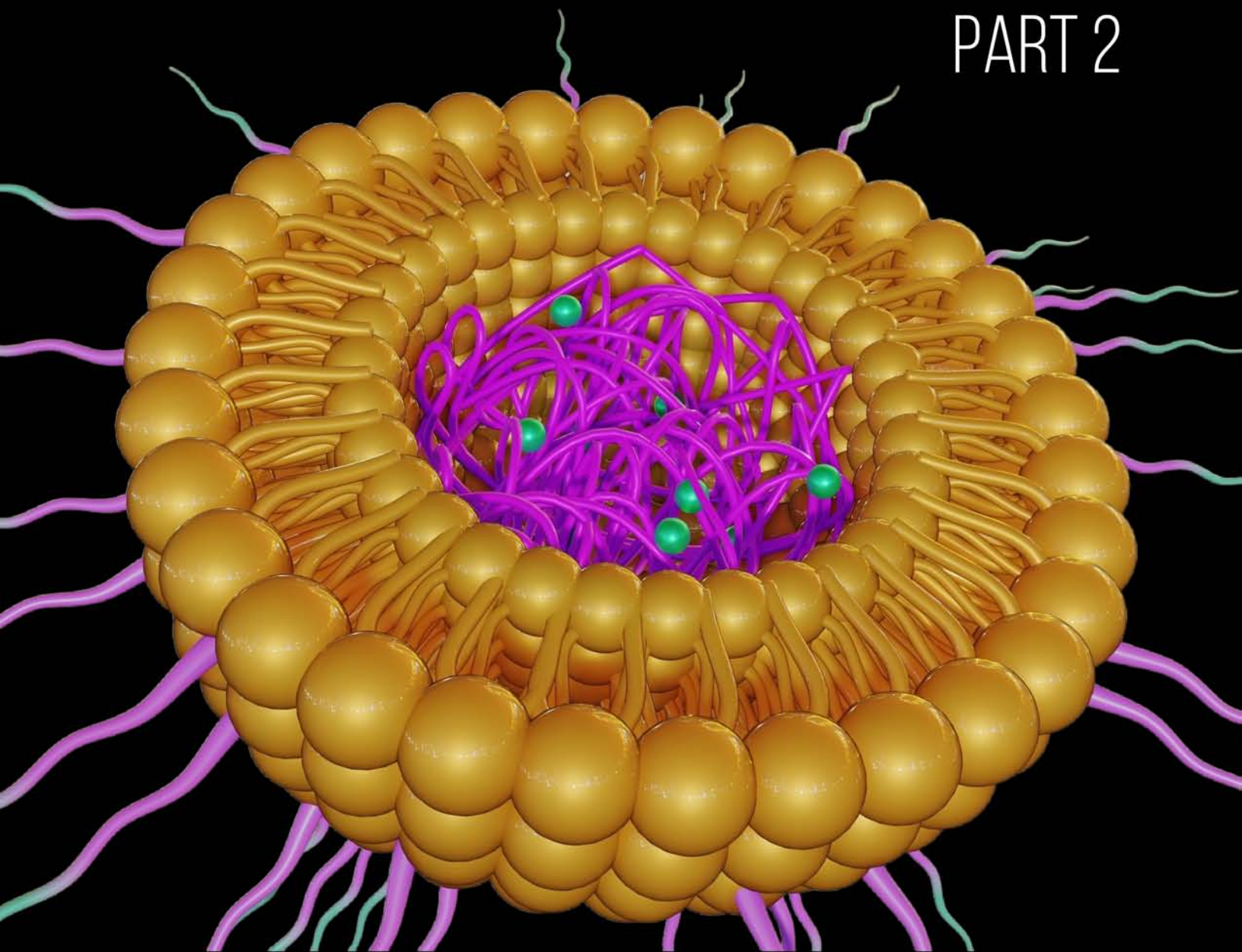


NOVEL DRUG DELIVERY SYSTEMS

PART 2



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Bentham Books

Novel Drug Delivery Systemu

(Part 2)

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FOREWORD

The field of pharmaceutical sciences is ever-evolving, driven by the pursuit of more efficient, targeted, and patient-friendly therapeutic solutions. At the forefront of this transformation are Novel Drug Delivery Systems (NDDS), which hold the potential to revolutionize drug administration and efficacy paradigms. This book provides a comprehensive exploration of NDDS, meticulously crafted for postgraduate students and researchers ready to lead this exciting frontier.

The authors delve into the principles and advantages of NDDS, emphasising their potential to enhance drug bioavailability, reduce side effects, and improve patient compliance. It sets the stage for subsequent discussions on how NDDS can address these challenges by providing more effective and targeted therapeutic options. This book introduces various NDDS platforms and their applications in managing chronic diseases. As you navigate through these chapters, you will encounter a blend of rigorous scientific analysis and practical insights. The discussions are enriched with illustrative figures, tables, and real-world examples that elucidate complex concepts and foster a deeper understanding. This book is more than just a compilation of knowledge; it is a call to action for the next generation of pharmacy professionals and researchers. The advancements in NDDS hold the promise of revolutionising healthcare, and it is through your dedication and innovation that this promise will be realised.

I am confident that this book will serve as a valuable guide and reference in your journey towards mastering NDDS. May it empower you to make significant contributions to the field of pharmacy and to the betterment of patient care worldwide.

V. K. Mourya
Chh. Sambhajinagar, Maharashtra, India

PREFACE

We are excited to present the second volume of our comprehensive book on novel drug delivery systems. Following the foundation laid in Volume 1, this volume delves deeper into specialized and emerging technologies that are reshaping drug delivery, broadening the scope of controlled release systems in diverse therapeutic areas.

This volume begins with Chapter 1, "Nasopulmonary Drug Delivery Systems", which explores the promising potential of nasal and pulmonary routes for drug administration. The chapter discusses the intricate dynamics of drug delivery to these regions, emphasizing their relevance in targeting respiratory diseases and systemic drug administration.

