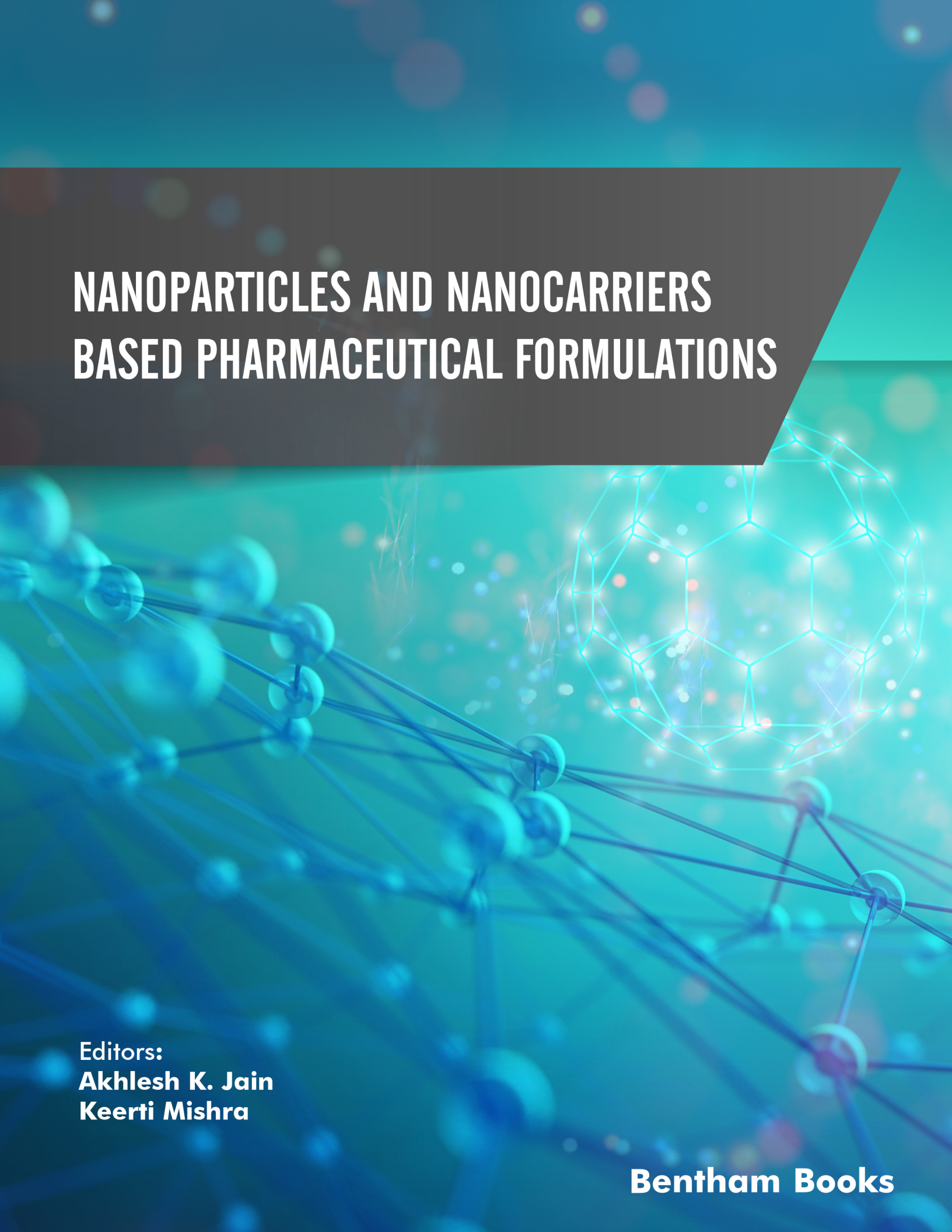
NANOPARTICLES AND NANOCARRIERS BASED PHARMACEUTICAL FORMULATIONS



Editors:
Akhlesh K. Jain
Keerti Mishra

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Nanoparticles and Nanocarriers Based Pharmaceutical Formulations

Edited by

Akhlesh K. Jain

Institute of Pharmaceutical Sciences
Guru Ghasidas University, Koni
Bilaspur, CG- 495009
India

&

Keerti Mishra

Institute of Pharmaceutical Sciences
Guru Ghasidas University, Koni
Bilaspur, CG- 495009
India

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Editors: Akhlesh K. Jain and Keerti Mishra

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PREFACE

Researchers working in pharmaceutical research have been interested in changing existing medication delivery systems for decades. Pharmaceutical industry research faces an unclear future due to the vast spread of numerous scientific disciplines and skill sets, such as polymer science, biotechnology, genetics, and molecular pharmaceutics. Higher clinical development costs, along with a lower rate of drug discovery and clinical success, result in a lower flow of new chemical entities (NCE) in research development.

The development of analytical tools and the ability to quantify particle size on a nanometre scale has shifted research in particulate drug delivery systems from the micro to the nanoscale. Nanocarriers are assisting in overcoming obstacles in conventional drug delivery due to their adaptability in targeting tissues, accessing deep molecular targets, and managing drug release.

The current book is an attempt to describe the global scientific community's research on this topic. Nanoparticulate drug delivery devices are difficult to develop and have been equipped with vivacious changes. The goal of this book is to explore current developments and upcoming technology in the field of nanoparticulate drug delivery systems.

We hope that the current multiauthored book on nanoparticles and nanocarriers will help and improve readers' understanding of the various types of nanocarrier-based formulations that are either existing or in development. We also hope that persons working in academic, industrial, and scientific fields concerned with pharmaceutical medication delivery would find the book useful. The book is organised so that each chapter covers a distinct topic of research that can be followed without referring to previous chapters.

To go with the flow, we have initiated this book with chapter one, which introduces readers to nanoparticles and nanocarriers. The chapter outlines the introduction of nanoparticles and nanocarriers, within which it describes their classification, including polymeric nanoparticles, metal nanoparticles, magnetic nanoparticles, inorganic nanocarriers, dendrimers, vesicular carriers, micelles and a lot more, along with their synthesis techniques and applications. Overall, this chapter is a comprehensive compilation of available information on recent advances in the field of nanomedicine through an elucidation of nanoparticles and nanocarriers systems. Second chapter focuses on various polymers and techniques engaged with the advancement of polymer-based nanoparticles and their applications in therapeutic intervention. Third chapter highlights the specific and targeted nanoparticles and the use of various nanocarriers for the targeted delivery of drugs in various diseases, along with their opportunities and challenges in targeted delivery. Chapter four mainly focuses on the role and benefits of nanocarriers in drug-targeting and nanocarriers as a prominent system for targeting and delivering drugs to achieve maximum effects with improved therapeutic response. Fifth chapter presents the state of various nanocarriers in the form of nanoparticles and nanodevices applications in medical diagnosis and disease treatments providing essential insights and recent progress on the exciting biomedical applications of nanoparticles, including bioimaging of biological environments, and their role as a critical tool for the early detection of many diseases.

Chapter six focuses on the targeting potential of nanocarriers for the effective treatment of *H. Pylori.* Seventh chapter covers various merits and demerits of gastro-retentive nanocarriers, including some gastro-retentive strategies and their applications in the therapy of various illnesses. In chapter eight, an overview of the recent developments in nanoparticle

formulations for cancer treatment is presented with a comprehensive outlook of the clinical studies and utilization in different prevalent cancers affecting the brain, lung, breast, colon, cervix, and prostate.

Chapter nine outlines the recent development in the area of nanoemulsion as a delivery system with respect to topical drug delivery can be studied. In chapter ten, a deep discussion about the micro/nano-sized lipid-based carriers can be studied. In continuation with chapter tenth, chapter eleven represents the various aspects of the liposomes which further relates to the growing advances and interest in the nanotechnology field. Chapter twelve contains a brief knowledge about structural components and integrity concerning the advanced method of niosome preparation and characterization techniques. Recent examples for different applications are also included in the chapter for therapy/diagnostic purposes based on the route of administration and disease state.

Chapter thirteen emphasizes the advantages, limitations, source, isolation, loading methodology, characterization parameters, and clinical applications, and future potential of resealed erythrocytes. Chapter fourteen summarizes the recent development of therapeutic gene delivery approaches for the effective management of ocular diseases and their use in ophthalmology. The last chapter highlights the green approach to synthesize nanoparticles using microorganisms, enzymes or plant extracts as an alternative to chemical synthesis and their further application in the delivery of herbal drugs process preferably green.

We would like to thank Bentham Science Publishers for inviting us to put this book together and for being patient with us throughout the long development process. Their encouragement and guidance were vital in ensuring the book's completion.

We would also like to extend our sincere gratitude to all of the authors who have taken time out of their busy schedules to be a part of this book and authored fantastic chapters that have brought depth and value to it. Their prompt contributions are greatly appreciated.

Akhlesh K. Jain
Institute of Pharmaceutical Sciences
Guru Ghasidas University, Koni
Bilaspur, CG- 495009
India

&

Keerti Mishra
Institute of Pharmaceutical Sciences
Guru Ghasidas University, Koni
Bilaspur, CG- 495009
India

List of Contributors

Abhimanyu Dev	Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, India
Aditi Pradhan	Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, India
Akhlesh K. Jain	School of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur-495009 (C.G.), India
Amber Vyas	University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, C.G, India
Amit Kumar Jain	Department of Pharmaceutics, Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur M.P. 458001, India
Atul Tripathi	People's Institute of Pharmacy & Research Centre, Bhopal, (M.P.), India
Ashish K. Parashar	Chameli Devi Institute of Pharmacy, Indore-452020, (M.P.), India
Aseem Setia	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, 142001, India
Atul Chaudhary	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, 142001, India
Awesh Yadav	Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Raebareli, India
Balaga Venkata Krishna Rao	Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, India
Balak Das Kurmi	ISF College of Pharmacy, Moga-142001, Punjab, India
Bhavisha Patel	School of Pharmacy, Parul University, Vadodara, Gujarat, India
Bina Gidwani	Columbia Institute of Pharmacy, Raipur (C.G.), India
Dilpreet Singh	ISF College of Pharmacy, Moga-142001, Punjab, India
G.D. Gupta	ISF College of Pharmacy, Moga-142001, Punjab, India
Gautam Singhvi	Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani, Rajasthan, India
Kesavan Karthikeyan	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India
Krishna Yadav	Raipur Institute of Pharmaceutical Education and Research (RIPER), Sarona, Raipur-492010, (C.G.), India
Kuldeep Rajpoot	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur (C.G.)-495009, India
Manu Singhai	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, 142001, India
Monika Kaurav	KIET School of Pharmacy, Ghaziabad-201206, (U.P.), India
Neha Gahlot	Department of Pharmaceutics, Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur M.P. 458001, India

Nivedita Gautam	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India
Olivia Parra-Marín	Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510, Ciudad de México, Mexico
Parasuraman Mohan	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India
Prem N. Gupta	CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India
Preeti Patel	ISF College of Pharmacy, Moga-142001, Punjab, India
Priya Namdeo	University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G.), India
Ranendra N. Saha	Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani, Rajasthan, India
Ravindra Kumar Pandey	Columbia Institute of Pharmacy, Raipur (C.G.), India
Sakshi Tiwari	University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G.), India
Saroj Dangi Rajpoot	Mahatma Gandhi Homoeopathic Medical College, Rani Durgavati Vishwavidyalaya, Jabalpur, M.P. 482001, India
Selvasankar Murugesan	Mother and Child Health Department, SIDRA Medicine, Doha, Qatar
Sneha Singh	Department of Bio-Engineering, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, India
Shiv Shankar Shukla	Columbia Institute of Pharmacy, Raipur (C.G.), India
Shyam S. Pancholi	Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, 384012, Mahesana, Gujarat, India
Sunil K. Jain	Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur (C.G.) 495 009, India
Suresh Thareja	Department of Pharmaceutical Sciences, Natural Products Central University of Punjab, Bathinda, 151001, Punjab, India
Tejashree Waghule	Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani, Rajasthan, India
Umesh Gupta	Department of Pharmacy, Central University of Rajasthan, Ajmer, Rajasthan 305801, India
Unnati Batra	Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani, Rajasthan, India
Varsha Sahu	University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G), India
Veenu Joshi	Center of Basic Science, Pt. Ravishankar Shukla University, Raipur (C.G.), India
Vikas Kumar Jain	Department of Chemistry, Government Engineering College, Raipur, C.G, India

Vishal Jain University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G.), India

Vivek Shrivastava School of Pharmacy, Parul University, Vadodara, Gujarat, India

CHAPTER 1

Introduction to Nanoparticles and Nanocarriers

Amit Kumar Jain[1,*] and **Neha Gahlot**[1]

[1] *Department of Pharmaceutics, Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur M.P. 458001, India*

Abstract: This chapter outlines the introduction of nanoparticles and nanocarriers, within which it delineates their classification into various categories of polymeric nanoparticles, metal nanoparticles, magnetic nanoparticles, inorganic nanocarriers, dendrimers, vesicular carriers, micelles, and a lot more, their synthesis techniques such as physical, chemical and biological, and their application in the medical sector. The chapter also focuses on various challenges faced by these nanocarrier systems in nanomedicine as well as their advantages over conventional drug delivery. Overall, this chapter is a comprehensive compilation of available information on recent advances in the field of nanomedicine through an elucidation of nanoparticles and nanocarrier systems. During the last decade, surplus new nano-based strategies for improved drug delivery and nanocarriers centered therapeutic approaches have been adopted for oral drug delivery, pulmonary drug delivery, cutaneous drug delivery, drug delivery into the brain, for cardiovascular diseases, intracellular targeting, gene delivery, protein delivery, insulin delivery, anticancer targeting and many more. Currently, nanoparticle-integrated diagnosis and imaging have been in abundant use seeing an urgent need for early detection and diagnosis of various lethal diseases.

Keywords: Anticancer drugs, Antidiabetic, Biomedical imaging, Brain drug delivery, Carbon nanotubes, Dendrimers, Ellipsometers, Encapsulation, Ethosomes, Gene delivery, Hybrid nanocarriers, Inorganic nanocarriers, Lipid carriers, Liposomes, Magnetic nanoparticles, Metal nanoparticles, Nano-composites, Nanovaccines, Quantum dots, Vesicular carriers.

INTRODUCTION

In recent years, a plethora of innovations based on nanotechnology has been introduced in the market through various sectors such as medicine, cosmetics, biotechnology, and the pharmaceutical industry. These innovations have improved the quality of life linked with human health perspectives through

[*] **Corresponding author Amit Kumar Jain:** Department of Pharmaceutics, Faculty of Pharmacy, B. R. Nahata College of Pharmacy, Mandsaur University, Mandsaur M.P. 458001, India; Tel: +919501846476; E-mail: director.brncop@meu.edu.in

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various developments in drug delivery through nanotechnology. Nanotechnology deals with substances at a nanometer scale that is the size equal to one billionth of something (range 10-1000 nm). This chapter focuses on the latest trends in nanotechnological research and nanomedicine through a comprehensive overview of nanoparticles and nanocarriers in drug delivery and other developments in the pharmaceutical sector. The whole system leads to the prevention, treatment, and diagnosis of diseases through various smart formulations or theragnostic. Many existing systems for the administration and release of drugs and therapeutics have been converted into nanotechnology-based systems for the delivery of genes, proteins, and cells for oral, pulmonary, and topical delivery of drugs and therapeutics for therapeutic effect. In addition, various diagnostic and imaging techniques based on nanotechnology have evolved for economic and rapid detection of diseases.

