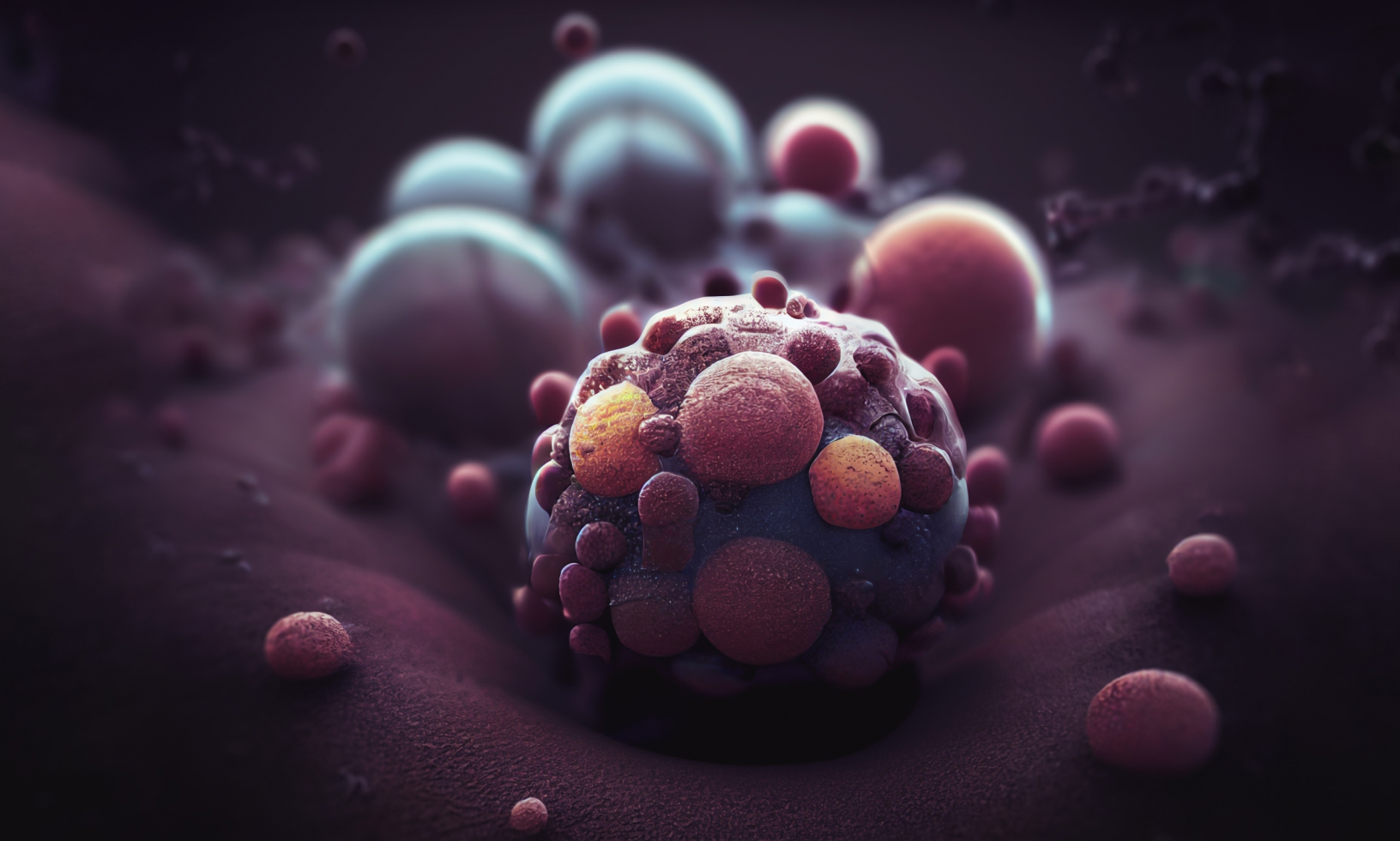
ROLE OF NANOTECHNOLOGY IN CANCER THERAPY



Editor:
Priya Patel

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Role of Nanotechnology in Cancer Therapy

Edited by

Priya Patel
Department of Pharmaceutical Sciences
Saurashtra University, Rajkot – 360005
Gujarat,
India

Role of Nanotechnology in Cancer Therapy

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FOREWORD

It gives me immense pleasure to write the foreword for the book "Role of Nanotechnology in cancer therapy" brought by expert academicians and researchers.

Pharmacy is the field where novel concepts arise by researchers frequently. Nanotechnology and nanocarriers have emerged as a big Iceland of good prospects in the pharmaceutical sector. A foundation of nanotechnology knowledge is one of the necessary aspects for building adequate knowledge, critical thinking, and problem-solving skills for pharmacy students, researchers, and educators to be successful in their careers.

Nanotechnology has lately created a buzz in the world, embracing the study and application of nanomaterials in the medical field. Nanotechnology and new drug delivery systems are becoming increasingly important in pharmacy curriculum, making it difficult for students to understand the concepts thoroughly in a short period of time.

Primarily aims at carrying out research on finding innovative nanotechnological solutions for a disease state like Cancer. Besides, it also endeavors to provide a platform to represent the experience and advanced knowledge of researchers and academicians across the globe.

Each chapter of this book includes the formulation approach of different nanocarriers and recent nano formulation developments in various cancers. The content of each chapter would be beneficial to all the readers, including students, faculty members and other persons working in the field of nanocarriers.

I wish this book to be a vital asset not only for the experts but also its effective resource for all researchers.

Dr. Pranav Shah
Maliba Pharmacy College
Uka Tarsadia University
Bardoli,
India

PREFACE

Nanotechnology has advanced at such a quick pace that major changes have been witnessed in recent years. In the early 2000s, there was a boost in public awareness and discussion around nanotechnology, which led to the first commercial applications of the technology. Nanotechnologies contribute to almost every field of science, including physics, materials science, chemistry, biology, computer science, and engineering.

On a global level, Cancer is a primary cause of death and poor quality of life. Despite the fact that various ways have been established to reduce mortality, chronic pain and improve quality of life, there is still a gap in the adequacy of cancer medicines. Early diagnosis of cancer cells and drug application with high specificity to prevent toxicities are two critical stages toward assuring optimal cancer treatment. Other techniques, such as nanotechnology, are being used to improve diagnosis and attenuate disease severity due to increased systemic toxicities and refractoriness with current cancer diagnostic and therapeutic tools. Nanoparticles are rapidly being developed and tested to circumvent various limitations of existing drug delivery systems, and they are emerging as unique cancer treatments. Nanotechnology has opened a new era of cancer targeting.

Cancer nanotechnology is being eagerly investigated and utilised in cancer treatment, signifying a significant advancement in the disease's detection, diagnosis, and treatment.

With the use of nanotechnology in medicine, scientists hope to prevent illness and more quickly diagnose, control and treat disease with fewer side effects. The current trend in nanoparticle research parallels these goals and concentrates on issues associated with drug delivery. As the area of nanoscience, nanotechnology and nanomaterials is a fast-developing one, an approach that equips the large volume of information is essential. With this view, while providing a broad perspective, the book emphasizes the basics of nanoscience and nanoscale materials and also introduces several different types of nanoparticles and their utility in various types of Cancer.

This report presents guidelines for enhancing nanotechnology's utility in cancer research in order to improve the understanding of cancer biology, prevention, detection, and treatment. The book Nanotechnology for Cancer Therapy focuses on the most promising nanoscientific and nanotechnological solutions for cancer imaging and treatment. Nanotechnology, among the several options examined, has significant promise for the targeted delivery of medications and genes to tumour areas, as well as the eventual replacement of chemotherapeutic agents plagued by side effects.

This collection brings together the knowledge of world-renowned academics and researchers to produce a complete treatise. The book is structured into eight sections and consists of 11 chapters.

- Basic cancer pathophysiology, includes the current challenges and opportunities in cancer treatment.
- Recent advances in multifunctional Nanomedicine include the development and advancement in microneedle-assisted drug delivery systems used in cancer treatment.
- Nanotechnology-Based Inhalation approach for the treatment of lung cancer along with their opportunities And challenges.
- Mesoporous Based Drug Delivery along with their methods and characterization for the

Prostate Cancer.
- Current opportunities and challenges of Nanotechnology in Skin Cancer Treatment along with future outlook.
- Nanofibre approach and its applicability in Gastric Cancer.
- Fundamentals of targeting strategies, Nanomedicine-based use of siRNA in Cancer along with the role of ligand and dendrimer in the tumour targeting.
- Various regulatory aspects of Nanoformulations, including past failure, current challenges and standards, along with the global strategies for nanoparticle regulation.