In Chapter 2, "Transdermal Route of Drug Delivery", the focus shifts to the innovative methods for delivering drugs through the skin. This chapter offers a detailed look at transdermal systems, their design, applications, and the advances that are transforming this route into a powerful tool for controlled drug delivery.

Ocular drug delivery presents unique challenges due to the sensitivity and complexity of the eye. Chapter 3, "Ocular Drug Delivery Systems", provides valuable insights into the technological advances that are improving the administration of therapeutics to the eye, ensuring precise and effective treatment for ocular conditions.

Chapter 4, "Nanotechnology and its Concepts", opens up the fascinating world of nanotechnology, a field that holds immense promise for revolutionizing drug delivery. This chapter delves into nanoscale materials and their applications in achieving targeted, controlled, and efficient delivery of therapeutics at the cellular and molecular levels.

Continuing the exploration of innovative approaches, Chapter 5, "Implantable Drug Delivery Systems", examines how implantable devices can provide long-term, controlled release of drugs, particularly in chronic conditions. This chapter offers a comprehensive look at the development, design, and applications of these devices in clinical practice.

The volume concludes with Chapter 6, "Controlled Release Injectables", which offers a thorough overview of the advancements in injectable formulations designed for sustained and controlled drug release. This chapter highlights the critical role injectables play in modern medicine, providing an in-depth understanding of the latest innovations in this area.

As with the first volume, our goal was to equip readers—whether students, researchers, or professionals—with a deeper understanding of the latest developments in controlled drug delivery systems. The content in this volume reflects the expanding horizons of drug delivery and presents cutting-edge research that is driving the future of pharmaceutical sciences.

We extend our deepest appreciation to the expert authors who have contributed to this volume. Their commitment to advancing knowledge in novel drug delivery has made this collection a valuable resource for readers worldwide. We hope that this volume, like the one before it, will inspire continued innovation and progress in the field of pharmaceutical sciences.

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DEDICATION

*I would like to dedicate this book
To
My Loving and Caring late Elder Sister, Shubhangi
To
My family*

Atish S. Mundada

*I would like to dedicate this book
To
My Friends & Family*

Alap Chaudhari

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Nasopulmonary Route of Drug Delivery

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Abstract: Nasopulmonary drug delivery has gained a lot of interest as a convenient, reliable, and promising technique for systemic drug administration. It is especially used for molecules that can only be delivered intravenously and are inefficient when taken orally. This is due to the high vascularization seen above the upper nasal cavity and alveolar region of the pulmonary system, wide surface area, avoidance of first-pass metabolism, gut wall metabolism, and/or destruction in the gastrointestinal tract. Numerous therapeutic compounds may be supplied intranasally for topical or systemic administration. Presently, the nose-to-brain administration route offers targeted delivery. Several further advantages are expected to emerge *via* the pulmonary route to achieve systemic effects and treat lung disorders. Barriers that prevent absorption through the nasal and pulmonary pathways must be overcome to achieve these therapeutic benefits. Numerous drug delivery devices are being researched for nasal and pulmonary administration of liquid, semisolid, and solid formulations to deliver the medications quickly and/or efficiently to the target area. They are especially suitable for the administration of biotechnological products like proteins, peptides, hormones, and vaccines, as well as poorly soluble drugs, to improve bioavailability. Pulmonary drug delivery has triggered intense scientific and biomedical interest in recent years, and it has made significant progress in the context of local treatment for lung disorders, owing to improved local targeting and fewer systemic adverse effects with the administration of minute therapeutic levels. The chapter attempts to provide some information regarding the nasopulmonary drug delivery system, including the anatomy of the nasal cavity and respiratory tract, the mechanism of drug absorption, characteristics that are considered during the selection of drugs for the nasopulmonary system, factors that affect nasal and pulmonary drug absorption, techniques to improve absorption, dose calculation specifically for intranasal delivery, formulation of dosage forms according to requirement, novel drug formulations, recent improvements of the nasal and pulmonary delivery systems, and some of the patents and commercially also available formulations. The impact of COVID-19 and intranasal vaccine development is discussed in this chapter.

Keywords: Barriers, Inhalers, Mucociliary clearance, Nasopulmonary, Nose-to-brain delivery, Nanoparticles.

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INTRODUCTION

The nasal mucosa is considered an effective route to deliver drugs for fast absorption and quick entry of drugs into systemic circulation. Nasal therapy, commonly known as “NASAYA KARMA”, is a recognized treatment in the Indian medical Ayurvedic systems.

The absorption of the drug is effectively facilitated by utilizing the significant surface area of the nose as a key for the absorption. Villi present on the epithelial surface in the nose are found to be in microns size, known as microvilli, while the layer below the epithelial, called the subepithelial layer, is densely vascularized. Vascularized areas of the nose blood streams immediately make it to the systemic circulation, which fends off the loss of drugs from first-pass metabolism. They offer low doses of drugs and quick attainment of therapeutic levels in the blood. The onset of pharmacological activity is faster and also gives fewer side effects [1 - 3]. Various notable drawbacks of the nasal route that impact the absorption include a modest volume of application (25-250 μ l) and drugs with high molecular weight (>1000 Da) passing through the nasal mucus layer. Physiological circumstances such as mucociliary drug clearance, enzyme-mediated barriers, and nasal mucosal irritations are also challenges for drug delivery [4 - 6].

The nasal mucosa is an endothelial basal membrane that is quite thin and porous in comparison to other biological membranes. Stratified squamous epithelium, basement membrane, and lamina propria are the systematic arrangements within the nasal mucosa. The nasal mucosa consists of the epithelium, basement membrane, and lamina propria. The nasal mucosa epithelium predominantly consists of four cells: goblet cells, basal cells, and ciliated and non-ciliated columnar cells [7]. Mucosal secretion is much more aqueous as it is composed of about 95% water, and the other 5% consists of mucin, salts, albumin, lysozyme, immunoglobulin, and lactoferrin, as well as some other proteins and lipids. Some of the antibodies, such as IgE, IgA, and IgG, are also found in the nasal mucus [6]. The epithelial layer is highly vascularized and around 150 cm^2 , with an absorption region featuring microvilli. It also has a quick blood flow. These qualities give it various benefits, including quick drug absorption, quick action, and low overdose risks [8, 9]. There are three mechanisms for drug or therapeutic substances to pass through the nasal mucosa: paracellular, transcellular, and transcytosis [10].