Overview of Nanoparticles (NPs)

Recent research in nanoscience and the application of nanotechnology in medicine has raised high expectations that technologies using nanosystems in medicine will make great strides in disease prognosis and treatment [1]. Nanotechnology is a relatively new advance in scientific research, but its basic concepts have been around for a long time. A Nobel prize-winning physicist Richerd P. Fineman introduced the term nanotechnology in his lecture at a meeting organized by the American Physical Society in December 1959. In 1974, a professor at the Tokyo University of Science described the term nanotechnology as a system encompassing dimensions in an ultra-fine range. In short, nanotechnology can best be defined as creating or manipulating materials on a nanometric scale. The class of particles in this very fine dimension is defined as nanoparticles and can be obtained by size reduction or clustering [2].

The unique properties of nanoparticles have a spectrum of uses that normally do not exist in particles of greater size (> 500 nm) or their bulk equivalents. Nanoparticles below 100 nm in size are widely used in medicine (targeted drug delivery, imaging, and personalized medicine), except for solid lipid nanoparticles, which are larger than 100 nm in diameter and have different physicochemical properties [3]. Nanoparticle applications in a variety of disciplines necessitate a low-cost, simplified method of producing high-quality shaped nanoparticles. In recent years, so many synthesis approaches have been employed or improved in an attempt to optimize physicochemical attributes and lower production costs [4].

Structure, Morphology, and Size Analysis

To understand the properties and performance of nanoparticles, a thorough study of size, shape, and surface structure is necessary which can be accomplished by morphological characterization by use of different techniques of microscopy such as transmission electron microscopy, scanning electron microscopy, scanning transmission electron microscopy, optical microscopy, and scanning probe microscopy. Diffraction techniques such as X-Ray diffraction of powder, small-angle X-ray scattering, electron diffraction, and small-angle neutron scattering are used to investigate the atomic and molecular structure of crystals [5, 6]. A widespread range of techniques can be used for the assessment of NPs size including Transmission electron microscopy, Scanning electron microscopy, Atomic Force Microscopy, X-Ray Diffraction, and Dynamic light dispersion. While the first four give a better estimate of size than the Dynamic light dispersion, only the zeta potential size analyzer/DLS can estimate NPs size at extremely low dimensions. The NTA model allows the size distribution of nanoparticles in a fluid medium with diameters between 10 and 1000 nm to be analyzed and visualized by comparing the Brownian motion rate with the size of the NPs [7]. AFM is used to measure the surface roughness of nanoparticles [8].

Electron Microscopy

TEM and SEM are widely used in various research areas to observe particles under high magnification. When an electron beam drops on the surface of the specimen in a TEM, the microscope measures the changes in the electron beam scattered within the test specimen. However, in SEM, electron beams drop on the specimen surface and scan it in a raster scan pattern; here, the electrons will interact only with the specimen surface, containing the information only about the specimen surface. Based on how the SEM image is formed, the image has a distinct three-dimensional (3D) appearance and is useful for analyzing the surface morphology of the target sample. Electrons scattered at very high angles are used in Z-contrast annular-dark-field (ADF) imaging in scanning transmission electron microscopy (STEM).

Optical Microscopy

The mechanism involved in the optical microscope particle size analysis is based on the 1000-fold resolution of particles in the sub-micron range at a wavelength of 2000-8000 A° of light rays [5].

CHAPTER 2

Polymeric Nanoparticles as Drug Delivery System: Basic Concepts and Applications

Sakshi Tiwari[1], Bina Gidwani[2], Priya Namdeo[1], Atul Tripathi[4], Ravindra Kumar Pandey[2], Shiv Shankar Shukla[2], Veenu Joshi[3], Vishal Jain[1], Vikas Kumar Jain[5] and **Amber Vyas[1,*]**

[1] *University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G.), India*

[2] *Columbia Institute of Pharmacy, Raipur (C.G.), India*

[3] *Center of Basic Science, Pt. Ravishankar Shukla University, Raipur (C.G.), India*

[4] *People's Institute of Pharmacy & Research Centre, Bhopal, (M.P.), India*

[5] *Department of Chemistry, Government Engineering College, Raipur, C.G, India*

Abstract: Delivering drugs through various delivery systems into the body for successful treatment of diseases is most entrancing deeds for the pharmaceutical analyst. Conventional drug delivery systems have various hindrances like loss of medication and poor bioavailability of drugs. Polymer-based nanocarriers such as polymeric nanoparticles upgrade bioavailability of drug, delivery of drug to specific site and improve solubility of drugs. They are widely explored as controlled, precise, sustained and continuous release systems for drug delivery and are easily incorporated and appropriate for practically all parts of nanomedicines and bring new trust in field of drug conveyance by redesigning drug viability and diminishing drug toxicity. This chapter mainly focuses on polymers and techniques engaged with advancement of polymer-based nanoparticles and their applications in therapeutic intervention.

Keywords: Bioavailability, Controlled release, Diagnosis, Dispersion, Drug delivery system, Drug efficacy, Drug toxicity, Diffusion, Polymeric nanoparticles, Macromolecules, Natural polymers, Nanoprecipitation, Interfacial polymerization, Synthetic polymers, Targeted drug delivery, Potent drug delivery, Polymerization, Sustained release, Treatment, Solvent evaporation.

INTRODUCTION

The intricacy of specific diseases and the related toxicity of certain therapies progressively request novel courses for drug conveyance [1]. In the mid of the twentieth century, Paul Ehrlich conjectured the concept of "Magic bullet" that has

* **Corresponding author Amber Vyas**: University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G); Tel: 9926807999; E-mail: ambervyas@gmail.com

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the capacity to target drugs with a high particularity and gave rise to advancement and improvement of nanoparticles (NPs) [2]. These novel carriers are characterized as particles range in size from 10–1000 nm and offer several advantages over conventional dosage forms such as improving the medication bioavailability by expanding their absorption or by working with their passage through the biologic films [3]. Nanoparticles can be integrated from lipids, proteins, carbohydrates, just as a few natural and synthetic polymers [4].

There are five fundamental sorts of nanoparticle frameworks for drug conveyance: dendrimers, liposomes, micelles, polymeric nanoparticles, and nanocrystals. In the course of recent many years, there has been significant interest in creating biodegradable nanoparticles (NPs) as successful medication conveyance gadgets. Different polymers are utilized for drug conveyance exploration because they viably convey medication towards an objective spot, also in this way limiting the side effects, incrementing the restorative advantages [5]. The significant objective in designing such devices is to obtain pharmacologically dynamic specialist control arrival to the particular location of activity at the restoratively ideal frequency. The critical goal in planning such gadgets is to acquire controlled arrival of pharmacologically powerful specialists to the specific site of movement at the therapeutically ideal rate and portion routine. The improvements in the nanotechnology field have created unique nanocarriers especially, polymeric nanoparticles, either nanospheres or nanocapsules, may prompt improved bioavailability profiles for well-established drug molecules and also to convey drugs for helpful purposes. The aim of medication conveyance is the controlled release of medications to their site of activity and diminishing medication dose and at the same time limiting the undesirable effects [6]. In the recent couple of years, polymeric nanoparticles (PNPs) attained uncommon significance considering development of drug delivery systems because of the capacity to encapsulate and secure substances just as to present explicit usefulness through surface modifications, polymer-based medication conveyance frameworks are the focal point of extraordinary clinical and scientific interest. Polymeric nanoparticles will in general be more steady than different transporters, like liposomes and micelles, and their conveyance properties can be changed by controlling the design, composition, chemical and physical properties of the polymer [7]. The chapter primarily emphases on polymeric nanoparticles and their applications in therapeutic interventions.

POLYMERIC NANOPARTICLES

Nanoparticles for pharmaceutical purposes are solid colloidal particles of macromolecular materials within active material, dissolved or attached resulting in ranging size from 1 to 1000 nm (1 μm) [8]. They are ideally comprised of polymers acquired from natural, synthetic and semisynthetic basis which might be

biodegradable or nonbiodegradable where the drug is entangled to a nanoparticle framework. In the previous many years, polymeric nanoparticles have arisen as a generally encouraging and reasonable innovation stage for targeted and controlled medication conveyance [9]. Appropriate information on the polymers is of most extreme significance because they are vital part in the medication conveyance framework for the therapy of different diseases like malignancy, neurodegenerative disorders, cardiovascular issues, and so forth [10]. The covalent association of macromolecular monomers into straight or extended chain is known as polymers. They are framed with at least two functional groups [11]. Nanoparticles, nanospheres or nanocapsules can be obtained contingent on the method of preparation [12]. Into the intended organ and cells, PNPs adequately convey medications and genetic materials as well as proteins. Their aim particularity and utilization in form of savvy polymer with decreased incidental properties expanded its development and utilization in treatment of certain diseases such as malignancy, which is no more a nightmare because of emergence of polymeric nanoparticles [8].

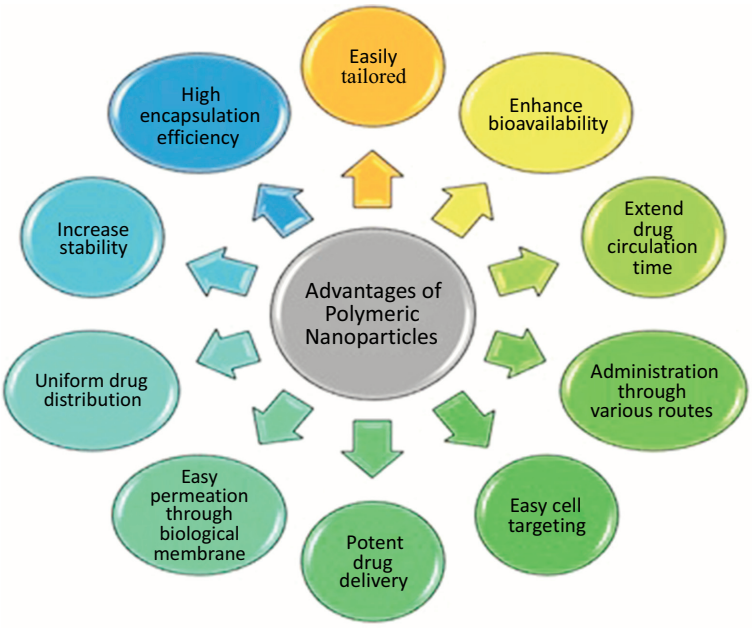

Fig. (2.1). Advantages of polymeric nanoparticles.

Types of Polymeric Nanoparticles

Polymeric nanoparticles are a united term which can be used for any polymeric arrangements but they are classified into two major types, which are Nanospheres and Nanocapsules [13, 14].

CHAPTER 3

An Overview on Nanoparticulate Drug Delivery System for its Specific and Targeted Effects in Various Diseases

Balaga Venkata Krishna Rao[1], Aditi Pradhan[1], Sneha Singh[2] and **Abhimanyu Dev[1,*]**

[1] *Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, India*

[2] *Department of Bio-Engineering, Birla Institute of Technology, Mesra, Ranchi-835215, Jharkhand, India*

Abstract: In modern-day medicine, nanoparticles and nanocarriers are rapidly evolving fields in therapeutics and are the building blocks of nanomedicine, which emphasize the use of nanoscale particles that have a wide array of functions from working as a diagnostic tool to the screening, monitoring, and controlling of various diseases to the delivery of drugs at specific targets in a controlled manner. With the advancement in technologies, it is proven that nanoparticles have a greater potential in wide biomedical applications. Due to their ability to bind with both hydrophobic and lyophilic substances, lower particle size, higher carrier capacity, nanoparticles serve as a favorable platform for specific and targeted drug delivery in disease treatment. Nanoformulations can improve the safety, pharmacokinetic characteristics, and bioavailability of administered drugs, and can improve the therapeutic effect when compared with conventional therapies. Besides, nanoparticles may also be effective in delivering nucleotides, vaccines, and recombinant proteins. Several varieties of nanoparticles are available: different metal and polymeric nanoparticles like gold/silver nanoparticles and micelles, dendrimers. Carbon-derived nanoparticles like quantum dots, carbon tubes, and many other nano assemblies. Numerous nanocarriers, nanoparticle-based drug delivery systems, and drug targeting systems are either developed or under development. In this chapter, we will emphasize mainly the specific and targeted nanoparticles and the use of various nanocarriers for the targeted delivery of drugs in various diseases. The opportunities and challenges of using nanoparticles/nanocarriers in targeted delivery along with its clinical applications are also discussed here.

Keywords: Autoimmune disorder, Cancer, Drug delivery, Infectious diseases, Nanoparticles, Polymers pulmonary diseases.

[*] **Corresponding author Abhimanyu Dev:** Department of Pharmaceutical Sciences & Technology, Birla Institute of Technology, Mesra, Ranchi-835215, India; Tel: 9955165915; E-mail: abhimanyudev@bitmesra.ac.in

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INTRODUCTION

For decades, pharmaceutical research is concentrated on modifying delivery systems. Tremendous advancements in technology and incorporation of multidisciplinary research faculties like polymer science, physics, biotechnology, genetics, molecular science and their use in the research and development setup have led to the development of newer technologies. Due to the advent of analytical techniques and our growing ability to measure particles in the nanoscale, the focus of current research is shifted from micro to nanoscale. The prefix *'nano'* word has been derived from the Greek word *'dwarf'*. The word nano has attained a lot of significance in recent days due to the existing materials as they exhibit unusual physical and chemical properties that change significantly when their size is reduced to nano levels. Nanoscience refers to the study of particles on an ultra-small scale, while the use of these small atomic particles for industrial applications is defined by the term nanotechnology [1].

There's plenty of room at the bottom were the words by Noble laureate, theoretical physicist Richard Phillips Feynman who envisioned the technology at the molecular level way back in 1959 and inspired the Japanese professor and scientist Norio Taniguchi, at the University of Tokyo, Japan in 1974 when he first referred to the materials in nanometre and was the first to use the word nanotechnology. A nanometre (nm) is 10^{-9}, which is one-billionth of a meter or around one-thousandth of a micrometer. Nanotechnology is the new key in the field of science and technology and if properly exploited to its full potential, would benefit different aspects of mankind for the better.

Nanoparticles (NPs) with their small size, have unique properties that have wide applications and greater potential to benefit wide areas in research. NPs along with nanodevices that form the basis of nanomedicine can be used for treatment, diagnosis, monitoring, and controlling various diseases including cancer. Exploiting nanotechnology has led to the surfacing of various nano particulates which are currently under use as drug delivery systems, often referred to as nanoparticulate drug-delivery systems (NPDDSs). The use of these NPs is also arising from newer challenges in the fields of ethical, safety, and regulatory aspects which need extensive research and revision wherever needed. Some issues need to be resolved, but still, it shows how intense and broad this area is and can be in the future and depicts why the nanoscale-based drug delivery strategies are making a significant impact in the global pharmaceuticals [2].