This book was written to provide comprehensive knowledge to all readers involved in pharmaceutical and nanotechnology sciences. Students, research scholars and research scientists may benefit from the material available in this book for the use of this knowledge in more advanced research that could be financially and socially advantageous.

Priya Patel
Department of Pharmaceutical Sciences
Saurashtra University, Rajkot – 360005
Gujarat,
India

List of Contributors

Akashdeep Singh	Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala- 147002 (Punjab), India
Arjun Joshi	Department of Pharmaceutics, Anand Pharmacy College, Anand- 388001, Gujarat, India
Anand J. Patel	Tarsadia Institute of Chemical Science, Uka Tarsadia University, Bardoli-394620 Surat, Gujarat, India
Bhavin R. Patel	Tarsadia Institute of Chemical Science, Uka Tarsadia University, Bardoli-394620 Surat, Gujarat, India
Chirag A. Patel	Department of Pharmacology, L M College of Pharmacy, Navrangpura, Ahmedabad-380009, Gujarat, India
Chetna Modi	Department of Pharmaceutics, Anand Pharmacy College, Anand- 388001, Gujarat, India
Devang B. Sheth	Department of Pharmacology, L M College of Pharmacy, Navrangpura, Ahmedabad-380009, Gujarat, India
Devyani Dave	Department of Pharmaceutical Sciences, Saurashtra University, Rajkot-360005, Gujarat, India
Jay M. Nimavat	Gujarat Biotechnology University, Gandhinagar- 382355, Gujarat, India
Kamal Singh Rathore	Bhupal Nobles, College of Pharmacy, BN University, Udaipur- 313001, Rajasthan, India
Mansi Faladia	Department of Pharmaceutical Sciences, Saurashtra University, Rajkot-360005, Gujarat, India
Mihir Raval	Department of Pharmaceutical Sciences, Sardar Patel University, Vallabh Vidyanagar-388 120, Gujarat, India
Nasir Vadia	Faculty of Pharmacy, Marwadi University, Rajkot-Morbi Highway, Rajkot-360003, Gujarat, India
Nikita Udhwnai	Department of Pharmaceutics, Anand Pharmacy College, Anand- 388001, Gujarat, India
Priya Patel	Department of Pharmaceutical Sciences, Saurashtra University, Rajkot-360005, Gujarat, India
Pranav Shah	Department of Pharmaceutics, Maliba Pharmacy College, Uka Tarsadia University, Surat, Bardoli - 394620, Gujarat, India
Pallavi M. Chaudhari	Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune- 411044, India
Pratibha Chavda	Department of Pharmaceutical Sciences Saurashtra University, Rajkot-360005, Gujarat, India
Sandip B. Patel	Department of Pharmacology, L M College of Pharmacy, Navrangpura, Ahmedabad-380009, Gujarat, India
Saloni Bhandari	Bhupal Nobles, College of Pharmacy, BN University, Udaipur- 313001, Rajasthan, India

Saloni Dalwadi	Department of Pharmaceutics, Anand Pharmacy College, Anand - 388001, Gujarat, India
Vaibhav D. Bhatt	School of Applied Sciences and Technology, Gujarat Technology University, Ahmedabad- 382424, Gujarat, India
Vikas Rana	Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala- 147002 (Punjab), India
Vaishali Thakkar	Department of Pharmaceutics, Anand Pharmacy College, Anand- 388001, Gujarat, India

CHAPTER 1

Cancer Pathophysiology

Devang B. Sheth[1,*], **Chirag A. Patel**[1] and **Sandip B. Patel**[1]

[1] *Department of Pharmacology, L.M. College of Pharmacy, Navrangpura, Ahmedabad 380009, Gujarat, India*

Abstract: Cancer prevalence across the globe has increased substantially in the last two decades despite significant progress in inpatient care. Cancer, a multifactorial disease, evolved several theories to establish pathophysiological conditions. Uncontrolled proliferation, dedifferentiation and metastasis mainly describe the cancer progression, which must be characterized by cellular and molecular changes. Understanding these processes helps devise the strategy for effectively delivering the drugs to the target sites. The present review described the essential features of cancer pathophysiology and challenges to achieving drug concentration in the targeted area.

Keywords: Dedifferentiation, Metastasis, Nanotechnology, Uncontrolled Proliferation.

INTRODUCTION

Cancer is a heterogeneous group of diseases that evolved from a complex multistage process resulting from genetic and epigenetic abnormalities, resulting in dysregulated gene expression [1 - 3]. All conditions categorised under *'Cancer'* share common phenotypic characteristics of uncontrollable cell growth and proliferation. 'Cancer' is derived from the Greek word *'Karkinos,'* meaning crab. The etymology correlates with the appearance of finger-like spreading projections from a tumor [4, 5]. Globally, cancer is the second leading cause of mortality below 70 years. Amongst the ranking of premature mortality across the globe, cancer stands 1st across 57 countries, 2nd across 55 countries and 3rd-4th across 23 countries [6]. The world has observed an alarming increase of nearly 100% in new cancer cases from 10 million in 2000 to 19.3 million in 2020. This trend continues to be kept in the last few decades in developed and developing countries with advancements in socioeconomic status and an increase in the average lifespan of human beings. As per Global Cancer Statistics, nearly 10 million deaths due to cancer were reported in 2020 against 6 million deaths in 2000 [6, 7].

[*] **Corresponding author Devang B. Sheth:** Department of Pharmacology, L M College of Pharmacy, Navrangpura, Ahmedabad-380009, Gujarat, India; Tel: +919879949977; E-mail: devangbsheth@gmail.com

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ETIOPATHOGENESIS

The transformation of a normal cell into a tumor cell is primarily due to one or more DNA alterations that dysregulate gene structure and expression [8, 9]. These alterations may either be inherited or acquired/provoked by exposure to a carcinogen(s).

Aetiology

Alteration(s) of DNA (*i.e.*, mutation) can be provoked by primary carcinogen, secondary carcinogen, co-carcinogen and promoter. Primary carcinogens, such as physical, biological and chemical agents, produce mutagenesis resulting in carcinogenesis. Secondary carcinogen (commonly referred to as pro-carcinogen) mediates the process of carcinogenesis after being converted into active metabolites. Co-carcinogen increases the process of carcinogenesis when administered with a carcinogen, while (tumor) promoter does the same when administered after a carcinogen. Both co-carcinogen and promoter do not possess carcinogenic potential when given alone (Fig. **1**). However, it is complicated to determine the etiology of cancer in clinical practice.

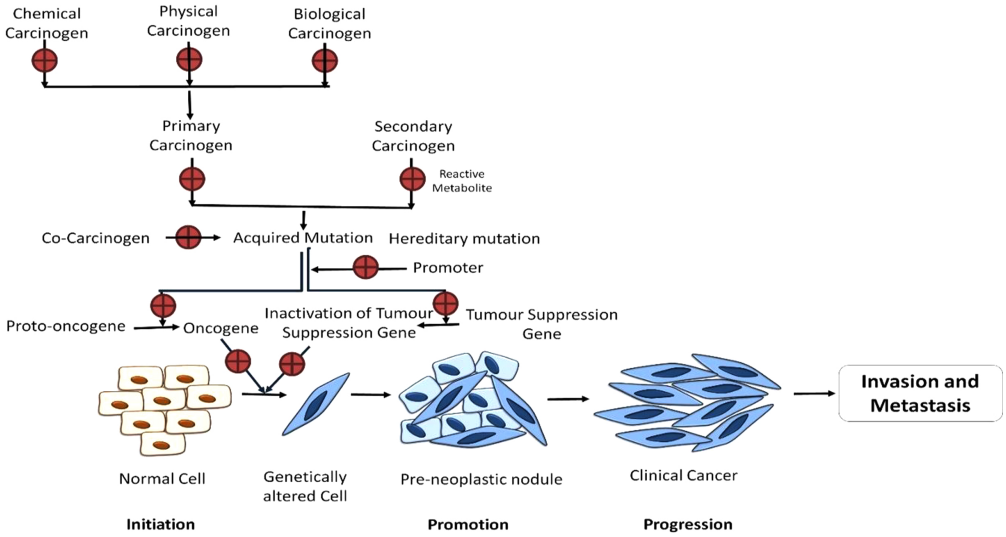

Fig. (1). Process of Carcinogenesis.