Paracellular transport is associated with tight junctions and intercellular gaps, and it is a considerable pathway, especially for protein and peptide absorption. According to reports, the paracellular pathway should be reversibly open to

improve the absorption of peptides by the nasal mucosa. Also, some of the reports state that drug absorption increases by taking up the hydrophilic character of the molecule [11, 12].

Active or passive transport mechanisms are used to achieve the transcellular pathway. It is essential for the absorption of molecules that are acknowledged by the membrane or those that are lipophilic [9].

The mechanism by which a particle is trapped into vesicles and delivered to the cell is called transcytosis. Finally, it gathers in the interstitial space [13].

There are three different routes through the nose for the drug to reach the brain [14]. The olfactory pathway is the very first point of entry for drugs into the brain. Drugs can move to the brain from the olfactory region, which it surpasses through the olfactory epithelium (Consists of basal cells, supporting cells, and olfactory nerve cells) and then promotes to the olfactory bulb *via* the olfactory nerve. The trigeminal pathway is another route through the nose for the entry of drugs to the brain [15]. In the trigeminal pathway, the drug can get into the brain to achieve nose-to-brain delivery using trigeminal nerves, which innervate the olfactory epithelium and mucosa [16]. The peripheral pathway is the third way to promote brain delivery *via* the nose (Fig. 1). Drugs are absorbed through the vascular pathways and enter into the systemic circulation by allowing them to bypass the blood-brain barrier (BBB) [17]. Drugs delivered nasally may also reach the lymphatic system and gastrointestinal tract [18].

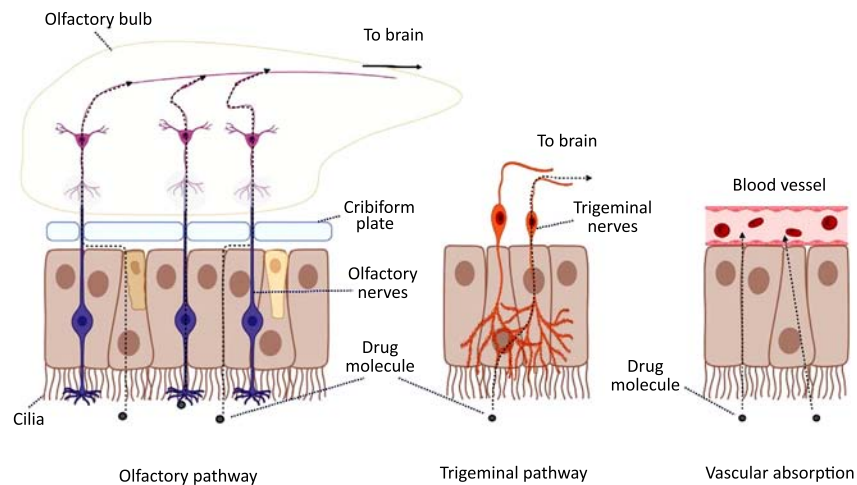


Fig. (1). Pathways followed by drug through nasal delivery.

Transdermal Route of Drug Delivery

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Abstract: Significant breakthroughs in transdermal delivery of drugs have occurred in recent years owing to new technology and strategies used for transporting drug across the skin. Transdermal drug delivery systems (TDDS) provide many benefits, such as the avoidance of hepatic clearance, ease of application, better patient acceptance, and regulated release of medication; yet, patients and physicians still face numerous challenges. Due to the skin's excellent barrier function and lipophilic nature, one of the main obstacles for TDDS is the restricted amount of drug placement, specifically for drugs with molecular weights > 500 Da. Many pharmacological molecules, including high molecular weight pharmaceuticals, have been the subject of much research, especially in relation to biotechnologically manufactured medications delivered using TDDS. This chapter covers the principles of transdermal drug delivery systems, including their types, components, evaluation, lab and large-scale manufacture. This chapter also emphasizes on new technologies that have improved skin permeability and the regulatory considerations for transdermal formulation.

Keywords: Drug delivery, Film formulations, Flux, Lab scale and large-scale production of transdermal patches, Penetration, Permeation coefficient, Skin as port of drug delivery, TDDS, Transdermal patch.

INTRODUCTION

The word 'transdermal' is coined from 'trans', means 'across', and 'dermal', means 'skin', indicating the transport of the drug from the outer layer of the skin to the bloodstream. The method of delivering drugs directly into the bloodstream through intact skin in a beneficial quantity after administering a therapeutic dose is known as transdermal drug delivery. It was not until 1950s that the utilization of the skin as a delivery route into systemic circulation was commercially explored. The idea that drugs might be delivered through the skin was confirmed by the salicylates and nitroglycerine ointment formulations, which were found to

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have therapeutic effects [1]. Early in the 1980s, a pharmaceutical transdermal patch for motion sickness was developed, which signaled the advantages and suitability of this mode of administration for contemporary commercial drug products. Subsequently, a plethora of different transdermal patches-including those for nicotine, nitroglycerin, clonidine, and estradiol-revolutionized TDDS and gave the pharmaceutical sector a new space of prospect to reap its benefits.

Over the past four decades, significant advancements have been made in the field of controlled transdermal medication delivery. TDDS has become increasingly popular, particularly in elderly and young people, as well as for all those who struggle to swallow and experience nausea and vomiting, owing to its simple and painless administration and better patient acquiescence for non-invasive skin routes. There are many TDDS available for sale in the form of films that contain low molecular weight pharmacological molecules. The development of transdermal products applying revolutionary systems and technologies to administer any API, including macromolecules and biologicals, is anticipated to have a significant impact in the near future. Compared to other medication administration methods, including oral, topical, and parenteral, great interest has developed in this area of drug delivery, possibly due to several advantages it offers.