The need for NPs is increasing rapidly. The research in the pharmaceutical industry is heading towards uncertain ways with a decline in the flow of incoming new chemical entities and drug discovery process coupled with higher rates of

clinical failure and clinical development cost. The main problems of the conventional delivery include issues related to but not limited to solubility, permeability, drug release profile, and bioavailability. However, by the application of nanotechnology-driven delivery systems, all these problems could be overcome [1].

Developing nanoscale distribution systems is a rapidly growing and most advanced technology in the field of NP applications.The potential advantage of using NPs is their ability to modify the physicochemical properties of drugs. Drugs with fewer side effects, enhanced biodistribution, and lower toxicity could be developed along with a convenient administration route. NPs are engineered particles that can deliver a drug at a particular (target) site in a controlled manner for a prolonged period. The main aim of these NPs is to develop a safer and effective therapeutic delivery system that can subsequently lead to targeted therapy in disease treatment [3].

The concept of NPs may have become a part of the discussion from the mid-twentieth century but its existence in the natural biological systems as the functional component of living cells cannot be ignored. Various natural NPs exist in nature ranging from organisms like viruses, bacteria, fungi, yeasts, and algae to the components like amino acids, carbohydrates, lipids, and proteins which not only act as a building block of the body but also help in the regular functioning of the body.

SPECIFIC & TARGETED NANOPARTICLES

Nanotechnology in medicine or widely termed nanomedicine comprises mainly two things nanodevices and nanomaterials. Nanodevices contain nanoscale robots, smart pills, microarrays, and other microscopic devices. Nanomaterials are classified as nanocrystalline and nanostructured, while the former contains nanocrystals (carrier-free drug particles), the latter is again classified based upon its core composition into polymer-based NPs, non-polymer based and lipid-based NPs. Polymer-based NPs include micelles, drug conjugates, protein NPs, nanogels, dendrimers, and nanoparticles. Non-polymeric NPs include carbon dots, carbon nanotubes, quantum dots, silica-based NPs, nanodiamonds, and metallic nanoparticles. Lipid-based NPs comprise liposomes, exosomes, and solid lipid nanoparticles. Apart from these main classes of NPs used, various modifications have been done to these existing materials to obtain newer carrier molecules [2]. Further, various nanomedicine used in the biomedical applications are depicted in Fig. (**3.1**).

CHAPTER 4

Nanocarriers For Drug Targeting

Bina Gidwani[1], Varsha Sahu[2], Priya Namdeo[2], Sakshi Tiwari[2], Atul Tripathi[4], Ravindra Kumar Pandey[1], Shiv Shankar Shukla[1], Veenu Joshi[3], Vishal Jain[2], Suresh Thareja[5] and **Amber Vyas[2,*]**

[1] *Columbia Institute of Pharmacy, Raipur (C.G), India*

[2] *University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G), India*

[3] *Center of Basic Science, Pt. Ravishankar Shukla University, Raipur (C.G), India*

[4] *People's Institute of Pharmacy & Research Centre, Bhopal, (M.P.), India*

[5] *Department of Pharmaceutical Sciences and Natural Products Central University of Punjab, Bathinda, 151001, Punjab, India*

Abstract: Drug targeting specific cells/tissues of the body without their becoming a part of the systemic circulation is a prominent area of research in drug delivery, with the main emphasis on improvement in formulation and development. Drug-targeting can improve the viability, lower/minimize the adverse/side effects, and can become cost-effective. Certain limitations like short circulating half-life, bioavailability issues, rapid metabolism and degradation, poor tissue distribution and penetration in the blood-brain barrier, intestinal absorption barriers, *etc*., are associated with the delivery of various therapeutic agents. Nanocarriers have arisen in the field of drug targeting with valuable delivery of drugs to site-specific/desired areas which is a significant therapeutic advantage since it keeps drugs from being conveyed to some unacceptable spots. Nanocarriers prevent the obstacles in clinical utilization of the therapeutic agents as they decrease the serious and critical side/adverse effects by targeted drug delivery and provide slow and sustained drug release. Nanocarriers bring new trust to drug targeting by upgrading the efficacy, defeating resistance, and minimizing toxicity. This chapter mainly focuses on the role and benefits of nanocarriers in drug-targeting and nanocarriers as prominent systems for targeting and delivering drugs to achieve maximum effects with improved therapeutic response.

Keywords: Bioavailability, Blood-brain barrier, Drug delivery, Drug efficacy, Drug resistance, Drug targeting, Half-life, Intestinal barrier, Metabolic degradation, Nanocarriers, Site of action, Site-specific targets, Sustained release, Targeted drug delivery, Tissue distribution.

[*] **Corresponding author Amber Vyas**: University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India; Tel: 9926807999; E-mail: ambervyas@gmail.com

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INTRODUCTION

In the world of medicine, there is continuous development in drug delivery, which involves the delivery of drugs to their particular site in a specific amount. Recent advances in pharmaceutical science are to discover a new therapeutic molecule ranging from micro molecules to macromolecules such as proteins and peptides. But the actual aim of drug delivery is to achieve disease-free conditions in the person's body; minimizing the physicochemical hurdles, and reducing the overdose to biological targets are necessary [1, 2]. Disease like cardiovascular, cancer, viral disease, inflammatory, microbial disease, and neurological diseases can be treated through conventional available drug delivery system, but there is some limitation like the short half-life of the drug, low efficacy, side effects, some biological barriers, low penetration, and low bioavailability, *etc.*, which limit their use [3]. To overcome this problem and enhance their *in-vivo* drug action, prepare such type of formulation that facilitates the improved pharmacokinetic and biodistribution of the drug, thereby enhancing the drug's safety and efficacy. The targeted delivery system is a newer system of drug delivery [4, 5]. In 1906, Paul Ehrlich suggested the targeted delivery through a magic bullet. The therapeutic efficiency is improved by reducing the non-specific drug distribution and minimizing the side effect. Drug targeting a particular site improves the therapeutic profile in the body. Delivering the drug at a specific site at the right time and the right place to maximize the therapeutic effect is the main aim of targeted delivery [6].

A targeted system is a type of specific delivery system, where the drug is precisely targeted or delivered to the specific or desired site. These results show minimum drug accumulation in non-targeted tissue [7]. It delivers a particular amount of drug for a longer period at the target site, which improves its efficacy and reduces the side effect [2, 8]. The pharmacokinetics and pharmacodynamics of the drugs are improved through targeted delivery. The major factor for drug delivery depends on the biological characteristic of the targeted area. The targeted delivery is achieved by:

1. Drugs directly apply to the site of action, such as topical application of drugs in skin disease.

2. Used external stimuli for targeted action of drugs such as ultrasound.

3. Modification of physicochemical properties of drugs.

4. Using nanocarriers for delivery of drug to a particular site such as liposomes, solid lipid nanoparticles, nanoemulsion, polymeric nanoparticles, *etc* [2].

Targeted drug delivery can be achieved by some direct invasive techniques such as direct injection, gene gun, catheter, *etc.* But these techniques are a bit expensive, not patient compliance, and not applicable to many conditions. Therefore, targeted drug delivery also involves chemical and physical modification of drugs [7, 9]. Changes in the physicochemical property of drugs make them suitable for targeted delivery. *E.g.*, prodrugs can be led to improvement in the kinetics of drugs. In prodrugs, the drug is chemically modified by attaching some moiety and makes them pharmacological inactive and *in vivo* metabolically active after reaching their target site. Some of the small molecule and lipophilic nature of drugs are suitable for brain drug delivery through the crossing of the blood-brain barrier [8, 10]. Another method for targeted drug delivery is to incorporate the drug into nanocarriers. This involves the use of drug carriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanogels, *etc.* These nanocarriers are effective for the delivery of drugs, genes, and proteins. The great advantage of this is the pharmacokinetic property of nanocarriers [2, 11]. This drug is added to nanocarriers, and the biodistribution of the drug depends on the pharmacokinetic property of nanocarriers in which targeting is controlled by further modification.

Some of the basic properties of drugs that are used for the preparation of targeted drug delivery [10]:

1. If a drug has a short half-life.

2. If a drug has low stability.

3. If a drug has poor absorption.

4. If a drug has a narrow therapeutic index.

5. If a drug has low specificity.

In the field of nanotechnology, various nanostructures have been involved that benefit conventional available systems for the delivery of medicine, such as nanoparticles, nanofibers, and nanocomposites which are used in the treatment of various diseases. This nanostructured molecule works as a carrier that carries various drugs, genes, proteins, enzymes, *etc.*, and is delivered to a particular targeted site or tissue [12, 13]. These nanocarriers provide a longer half-life, minimize drug degradation, overcome first-pass metabolism, provide sustained or targeted drug release, reduce the side effect and improve the pharmacological response of the drug [9]. All these properties provide better treatment of diseases. The targeted drug delivery system is designed to overcome the drawback and limitations associated with conventional drug delivery systems.

CHAPTER 5

Nanomaterials as Diagnostic Tools and Drug Carriers

Ashish K. Parashar[1], Preeti Patel[2], Monika Kaurav[3], Krishna Yadav[4], Dilpreet Singh[2], G.D. Gupta[2] and **Balak Das Kurmi[2,*]**

[1] *Chameli Devi Institute of Pharmacy, Indore-452020, (M.P.), India*

[2] *ISF College of Pharmacy, Moga-142001, Punjab, India*

[3] *KIET School of Pharmacy, Ghaziabad-201206, (U.P.), India*

[4] *Raipur Institute of Pharmaceutical Education and Research (RIPER), Sarona, Raipur-492010, (C.G.), India*

Abstract: Nanotechnology is a multidisciplinary field of study that bridges chemistry, engineering, biology, and medicine. The utilization of the nanotechnological approach for the development of theranostic nanocarrier system is capable of being loaded as drug therapy/delivery and diagnostic vehicles/means. A very recent term, theranostic nanomedicine, has gained much attention as a favorable model for various types of progressive disease. Theranostic nanocarriers' strategy utilizes the diagnostic excellence mediated treatment of such illnesses that required individual therapy, such as in cancer. These can impart an essential role in improving public health regarding high-stress lifestyle-related challenges in diabetes, asthma, cancer, hypertension, and many infectious diseases, as the diagnosis of these circumstances and the treatment strategy, are also possible with biomedical applications of these nanomaterials. It includes benefits from both worlds: highly powerful nanocarriers to drug delivery and diagnosis spawned the concept, enabling the emergence of personalized medicine. This chapter discusses the state of various nanocarriers' art in the form of NPs and nanodevices applications in medical diagnosis and disease treatments. It presents key insights and current advancements into the intriguing biomedical applications of NPs, including bioimaging of biological surroundings and their significance as a critical early detection tool for various diseases. It also describes their types and limitations concerning conventional means. The topic has attracted significant attention and interest as diagnostic and treating nanocarriers' can target various illnesses faced by the healthcare providers suggested by several researchers over the past decade. Additionally, with recent advances in nanoscience and nanoscale materials, the creation of different diagnostic or therapeutic devices is also discussed briefly. Along with nanocarrier systems' therapeutic and diagnostic aims, physicochemical advantages even considerable potential to be studied concerning health system, which is useful for protecting active drug molecules from degradation, targeted and site-specific drug deli-

* **Corresponding author Balak Das Kurmi:** ISF College of Pharmacy, Moga-142001,(Punjab), India; Tel: +919754275553; E-mail: bdkurmi@gmail.com

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veries are also discussed. Despite the numerous technological, scientific, regulatory, and legal hurdles that nanomedicine faces, researchers are driven to develop new medications and nanomedicine devices. As a result, the development of nanoparticle-based drug delivery and diagnostic devices could help improve patient comfort and convenience while also lowering treatment costs.

Keywords: Bio-imaging, Cancer, Carbon nanotube, Cardiovascular diseases, Central nervous system diseases, Dendrimer, Drug targeting, Drug delivery, Diagnosis, Liposome, Metallic nanomaterials, MRI imaging, Nanocarriers, Nano-engineering, Nanomedicine, Nanoprobes, Photodynamic therapy, Polymeric micelle, Polymer conjugates, Pharmaceutical technology, Quantum dots, Theranostic.

INTRODUCTION

Diagnostics, nanomedicine, and pharmaceutical technology advancements have accelerated the drug discovery and development process, resulting in various innovative, compelling, and therapeutic candidates with a specific target for theranostic uses. Additionally, recent developments in pharmaceutical technology and nanotechnology have enabled theranostics to be used as realistic programmable moieties capable of performing sophisticated operations in order to correctly detect each patient's sickness status [1]. In 2002, Funkhouser invented the term "theranostics," which he defines as the product that combines two modalities, that is therapy and diagnostic imaging, along with a single set" to overcome unwanted biodistribution and therapeutic efficacy differences [2].

Using theranostic nanomedicine incorporates theranostic NPs with multiple capabilities, including stimuli-responsive systems, sustained or controlled release dosage form, increased endocytosis mediated transport efficiency, and multimodality diagnosis and therapy, to treat lethal cancers and other serious illnesses. Thus, theranostic nanomedicine has the potential to revolutionize cancer treatment and other serious diseases. Pharmacokinetics, pharmacodynamics, and biodistribution of each therapy may be optimized by using theranostic nanomedicine to deliver medicines at the right time, place, and quantity [1].

Theranostic nanomedicine allows for systemic circulation, circumvents host defence systems, and distributes medicines and diagnostic materials directly to the place of need, allowing for cellular and molecular diagnosis and therapy. When used in conjunction with theranostic nanomedicine, precise spatial and temporal regulation of therapeutic molecule development can achieve drug release based on the specific patient's sickness state, increasing therapeutic benefits while decreasing adverse effects.

Nanomedicine combines therapeutic and diagnostic agents into a single theranostic scaffold that may subsequently be attached with biological ligands to transport the agents to their targeted targets. The theranostic efficacy of NPs will steadily improve using "smart and distinctive" biomaterials in combination with NPs. Numerous biological factors, including temperature, pH, enzyme activity, or the presence of a particular targeting moiety, might result in the production of theranostic NPs that enable system-specific drug delivery while limiting damage to healthy tissues [1 - 3].

CONCEPT OF NANOTHERANOSTICS

Nanotheranostics is distinguished by three key characteristics: nanoscale size, diagnostic and therapeutic properties. By integrating several functionalities within a single particle, nanotheranostics have been shown to improve the solubilization and release profile of the medicaments, as well as the accumulation of contrast and medicinal chemicals at the site of action. Fig. **(5.1)** demonstrates the easy and simple concept of theranostics [1].