Examples of physical carcinogen include ionizing radiation (*e.g.* γ-rays, X-rays) and non-ionizing radiation (*e.g.* UV-rays) [10 - 13]. Squamous cell carcinoma resulting from sun-exposed areas and Kangari cancer due to the use of traditional fire-pot in some areas of Kashmir are examples of cancer produced by physical carcinogens [14 - 16].

Biological agents such as bacteria, fungus and more commonly viruses can cause direct DNA damage, produce carcinogens or introduce oncogenes in the host cell. Cervical, penile, anal, oral and pharyngeal cancer caused by Human Papillomavirus (HPV); Burkitt's Lymphoma caused by Epstein-Barr Virus (EBV) and Kaposi's Sarcoma caused by Human Herpes Virus 8 (especially in patients of HIV infection) are some examples of biological carcinogen. Growth of *Aspergillus flavus* resulting in the release of aflatoxin can lead to hepatocellular carcinoma. Infection with *Helicobacter pylori* is a recognized etiopathological factor for incidences of gastric adenocarcinoma.

Chemical carcinogens can be classified into genotoxic and non-genotoxic carcinogens based on their biological activity [17, 18]. Genotoxic carcinogens cause mutation by covalently modifying the nitrogenous bases of DNA (particularly guanine) [19, 20]. O6 and N7 positions of guanine base can readily and covalently associate with reactive metabolites of chemical carcinogens. Substitutions at N7 positions may get repaired quickly, but O6 positions are not. Thus, permanent mutagenic effects are usually due to substitutions at O6 positions [20, 21]. Chemicals present in tobacco like polycyclic aromatic hydrocarbons, nicotine, coal tar and nitrosamine NNK (4-(methylnitrosamino)-1-(3-pyrid-l)-1-butanone) when consumed through chewing, smoking or sniffing, greatly increases the possibility of such substitutions [22]. Tobacco products are the leading cause of lung and oropharyngeal cancers. Association of asbestos in lung cancer; heavy metals like arsenic in liver, lung and skin cancer and benzene in leukemia is well documented [20, 21, 23 - 29]. Non-genotoxic carcinogens mediate their action by modifying epigenetic mechanisms [17, 18].

Pathogenesis

Damage to the genomic structure of cells or altered phenotypic expression of genes is a common feature for all neoplasms. Despite the high fidelity of DNA replication, it is a fact that spontaneous mutation in eukaryotic cells occurs at the rate of 10^{-10}-10^{-12} errors per base pair per generation [30]. Although low, it is an inevitable and inherent error rate in DNA replication. Thus, all multicellular organisms face the near-certainty of developing a neoplasm if their survival tenure is long enough [31]. Many non-lethal and inconsequential mutations in a minor subset of the coding and non-coding regions of the genome can give rise to carcinogenesis [32]. Oncogene is a mutated gene that can cause cancer by accelerating proliferation through dysregulating the cell cycle or inhibiting apoptosis [33 - 35]. Major 2 categories of genetic change that lead to cancer include:

(a) Activation of proto-oncogenes to oncogenes

CHAPTER 2

Recent Advances of Multifunctional Nanomedicine

Pallavi M. Chaudhari[1,*]

[1] *Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune- 411044, India*

Abstract: The revolution of nanomedicine has emerged as an array of biological products in the pharmaceutical field. Their peculiarity of nanosize has been a benefit for the detection and prevention of diseases by application of engineered nanodevices and nanostructures. This presents range of opportunities, that are suitable for most drugs, prevents side effects, and enhances patient compliance. Nanomedicine has fascinated medical research in developing different multifunctional nanostructures like dendrimers, nanoparticles, micelles, quantum dots, carbon nanotubes, *etc*. However, there are still certain impedes to bringing out the best amongst these nanomedicines. This chapter will spotlight the recent advances of multifunctional nanomedicine, solely to combat cancer disease conditions, that can offer improvement in the pharmacokinetic and pharmacodynamic profiles of the conventional approaches and optimize the efficacy of the existing anticancer drugs. In recent years, combination therapy has also shown good improvement in cancer therapy as compared to monotherapy. The theranostic application can offer a good alternative to cancer treatment. So, when the insights are combined with new nanotechnology-based therapy, targeted drug delivery can be obtained to avoid the side effects, but the concern of their toxicity should also be noted. Hence, nanomedicine represents one of the advanced fields that combine nanotechnology and medicine for improved efficiency and safety to human health, through the study of elucidation of cellular and molecular mechanisms, to design performant nano-delivery as an efficient tool for the treatment of cancer. Thus, the exploration of the properties needs to be understood to execute the unmet needs and attain project cost benefits.

Keywords: Cancer, Carbon Nanotubes, Dendrimers, Micelles, Multifunctional, Nanomedicine, Nanoparticles, Nanosize, Nanostructures, Pharmacodynamic, Pharmacokinetic, Quantum dots, Theranostic, Toxicity.

INTRODUCTION

The advancement in diverse fields of cellular and molecular biology, proteomics, genetics, and bioengineering has led to rise in the field of nanomedicine. Thus, nanomedicine is the convergence of nanotechnology and medicine with applicat-

[*] **Corresponding author Pallavi M. Chaudhari:** Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune- 411044, India; E-mail: pallavichaudhari26@gmail.com

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ions to cancer research [1]. The term nanotechnology is derived from the Greek word Nanos, meaning dwarf.

Nanomedicine is an application of controlled materials at the 1 – 100 nm length scale [2]. Emerging nanomedicine is an interdisciplinary science that comprises different fields like physics, chemistry, biology, medical sciences, engineering and pharmaceutical sciences, including biomedical applications of nanotechnology [3].

The field of nanotechnology is concerned with materials and systems, their structures and components exhibit novel and significantly improve physical, chemical, and biological properties due to their nanoscale size [4]. These nanoscale size have wide applications in the treatment of disorders, increase efficacy with safety, enhance bioavailability, reduce toxicity, *etc.* The different nanomaterials (Fig. **1**) offer ample research opportunities, and with an interdisciplinary approach, can assist in treating different disease conditions [5].

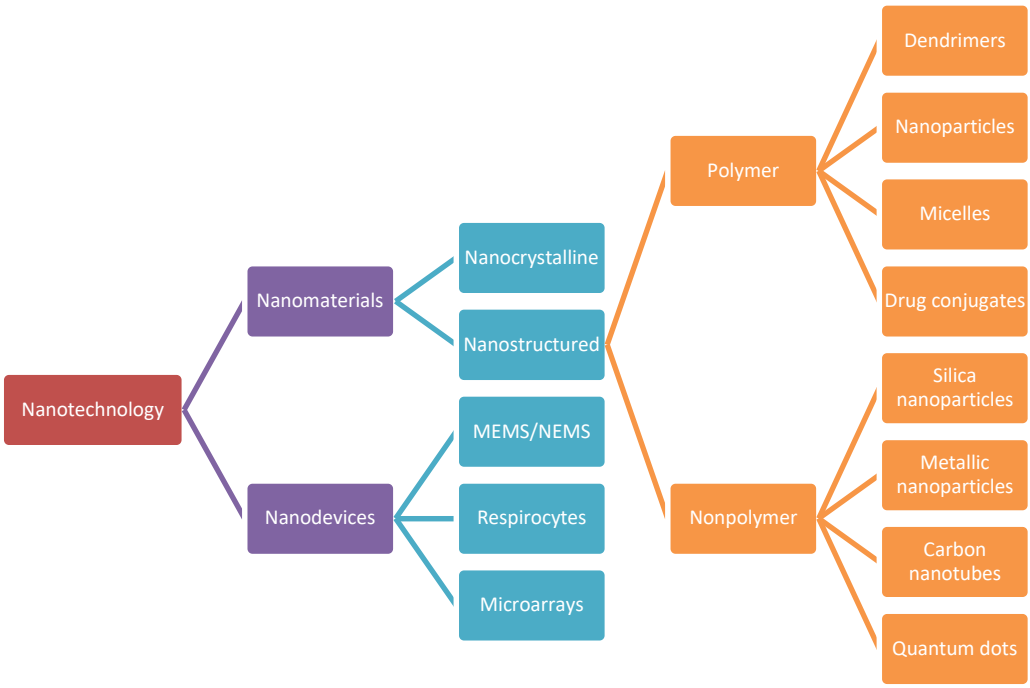

Fig. (1). Flowchart to illustrate the classification of nanotechnology.