Advantages

The perceived advantages of TDDS [2, 3] include:

1. Devoid of the hazards and drawbacks associated with intravenous therapy.
2. Transdermal medicine provides a consistent infusion of a substance for an extended period. It is also possible to prevent side effects or treatment failures that are commonly linked to sporadic dosing.
3. The transdermal route of delivery can enhance the efficacy of many drugs by avoiding certain drug-related problems such as gastrointestinal irritation, poor absorption, hepatic “first-pass” effect-induced decomposition, metabolite formation that causes side effects, short half-life requiring frequent dosing, *etc.*
4. Self-administration, ease of stopping therapy, and fewer opportunities for over- or under-dosing result in increased patient acceptance and decreased variability between and among patients.

Limitations

Apart from the advantages mentioned above, TDDS has some limitations [4, 5].

1. For the medicine to pass through the stratum corneum, it needs to possess the following favorable physicochemical characteristics.

- Molecular mass should not be greater than 500 Da.
- Efficient oil-water partitioning to achieve the necessary gradient in membrane concentration, which catalyzes the drug's passive diffusion through the uppermost barrier layer of the skin.
- A suitable partition coefficient (1-4) to facilitate better separation of a vehicle from the stratum corneum, the skin barrier.
- A suitable melting point (less than 200 °C), a crucial factor influencing solubility.

1. Another drawback is that certain medications, excipients, and boosters that are used to boost percutaneous absorption might cause skin irritation or contact dermatitis.
2. Clinical necessity is another vital factor that needs to be carefully taken into account before electing to produce a transdermal patch.
3. The barrier function of the skin changes with age, individual variation, and location within a single person.

SKIN AS THE PORT OF DRUG ADMINISTRATION

The skin is the largest organ of the human body, with a surface area of around 1.5 to 2.0 m² and thickness ranging from 0.05 mm to 2 mm [6]. Approximately one-third of the blood that flows through the human body passes through the skin, making it one of the largest and easiest organs to reach. It is tough, elastic, and self-regenerating under typical physiological circumstances. The internal fatty matter and the duct system regulate body temperature. The mechanical strength of the skin protects the body against mechanical stress. Because of its limited permeability, the body's trans-epidermal water loss is inhibited, preventing dehydration. Skin cells called melanocytes provide defense against damaging UV rays. In addition, the skin carries out endocrine tasks like pheromone synthesis and vitamin D synthesis [7].

Skin Anatomy

Microscopically, the skin is made up of three distinct layers, as shown in Fig. (1). These layers are the epidermis, the dermis, and the hypodermis.

Ocular Drug Delivery Systems

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Abstract: Ophthalmologists and drug delivery scientists face considerable challenges in the realm of ocular drug delivery, primarily attributable to the intricate structural and barrier complexities inherent in the eye. The presence of various barriers, including the multilayered cornea, sclera, conjunctival blood flow, and tear dilution, imposes limitations on the efficacy of drug delivery, affecting both the anterior and posterior segments of the eye. To overcome these challenges, researchers have explored diverse delivery systems to enhance drug delivery and treatment outcomes. Among the conventional ocular drug delivery systems, the ophthalmic solution or eye drop stands out as a widely utilized and consumer-preferred option. Existing market formulations include emulsions, suspensions, and ointments. Concurrently, scientists have been investigating innovative formulations such as liposomes, solid lipid nanoparticles, nanostructure lipid carriers, nanoparticles, hydrogel, and contact Lenses as potential future treatments, offering advancements in ocular drug delivery and serving as alternatives to traditional delivery methods.

This book chapter aims to provide a comprehensive summary of both conventional and novel topical formulations for ocular drug delivery. By examining the current landscape of ocular drug delivery systems, this chapter seeks to contribute valuable insights into the ongoing efforts to improve treatment efficacy and patient outcomes in the challenging domain of ocular therapeutics.

Keywords: Bioavailability, Conventional drug delivery, Nanotechnology, Novel approaches, Ocular drug delivery.

INTRODUCTION

The distribution of drugs to the eye, an area that is notorious for its difficult treatment, has improved recently. The eye is an organ that is relatively separated from the rest of the body. It is equipped with several systems and barriers that

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prevent things from entering it. These include the nasolacrimal drainage system, blood-aqueous barrier, blood-retina barrier, cornea, and blinking reflex as shown in Fig. (1). When combined, these systems provide barriers to the efficient administration of medications to the anterior and posterior parts of the eye [1]. Therefore, there is a current emphasis on advancing ocular particulate drug delivery systems (DDSs) that demonstrate sustained release capabilities or enhance permeability. This area represents a recent and intense focus of research. The particulate DDSs include liposomes, emulsions, micelles, dendrimers, and microspheres. The conventional method for administering an ocular DDS mainly involves the ocular surface, intraocular regions (such as intravitreal and suprachoroidal space), and periorbital tissues as depicted in Fig. (2). Due to the distinctive barrier effects of each eye segment, the factors influencing administration for each route vary. Designing an innovative ocular DDS is now recognized as a crucial factor in achieving effective drug delivery to different parts of the eye [2].