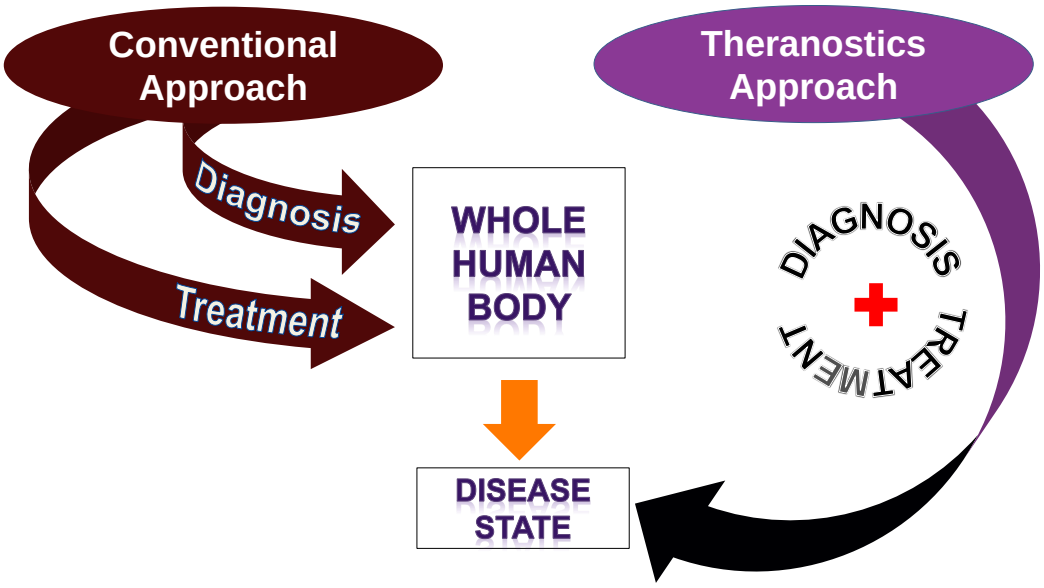

Fig. (5.1). Nanotheranostics concept.

Nanomedicine is currently generating innovative and promising uses in diagnosing and non-invasive treatment of many diseases. Although still important, developing innovative devices with superior imaging properties, which can aid in the early identification of diseases, is still a top priority. Nanotherapeutics, in

CHAPTER 6

Targeting Potential of Nanocarriers for Efficient Treatment of *H. Pylori* Infection

Sunil K. Jain[1,*], Kuldeep Rajpoot[1], K. Kesavan[1], Awesh Yadav[2], Umesh Gupta[3] and **Prem N. Gupta[4]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur (C.G.) 495 009, India*

[2] *Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Raebareli, India*

[3] *Department of Pharmacy, Central University of Rajasthan, Ajmer, Rajasthan 305801, India*

[4] *CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India*

Abstract: *Helicobacter pylori* (*H. pylori*), a prevalent human-specific pathogen, plays a key role in the development of peptic ulcer disease, gastric carcinoma, and gastric mucosa associated lymphoid tissue lymphoma. Once infected, those bacteria reside below the gastric mucosa adherent to the gastric epithelium, and entry of drugs to this target site is very difficult. The bacteria can also acquire resistance to commonly used antimicrobial drugs. Thus, an effective antimicrobial concentration cannot be achieved in the gastric mucous layer or on the epithelial cell surfaces where *H. pylori* exist and caused inefficient treatment. Such challenges have encouraged researchers into developing some therapies based on nanotechnology.

Keywords: Antibiotics, Gastro-retentive delivery system, *H. pylori*, Nanoparticles, pH responsive nanoparticles, Herbal approach, Liposomes, Lectins, Nanogels, Nanoparticulate vaccine, Mucoadhesion, Nanocarriers, Nanolipobeads, Polymeric nano-micelles, Receptor mediated targeting.

INTRODUCTION

The incidence of Helicobacter pylori (*H. pylori*) is found to be between 85 to 95% in developing countries such as India, Malaysia, *etc* and 30 to 50% in developed countries such as the USA, Australia, UK, *etc*. The epidemiology of *H. pylori* infection has been changed with improved sanitation and methods of eradication.

[*] **Corresponding author Sunil K. Jain**: Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur (C.G.) 495 009, India; Tel: +91 94254 52174; E-mail: suniljain25in@yahoo.com

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On the other hand, the occurrence of *H. pylori* is still plentiful all around the world [1, 2]. The incidences of *H. pylori* remain at the maximum in developing countries, and it is very much directly related to socioeconomic conditions and levels of sanitation. It was observed that after the year 2000, the prevalence of *H. pylori* was found to become lower than before in European countries. However, in Asia, the status/condition remains the same [3, 4]. The highest reported occurrence was reported in Africa (70.1%) and the lowest occurrence was reported in Switzerland (18.9%). Pakistan and India have shown the highest *H. pylori* prevalence 81% and 63.5%, respectively.

H. pylori is classified as a Class I carcinogen by the World Health Organization (WHO) and considered as an infectious disease. It is associated with dyspepsia, gastritis, peptic ulcer disease, gastric carcinoma, and mucous associated lymphoid tissue (MALT) lymphoma [5, 6]. It is a gram-negative spiral, 3.5 mm long, 0.6 mm thick, with 4-7 sheathed flagella at one end, which colonizes on the surface of the epithelium (beneath the mucus layer) of the gastric antrum [7, 8]. It is usually adhered to the inner lining of the gastric region and developed suitable surroundings to cultivate [9]. During *H. pylori* infection, urease hydrolyses the urea that is present in gastric epithelium into the ammonia and carbamate, which ultimately augmented the pH of the gastric region [10, 11].

All research communities and healthcare professionals are continuously involved to develop controlled release formulations of antimicrobial agents with the combination of certain newer drug molecules. Both unit dosage forms and multiunit dosage forms were developed and it was found that nanocarriers are getting more success in the effective treatment of *H. pylori* infection [12]. Gastro retentive drug delivery systems (GRDDS) have the immense potential and ability to effectively answer the problem of high bacterial load.

NANO APPROACHES

Nanocarriers are getting much attention from formulation scientists/researchers due to their effective surface area, uptake ability and penetration power. Several researchers have found the possibility of immunologically mediated prevention of *H. pylori* infection using an oral vaccine. Various nanocarriers *i.e.* nanoparticles, nanocapsules, nanolipobeads, nanosize liposomes with the various novel concepts with a target to treat *H. pylori* infection effectively were developed in past by researchers. There were various approaches utilized for the effective treatment of *H. pylori* (Fig. **6.1**).

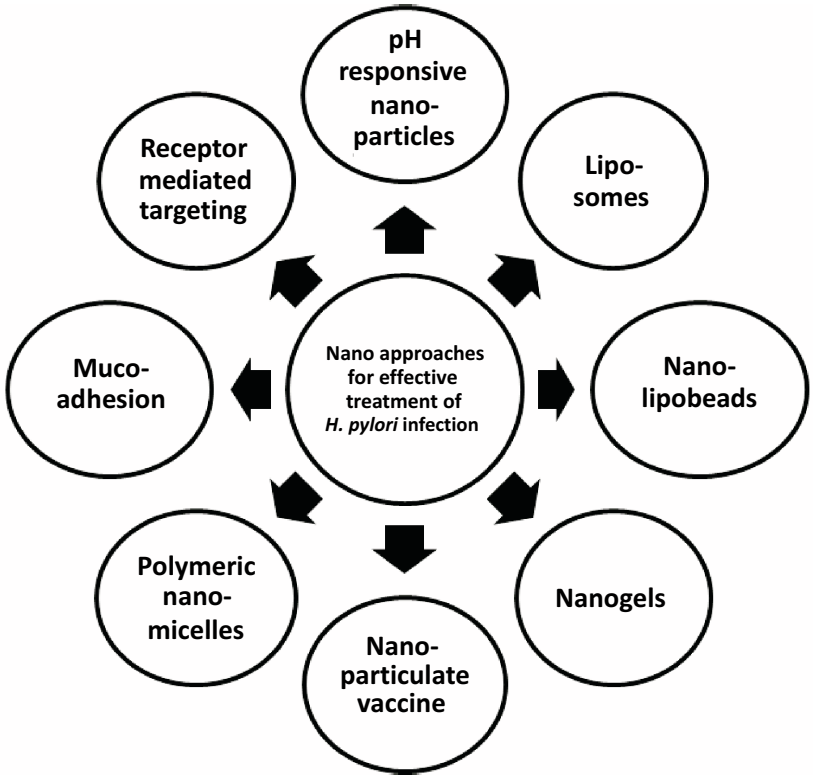

Fig. (6.1). Schematic showing various nano approaches for effective treatment of *H. pylori*.

Mucoadhesion Approach

Mucoadhesion has played a very important role in developing treatment strategies for *H. pylori* infection [13]. Different polymers have varied mucoadhesive abilities because of their inherent nature and properties. Fig. **6.2** is showing the mechanism of mucoadhesion of polymers. Nowadays, a variety of polymers such as methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, sodium alginate, karya gum, guar gum, retene, tragacanth and poly(ethylene glycol) (PEG) have been found to exhibit mucoadhesive properties and are widely used (Table **6.1**).

Since most of the existing drug delivery systems have failed on account of either improper mucoadhesion or muco-penetration. Now research is focused on the use of mucoadhesive nanocarriers that are based on the fact that these mucoadhesive nanoparticulate delivery systems show longer retention in the gastric region and deliver the antibiotic locally in the gastric mucosa for a longer period of time [14, 15].

CHAPTER 7

Gastro-retentive Nanocarriers in Drug Delivery

Kuldeep Rajpoot[1,*], Sunil K. Jain[1] and **Saroj Dangi Rajpoot[2]**

[1] *Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, C.G. 495009, India*

[2] *Mahatma Gandhi Homoeopathic Medical College, Rani Durgavati Vishwavidyalaya, Jabalpur, M.P. 482001, India*

Abstract: The oral route is an extremely accepted route for the administration of several drug delivery systems. This route exhibits several merits for the controlled and sustained release of different formulation types to attain enhanced therapeutic responses. Gastro-retentive nanocarriers (NCs) (GRNCs) have advantages due to their aptitude for extended retaining potential in the stomach environment and thereby elevate gastric retention and augmenting bioavailability of the drug molecules. This chapter covers various merits and demerits of gastro-retentive NCs. Further, it also discusses some gastro-retentive strategies and their applications in the therapy of various illnesses, for instance, swelling NCs, porous NCs, floating/non-floating NCs, lipid NCs, Polymeric NCs, bioadhesive NCs, and magnetic NCs, *etc.*

Keywords: Bioavailability, Controlled drug release, Drug delivery, Eudragit L100, Floating systems, Gastric cancer, Gastro-retentive carriers, Gastric retention time, Gastric emptying time, Gastrointestinal, HPMC, Ion-exchange resin, Lipids nanocarriers, Mucoadhesive nanocarriers, Magnetic nanocarriers, Polymer, Polymeric nanocarriers, Stomach, Sustained drug release, Super porous systems.

INTRODUCTION

Oral administration of formulations exhibits several merits such as flexibility in preparation, low price, ease of delivery, easy transport, as well as elevated patient compliance. Despite this, it is associated with some demerits like low bioavailability of drugs owing to the heterogeneity of the gastrointestinal (GI) environment, the poor gastric retention time (GRT) of the product, enzymatic actions, pH conditions of the GI tract (GIT), and surface area [1]. Furthermore, traditional drug delivery systems (DDS) have not shown great potential to combat the challenges levied by the GIT, for instance, imperfect drug release, less

[*] **Corresponding author Kuldeep Rajpoot**: Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur (C.G.) 495 009, India; Tel: +919993965153; E-mail: kuldeep_sagar06@rediffmail.com

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efficiency of the drug, as well as the compulsion of recurrent dosing. Hence, to overcome these issues associated with traditional DDS and for enhancing the retaining aptitude of drugs in gastric conditions, it becomes essential to develop gastro-retentive nanocarriers (NCs) (GRNCs) [2].

GRNCs may offer various advantages like prolonged GRT of developed products especially in the harsh conditions of the stomach for many hours, improving therapeutic efficiency of drugs in different ways such as by elevating drug absorption and bioavailability, as well as *via* opening the door of possibilities for targeted delivery of the drug in the stomach using different NCs. Besides, GRNCs can augment sustained and controlled delivery *via* constantly releasing many drugs at the desired rate at preferred absorption sites [1, 3, 4]. GRNCs show good feasibility for drugs, which usually have poor absorption ability in the inferior part of the GIT and are not stable in the harsh condition of the stomach. Further, they are also a strong candidate for drugs that are poorly soluble in the basic pH environment, and having a short half-life. In this regard, numerous formulation approaches are being implemented and developed for attaining controlled release of the drug, for instance, porous NCs (*e.g.*, hydrogel (HG), porous silicon NCs) [5, 6], mucoadhesive NCs [7], raft-forming nanosystems [8], magnetic NCs [9], *etc.*

PHYSIOLOGICAL ASPECTS OF STOMACH

The physiology of the stomach plays a vital role in the development of NCs. Hence, for the successful development of GRNCs, deep insight into anatomy as well as the physiology of the stomach is essential. Moreover, anatomically, the stomach is classified as proximal stomach and distal stomach. The proximal part represents the fundus and body, while the distal region includes the antrum as well as pylorus (Fig. **7.1**).

In the stomach, food content is crushed, and then, it transfers slowly into the next part (*i.e.*, duodenum) [10]. On the other hand, the fundus along with the body mainly reserves the undigested food contents. In contrast, the antrum pumps the content *via* utilizing a propelling action and facilitates gastric emptying [10, 11]. Diverse phases in the mobility of food content through the stomach are called migrating myoelectric complex (MMC) (Fig. **7.2**). The gastric emptying pattern significantly fluctuates during fed and fast states [1, 10, 12]. In the fast state, particles having a smaller size over the diameter of the pyloric sphincter can effortlessly clear from the pylorus and reach into the duodenum [12]. In contrast, in the fed state, motor action plays a crucial role and can produce its motor effect after 5–10 min following ingestion of food. Further, this effect remains until the food is present in the stomach, which can interrupt gastric emptying speed.

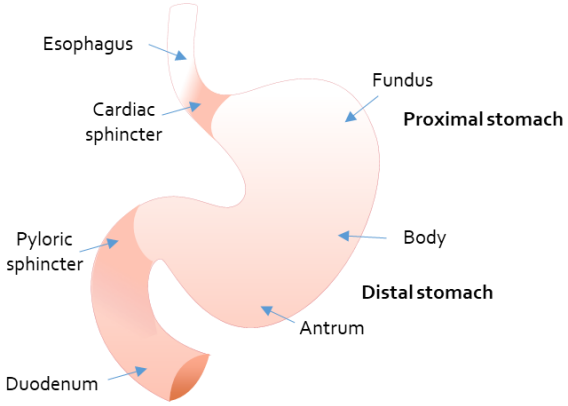

Fig. (7.1). Schematic view on the anatomy of the stomach.

