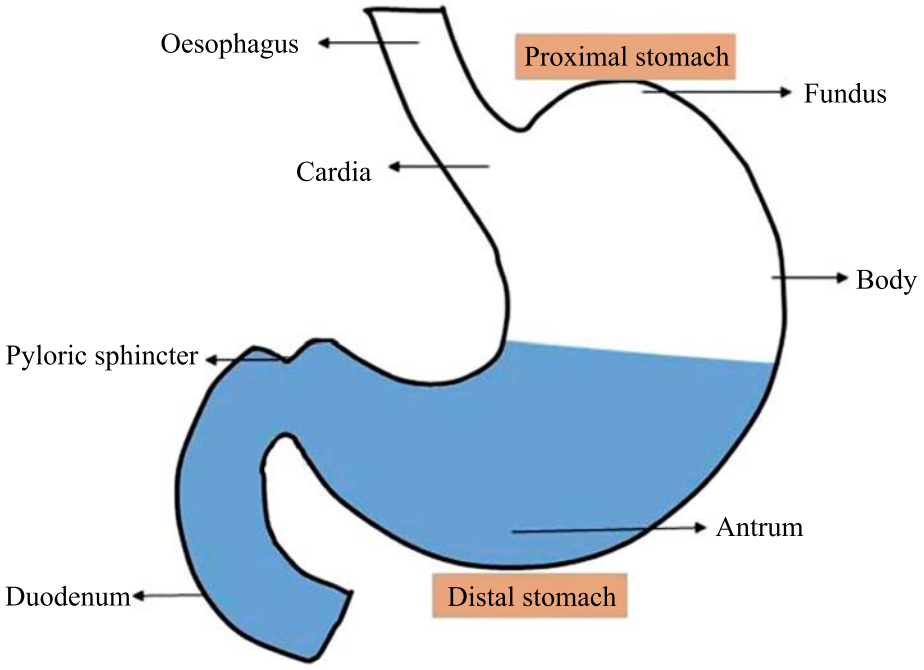

Fig. (1). Anatomy of Stomach [10].

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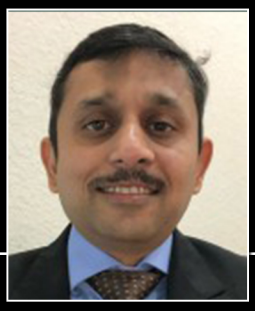

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