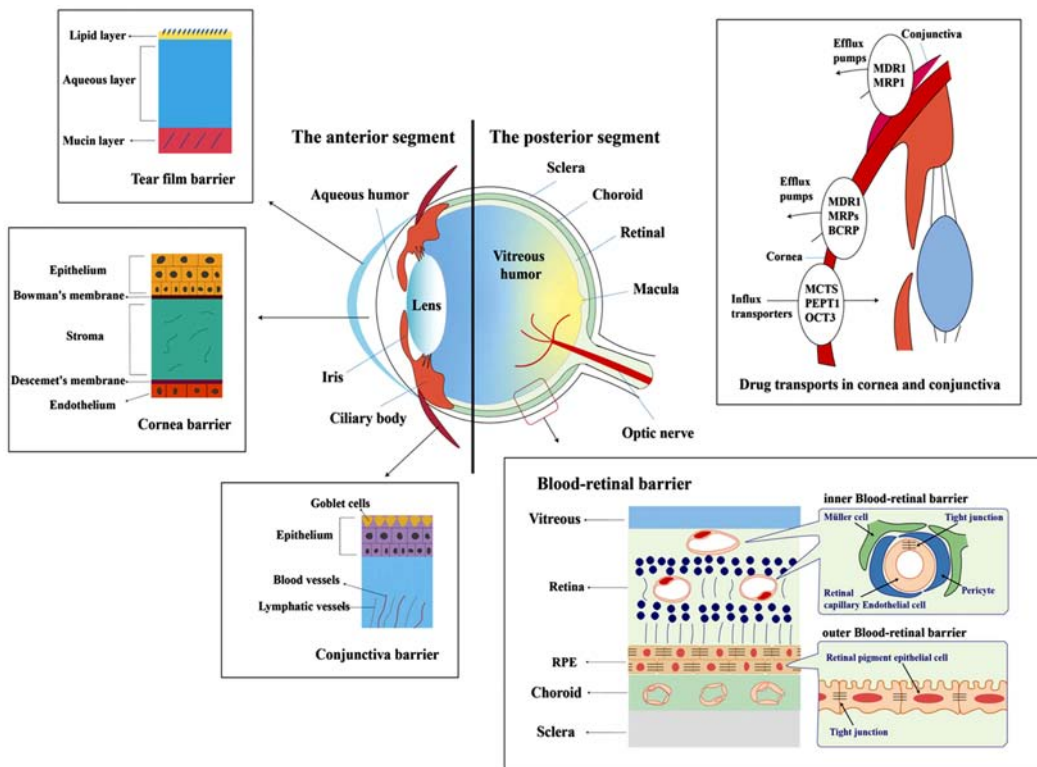


Fig. (1). An overview of ocular anatomy and physiological barriers [3].

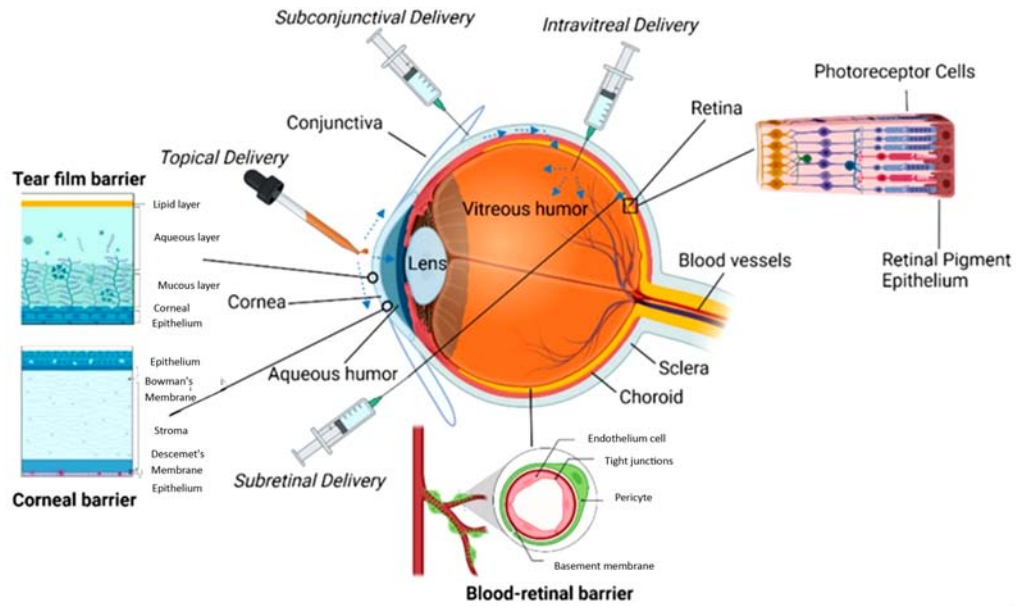


Fig. (2). The ocular anatomy, key barriers, and four primary routes of delivery, including topical, intravitreal, subretinal, and subconjunctival [4].

Classification of Ocular Dosage Forms

Classification of dosage form for ocular drug delivery are listed in Fig. (3).

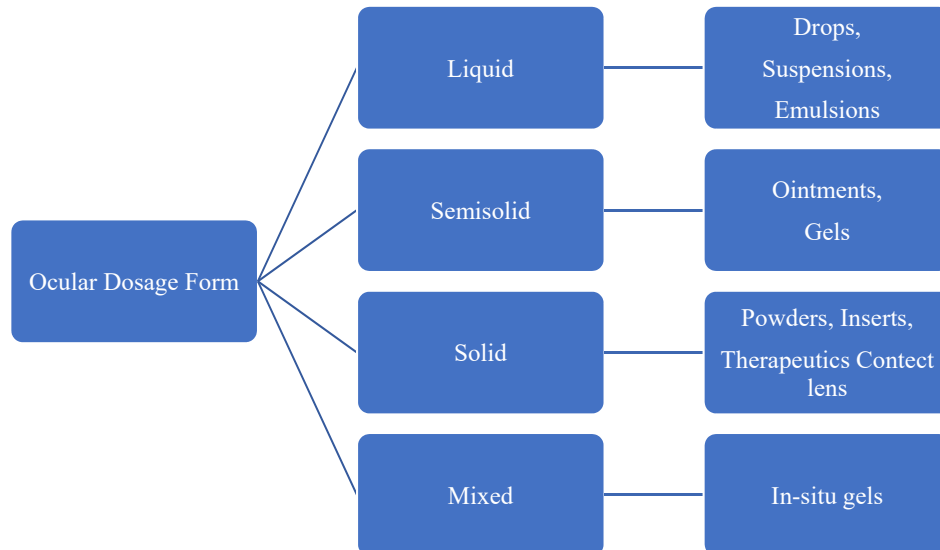


Fig. (3). Flow chart of different Ocular dosage forms [5].