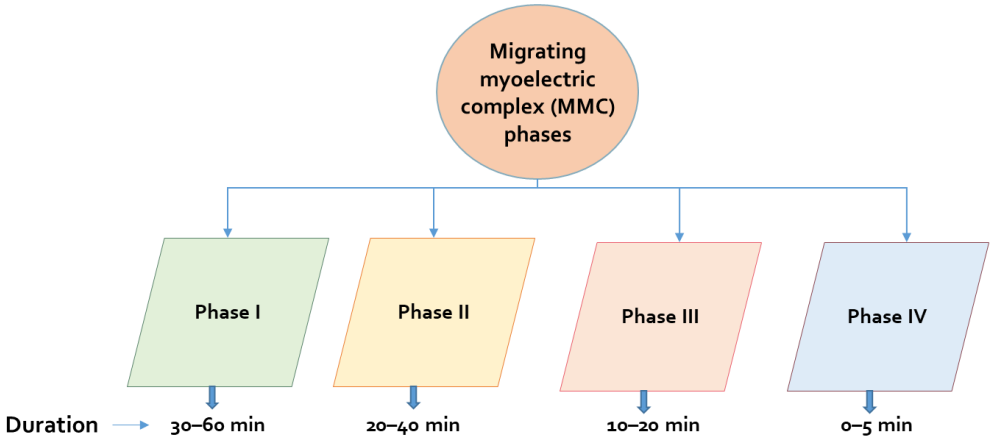

Fig. (7.2). Four phases of the MMC.

FACTORS INFLUENCING THE ACTIVITY OF GRNC$_S$ IN THE STOMACH

Various factors affect the performance of GRNCs. These factors are mainly categorized into pharmaceutical factors, physiological factors, and patient-related factors (Fig. **7.3**).

Physiological Factors

In the stomach, several extrinsic factors may affect GRTs of drugs, for example, nature and content of meal, nature, and density of calories, eating habits, exercise, position and movement of the body, and duration of sleep [1, 13 - 15]. During MMC phases (every 1.5-2 h) in a fast state, the undigested food content is swept

CHAPTER 8

Nanocarrier-based Targeted Delivery in Cancer

Shyam S. Pancholi[1,*], Aseem Setia[2], Manu Singhai[2] and **Atul Chaudhary[2]**

[1] *Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, 384012, Mahesana, Gujarat, India*

[2] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, 142001, India*

Abstract: Anticancer agents are known for their cytotoxic action against tumors, but the spread of their activity to noncancerous tissue is highly undesirable and may be toxic. The conventional methods of drug delivery pose numerous restrictions, involving side effects, lack of patient compliance, *etc.* Nanocarrier-based drug delivery alternatives offer the potential for the management of cancer, as they not only confer better delivery but also efficient targeting to the tissues with limited toxicity. Nanoparticles offer localization in tumors in the vicinity of capillaries, that accounts for improved penetration and prolonged detainment of drug in tumors. Under the tremendous potential of nanoparticles. The exploitation of multi-functional nanocarrier approaches is a burgeoning research subject, driven by increasing medical needs in the area of cancer therapy. Several nano-formulation have been approved for the treatment of cancer. This chapter is an attempt to provide an overview of the recent developments in nanoparticle formulations for cancer treatment and presents a comprehensive outlook of the clinical studies and utilization in different prevalent cancers affecting the brain, lung, breast, colon, cervix, and prostate, *etc.*

Keywords: Brain, Breast, Cancer, Cervical, Chemotherapeutic agents, Colon, Nanocarriers, Lung, Localized delivery, Prostate.

INTRODUCTION

Cancer is a disorder in which aberrant cells proliferate uncontrollably and it remains the most deadly ailment humanity is suffering from [1], accounting for one out of every six fatalities globally [2]. The latest data published in 2020 shows that 10 million people suffer from malignancies of various forms as shown in Fig. (**8.1**) the breast cancer tops the tally followed by prostate (https://gco.iarc.fr/). Low- and middle-income countries account for over 70% of deaths (WHO). Cancerous cell properties that make them challenging to deal with

[*] **Corresponding author S.S. Pancholi:** Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, 384012, Mahesana, Gujarat, India; Tel: 7023459497; E-mail: sspancholi@gmail.com

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include–uncontrolled, limitless replication potential, angiogenesis stimulation,and resistance to cell death with the ability to elude growth suppressors, and invasive metastasis, *etc.* This allows them to enter far-flung locations and cause cancer in areas other than the primary ones [3].

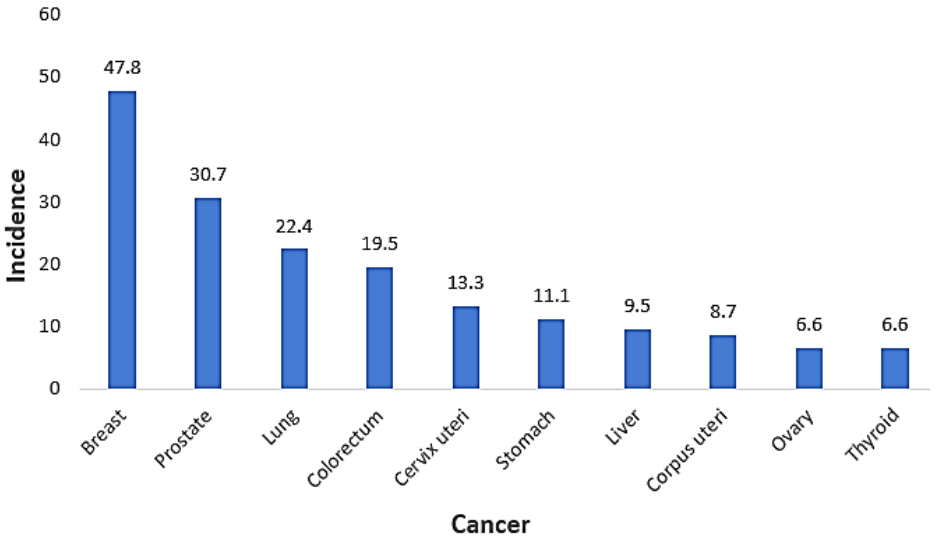

Fig. (8.1). Estimated cancer incidences in 2020. (Source: https://www.gco.iarc.fa/).

Chemotherapy remains the most effective cancer treatment approach though associated with several limitations of delivery and toxic effects. Chemotherapeutic agents are intended to eliminate the malfunctioning of cancer cells while causing no harm to healthy cells in the body [4]. Nano-pharmaceuticals have several advantages over traditional medicines, including superior targeting capabilities with high precision, as well as improved stability and sustainability in the target areas [5]. The exploitation of multi-functional nanocarrier approaches is a burgeoning research subject, driven by increasing medical needs. Several nano-formulation have been approved recently by USFDA as summarized in Table **8.1**. Nanocarriers technology has been adapted not just to deliver pharmaceuticals to target sites but also in diagnostics and drug monitoring throughout cancer treatment [6] for example image-guided drug delivery involves monitoring biodistribution, circulation, and targeting behavior of drug nanoparticles using magnetic resonance imaging (MRI) [7]. This chapter deals with available information regarding various nanocarrier systems, and their site-specific utilization for the treatment of various cancers. We have also tried to bring to the readers' knowledge various recent clinical trials on nano carrier-based formulations and their outcomes for the management of carcinoma.

Table 8.1. Anti-cancer Nanoformulations recently approved by FDA.

S. No.	Drug Product	API	Manufacturer	Indications
1.	TRODELVY	Sacituzumab Govitecan	Immunomedics Inc.	Locally advanced or metastatic triple-negative breast cancer
2.	ERBITUX	Cetuximab	ImClone LLC	EGFR-expressing colorectal cancer
3.	LORBRENA	Lorlatinib	Pfizer Inc.	Metastatic non-small-cell lung cancer
4.	LIBTAYO	Cemiplimab	Regeneron Pharmaceuticals, Inc.	Advanced non-small cell lung cancer
5.	TEPMETKO	Tepotinib	EMD Serono Inc.	Metastatic non-small-cell lung cancer
6.	TAGRISSO	Osimertinib	AstraZeneca Pharmaceuticals LP	Non-small cell lung cancer
7.	ORGOVYX	Relugolix	Myovant Sciences	Advanced prostate cancer
8.	MARGENZA	Margetuximab	MacroGenics	Metastatic HER2-positive breast cancer
9.	KEYTRUDA	Pembrolizumab	Merck & Co.	Metastatic triple-negative breast cancer
10.	GAVRETO	Pralsetinib	Blueprint Medicines Corporation	Non-small cell lung cancer
11.	KEYTRUDA	Pembrolizumab	Merck & Co.	Colorectal cancer
12.	ZEPZELCA	Lurbinectedin	Pharma Mar S.A.	Metastatic small cell lung cancer
13.	CYRAMZA	Ramucirumab	Eli Lilly and Company	Metastatic non-small-cell lung cancer
14.	OPDIVO	Nivolumab	Bristol-Myers Squibb Co.	Metastatic or recurrent non-small cell lung cancer
15.	ALUNBRIG	Brigatinib	ARIAD Pharmaceuticals Inc.	Metastatic or recurrent non-small cell lung cancer
16.	LYNPARZA	Olaparib	AstraZeneca Pharmaceuticals, LP	Gene-mutated metastatic castration-resistant prostate cancer
17.	TECENTRIQ	Atezolizumab	Genentech Inc.	Metastatic non-small-cell lung cancer
18.	RUBRACA	Rucaparib	Clovis Oncology, Inc.	Metastatic castration-resistant prostate cancer
19.	OPDIVO+ YERVOY	Nivolumab+ Ipilimumab	Bristol-Myers Squibb Co.	Metastatic non-small-cell lung cancer

CHAPTER 9

Nanoemulsion: A Potential Carrier for Topical Drug Delivery

Karthikeyan Kesavan[1,*], Parasuraman Mohan[1], Sunil K. Jain[1], Olivia Parra-Marín[2] and **Selvasankar Murugesan[3]**

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India*

[2] *Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510, Ciudad de México, Mexico*

[3] *Mother and Child Health Department, SIDRA Medicine, Doha, Qatar*

Abstract: Nanoemulsions (NEs) are stable nanocarrier systems consisting mainly of oil and water, which are stabilized by surfactant with cosurfactant. Due to their typical size, nano-emulsions are transparent or translucent, and minute droplet size makes them stable against sedimentation or creaming. The nanoemulsion system may be in the form of oil-in-water (O/W) or water-in-oil (W/O). The recent literature revealed that NEs as a colloidal carrier system has been confirmed to be a valuable strategy to improve the bioavailability of topically applied drugs. NE has been proposed as a viable alternative to conventional topical dosage forms due to the ability to overcome the skin/ocular barriers faced after administration. Better permeation rate, improved therapeutic efficacy and reduction of dose, non–specific toxicity, and targeted drug delivery system can improve drug effectiveness when drugs are incorporated into NEs. In recent years, research studies have focused more on ion nanoemulsion systems using a mixture of surfactants to solve critical factors, such as solubility, stability, and drug delivery applications. This chapter outlines the recent development in nanoemulsion as a delivery system to study topical drug delivery.

Keywords: Nanocarrier, Nanoemulsion, Ocular, Skin, Topical drug delivery.

INTRODUCTION

Oil and water are immiscible liquids for blending two phases; the phases are miscible with the addition of the third substance like an emulsifier [1]. Uniting the combination of these phases requires energy contribution to make up dissimilar contacts with in water-oil systems that can restore similar phase

* **Corresponding author Karthikeyan Kesavan:** Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India; E-mails: kesavanmpharm@gmail.com; k7_76@rediffmail.com

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systems like water-water and oil-oil connections. The immiscible oil and interfacial water tension are as high as 30-50 dynes/cm [2]. The reduction of interfacial tension to the addition of a surface-active agent or surfactant, or emulsifier can be utilized based on a polar head (water-loving) and non-polar tail (oil-loving) groups with the ability to absorb the oil-water interface [3]. The lower concentration of surface-active agent adsorbs at the oil-water interface, expands the interfacial area, or diminishes the interfacial tension [2]. A stable emulsion system is formed by a minute amount of suitable surface active agent added and mechanically mixed with oil and water components. The consequence of the biphasic dispersion system shows that oil globules coated with a surface-active agent are promptly distributed throughout the distribution medium. These emulsified systems are opaque or milky because the globule diameter ranges from 0.1 to 1 micron [3]. As a general rule, the class of emulsion systems is formed based on the type of emulsifier used [4]. W/O type of emulsion is generated by the surfactant used in the system that is more soluble in the oil phase than water, and *vice versa*. In another way, the continuous phase of the emulsion system is in which the surface-active agents are predominantly soluble. The emulsified system is called emulsions, nanoemulsions, submicron emulsions, or mini emulsions. There are numerous identical properties among these systems. Nevertheless, every emulsified system has its physical properties and thermodynamic stability for making a specific application compared with other systems [5].

The emulsified systems have three main compositions: aqueous phase, oily phase, and a combination of surface-active agents. An appropriate emulsifying agent is vital for the system to formulate a stable emulsion from the discontinuous and continuous phases. There are fundamental emulsions like oil-in-water (O/W) emulsion, in which oil droplets are dispersed into the continuous water phase, and water-in-oil (W/O) emulsion, wherein water droplets are dispersed into the continuous oil phase. The multiple types of emulsion, like oil-in-water-in-oil (O/W/O) or water-in-oil-in-water (W/O/W) emulsion, are formed by the overlap of O/W and W/O types of emulsion in which minute globules are within larger ones [6, 7]. Significant differences exist among the systems like emulsion, nanoemulsion, and microemulsions. Emulsions appear to be milky, and their globule size ranges between 100 nm and 1mm [8]. The systems are thermodynamically unstable due to physical contact between the oil and water phase.

Conversely, emulsions are kinetically stable systems because the statement of the energy formation is more significant than zero. The surface-active agent is tightly adsorbed between the oil /water interface, so the system is kinetically stable [9]. Expressly, the microemulsion is noted as thermodynamically stable, isotropic, clear, and usually has a globule size less than 100 nm in diameter and is

commonly close to the matching micelles system [10]. Low energy input is required to form the microemulsion, and an immense amount of surfactant is needed to form the system compared to nanoemulsion.

A nanoemulsion with globule size in the nanometric scale (less than 1 micron) is denoted as nano, submicron, mini, or ultrafine emulsions [11 - 13]. The term nano-emulsion is preferred because it provides a nanoscale size range of droplets and avoids misapprehension when compared with microemulsion, which alters their physicochemical properties and leads to superior kinetic stability. The different instability processes such as flocculation and coalescence are insignificant in the form of nano-emulsified systems. The formulation requires a high-speed homogenizer with high energy inputs, and a lower amount of surfactant is sufficient [14 - 17]. The choice of nanocarrier system is widely used for topical delivery systems like liposomes, niosomes, transferosomes, ethosomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) [18 - 21]. Even though nanoemulsion systems have numerous pharmaceutical applications in the field of pharmaceutics, cosmetics, *etc.*, it likewise assumes an imperative part as reaction initiation for many polymer dispersions and nanoparticle synthesis, owing to the smaller size globule, reasonably long-term stability, and effective solubilization capacity, acting as a medium for active pharmaceutical substance, improving the therapeutic efficiency, minimizing the drug dose, and by this means side effects and toxicity. The presence of surfactants in the emulsified system has to alter the membrane fluidity that helps to enhance the absorption of active drug molecules [22].