DENDRIMERS

The word dendrimer originates from the Greek word *dendron*, meaning branch or tree, while *mer* means part. Dendrimers are 3D, extremely branched

macromolecules obtained by a polymerization reaction mechanism resembling the branches of trees (Fig. **2**) [6]. These possess nanoscale dimensions, and their size of it is dogged by their number of generations. So, if the generation number is increased, the size of dendrimers is also increased. The effects of dendrimer size and central metal ions on the photosensitizing properties of dendrimer porphyrins were reported [7]. The structure of the dendrimer originates from a central core, into branches that are known as dendrons. A study demonstrated that when Paclitaxel was encapsulated in hydrophobic nanodomains of PPI dendrimers, about 30% of the drug was entrapped, and mAbK1-PPI-PTX was tested in an ovarian cancer model, and results depicted reduced tumor volume and extended animal survival significantly through enhanced drug uptake in the tumor [8]. The anticancer drugs when encapsulated in FA-modified dendrimers displayed precise efficacy against cancer cells with high-affinity of FA receptors [9].

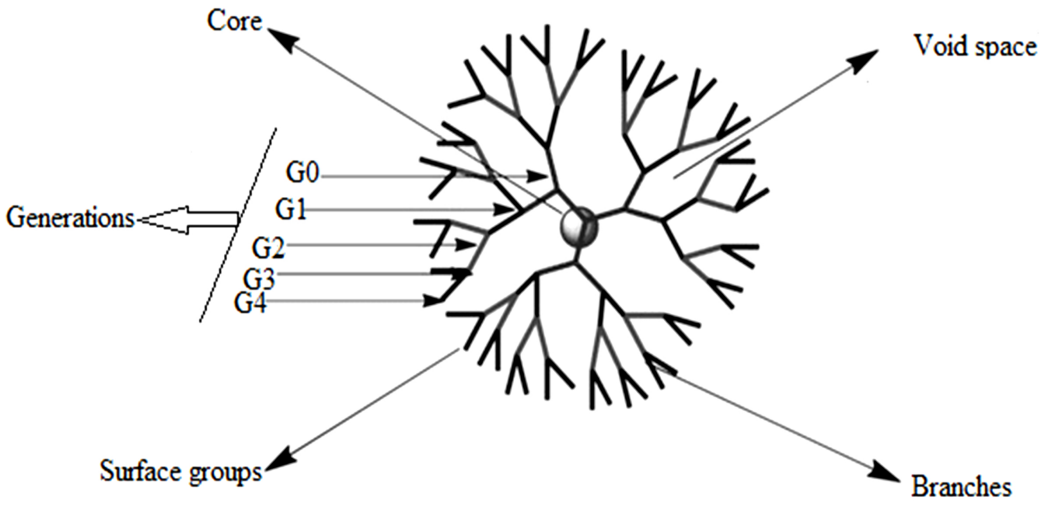

Fig. (2). Representation of a dendrimer with core, branches, and surface.

The elite characteristics of the dendrimers reflect it as a potential drug delivery system for drugs for cancer treatment. The branched structure of these dendrimers can be utilized for entrapment and targeting of anticancer drugs. Thus, they offer attractive polymers in terms of drug delivery [10, 11]. Kelly E. Burnsa synthesized a pHLIP-dendrimer-DOX, a peptide dendrimer-drug conjugate system for pH-triggered direct cytosolic delivery of cancer chemotherapeutic doxorubicin (DOX) using the pH Low Insertion Peptide (pHLIP). The biophysical analysis showed the dendrimer and a single DOX conjugate inserted into membrane bilayers in a pH-dependent manner [12].

CHAPTER 3

Dendrimers in Anticancer Drug Delivery

Saloni Bhandari[1,*] and **Kamal Singh Rathore**[1]

[1] *Bhupal Nobles, College of Pharmacy, BN University, Udaipur- 313001, Rajasthan, India*

Abstract: Recent development and advances in the application of nanotechnology in the field of medicine have led to the evolution of multifunctional "smart" nanocarriers that are capable of delivering one or more therapeutic agents effectively, safely and selectively to tumor cells, including intracellular gene-specific targeting. Dendrimers have a high level of control over the synthesis of dendritic architecture, well-defined size, shape, molecular weight, membrane interaction and monodispersity, making them a perfect example of one such multifunctional smart nanocarrier.

The 3D nano-polymeric architecture of dendrimer makes it an appropriate choice for drug and gene delivery vectors. The functional groups attached on the surface of dendrimers permit the addition of other moieties that can actively target certain diseases, which are now widely used as tumor-targeting strategies. Along with being compact and globular in structure, dendrimers also exhibit interior cavity spaces and multiple surface functional groups, which play a vital role in encapsulating drug molecules both in the interior of the dendrimers (physical encapsulation) as well as in the surface functional groups (covalent conjugations). The application of dendrimers in biomedicine has recently attracted much attention worldwide. Dendrimers are interesting in the field of biomedical applications due to their unique characteristics.

Keywords: Biomedical Applications, Dendrimers, Drug Delivery, Drug Encapsulation, Gene Specific Targeting, Nanocarriers, Nanotechnology, Tumor Targeting.

INTRODUCTION

Cancer is one of the most excruciating diseases without any successful treatment of several types of tumors [1]. Cancer is the uncontrolled and abnormal growth of the cells within the body. These abnormal cell growths are termed as cancer cells, malignant cells or tumor cells. Tumor having the potential to invade or spread to other body parts is known as a malignant tumor, whereas a tumor confined to a specific organ or body part is referred to as a benign tumor. There are several obstacles that hinder the efficacy of conventional chemotherapeutic agents, such

[*] **Corresponding author Saloni Bhandari:** Bhupal Nobles, College of Pharmacy, BN University, Udaipur- 313001, Rajasthan, India; Tel: 8094927056; E-mail: salonibhandari1996.sb@gmail.com

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as low aqueous solubility, poor bio-distribution, unfavorable pharmacokinetics, narrow therapeutic index, poor membrane permeability, instability, rapid clearance, severe toxicity, and the emergence of multidrug resistance phenotypes [2].

Drug delivery through dendrimeric systems, particularly *via* ligand or receptor-mediated endocytosis targeted to the cancerous cells, appears promising due to various properties (including surface properties). Dendrimeric drug delivery also by-passes the above-mentioned limitation of the conventional chemotherapeutic agents. Dendrimers prevent the degradation of the drug during transit, enhance targeting efficiency and reduce adverse toxic effects caused by cytotoxic drugs [2, 3].

Chemistry of dendritic polymers was initially discovered in the early 1978s by Fritz Vögtle and coworkers [4], and they named them as "cascade" molecules. Later in the 1980s, Donlad Tomalia and coworkers synthesized the first dendritic family [5]. George R. Newkome used divergent synthesis approaches to synthesize similar macromolecules, which he referred to as arborols, from the Latin term "arbor" meaning a tree [6]. Dendritic polymers are now commonly referred to as "dendrimers", and originated from two Greek words, "dendron," meaning tree and "meros", meaning a part [7]. Dendrimers are a novel class of highly ordered, spherical, branched polymeric macromolecules, having a three-dimensional well defined globular structure with low polydispersity and high functionality [8].

STRUCTURE AND PROPERTIES

Dendrimers are made up of three components; a central core, repetitive branching units and multiple active terminal groups. The structure of the dendrimer is shown in Fig. **(1)** [2].