CHAPTER 4

Nanotechnology as a Novel Approach to Drug Delivery Systems

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Abstract: Nanotechnology is a new platform through which the delivery of therapeutics takes place using nanoformulation to overcome the pharmacokinetics challenges of the drug. This chapter presents an overview of nanotechnology-based delivery systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid polymer hybrid nanoparticles. The potential advantages of the use of a nanotechnology-based delivery system over the conventional drug delivery system are highlighted. The rationale for the development of a nanotechnology-based delivery system is discussed in detail. The aspects of various characterization studies of nanoparticles and their effect on performance behavior are discussed. The potential applications of nanotechnology-based delivery systems and nonparticulate drug delivery systems, such as oral, dermal, ocular, and parenteral, are currently being explored.

Keywords: Characterization, Liposomes, Lipid-polymer hybrid nanoparticles, Nanotechnology, Nanoparticles, NLC, Oral delivery, Ocular delivery, SLN, Therapeutic applications.

INTRODUCTION

The concept of nanotechnology was presented initially by the Nobel Prize laureate and American physicist Richard Feynman in 1959. After fifteen years, in 1974, the Japanese scientist Norio Taniguchi used and studied the details of 'nanotechnology'. He defined the term "nanotechnology" in his own words. He described that "nanotechnology is mainly composed of various processes such as

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the separation, consolidation, and deformation of materials by one atom or one molecule” [1]. Nanotechnology is a newer platform through which the delivery of drugs can be achieved in nanosize range. Several scientists are working on nanotechnology-based delivery systems for the therapy of various diseases such as cancer, HIV-I infection, arthritis, psoriasis, diabetes, and bacterial and fungal infections. A few examples are polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid drug conjugates (LDCs), self-microemulsifying drug delivery systems (SMEDDS), gold nanoparticles, nanosuspension, nanoemulsion, *etc* [2]. With respect to nanotechnology, the nanotech-based delivery system has entered the science, medical, and engineering fields in order to enhance various activities in various fields. In addition, the nanotech-based delivery of medicine is utilized for medical therapy and treatment of diseases [1].

Advantages

The nanotechnology-based delivery system offers several advantages over the conventional delivery system. They are:

1. Delivery of drugs at a predetermined rate.
2. Enhanced targeting of a group of cells.
3. Targeting the sites to minimize the unwanted side effects.
4. Delivery of drugs to various targeted sites, tissues, and specific cells to minimize the side effects.
5. Improved drug solubility and bioavailability to enhance therapeutic efficacy.
6. Controlled and sustained release behavior of the nanoparticles, maintaining optimal drug concentration and reducing the frequency of drug administration.
7. Protection of drugs from the gastric environment to improve their overall effectiveness.
8. Versatility is a virtue of the nanoparticles since they can deliver a wide variety of drugs, such as proteins and nucleic acids (DNA and RNA).

Currently, micro and nano-scale nanoparticles have been fabricated to deliver the drug in target sites with minimum side effects and maximum efficacy. It is also useful for detecting and responding to the disease state and tissues to improve the particles' life [3]. In recent years, a nanotechnology-based delivery system has

developed multifunctional pharmaceutical nanocarriers, which have reached a higher level [4].

Nanotechnology refers to the manufacturing of particles in nanometric sizes less than 100 nm. Nevertheless, this size, *i.e.*, 100 nm, of nanoparticles is not a constraint, but it varies with the various applications of medicines, cosmetics, and tissue engineering. Thus, a nanoparticulate drug delivery system is beneficial over a traditional drug delivery system. The main application of nanotechnology is the manufacturing of nanomedicine or nanocarriers for the treatment of various diseases [5].

The nanotechnology-based lipidic drug delivery system includes liposomes, polymeric nanoparticles, SLNs [6, 7], NLCs [8], LDC [9], and SMEDDS [10, 11]. The 'liposomes' are drug delivery systems composed of phospholipid vesicles. The first pharmaceutical liposomal product (for pulmonary instillation) entered the cosmetics market at the beginning of the nineties [12]. However, liposomal products fail to grab the market due to the stability issues of the liposomes. Moreover, the liposome is associated with some kinds of lacuna *i.e.*, difficulty in liposome production, issues of scale-up in formulation, and high cost, which are some major drawbacks that prevent the commercialization of liposomes [13]. Many researchers are still working on liposomes to improve storage stability [14]. Polymeric nanoparticles have emerged as a promising delivery system with potential applications in the pharmaceutical field due to their unique properties. The polymeric nanoparticles are biodegradable and made up of synthetic polymers with repeating chain units. Examples of synthetic polymers are poly (L-lactide) (PLA), polyglycolide (PGA), and polyurethane. The targeted delivery at specific sites can be made possible by using nanotechnology to improve the absorption and bioavailability [15]. The drug release from these nanoparticulate systems can be achieved through various physical processes such as desorption, diffusion, or erosion [2]. The poor encapsulation capacity and drug expulsion are the main drawbacks of the SLNs. However, SLNs, as a leading drug delivery system for poorly soluble drugs, are described by several researchers. To overcome these drawbacks, second-generation NLCs have been discovered, which have a high drug payload, improved stability, and high encapsulation capacity and can cause controlled release of a drug. They are prepared by lipidic excipients of a GRAS nature. There are multiple types, amorphous types, and imperfect lattice arrangements of the particles [2].