The nanoemulsions system is used for parenteral, oral, ocular, and topical administration [23 - 26]. Nanoemulsion offers significant advantages in topical drug delivery systems, including (i) less surfactant concentration leads to offer minor skin irritation, (ii) adequate penetration capacity, and (iii) high drug-loading efficiency, and topical administration may be beneficial when compared to oral administration to avoid chemical or enzymatic degradation from the gastrointestinal tract and first-pass metabolic effect of drug molecule [15, 27 - 29]. It is an ideal route of drug administration because of various apparent benefits compared to parenteral and oral routes in which patient compliance and therapeutic drug efficacy are considered in the report. This system is most pertinent for encapsulating poorly soluble drugs with superior stability [30, 31]. It is mainly suitable for topical drug delivery to circumvent systemic side effects, and it acts as potential cargo for the delivery of drugs to the specific site of action [32, 33].

Moreover, due to the smaller droplet size, the system has advantages such as good rheological properties, excellent colloidal stability, and a low sedimentation rate.

CHAPTER 10

Lipoidal Carrier as Drug Delivery System

Bina Gidwani[1], Priya Namdeo[2], Sakshi Tiwari[2], Atul Tripathi[4], Ravindra Kumar Pandey[1], Shiv Shankar Shukla[1], Veenu Joshi[3], Vishal Jain[2], Suresh Thareja[5] and **Amber Vyas[2,*]**

[1] *Columbia Institute of Pharmacy, Raipur (C.G), India*

[2] *University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (C.G), India*

[3] *Center of Basic Science, Pt. Ravishankar Shukla University, Raipur (C.G), India*

[4] *People's Institute of Pharmacy & Research Centre, Bhopal, (M.P.), India*

[5] *Department of Pharmaceutical Sciences and Natural ProductsCentral University of Punjab Bathinda, Punjab-151001, India*

Abstract: The delivery system plays a vital role in managing the pharmacokinetics and pharmacodynamics of a drug. The size of the carrier system contributes to its pharmacological action. Lipid-based carriers refer to the formulations containing a dissolved or suspended drug in lipidic excipients. Lipoidal systems as carriers are achieving heights due to their significant lipid nature and the size of particles in the delivery system. The micro/nano-sized lipid-based carriers possess versatility in improving the physic-chemical properties of drugs. Also, they are biocompatible and can be administered through all possible routes. Lipid-based drug delivery carrier systems of new and existing formulations can be commercialized to achieve the desired range of product specifications. Solubility of the drug in various lipids is a key factor in the development of the delivery system. Lipids as functional excipients are compatible with solid, liquid, and semi-solid dosage forms. Besides improving/enhancing the solubility and bioavailability, lipids provide multiple broad-based applications in the pharmaceutical delivery system.

Keywords: Bioavailability, BCS Class, Cancer, Carriers, Delivery system, Lipids, Micro/nano, Pharmacokinetics, Pharmacodynamics, Solubility, Liposomes, Solid Lipid Nanoparticles, Nanostructured lipid carrier, Lipid-drug conjugate, Liposphere, Topical, Oral, Parenteral, Pulmonary, Protein/peptide.

INTRODUCTION

Lipoidal carrier is a versatile delivery platform, which has achieved a lot of attention in the current era. Lipoidal carriers are systems with significant

[*] **Corresponding author Amber Vyas:** University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh, India; Tel: 9926807999; E-mail: ambervyas@gmail.com

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biopharmaceutical and technological benefits, making them suitable for effective & optimum therapeutic delivery of drugs. These carriers are based on the concept that ingested fats (lipids) improving lipophilic drug absorption. Monoglycerides, diglycerides, and triglycerides are the most widely accepted lipid excipients, followed by oils containing different combinations of glycerides, sphingolipids, & phospholipids [1]. Typically, the most common use of lipoidal carrier has been to boost the solubility of aqueous insoluble drugs, particularly those classified as Biopharmaceutics Classification System (BCS) Class II & IV [2]. The lipoidal carriers have several unique features that include effective encapsulation of lipophilic and hydrophilic drug candidates, enhanced bioavailability of drug-loaded in the carrier, prolonging of circulation period, targeted distribution to cells and/or organs, increased therapeutic efficacy along with reducing toxicity by modifying the drug pharmacokinetics and biodistribution [3].

When these amphiphilic building blocks are exposed to water, they create highly organized assemblies of one or more concentric lipid bilayers. Carrier particles can be made from a variety of building blocks of amphiphilic drugs [4]. The use of lipoidal carriers for drug delivery emerged in the early 1960s when fatty emulsions were provided *via* parenteral administration of nutrition [5]. In 1965, the first closed bilayer phospholipid system was discovered, thus, encouraging experts worldwide to produce significant technical innovations in the delivery of the lipoidal carrier; as a result, a large number of clinical trials have been conducted [6]. There are several licensed & commercialized lipid-based drug preparations; however, due to the unique features of the lipoidal carrier system, overcoming the delivery of drugs is a challenge for pharmaceuticals with considerable formulating obstacles [7].

Lipoidal carrier-based delivery systems are a broad category of products that can incorporate a drug that has been suspended or dissolved in lipidic excipients. Lipids are fatty acid esters, which are lipophilic hydrocarbon chains connected to a hydrophilic group such as polyalcohol, polyglycerol, and glycerol. The lipoidal carrier system consists of the simple drug in oil to a more complex preparation that is meant to emulsify spontaneously when exposed to an aqueous medium [8]. The temperature, *i.e*., melting point of lipids, typically increases with molecular weight (hydrocarbon chain length) & decreases with fatty acid unsaturation. Lipids are insoluble in water and are frequently characterized by their fatty acid composition, solubility for non-polar organic solvents, melting temperature & Hydrophilic-Lipophilic Balance (HLB). Lipoidal carriers, including liposomes, submicron lipid emulsions & lipid microspheres, are strongly desired and are now being researched in several ways, with several items being commercially accessible [9].

Need for Lipoidal Carrier System [10]

• If conventional preparations deliver poor bioavailability (Fig. **10.1** shows the reasons for poor bioavailability), a Lipoidal Carrier System is essential.

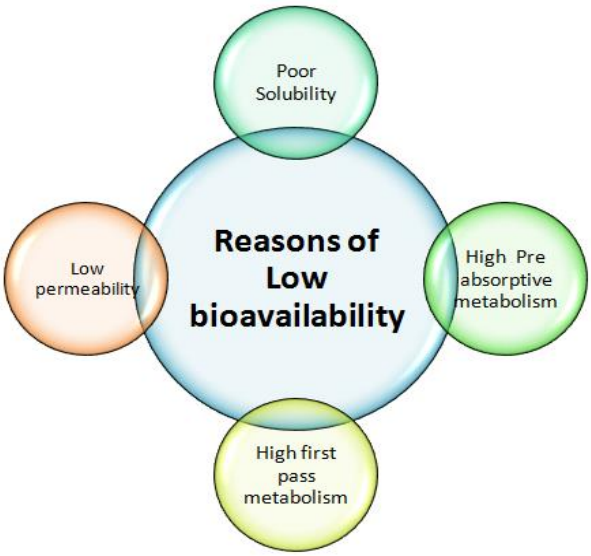

Fig. (10.1). Reasons for low bioavailability.

• Lipoidal Carrier Systems are versatile; they involve the usage of lipids & lipid-based technology in pharmaceutical preparations designed for a wide range of administration routes such as oral, parenteral, transdermal, ophthalmic, *etc*.

• To modify local or systemic drug distribution by solubility, penetration, absorption, circulation & metabolism.

• To develop physiologically & chemically stable preparations that provide an effective and safe method of delivering pharmaceuticals at the targeted location for absorption or activity.

• Improving taste, general consumer acceptability, dose frequency, and/or toxicity to achieve patient compliance barriers [11].

CHAPTER 11

Liposomal Drug Delivery

Unnati Batra[1], Tejashree Waghule[1], Ranendra N. Saha[1] and **Gautam Singhvi[1,*]**

[1] *Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani, Rajasthan, India*

Abstract: Liposomes are emerging as uni or multilamellar micro particulate phospholipid bilayer sphere vesicles, which can be produced synthetically and have the ability to encapsulate any kind of drug molecule. Either hydrophilic or lipophilic drug substances can be easily entrapped in these vesicles for efficient delivery of a drug. Over the past decades, these have been under investigation to develop novel and revolutionary drug delivery aspects in the pharmaceutical field. Liposomes are based on a simple mechanism of formation of the enclosed sphere formed when amphiphilic lipid comes in contact with the aqueous layer. The advancements in liposomes have paved pathways towards efficient drug delivery through alteration in the bioavailability and bio-distribution of drugs. Classified into various types, liposomes can be prepared using various techniques involving mechanical dispersion, solvent dispersion, and detergent removal methods. The development of these liposomes has profound the advanced delivery characterization. This helps deliver the molecules at the target site, and the number of liposomal products in clinical use has now increased. Recent advances are incorporating the emergence of second-generation liposomes over conventional liposomes, which will help modulate the encapsulation efficiency and drug release from liposomes. This literature briefly focusses on various aspects of liposomes, which further relates to the growing advances and interest in this field.

Keywords: Bio-distribution, Drug delivery, Drug release, Encapsulation efficiency, Liposomes, Liposomal products, Mechanical dispersion, Multilamellar vesicles, Phospholipids, Second generation liposomes, Solvent dispersion, Targeting, Unilamellar vesicles.

INTRODUCTION

Liposomes are the simple spherical structures that can encapsulate any type of material, either hydrophilic or lipophilic, like nutrients, drugs, or any biotechnological agents. Constituting lipid bilayer obtained from phospholipids

* **Corresponding author Gautam Singhvi:** Department of Pharmacy, Birla Institute of Technology and Science (BITS), Pilani, Rajasthan, India; Tel: +919314490535; E-mail: gautam.singhvi@pilani.bits-pilani.ac.in

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which are non-toxic natural lipids, form concentric spaces for entrapment of the formerly stated substances [1, 2]. Not new as emerging vesicles that need to be established for their roles in drug delivery, these were discovered and described around 60 years ago by British hematologist Alec D Bangham, which were later published after 3-4 years. The idea of naming them was created from the idea of these spheres being fat bodies comprising lipids. Lipo means "fat," and soma represents "body," and this states its composition of phospholipids [3, 4].

The discovery of the liposomes was attributed to Bangham and R.W. Horne when they were testing the new electron microscope they received at Babraham Institute in Cambridge. During this study, they added a negative stain to the phospholipid. Along with the simple plasmalemma, they observed the cell membrane structure, which was the first of its kind. They studied the integrity of the lipid bilayer and further worked on it to find out what that bilayer was. Sooner they recognized the layer as an integrated bilayer lipid that can release its content upon treatment with the surfactants. In the next year, Weissmann, who was of the Babraham Institute, in a meeting with Bangham, named the structure of one of its special kind as "Liposome." This was somewhat influenced by the word lysosome, on which the people were already working. Bangham called these structures "Multilamellar smectic mesophases" or "Banghasomes." This all led to the beginning of the liposome industry, which today has spread its legs almost to every area of drug delivery and its processes [5].

The assembly of liposomes was nothing but just a simple observation of the natural cell membrane which is comprised of the bilayered lipid. These observations led to the development in this field that enhanced its usage in various fields. The composite structure includes the lipids arranged in such a way that they form a bilayer with the hydrophilic head of the lipid molecules facing outside in the region of the aqueous state [6]. The lipophilic tails of the lipid molecules of two individual layers face inwards towards each other, forming a bilayer of lipid molecules. The two layers are just oppositely overlapping each other. They are in the formation in such a way that the circular position of these structures leads to the development of concentric space. Fig. (**11.1**) below illustrates the complete structure of liposomes and the drug entrapment in liposomes [7, 8].

The physicochemical nature of liposomes states the amphipathic nature that inculcates their strong tendency to strengthen the structure. These inclusive properties enhance the structuring of lipid layers and act as a barrier to the permeation of the entrapped molecules. The occurrence of the hydrophilic layer provides the stability of this structural organization to remain in contact with the dispersion media and inner substance. The latter only emerges out of the vesicle on the changes in the solution or dispersion, pH, temperature, or ultimately

diffusion of the membrane [9, 10]. The concentric space thus formed can be utilized as a loading area for any type of molecule to deliver them to the targeted site of action. In addition to this, they can easily add up with different bilayer membranes and can diffuse their content easily, making it a way much easier to deliver drugs into the biological system [11]. Many approaches are now coming up, which are easing the content delivery through liposomes by just inculcating the simple phenomenon of the pH or charge systems of the fluids which need to be delivered at the targeted site [5].

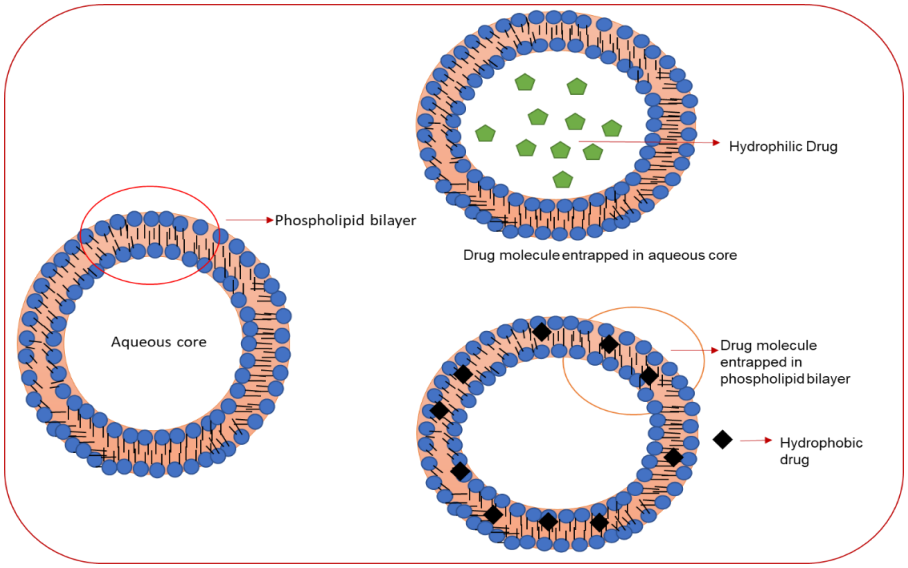

Fig. (11.1). Structure of liposomes and entrapment of drug molecules.