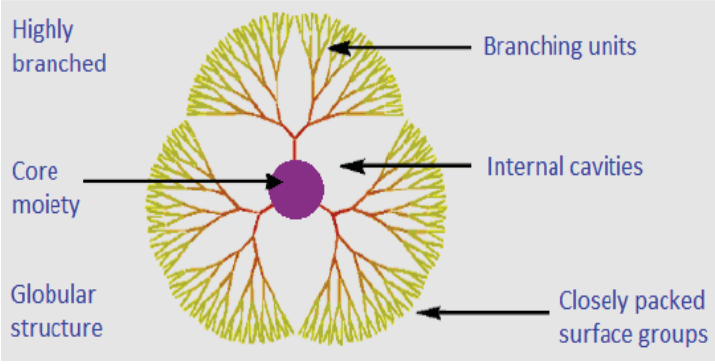

Fig. (1). Structure of Dendrimer [2] (ref no. IJAP/2021/fig1/11/6/21).

Dendrimers have well-defined architecture and are synthesized carefully in a stepwise manner where each additional reaction step leads to a higher generation dendrimer with a double number of active sites (known as end groups) and double weight than the previous generation [7]. The "Generation number" of dendrimer is determined by the increase in the number of branching units, resulting in globular structure formation due to steric crowding of branches at the surface [9 - 12]. Dendrimers form a closed membrane-like structure and become densely packed as they extend out to the periphery. Upon reaching the critical branched state, they stop growing due to a lack of space. This is known as the "starburst limit" [13]. The surface area of the dendrimer increases with the square of generation, and the number of branch ends on a dendrimer increases exponentially as a function of generation [7].

Based upon their structure, dendrimers can be broadly classified into simple dendrimers, liquid dendrimers, chiral dendrimers, micellar dendrimers, amphiphilic dendrimers, metallo dendrimers and hybrid dendrimers [14].

1. Simple Dendrimers: They have simple monomer units. The convergent synthesis of a sequence of mono-disperse Lester dendrimer, based upon symmetrically substituted benzene tricarboxylic acid ester, is described. These materials consist of 4, 10, 22 and 46 and have molecular diameters of 45A.

2. Liquid Crystalline Dendrimer: These are made up of mesogenic monomers, *etc.*, mesogen functionalized carbosilane dendrimer. Functionalization to the end group of carbosilane dendrimers with 36 mesogenic units, which can be attached through a C-5 spacer, leads to liquid crystalline dendrimers that form broad smectic phase in the temperature range of 17°C to 130°C.

3. Chiral Dendrimer: In chiral dendrimers, the chirality is based on the building of 4 constitutionally assorted but chemically alike branches to an achiral core, *etc.*, chiral dendrimers obtained from pentaerythritol.

4. Micellar Dendrimers: These are unimolecular micelle arrangement dendrimers. Fully aromatic, water-soluble dendrimers form a collection of aromatic polymeric chains that generate an environment that resembles some micellar structures, which form a complex with small organic molecules in water.

5. Hybrid Dendrimers: These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form, which provide an opening to use them as surface active agents, compatibilizers or adhesives, *etc.*, hybrid dendritic linear polymers.

CHAPTER 4

Nanomedicine-based use of SiRNA in Cancer

Jay M. Nimavat[1,*], Vaibhav D. Bhatt[2] and **Devyani Dave[3]**

[1] *Gujarat Biotechnology University, Gandhinagar- 382355, Gujarat, India*

[2] *School of Applied Sciences and Technology, Gujarat Technology University, Ahmedabad-382424, Gujarat, India*

[3] *Department of Pharmaceutical Sciences, Saurashtra University, Rajkot-360005, Gujarat, India*

Abstract: People have been suffering from cancer and associated problems for many years. A great amount of improvement has occurred in the field of medical science, and it certainly has benefitted humankind to help live a happy and prosperous life. Despite all these things, cancer treatment remains a provocative question as every year cases are increasing; on the contrary, there are a lot of difficulties associated with cancer treatment. To cope with these unique and mischievous problems, nanotechnology is considered a boon. Various nanoparticle facilitates the required characteristics to deliver a specific active therapeutic agent against the cancer cells. They can be targeted and even modified to fulfill specific pharmacokinetic parameters vital for *in vivo* delivery of drugs along with Nano-systems. This chapter here focuses on various types of nanoparticles and nanoparticle-mediated drug delivery of certain therapeutic agents.

Keywords: Cancer, Clinical trials, Combined therapy, Liposomes, Metal-based nanoparticles, Nanoparticles, Nanotechnology, SiRNA, Targeted therapy.

INTRODUCTION

Regardless of considerable advancements in the diagnostics and therapeutic field, cancer has been and still is a major cause of death around the globe. Considering WHO data, in 2019, cancer was among the leading causes of death before the age of 70 [1]. According to the study conducted by the International Agency for Research on Cancer from data provided by GLOBOCAN (Global Cancer Observatory), worldwide, an estimated 19.3 million new cases and almost 10 million deaths occurred due to cancer in 2020 [1]. Female breast cancer surpassed lung cancer as the most commonly diagnosed cancer type, with approximately 2.3 million new cases, followed by lung cancer and colorectal cancer. However, lung cancer remained the leading cause of death by cancer with estimated 1.8 million deaths (18%), followed by colorectal cancer (9.4%), liver (8.3%), stomach (7.7%)

[*] **Corresponding author Jay M. Nimavat:** Gujarat Biotechnology University, Gandhinagar, Gujarat, India; Tel: +91 9624233282; E-mail: jainimavat36@gmail.com

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and female breast cancer (6.9%). According to the study, the global cancer burden is expected to be 28.4 million cases by 2040, about a 47% rise from 2020 [1]. The incidence rate for all cancers combined was 19% higher in men than in women in 2020, though the rates varied widely in different geographical areas.

The human body has trillions of cells. Some of them may relate to some mutations which lead to void in the cell's regulatory processes. *e.g*., Uncontrolled cell proliferation (Cancer). Damage to DNA can render a cell useless or even harmful to an organism. Apoptosis, or programmed cell death, evolved as a rapid and irreversible process to efficiently eliminate dysfunctional cells. Tumors have several structural layers: necrotic core, intermediate or hypoxic layer, and peripheral or vascularized layer. Cancer that has spread to other body parts needs arduous and broad treatment approaches, which require chemotherapy as a first-line approach [2, 3]. However, chemotherapeutic agents are primarily hydrophobic and thus challenging to administer directly. Furthermore, these drugs are toxic to healthy cells and tissues and may produce side effects. As an emerging treatment approach, gene therapy is one of the most promising inventions. It uses nucleic acid tools, such as oligonucleotides and small interfering RNA (siRNA), to silence the genes that cause cancer. This approach can also be used to increase the expression of proteins that can prevent cancer cell growth and metastasis [4].

Cancer progression is also associated with multidrug resistance as it has many ways to evade these chemotherapeutics and the immune system. Drug resistance in cancer occurs due to increased drug efflux, drug inactivation, drug target alteration, cell death inhibition, and epithelia-mesenchymal transition. During drug inactivation, drug molecules interact with different proteins that might partly modify or degrade or make drug-protein complexes, ultimately leading to drug inactivation. For instance, it is observed in treating acute myelogenous leukemia with a nucleoside drug called Cytarabine (AraC), activated by multiple phosphorylation events converting it to AraC-triphosphate [5, 6]. Mutation or down-regulation of this pathway can lead to decreased activation levels of AraC and hence to AraC drug resistance. Another critical example observed is the GST superfamily, a group of detoxifying enzymes. Their primary function is to protect cellular macromolecules from electrophilic moieties. These assist in drug resistance through direct detoxification and inhibiting the mitogen-activated protein kinase pathway (MAPK). Elevation of GST in cancer cells increases the detoxification of anticancer drugs, resulting in lower cytotoxicity exertion of drugs [7, 8].

A drug's efficiency is affected by its molecular target and alteration/modification of the target. In cancer cells, such types of alteration may lead to drug resistance.

For example, some active agents target topoisomerase II, which is an enzyme that stops DNA from becoming under- or super-coiled. The complex formed between DNA and Topoisomerase II is short-lived, and these drugs stabilize this complex, ultimately leading to the stoppage of the cell cycle. It has been observed that some cell lines become resistant to topoisomerase II inhibitors through mutations in the topoisomerase II gene [9, 10].