Thus, in this chapter, we present the concept of nanotechnology and nanotechnology-based delivery systems. The use of nanotechnology for the development of nanoformulation to deliver the right drug at the right target is discussed along with their applications are discussed. We especially discuss the

Implantable Drug Delivery

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Abstract: Miniaturized systems, known as implantable drug delivery systems, are used to administer medicinal medicines to specific sites within the body. They are made of biocompatible substances that enclose the drug payload and control its kinetics of release, enabling sustained delivery. These systems provide a number of benefits by avoiding the drawbacks of oral drugs and conventional injectable techniques, including increased bioavailability, fewer systemic side effects, and improved patient adherence. The key characteristics and elements of implanted drug delivery systems, such as the drug reservoir, release mechanism, and sensing capabilities, are highlighted in this chapter. It explores several implant design techniques that allow for exact control of drug release rates, including micropumps, microelectromechanical systems, and biodegradable polymers. Potential uses for implantable drug delivery systems (IDDSs) include the management of chronic pain, hormone replacement therapy, the management of cardiovascular diseases, and cancer. The challenges and considerations to be taken into account when developing IDDSs, such as biocompatibility, device integration, and long-term dependability, are also covered in this chapter. Furthermore, it explores ongoing studies aiming at enhancing remote monitoring capabilities, drug loading capacity, and device performance. By enabling accurate and localized administration, IDDSs have the potential to revolutionize the field of targeted treatments. These technologies have promising potential for enhancing the patient's quality of life, lowering healthcare costs, and improving treatment outcomes.

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Keywords: Biocompatible materials, Chronic pain management, Cancer treatment, Implantable drug delivery systems, Microelectromechanical systems, Sustained drug release.

INTRODUCTION

Controlled and focused drug distribution is highly valued in contemporary medicine. Conventional oral and intravenous medication administration often faces limitations in terms of therapeutic windows due to the presence of unwanted impact on tissues not intended for targeting and insufficient hepatic metabolism [1]. Additionally, the medication is hampered by the patient's complicated regimens, which require them to administer injections or take multiple pills. This results in low adherence and unstable therapeutic concentrations [2, 3]. Systemic side effects cause a significant number of medication candidates to fail to progress beyond the initial phase of clinical trials. On the path to precision medicine, there is a need for alternate medication delivery techniques that overcome biological and psychological obstacles. The implantable drug delivery system (IDDS) is a surgically placed device that regulates medication release rate, timing, and location in the body. Its purpose is to deliver therapeutic materials, thereby enhancing their efficacy and safety [4].

Clinical management techniques have been revolutionized by IDDSs, which have also established themselves as good therapies and/or industry standards with the peculiar qualities listed below:

- Regional medication delivery
- Increased patient adherence
- A decline in the frequency of systemic side effects
- A low dosage range
- Improved medication stability

The development of an exceptional IDDS is essential in significantly reducing the prerequisite for repeated drug administration throughout the recommended treatment period. In fact, it needs to be sterile, biocompatible, and easily accessible. To begin or stop the therapy, medical practitioners can implant and remove these devices. It also needs to be easy to make, provide economical therapy for the duration of the treatment, and allow rate-controlled medication release at the optimal dose. The form of an implantable system is typically cylindrical, with monolithic components utilized most frequently at the millimeter or centimeter. Surgical methods, needles, or specialized implantation equipment are typically employed to perform implantation in intramuscular or subcutaneous tissue [5].

In the 1930s, the subcutaneous implantation of pellets containing hormones in livestock and poultry was observed. This is regarded as one of the earliest applications of IDDSs. Bishop detailed the first clinical application of IDDS for female hormone therapy. Blakshear claims that the concept of IDDSs in contemporary medicine has been developed by Deansby and Parkes. In order to study the effects on castrated male chickens, they conducted an experiment in 1938 by subcutaneously implanting compressed pellets of crystalline estrone [6].

In the 1960s, Folkman and Long created implantable formulations in which a polymeric membrane controlled the rate of drug release. They talked about how a silicone rubber (Silastic) capsule was inserted into the canine cardiac muscle and how slowly drugs diffused through it [7]. In the 1990s, the FDA granted approval to Norplant[®], a contraceptive implant that contains Levonorgestrel (LNG) and is a “Silastic” capsule design. This approval marked the commencement of the clinical expansion of IDDSs. An extensive category of passive implants, including non-biodegradable implants consisting of the drug and biodegradable material, were developed as a result of the early studies on the diffusion of low-molecular-weight substances.

Intramuscular tissue is regarded as a perfect site for the implantation of a drug reservoir system because of its high-fat content. These sites encourage sluggish medication absorption, limited innervation, adequate blood flow, acceptable hemoperfusion, and a reduced risk of inflammation at the site of implantation (short response to external attachment) [8]. Other successful implantation sites outside of the skin include the intravaginal, intravascular, intraocular [9], intrathecal [10], intracranial, and peritoneal regions of the body [6, 11].

Glimpse into Implantable DDS

In the past, the two main types of IDDSs have been utilized- drug implants and drug-contained implantable pumps. The drug implants control how quickly drugs are released from delivery systems using a variety of polymers [12]. The first type of implant is further categorized into two subcategories: non-biodegradable and biodegradable systems. The drug-contained implantable pumps consist of mechanical pump-type devices that regulate drug release through an infusion pump-like mechanism. The ongoing technological developments in this area lead to the emergence of a new category of atypical implants [13].

Advancements in IDDS

Currently, commercially produced IDDSs are used for guided regeneration, pain management, and the treatment of chronic disorders. They are also used for women's health and pregnancy control. An IDDS primarily delivers hormonal,