Some advantages of liposomes include an increase in efficiency of the targeted drug delivery, site avoidance effect, passive targeting to the desired site of action, improvised pharmacokinetic parametric effects on the human body, flexibility of coupling with certain kinds of site-specific ligands, increase in the therapeutic efficiency of drugs, and most importantly increasing stability of the molecule being administered by encapsulation [1]. The applications of liposomes are emerging as a variety of drug delivery in oral systems, sustained-release drug delivery systems, immunological adjuvants, site-specific targeting in gene delivery, tailored drug release, and recent advances in anti-HIV, and anticancer drug delivery. In addition to this, they have been into the delivery of fabrics to the dying industry, nutritional supplements to the food industry, and cosmetics to the skin. The list is increasing with the upsurge in the studies going on liposomes. These have now been one of the greatest achievements in the area of clinical

CHAPTER 12

Niosome: A Vesicular Drug Delivery Tool

Preeti Patel[1], Ashish K. Parashar[2], Monika Kaurav[3], Krishna Yadav[4], Dilpreet Singh[1], G.D. Gupta[1] and **Balak Das Kurmi[1,*]**

[1] *ISF College of Pharmacy, Moga-142001, (Punjab), India*

[2] *Chameli Devi Institute of Pharmacy, Indore-452020, (M.P.), India*

[3] *KIET School of Pharmacy, Ghaziabad-201206, (U.P.) India*

[4] *Raipur Institute of Pharmaceutical Education and Research (RIPER), Sarona, Raipur-492010, (C.G.), India*

Abstract: Niosomes, which are well recognized for their non-ionic surfactant characteristics, are considered to be innovative drug delivery methods since they improve the solubility and stability of medicinal compounds when administered orally. It has been shown that niosome vesicles are closed bilayer structures that may exist in aqueous fluids and are produced by the self-assembly of different types of hydrated non-ionic surfactants and amphiphile monomers in aqueous media. Because the monomers maintain a wide range of kinetic activity inside the assembly, they are referred to as liquid crystal structures in terms of thermodynamics. It is just the total of different processes for the dispersion of monomers and solvents that results in the formation of the final systems. Niosomes are made up mostly of lipid molecules and nonionic surfactants, which are the two most important components in the process of making them. Nonetheless, as the name suggests, component surfactants play a key role in the creation of niosomes, owing to the fact that non-ionic surfactants were often employed to organize niosomes during their formation. They are especially well-suited for drug delivery because they have the ability to encapsulate medicines that are both lipophilic and hydrophilic in nature. These materials are appealing for a number of drug delivery goals, including drug targeting, controlled release, and permeability enhancement, because of their chemical stability, cheap production costs, and composed of biodegradable and non-immunogenic components. Niosomal vesicular carriers can also help to minimize problems such as physical and chemical instability. This book chapter contains a brief knowledge about structural components and integrity concerning the advanced method of noisome preparation. The characterization techniques essential for noisome have also been discussed in detail. The recent examples for different applications are also included for therapy /diagnostic purposes based on the route of administration and disease state.

[*] **Corresponding author Balak Das Kurmi:** ISF College of Pharmacy, Moga-142001, (Punjab), India; Tel: +919754275553; E-mail: bdkurmi@gmail.com

Akhlesh K. Jain & Keerti Mishra (Eds.)

Keywords: Anticancer, Drug delivery, Diagnostic, Drug targeting, Lipid nanocarriers, Niosome, Non-ionic surfactant, Transdermal delivery.

INTRODUCTION

Niosomes (NS) are carriers that were discovered for the first time in the 1970s. They are made up of closed bilayer structures generated by the self-assembly of non-ionic (NIC) amphiphiles in aqueous environments. Non-ionic surfactant vesicles (NISVs) are known as niosome. Handjani Vila and co-investigators were the first to describe vesicles generated by NIC surfactants. They were first mentioned as a beauty industry characteristic, but they are now widely employed as medicine delivery methods [1]. They are composed of biocompatible, non-toxic, non-immunogenic, and non-carcinogenic materials. NISVs are formed when hydrated surfactant monomers self-assemble. In aqueous conditions, the surfactant molecules self-assemble so that the hydrophobic tails face each other, reducing the high-energy interactions between the solvent and the tails. The hydrolytic breakdown is not a problem for NISVs. They're similar to liposomes, but they have a few advantages. The main benefit is that they can be used for various pH values [2]. Chemical stability, increased oral bioavailability, lower toxicity, greater therapeutic effectiveness, and convenience of handling and storage are other benefits [3 - 5]. Because of their low cost, they are more appealing for industrial production, particularly in pharmaceutical and cosmetic applications. Furthermore, no pharmaceutically undesirable solvents are used in the preparation process [6].

Encapsulation of medicines in NS has been proven to decrease drug toxicity, enhance drug absorption, enhance the therapeutic effectiveness, stability, or activity, and extend the time removing the drug from circulation when utilised in slow-release formulations. According to the research, NS may extend the circulation of occluded medicines [7, 8] and diagnostic markers [9]. NS are microscopic lamellar structures that form with the combination of cholesterol and a NIC surfactant of either the alkyl or dialkylpolyglycerol ether class [10]. The amphiphilic nature of NIC surfactants causes them to form a confined bilayer vesicle when used in aquatic circumstances. The introduction of input, such as heat or physical agitation, results in the formation of this structure. In contrast, the hydrophobic parts of the bilayer structure are oriented away from the aqueous solvent, while the hydrophilic components of the bilayer structure remain in direct contact with the aqueous solvent. There are a variety of ways to change the features of vesicles, including changing their composition, as well as their size, lamellarity, tapped volume, surface charge, concentration, and other characteristics. Internally, a number of forces are at work, including van der Waals forces between surfactant molecules, repulsive forces resulting from

electrostatic interactions between electrostatic interactions of surfactant molecules, entropic electrostatic repulsion of the head groups of surfactants, and so on. It is the responsibility of these forces to ensure that the vesicular structure of NS is sustained. It is possible to use niosomal drug delivery for a broad variety of pharmacological substances in the treatment of numerous diseases. Niosomal drug delivery is now being used in the treatment of a wide range of disorders. It may also be used as a carrier for medicines that are poorly absorbable, allowing for the development of a drug carrier for poorly absorbable medications. The transcytosis of M cells from Peyer's patches in the intestinal lymphatic tissues has the potential to enhance bioavailability by overcoming the anatomical barrier of the gastrointestinal tract, as shown in this study. The reticuloendothelial system is in charge of transporting niosomal vesicles throughout the body [11]. This type of localized drug accumulation is utilized to treat disorders such as leishmaniasis, in which parasites infiltrate the liver and spleen [12, 13]. Other systems, such as immunoglobins that do not recognize the reticuloendothelial system, can also recognize the lipid surface of this delivery system [14, 15]. Various anti-neoplastic drugs have been encapsulated in this carrier vesicle, which has reduced drug-induced harmful side effects while maintaining or, in some cases, improving anti-tumor activity [16 - 18].

It is a common practice to administer specific anti-inflammatory drugs, such as flurbiprofen and piroxicam, plant extracts, and sex hormones, such as estradiol and levonorgestrel, through an NS *via* the transdermal route in order to improve their therapeutic efficacy [10, 19, 20]. The use of NS makes it possible to develop more comprehensive drug delivery strategies. One of the accomplishments is the localised drug action that is possible due to the small size of the drugs and their low penetrability through the epithelium and connective tissue. This has the potential to keep the drug localised at the administration site, and localised drug action strengthens the efficacy or potency of the drug while at the same time reducing its systemic toxic contribution of different therapeutically active agents, according to the National Institutes of Health [21, 22]. This book chapter contains a brief knowledge about structural components and integrity concerning the advanced method of noisome preparation. The characterization techniques essential for noisome have also been discussed in detail. The recent examples for different applications are also included for therapy /diagnostic purposes based on the route of administration and disease state.

SILENT FEATURES OF NSS

NS are capable of entangling solute molecules, leading to an increase in their stiffness, and are also osmotically stable.

CHAPTER 13

Resealed Erythrocytes: As A Drug Delivery Tool

Krishna Yadav[1], Monika Kaurav[2], Preeti Patel[3], Ashish K. Parashar[4] and **Balak Das Kurmi[2,*]**

[1] *University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur, Chhattisgarh-492010, India*

[2] *KIET School of Pharmacy, Ghaziabad-201206, (U.P.) India*

[3] *ISF College of Pharmacy, Moga-142001, Punjab, India*

[4] *Chameli Devi Institute of Pharmacy, Indore-452020, (M.P.), India*

Abstract: Being the most abundant cell in the human body, resealed erythrocytes have been utilized as a promising natural biological carrier for therapeutic delivery. In various therapeutics, delivery resealed erythrocytes are found to be an alternative delivery approach with overcoming toxic and rapid clearance effects, such as enzyme-loaded bioreactors performing vital reaction along with improving the enzymes circulation time, as drug-loaded carrier affords sustained release of drug and in drug, targeting delivers drugs release in specific target organs without recognition by the immune system. From the research level to clinical development, it has been observed that the drug carrier expedition faces many regulatory and industrial process development challenges. Resealed erythrocytes possess many remarkable properties such as biocompatibility, biodegradability, long circulation and flexibility to encapsulate a wide variety of therapeutic compounds *via* employing different chemical and physical methods. It is possible to obtain resealed RBCs by collecting them from the source of concern (*e.g.*, humans, rats, rabbits, pigs, and so forth) through blood samples following the separation of RBCs. A number of techniques are then used for effective drug loadings, including hypotonic dialysis, hypotonic dilution, hypotonic preswelling, endocytosis, lipid fusion, electric cell fusion, and chemical disturbance. Up to date, resealed erythrocytes have been explored as a carrier for various therapeutic drug substances (antiviral, anti-inflammatory, steroids and anticancer, *etc.*), enzymes, antibiotics, and diagnostic agents. The main objective of this chapter is to emphasize the advantages, limitations, source, isolation, loading methodology, characterization parameters, and finally, to pay attention to *in-vivo* studies, clinical applications, and future potential of resealed erythrocytes.

* **Correspondence author Balak Das Kurmi**: KIET School of Pharmacy, Ghaziabad-201206, (U.P.) India; Tel: +919754275553; E-mail: bdkurmi@gmail.com

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Keywords: Advantages, Biodegradability, Carrier erythrocyte,RBC, Cellular carrier, Characterization parameters, Clinical applications,drug-loaded carrier, Development challenges, Drug delivery, Drug targeting, Diagnostics, Limitations, Isolation, *in-vivo* studies, Loading methodology, Release of drug, Resealed erythrocyte, Source, Therapeutics delivery.

INTRODUCTION

Currently, the industry is dominated by more than 30 powerful therapeutics formulations, with a gross turnover of about 33 billion US dollars and a steady annual increase of around 15%. The resurgence of the need for safe medications fortified to achieve the goal, and with minimal/trivial side effects is the crucial rationale for such emerging considerations for the conveyance of therapeutics. The biodistribution of medications and APIs in the body is one of the first concerns accompanying the systemic conveyance of therapeutics. An idyllic pharmaceutical should only perform its pharmacological activity on the target location while still employing the lowest feasible dose of medication without any side effects on the non-target areas. The purpose should be to increase therapeutic suitability by reducing dose and its frequency [1].

Researchers are currently focusing on a new effort to design a mechanism for medication conveyance that has the greatest therapeutic benefit. The basic idea is based on the controlled dispersal of pharmacological, bioactive, and biotechnological medicines. Therapeutic targeting is a notion that works to transmit therapeutics to (activity) receptors or bodies or other explicit pieces inside the body to transfer medicines completely. Accordingly, it focuses on a functioning bio-atom from efficacious medication conveyance where pharmacological specialists coordinate explicitly to its objective location. Medication targeting can be accomplished either by chemical transformation or by an apposite conveyance carrier [2]. The fundamental measures accompanied by the determination of the transporter in therapeutic targeting are that transporters utilized in the conveyance of the medication ought to have the option to shield the medication from untimely bio-inactivation and uninterrupted the arrival of the medication to the objective location. The transporter satisfying these standards expands the dose-effect of the medication by diminishing the dose and recurrence of the administration.

Natural transporters, such as antibodies, liposomes, macromolecules, erythrocytes (ERS, Red blood cells, RBCs), and others, achieve these optimal qualities. Unlike synthetic transporters, which must be delivered orally or parenterally, these biological transporters may be introduced unswervingly into the circulatory system, allowing for regulated and sustained pharmaceutical conveyance. The

cellular transporters/carriers provide significant prospective benefits in biodegradability, biocompatibility, non-immunogenicity, non-pathogenicity, and self-degradability, combined with excellent therapeutic loading skills for different transporters utilized for therapeutic targeting [1]. The various currently available transport systems of medications are either simple or decomposable, such as microparticles, cells, cell phantoms, lipoproteins, liposomes, leucocytes, platelets, and RBCs dissolvable macromolecules, such as monoclonal antibodies, polysaccharide polymers, and decomposable polymers and unpredictable multi-composing designs.

Every different kinds of transporters utilized RBCs in light of their remarkable conduct and feature in giving an idyllic medication conveyance system. Blood is the main fluid in the body that provides vital nutrients and oxygen to cells while also transporting metabolic waste away from them. The plasma in blood makes up around fifty-five percent of the total, with corpuscles accounting for the other forty-five percent. RBCs, leucocytes (WBC) and platelets constitute forty-five percent of blood corpuscles, suspended in blood plasma, which constitutes fifty-five percent of the body's fluid. The bone marrow is where blood cells are formed. All blood cells, such as stem cells, are made from bone marrow. Stem cells are immortal (*i.e.*, they do not perish). Stem cells are also undifferentiated cells that have not yet been converted into a specific cell kind [1]. As they are pluripotent, they have the command to convert into any kind of blood cell. The RBCs are the most prevalent in the blood, and these endless, undifferentiated pluripotent stem cells grow up to RBCs, Leukocytes(LUE), and platelets of the complete cell. LUE, often known as white platelets, is a collection of closely related cell kinds that participate in immunological responses. Monocytes, basophils, eosinophils, lymphocytes, and neutrophils are all kinds of LUE. The chief function of RBCs is to transfer gases during the respiratory cycle. Erythropoiesis is the process through which RBCs are created. Platelets are responsible for converting fibrinogen into fibrin, which has the important function of clotting the blood [1].

RBCs are the most numerous cells of the human body, with possible transporter capacities for the conveyance of therapeutics. These are biocompatible, decomposable, and have impressively long circulatory ½-lives. They can also be filled with some biologically active substances by a range of physical and chemical methods. RBCs have been thoroughly evaluated based on their drug-carrying capability and loading efficiency. Simply collect blood samples from the organism of interest, remove RBCs from plasma, ensnare the medicine in the ERS, and reseal the resultant cell transporters, and you have drug-loaded transporter ERS [1]. As a result, they are known as resealed erythrocytes(R-ERS). This entire cycle is dependent on how these cells respond under osmotic environ-

CHAPTER 14

Gene Therapy: A New Avenue for the Management of Ophthalmic Diseases

Kesavan Karthikeyan[1,*], Nivedita Gautam[1], Olivia Parra-Marín[2] and Selvasankar Murugesan[3]

[1] *Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India*

[2] *Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510, Ciudad de México, Mexico*

[3] *Mother and Child Health Department, Sidra Medicine, Doha, Qatar*

Abstract: Gene therapy aims at intercellular delivery of functional genetic material to the affected area to restore its function or block a dysfunctional gene using viral vectors (Adeno-associated virus) or non-viral vectors (liposomes, SLNs). Gene therapy for the management of ocular diseases is emerging with improved and encouraging results. The Eye has well-defined anatomy, tight ocular barriers, and immune-privileged. It is a perfect target for gene therapy. Recently, many clinical trials are underway or have been completed. The success of these clinical trials promotes the treatment of several ocular diseases (Age-related macular degeneration, glaucoma, retinitis pigmentosa, and choroideremia). Gene therapy should possess an efficient targeting capacity and longstanding gene expression. Viral vectors are mainly used for gene therapy, but due to the risk associated with immunogenicity and mutagenesis, non-viral vectors are widely utilized. This chapter summarizes the recent development of therapeutic gene delivery approaches for the effective management of ocular diseases and their use in ophthalmology.