Drug efflux is one of the most studied mechanisms of cancer drug resistance that reduces drug amassing inside the cells. Members of ATP binding cassette (ABC) transporter family proteins enable this efflux and are essential regulators at the plasma membrane of healthy cells. ABC transporters are transmembrane proteins and are present in humans as well as extant phyla, operating to transport a wide range of substances or molecules across cellular membranes. There are about 49 known members of the ABC family in humans, and their structure varies from protein to protein. However, they have two distinct domains that help classify a highly conserved nucleotide-binding domain and a variable transmembrane domain [11]. Substrate binding to the transmembrane domain causes ATP hydrolysis at the nucleotide-binding site, driving a change in conformation that pushes the substrate out of the cell. This efflux mechanism plays a vital role in preventing the excess accumulation of toxins inside the cells [12]. While efflux is a normal physiological process, it is known to cause drug resistance in cancer cells. Three transporters, MDR1 (multidrug resistance protein 1), MRP1 (multidrug resistance-associated protein 1) and BCRP (breast cancer resistance protein), are associated with many drug-resistant cancers. They have broad substrate specificity and can efflux many xenobiotics, including anthracyclins, Taxanes, kinase inhibitors and vinca alkaloids from the cells. Hence, protecting cancer from many other drugs. MDR1, which produces Pgp, was first to be identified. Normal expression of the MDR1 gene in colon, liver, and kidney increases when these tissues become cancerous. One study showed that treatment with doxorubicin tempted a significant increase in MDR1 expression in lung cancer cells. However, no major change was observed in normal lung cells [13 - 16].

Combine therapy of chemo agents and genes has been found to be very effective in overcoming this hurdle. However, delivering these agents alone or in combination is typically a more significant problem due to their lack of tumor selectivity, poor stability, and clearance from the body [17, 18]. Alternative options for cancer treatments involve chemical or natural products that work as anticancer agents or small molecule inhibitors but also have complications regarding their delivery. For instance, Photodynamic therapy uses photosensitizers that are generally hydrophobic, need soluble formulation agents for *in vivo* application and lacks tumor selectivity [19]. Hence, many anticancer

CHAPTER 5

Ligands for Tumor Targeting

Akashdeep Singh[1] and **Vikas Rana**[1,*]

[1] *Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala-147002 (Punjab), India*

Abstract: Cancer is the world's second leading cause of death, and new cancer cases are expected to increase dramatically in the next decades. Many biotechnologists and medical researchers are actively involved in finding issues related to cancer detection and treatment efficacy. Given the difficulties of traditional chemotherapy, the targeted drug delivery system (DDS) of chemotherapeutics for cancer therapy through nanoparticles (NPs) carriers is a growing field of research. Researchers have concentrated on surface modification of NPs or nanocarriers using biological ligands in addition to optimizing their physicochemical characteristics. Several *in-vivo* investigations have shown that virus-sized stealth NPs may circulate in the blood for a longer period and preferentially concentrate at tumor sites due to the increased permeability and retention (EPR) effect, also known as the passive targeting strategy. Surface modification of stealth NPs with specific biological ligands may result in enhanced retention and accumulation of NPs in tumor sites, referred to as an "active targeting strategy". This chapter outlined some key points regarding each strategy's impact and how combining some or all of them has proven beneficial in tumor targeting. After a brief introduction to existing cancer treatments and their drawbacks, we discussed the biological obstacles that NPs must overcome, followed by several forms of DDS to increase drug accumulation in the tumor site. Then, using active targeting strategies, we also describe various receptors present on cancer cells that enhance cellular drug targeting. A substantial quantity of information has been summarized in tables on different polymeric NPs conjugated with selective targeting ligands such as proteins, polysaccharides, peptides, and aptamers to small molecules. With the potential of maximizing therapeutic efficacy and reducing side effects, ligand-mediated-DDS has emerged as an essential platform for safe and effective tumor treatment.

* **Corresponding author Vikas Rana:** Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala- 147002 (Punjab), India; Tel: +91-9872023038; E-mail: vikas_pbi@rediffmail.com; vikas@pbi.ac.in

Priya Patel (Ed.)

Keywords: Active Targeting, Antibodies, Aptamers, Biological Ligands, Cancer, EPR Effect, Folic Acid, Human Epidermal Growth Factor Receptor, Leaky Vasculature, Multiple Drug Resistance, Nanoparticles, Nanostructures, Passive Targeting, Peptides, Proteins, Polysaccharides, Receptor-mediated Endocytosis, Reticuloendothelial System, Small Molecules, Targeted Drug Delivery System, Tumor Targeting.

INTRODUCTION

Worldwide, cancer is a big public health problem and the second leading cause of death in the United States. In 2020, there will be an estimated 1.8 million new cases of cancer diagnosed in the United States, and 606,520 people will die from cancer, with an overall of about 4950 new cancer cases and over 1600 deaths daily (www.cancer.org). An estimated 43% of lung, prostate, and colorectal cancer cases of all cancers are investigated in men, and an estimated 50% of lung, breast and colorectal cancer cases of all new cancers are investigated in women in 2020 (www.cancer.org, www.cancer.gov).

In modern medical practice, surgery, radiation therapy (RT), and chemotherapy are the chief treatment approaches used to treat cancer. Surgery is normally suggested when all cancer cells have been excised at an early stage of the disease and at a later stage with RT and chemotherapy to improve the quality of life [1 - 3]. In comparison to surgery, RT and chemotherapy are the most commonly used interventions as they are capable of killing a small portion of cancer cells with each treatment procedure. Many anticancer drugs are utilized primarily in chemotherapy for killing metabolically active cancer cells. Despite, improving the quality of patient life or prolonging it by using chemotherapeutic agents, they are also usually associated with serious systemic side effects due to a lack of cancer selectivity [3 - 7]. Similarly, RT also causes damage to healthy cells, tissues, and organs. Mucositis is one of the major adverse effects caused by chemotherapy and RT therapy. In addition, multiple drug resistance (MDR) is a major cause of treatment failure or reduction in therapeutic effect acquired during prolonged use of chemotherapeutic agents [8 - 12]. For the following reasons, rapid drug innovations have not had a significant clinical impact on cancer treatment: a) Many potent entities have very poor aqueous solubility, thereby exhibiting poor *in-vivo* bioavailability and pharmacokinetic performance. (b) Cytotoxic anticancer drugs typically lack cancer cell selectivity, thereby making them highly toxic to healthy cells; and (c) inappropriate biodistribution of many drugs following the intravenous route results in less therapeutic efficacy with significant side effects.

As many anticancer drugs have serious side effects, the use of ligand-based drug delivery systems (DDS) for addressing and delivering drugs to specific sites by recognizing their receptors or biomarkers (refer to Table **3**) overexpressed on tumor sites is very important. The receptors overexpressed on tumor cells to attain

nutrition for their hypermetabolism are usually different from normal cells or tissue [13]. To target these receptors, various conjugating ligands like proteins and polysaccharides, peptides, antibodies, aptamers, and small molecules have been attached to the surface of DDS or nanoparticles (NPs) to enhance the selective uptake of DDS by target cells. The DDS has a greater surface-to-volume ratio, which possibly increases the density of ligands over the surface for targeting and results in better stability and efficacy against tumor cells [14]. The definite interaction between receptors overexpressed on tumor cells and ligands conjugated to the DDS surface promotes the internalization of DDS by receptor-mediated endocytosis and endosomal-vascular transport (refer to Fig. **1**). The drug molecule either physically dissolved into the DDS or chemically attached by hydrophobic and electrostatic interactions. The human body's immune system, also known as an opsonin, stimulates the complement system and eliminates the DDS from blood circulation through the reticuloendothelial system (RES) [15]. The hydrophobic DDS can be more easily cleared from blood circulation than the hydrophilic DDS [16]. On the other hand, positively charged DDS can increase endocytosis but is identified by RES faster and cleared from blood circulation faster than neutral DDS [17]. Therefore, the coating of DDS with polyethylene glycol (a hydrophilic agent) is the prevalent approach used for increasing circulation time in the blood and reducing toxicity due to loaded drugs [18]. Further, the DDS in size range of 10-100 nm and targeting ligand can help to enhance endocytosis of particles by tumor cells, thereby enhancing their therapeutic response [19]. The internalization of DDS is important for the efficient delivery of fewer anti-cancer drugs, particularly in gene delivery [20]. Failure to sustain a sufficient concentration of anticancer drugs in the tumor site results in tumor cell regrowth that leads to drug resistance development. Drug resistance is the activity of membrane transporter proteins like P-glycoprotein, which throw anti-cancer drugs out of tumor cells and develop resistance to cancer therapy [21]. Active targeted DDS can overcome the above limitations and help to increase the concentration of drugs and their efficacy at the tumor site [22].