Controlled-Release Injectables

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Abstract: The importance of controlled-release injections in drug delivery, including the recent technological developments in injectable emulsions, liposomes, and nanosuspensions for parenteral drug delivery, is discussed in four major sections in the current chapter. The 1st section delves into the application of these systems for poorly soluble drugs, proteins/peptides, vaccines, and gene therapeutics, highlighting their potential to overcome challenges associated with bioavailability, stability, and targeted delivery. In the 2nd section, injectable emulsions are discussed as a formulation to overcome key formulation tasks such as solubilization of poorly water-soluble drugs as well as drugs susceptible to hydrolysis. The utility of injectable nanoemulsions exhibits enhanced stability and tissue penetration, while multiple emulsions show promise despite inherent complexity. Microemulsions offer a thermodynamically stable option for parenteral drug delivery. Tactics for improving poorly water-soluble drug delivery, sustained release, and targeted delivery using injectable emulsions are discussed. It also offers an overview of the physical and chemical properties and approaches used for the preparation of emulsion formulations. Emulsion stability assessments and characterization parameters essential for formulation development are also highlighted. An overview of the physicochemical characteristics of liposomes and the process by which drug-containing liposomes are formed is given in the 3rd part. It reviews a number of liposome preparation techniques, along with the number of drug loading and encapsulating methods. Examples of marketed and experimental products are provided while discussing the usage of injectable liposomes as a medication delivery vehicle. In the 4th section, nanosuspensions as a promising tactic for the formulation using the poorly water-soluble and poorly bioavailable drug candidates is discussed. The section navigates the complexities of manufacturing, emphasizing the importance of particle size distribution for stability. It explores diverse nanoparticle manufacturing techniques for formulating injectable nanosuspensions. Focusing on injectable nanosuspensions, it involves the application in controlled release, highlighting the significance of excipients, particle size, syringeability, and sterility for successful formulation.

Keywords: Controlled-release injections, Injectable nanoemulsions, Injectable nanosuspensions, Injectable liposomes, Microemulsions.

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INTRODUCTION

Prolonged administration of drugs can enhance their therapeutic efficacy and reduce their side effects. Various methods can sustain drug levels, such as repeated oral, pulmonary, topical, and parenteral administration, including controlled-release injections. In contrast to the inconsistent medication levels caused by recurrent bolus injection, controlled-release delivery keeps drug levels consistently above the minimal threshold for effectiveness and below the hazardous threshold. Hence, controlled-release injections offer an extended duration of action.

Controlled-release injection becomes a logical choice when drugs have extensive first-pass metabolism or low oral bioavailability. Controlled-release injections can be used for local delivery, such as applying an analgesic system straight to an invasive opening or a chemotherapeutic molecule to a brain tumor site, or for systemic delivery, such as delivering anti-metastatic chemotherapeutic agents. Controlled-release injections offer significant convenience to both patients and healthcare providers by reducing the frequency of drug administration. This decreased frequency saves costs for the healthcare system and improves patient compliance with the prescribed treatment, which in turn will increase the prospect of achieving the anticipated therapeutic result. Moreover, patient compliance is also enhanced with controlled release injections and minimizes unwanted side effects. While side effects may be inconvenient for some therapies like cancer chemotherapy, the benefits can be substantial.

One early controlled-release injection is lipophilic (oily) suspensions and solutions. These systems consist of edible oil, like castor or sesame, with the drug in dissolved or suspended form. These are manufactured with a simple process and have been used for delivering various drugs, including antipsychotics and steroids, with durations of action lasting up to 6 weeks. Liposomes, one of the injectable drug delivery systems, can either entrap the drug inside its interior or within the lipid bilayers. Liposomes are self-closing structures that contain one or more lipid bilayers that fill their interiors with part of the solvent. By attaching polyethylene glycol (PEG) to the lipid molecules in the bilayers, known as "Stealth" liposomes, the circulation time of liposomes can be extended.

Microemulsions and nanoemulsions are dispersed in a liquid carrier before injection. They offer solutions for hydrophobic and hydrophilic drugs. Emulsions can be water-in-oil (W/O) or oil-in-water (O/W). Multiple emulsions have also been developed for the incorporation of the combination of drugs. Suitable emulsifiers and viscosity-enhancing agents can be used to improve the stability of the formulation. The drug release rates and droplet size distribution are influenced

by the method of preparation. Nanosuspensions are another kind of dispersed system. It consists of particles with mean diameters that are less than 1,000 nm. This system addresses the challenge of poorly water-soluble drug candidates with low bioavailability. Nanoparticles can be produced using scalable techniques. Nanosuspension formulations have been approved for breast cancer treatment (Abraxane[®]) and antipsychotic therapy (Invega Sustenna[®]), which utilizes albumin-mediated uptake for targeted delivery of paclitaxel to tumors. Surface modification of nanoparticulate carriers is commonly employed to prolong their lifespan in the body, enhance stability under physiological conditions, and avoid uptake by the mononuclear phagocytic system. Synthetic polymers, particularly PEG, are frequently used as surface modifiers due to their favorable properties. Especially when the target tissue overexpresses specific receptors, such as in certain cancer cells, the targeting drug can be attached to PEGylated nanoparticles.

Oral delivery is the preferred method of drug administration, but achieving good oral bioavailability can be challenging. Factors such as poor absorption, first-pass metabolism, and rapid clearance can limit the amount of drug reaching the systemic circulation. The absorption of orally administered drugs is influenced by physicochemical properties and physiological barriers [1]. Many compounds, more than 40%, identified through screening programs have poor water solubility, making formulation difficult and causing performance issues. Injectable controlled drug delivery systems are commonly used for poorly soluble drugs like chemotherapeutic and anesthesia agents [2]. These systems bypass oral absorption barriers, allowing direct entry into the bloodstream or target sites. Highly lipophilic anticancer drugs pose challenges in formulation due to their limited water solubility. Injectable or implantable formulations offer a solution by facilitating direct circulation or targeted delivery. Paclitaxel (PTX), an effective drug for solid tumor malignancies, faces clinical limitations due to its poor water solubility [3].

Proteins and Peptides

With the advancements in pharmaceutical biotechnology, therapeutic proteins and peptides have gained prominence as effective drugs for various diseases due to their high selectivity and potency at low doses [4]. However, their use is hindered by their physicochemical properties, biological instability, and limited permeation and absorption. Proteins and peptides are vulnerable to enzymatic degradation, making oral delivery challenging [5 - 7]. Even parenteral administration results in short half-lives and necessitates repeated dosing. To address these limitations, controlled release systems have been developed, including microspheres, liposomes, nanosuspensions, and microemulsions [8]. However, the instability of

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