Keywords: Gene therapy, Non-viral, Ocular delivery, Ocular gene therapy, Viral.

INTRODUCTION

The human eye is an inaccessible, unique, and highly complex organ specified for photoreception. Its complex anatomy and physiology make it a vastly protected organ [1]. The eye ball consists of three primary layers, i) sclera and cornea (on the outside), ii) the retina (on the inside), and iii) in between is the uvea layer.

[*] **Corresponding author Kesavan Karthikeyan:** Department of Pharmacy, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India; Tel: +917587483123; E-mails: kesavanmpharm@gmail.com and k7_76@rediffmail.com

Akhlesh K. Jain & Keerti Mishra (Eds.)

Generally, the whole human eye is partitioned into two chambers: the anterior (at the front lobe) and the posterior (at the back lobe) [2]. The eye chambers (anterior and posterior) function individually after the ocular administration of any drug [3]. The most popular and accepted administration route for ocular disorders, especially for the eye's anterior segments, is the topical route, as it offers easy administration, low cost, and patient compliance [4]. But the topical route is associated with problems like attaining the optimum amount of drug at the target action. Moreover, conventional ocular dosage forms have poor or low bioavailability because of precorneal loss aspects: tear drainage, brief residence time in the cul-de-sac, non-productive absorption, and relatively low permeability feature of the corneal epithelial membrane [5]. Consequently, of these factors, not more than only 5% of administered drugs penetrate the eye [6].

Ocular disorders like diabetic retinopathy, glaucoma, age-related macular degeneration (AMD), and different types of retinitis pigmentosa cause damage to the eye's posterior segment, leading to impaired vision and blindness [7]. Approaches like topical (local), systemic, intravitreal, and periocular (comprising subconjunctival, sub-Tenon's, and retrobulbar) routes are the different administration routes for the treatment of posterior eye segment diseases. But the delivery of drugs to the rear section of the eye is the most challenging task due to protecting biological barriers. In contrast, the current approaches for managing ocular diseases have had limited achievements [8, 9]. Due to instant drainage *via* nasolacrimal ducts, impermeability of the corneal epithelium, absorption in the systemic circulation, and the blood-aqueous barrier restrict the topical route of administration.

On the contrary, the systemic route of administration to the posterior segment gets obstructed by the blood-retinal barriers and toxicities caused due to repeated systemic administration of drugs which are liable to aggravate because of nonspecific absorption [10, 11]. Therefore, intravitreal injections are the most preferred to deliver the drug to the tissues of the posterior section, and effective drug concentration can be achieved. Still, retinal detachment, hemorrhage, endophthalmitis, and cataract are some of the inbuilt side effects associated with this route of administration. Recently, intravitreal sustained-release devices, including implant devices, liposomes, and microspheres, offer effective treatment of posterior segment diseases. However, they necessitate intraocular surgery, and periodical substitution and are liable to side effects like intravitreal injections [12]. Different approaches such as permeation enhancers/cyclodextrins addition and viscosity enhancers were less significant to improve bioavailability. In recent times, enhanced ocular drug absorption was achieved by evasion/inhibition of drug efflux pumps. However, unwanted effects are evident due to their long-term use [13].

Many vivid changes have been observed in ocular drug delivery areas over a period. Understanding various approaches to gene delivery on the eye is a new opening of opportunities. The human eye is a highly immune-privileged spot with unique characteristics for designing successful ocular gene therapy. The anterior segment of the eye is protected from total immunological responses. Transportation of exogenous genes (*in vivo*) to the eye possesses high potential for ocular disease prevention and cure, employing genes as drugs. Genes are advantageous compared to conventional drugs as when the genes are inserted into the cells, they can release products for a longer period, which will enhance the duration of action of the commercial drugs available. The potential use of specific promoters targets the desired transgene expression. Restricting the gene expression to the particular cell type would prevent the adjacent tissues and reduce the subsidiary effects. In addition to this, gene expression can be easily regulated [14].

Ongoing studies in developing an improved gene-drug delivery system for ocular diseases will enhance drug delivery to the cell-specific targeting to minimize the immune responses. Therefore, this chapter is formed to summarize the latest development in the field of gene-drug delivery, surveyed in relevance to their application in ophthalmology.

Anatomy and Physiology of Eye

The human eye has distinctive anatomy and is a complex organ. Structurally, the whole eye is categorized into two major parts: the anterior and posterior segments (Fig. **14.1**). Approximately $1/3^{rd}$ of the eye covering the conjunctiva, cornea, aqueous humor, ciliary body, iris, and lens make up the anterior segment. On the other hand, the remaining back portion of the eye, *i.e.*, choroid, sclera, retinal pigment epithelium, optic nerve, neural retina, and vitreous humor, frame the posterior segment. Some diseases cause significant risk to the eye's vision, such as the anterior segment suffering from allergic conjunctivitis, glaucoma, anterior uveitis, and cataract. In contrast, diabetic retinopathy and age-related macular degeneration (AMD) affect the posterior segment of the eye [15].

In contrast with the other drug delivery systems of the body, more significant challenges are being faced by the ocular drug delivery system, due to the manifestation of various ocular barriers. Usually, these innate and unique ocular barriers are anatomically and physiologically meant to protect the eye from foreign materials [16] and maintain vital ocular functions [17]. These barriers are particular, *viz*. topical, systemic, and injectable, based on the route of administration [16].

CHAPTER 15

Biological Approaches to Nanoparticles Synthesis and their Applications in the Development Of Herbal Formulations

Vivek Shrivastava[1], Bhavisha Patel[1] and **Akhlesh K. Jain[2,*]**

[1] *School of Pharmacy, Parul University, Vadodara, Gujarat, India*

[2] *School of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur- 495 009 (C.G.), India*

Abstract: This chapter focuses on the sustainable environment for the synthesis of nanoparticles using microorganisms, enzymes, or botanical extracts as an alternative to chemical synthesis, and their subsequent application in herbal drug delivery systems. The objective is to emphasize the rapid, straightforward, and reliable synthesis of nanoparticles using a novel, preferably eco-friendly process. Herbal drugs are gaining prominence due to their ability to treat chronic diseases, such as arthritis and hypertension. However, several constraints, such as poor solubility, poor bioavailability, and low oral absorption, have restricted their use. Nanoparticle-loaded phytochemicals disperse conveniently in liquid and thus perforate easily. Merging nanotechnology with herbal medicine is required to produce better therapeutics with improved activity in the fight against long-term chronic disorders. Tissue engineering is another significant application of nanotechnology.

Keywords: Drug delivery, Gold nanoparticles, Green synthesis of Nanoparticles, Herbal nanoparticles, Microbial synthesis of nanoparticles, Nanotechnology in tissue engineering, Nanoparticles synthesis, Plant mediated nanoparticles. Therapeutic efficacy of Medicinal plants using nanoparticles, Synthesis of Nanoparticles of plants extracts, Viral nanotechnology.

INTRODUCTION

The chemical and physical methods (non-biological) used in the production of nanoparticles, show explicit health hazards and have high toxicity for living organisms. However, the biological production of nanoparticles is one step, low-cost, and eco-friendly method. There are several techniques for developing nano-

* **Corresponding Author Akhlesh K. Jain**: School of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur- 495 009 (C.G.), India, Tel: +91-8871211758; E-mail: akjain.ie@gmail.com

particles using environmentally friendly methods. Recently, phyto-nano synthesis has emerged as a major area of nanoscience, encompassing green approaches to synthesis [1]. Instead of using chemical reducing agents, biological methods for nanomaterial synthesis uses microbial enzymes or phytochemicals as reducing and capping agents. The advantages of synthesizing nanoparticles in this way are that the method is enviormental friendly (green synthesis), economical (not using any costly chemical), plants or microbes are readily available, and it is easy to tailor the size, shape and nature of the produced nanoparticles by simply modifying the culture conditions like pH, temperature or the nutrient media. We can further purify and characterize nanoparticles for their size, shape, and morphology by using techniques of optical spectroscopy, Fourier transforms infrared spectroscopy (FTIR), X-ray diffraction (XRD) analysis, transmission electron microscopy (TEM), and various other methods. Once these nanoparticles have been characterized, we can bio-functionalize them (by adding a moiety to these nanoparticles) and thus broaden their applications [1].

Synthesis of Nanoparticles using Microbes

The bacteria are potential biofactories for the synthesis of gold, silver, and other metal nanoparticles and can produce the nanoparticles either intracellularly or extracellularly. In the periplasmic space of bacteria, the pseudomonas bacteria isolated from silver mines have the ability to convert silver nitrate into silver nanoparticles. Similarly, bacteria in soil samples can convert copper into copper nanoparticles. Morganella species bacteria isolated from the midgut of an insect are proficient in secreting nanoparticles extracellularly. Magnetotactic bacteria are a heterogeneous class of prokaryotes. They lack flagella; they move in accordance with the geomagnetic field, and their migration is based on the intracellular magnetic structure (magnetosomes). When Fe^{3+} is added to this bacteria's culture, it converts into iron oxide nanoparticles.

Yeast (Candida) can be used to synthesize cadmium sulphide nanoparticles, and recently the yeast strains have been identified for making gold nanoparticles and other metal nanoparticles. We can manipulate the size and shape of nanoparticles by using yeast. The yeast is widely available and simple to cultivate, and the production of nanoparticles is inexpensive. Fungi (Verticillium spices) can be used to produce gold nanoparticles with elevated monodispersity. Furthermore, fungi are known to secrete a much higher amount of proteins, allowing for greater productivity of nanoparticles [1].

The Mechanism of Synthesis of the Nanoparticle by Microbes

The broadly acknowledged mechanism of synthesis of silver nanoparticles in the presence of nitrate reductase is well studied in the bacillus microbes. Nitrate

reductase (An enzyme present in the nitrogen cycle) is accountable for the conversion of nitrate to nitrate. The nitrate is converted to nitrate, and an electron is released, which is accepted by the incoming silver irons. The bacillus microbe secretes cofactors like NADH and NADH-dependent enzymes and converts Ag^{+} to $Ag^{0,}$ and the production of silver nanoparticles takes place. Fig. (**15.1**) depicts the mechanism of nanoparticle synthesis by microbes.

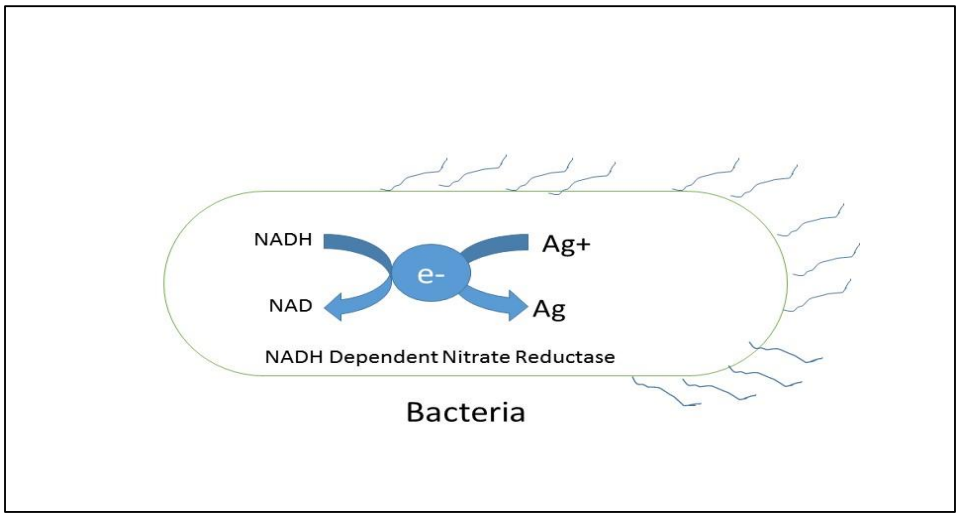

Fig. (15.1). Mechanism of nanoparticle production by bacteria.

Viral Nanotechnology

It entails the use of viruses and their nanostructure for a variety of applications. The attachment of the virus to the cells is the first step in the virus's life cycle. Once attached, their nucleic acid is injected into the host cell, where it uses the host machinery to integrate with the host cell's genome and replicate the viral genetic material multiple times. The viral genetic material, whether DNA or RNA, produces the proteins required for virus and replication in millions, and eventually destroys the entire cell. If the nucleic acid of the virus is removed, the virus's protein cage architecture can be used for a variety of purposes. Fig. (**15.2**) depicts several applications of the virus cage structure. Protein cage architecture can be used in the following ways.

The interior of the capsid can be loaded with a therapeutic agent, such as an anti-cancer drug, and thus used for therapeutic purposes.

The addition of gadolinium metal ions to the capsid wall makes it suitable for cancer imaging. We can target specific cells by adding RGD peptides (three amino acid peptides) to the surface of protein cage architecture.

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Akhlesh K. Jain

Dr. Akhlesh K. Jain is currently working as an Assistant Professor of Pharmaceutics at School of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur, India and having 20 years of teaching and research experience. He has graduated from Dr. H S Gour University and received his P h D degree in Formulation Science from Indian Institute of Chemical Technology Hyderabad, India (2007) and Postdoctoral training at Dublin City University, Dublin, Ireland, University College Cork, Cork, Ireland and National University of Singapore, Singapore (2008-2011). He also worked as Senior Scientist at Central Drug Research Institute, Lucknow India. He is the recipient of many reputed fellowships including Junior Research Fellowship and CSIR- SRF for research. Dr. Jain has authored more than 50 scientific publications in peer reviewed journals with total citations of more than 1700 and h-index 15. He has also authored five Book chapters at international level and four text book. He has successfully Investigated two Research project and guided two PhD. Students. He is an inventor of one international Patent and three Indian patents. His research focused on Nanoparticles, Nanocarriers based delivery systems, Mucosal vaccination, Non invasive protein delivery and Ligand conjugated colloidal carriers for cancer therapy.

Keerti Mishra

At present Keerti Mishra is a visiting Assistant Professor in Shambhunath Institute of Pharmacy, Prayagraj, India. She has completed her M. Pharm from School of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur, India. She has published 5 research and 2 review articles in reputed international journals. She twice cleared GPAT with high ranks before her B. Pharm degree. Mainly her research is focused on the nanocarriers based drug delivery system for the cancer treatment.