In this chapter, we will highlight some novel developments in targeted drug delivery for tumor treatment, including both preclinical and clinical data. We will also focus on the use of different nanoparticulate systems for promoting drug delivery through passive and active targeting within the field of tumor therapy. The pros and cons of different targeted systems are explained. In the end, conclusions, as well as future viewpoints on the active targeting of NPs for tumor chemotherapy, are discussed.

CHAPTER 6

Nanotechnology-Based Inhalation Approach for Lung Cancer

Priya Patel[1,*], **Mansi Faladia**[1] and **Mihir Raval**[2]

[1] *Department of Pharmaceutical Sciences, Saurashtra University, Rajkot-360005, Gujarat, India*

[2] *Department of Pharmaceutical Sciences, Sardar Patel University, Vallabh Vidyanagar-388 120, Gujarat, India*

Abstract: Ever since the success of producing inhalable insulin, drug delivery *via* pulmonary administration has been an intriguing way to treat chronic disorders. Pulmonary delivery system for nanotechnology is a relatively recent approach, especially when related to lung cancer therapy. The therapeutic ratio is increased by inhalation delivery, which delivers a high dose of the drug directly to the lungs without damaging other body organs. Despite extensive studies into targeted delivery and specific molecular inhibitors (gene delivery), cytotoxic drug delivery *via* inhalation is still considered a critical component of lung cancer treatment. Nanotechnology-based inhalation chemotherapy has been proven to be practical and more successful than conventional chemotherapy, with fewer adverse effects. Many nanocarriers have recently been studied for inhalation treatments of lung cancer, including liposomes, polymeric micelles, polymeric NPs, solid lipid NPs, and inorganic NPs. The potential for NPs-based local lung cancer targeting *via* inhalation, as well as the challenges that come with it, are explored here.

Keywords: Inhalable Approach, Lung Cancer, Nano Formulation.

INTRODUCTION

At present, lung cancer causes 23% of total cancer-related mortality worldwide, surpassing the combined mortality caused by breast, colon, and prostate cancer (Fig. **1**) [1 - 4]. Moreover, it is also recognized as cancer having the most intense fatality, with minimal survival rate. Lung cancer is the leading cause of cancer-related death worldwide due to late diagnosis and limited treatment [3, 4]. Lung cancer is a disease characterised by uncontrolled cell proliferation in lung tissues. This progression could lead to metastasis, or the invasion of nearby tissue and infiltration beyond the lungs. Lung carcinomas, which are formed from epithelial cells, account for the great majority of primary lung malignancies. The rapid cha-

[*] **Corresponding author Priya Patel:** Department of Pharmaceutical Sciences, Saurashtar University, Rajkot- 360005, Gujarat, India; Tel: +91 9825480989; E-mail: patelpriyav@gmail.com

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nges in lifestyle, urbanization, smoking habit and environmental degradation are all contributing towards the increase in patients with airway disease. Lung cancer is a heterogeneous disease that arises from genetic and epigenetic alterations in lung exposure [3, 5].

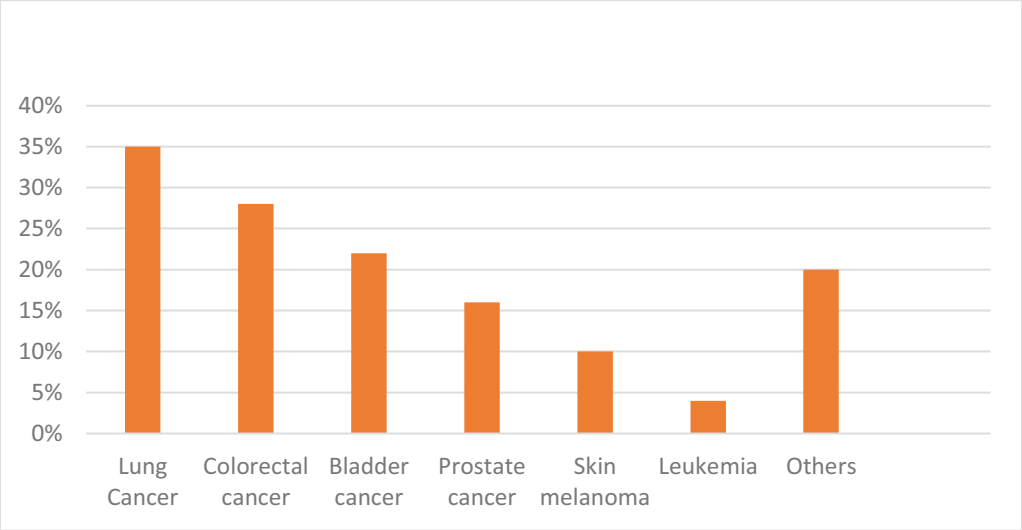

Fig. (1). Cancer occurrences.

Lung cancer is categorised into two types based on clinical and therapeutic characteristics: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (main and common form that accounts for 85 percent of cases) NSCLC). Squamous cell carcinoma (SCC), adenocarcinoma (ADC), and large cell carcinoma are the three types of NSCLC. SCLC commonly develops in the main bronchus, whereas SCC develops in the main stem lobar or segmental bronchi. On the periphery of the lungs, ADC and LCC appear [6 - 8]. Histologically, these NSCLC types are different from one another. It responds to chemotherapy; however, their reaction varies depending on which therapy is used. SCLC, on the other hand, appears seldom but exhibits rapid metastasis and aggressive growth, with an average survival time of only 4 months if untreated. As SCLC develops from neuroendocrine tumours, it contains neurosecretory vesicles and neurofilaments in its pathophysiology. Despite the fact that SCLC is a fairly aggressive cancer, it responds better to radiation and chemotherapy than NSCLC. Regardless of the many kinds of lung cancer, the failure of early detection and confirmation only at stage IV is the major reason for the poor survival rate, as it is in most other cases of cancer [1, 6, 8]. Long-term survival and enhanced quality of life for lung cancer patients are still unmet under conventional cancer treatments. The majority of chemotherapeutics come in

intravenous (iv) forms. Furthermore, some key chemotherapeutics used to treat lung malignancies are extremely lipophilic, requiring greater doses and surfactant-based solubilization to increase systemic drug availability. Drug bioavailability in the system isn't the only issue here; even at higher doses or with greater systemic availability, only a few medications are delivered to lung tumours [9, 10]. The bulk of chemotherapeutics acts on normal tissues due to their nontargeting nature, causing side effects. Local targeting in lung cancer with the potential for little systemic exposure can help to make chemotherapy safer and more patient-friendly. In this direction, medication delivery *via* inhalation holds tremendous promise for lung cancer treatment [10 - 12].

Lung cancer is difficult to diagnose early, and most lung tumours are progressed metastatic at the time of diagnosis. Depending on the stage of cancer, respectability, and overall performance, surgery, chemotherapy, and radiation are common treatment options for lung cancer [13]. The treatment regimen chosen is determined on the stage of cancer and the patient's health. As only a few numbers of chemotherapeutic medicines target lung tumour sites, even when given at high doses, systemic drug delivery is rarely successful [6, 13]. Chemotherapy is the first-line treatment for advanced lung cancer that involves the administration of chemotherapeutic medicines intravenously for systemic circulation. Most chemotherapy medications work by suppressing the growth of normal cells, making the patient exceedingly weak and perhaps dead. Improved medication delivery can help in the fight against cancer by delivering anticancer treatments locally to the tumour site in the lungs, reducing systemic drug exposure [14, 15]. The use of chemotherapeutic drugs is based on the principle of toxic compounds to inhibit the proliferation of cells growing at an abnormal rate. The combination of gemcitabine (an FDA-approved chemotherapeutic drug) and cisplatin has been widely utilised to treat patients with advanced or metastatic lung cancer as a first or second-line treatment. Furthermore, standard chemotherapeutic medicines, including paclitaxel, docetaxel, gemcitabine, and vinorelbine, are frequently used in conjunction with platinum-based medications to increase therapeutic index (*e.g.*, cisplatin). It should be mentioned, however, that the majority of chemotherapy medications include side effects such as pain, nerve damage, and skin allergic responses. Therefore, minimizing the side effects of chemotherapy drugs remains a challenge in the field of cancer chemotherapy [16 - 18].

Pharmaceutical nanotechnology has made significant progress in addressing the issues of drug delivery in cancer chemotherapeutics. Nanoparticles (NPs) have significant benefits over conventional delivery systems because they have extraordinary qualities such as small particle size, vast surface area, and the ability to change their surface properties [19]. Furthermore, it has been demonstrated that NP-based drug delivery systems ensure passive (size-based

CHAPTER 7

Mesoporous Based Drug Delivery: A Smart and Promising Approach for Prostate Cancer

Nasir Vadia[1,*] and **Priya Patel**[2]

[1] *Faculty of Pharmacy, Marwadi University, Rajkot-Morbi Highway, Rajkot-360003, Gujarat, India*

[2] *Department of Pharmaceutical Sciences, Saurashtra University, Rajkot-360005, Gujarat, India*

Abstract: Mesoporous silica has been gaining popularity as a drug delivery medium in recent years. Materials scientists have used these inorganic carriers successfully in other fields, including catalysis, purification, and adsorption. A major challenge in medicine is delivering drugs to defective cells or tumor cells in a way that has minimal toxic side effects. Due to the poor physicochemical and biological properties of a drug molecule like solubility, permeability, absorption and bioavailability, patients may have to take high doses of the drug to achieve the desired therapeutic effect. Various drug carriers are available in the pharmaceutical industry to help solve this problem. Biocompatible, chemically, and thermally stable nanoparticles, mesoporous silica nanoparticles (MSNs), are ideal for this application. During the last few years, research on the mesoporous-based delivery system has been studied vigorously. These materials act as drug carriers for the delivery of different therapeutic agents. This versatility is because they are used for the loading of small molecules and macromolecules such as proteins and siRNA. Mesoporous materials as a drug delivery system were discussed in this chapter. Specifically, it provides an overview of the synthesis, structural configurations, and their roles in loading and delivering therapeutic agents for the anticancer agents used in prostate cancer. The applications of these materials in prostate cancer for the detection, diagnosis, and treatment, were explored.

Keywords: Mesoporous Material, Nanoparticulate System, Prostate Cancer.

INTRODUCTION

Cancer is the leading cause of death in most developed and developing countries. The burden of cancer continues to rise globally, placing immense physical, emotional, and financial pressure on people, families, societies, and health systems. The prevailing health systems are less equipped to handle this burden in low- and middle-income nations, and significant numbers of cancer patients

* **Corresponding author Nasir Vadia:** Faculty of Pharmacy, Marwadi University, Rajkot-Morbi Highway, Rajkot-360003, Gujarat, India; E-mail: nasirvadia@rediff.com

Priya Patel (Ed.)

globally do not have access to prompt, quality diagnosis and care. Survival rates of many types of cancers are improving in countries where health systems are solid, thanks to affordable early detection, quality treatment and care for survivors. According to WHO, cancer is the first or second leading cause of death before 70 years of age in 112 out of 183 countries and ranks third or fourth in a further 23 countries (Fig. **1**) [1].

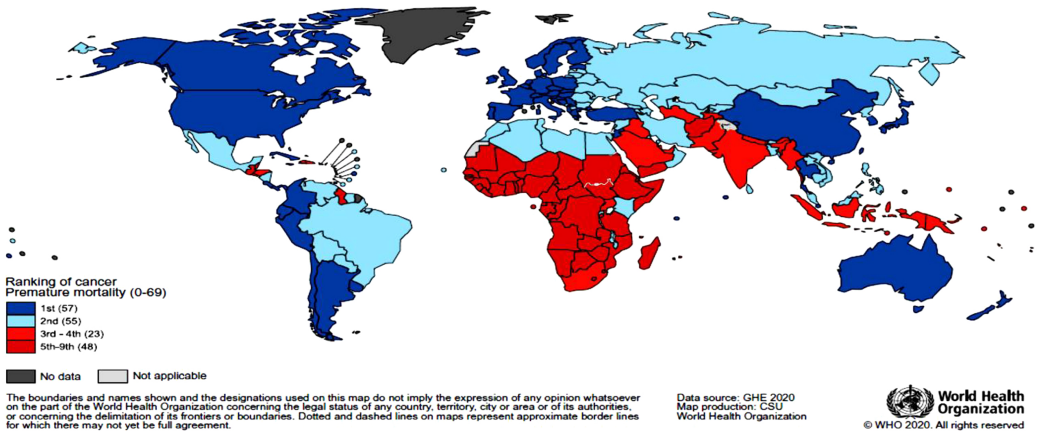

Fig. (1). National ranking of cancer as a cause of death at ages <70 years in 2019. The numbers of countries represented in each ranking group are included in the legend. Source: World Health Organization.

Cancer is the leading cause of death worldwide, with 9.6 million deaths estimated in 2018 [2]. According to the WHO report, the occurrence of most common cancers and the common causes of cancer are presented in Fig. (**2**) and Fig. (**3**), respectively. Cancer develops as normal cells turn into tumor cells in a multistage phase that usually progresses from a precancerous lesion to a malignant tumor. Cancer is caused by damage or mutations due to environmental or hereditary influences in the genetic material of the cells. Cancer-producing substances are known as carcinogens. According to the International Agency for Research on Cancer (IARC), a WHO cancer research committee maintains a classification of cancer-causing agents. Different carcinogens are presented in Fig. (**4**).

Another important factor in the development of cancer is age. The prevalence of cancer increases significantly with age; the accumulation of risk is compounded by the fact that cellular repair mechanisms become less successful as individuals age. Besides age, tobacco use, alcohol use, an unhealthy lifestyle, and physical inactivity are all significant cancer risk factors [3]. Some chronic infections are known to be cancer risk factors, particularly prevalent in low- and middle-income countries. In many cases, infections such as *Helicobacter pylori*, Human

papillomavirus (HPV), Hepatitis B virus, Hepatitis C virus, and Epstein-Barr virus were implicated in cancers diagnosed [4].

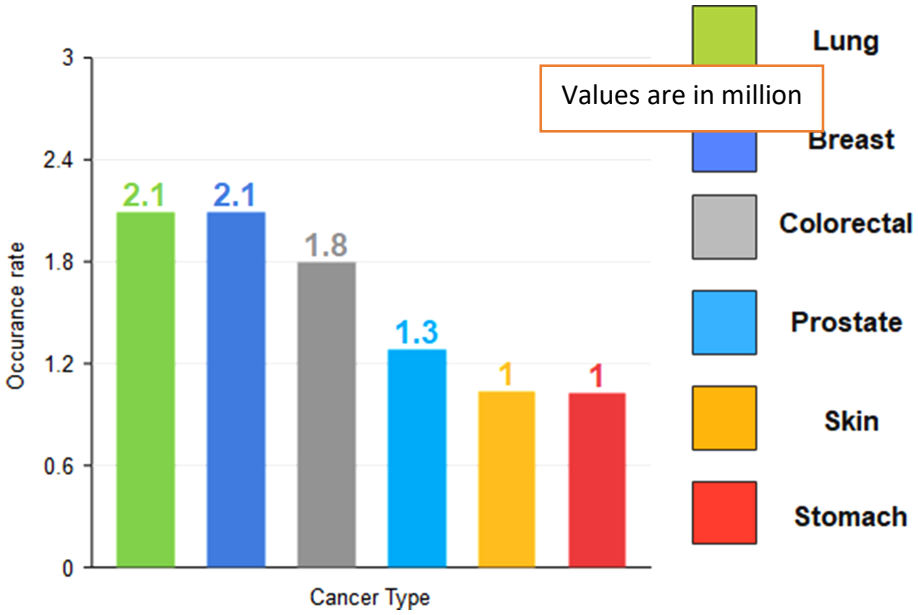

Fig. (2). The common occurrence rate of different types of cancer according to WHO.

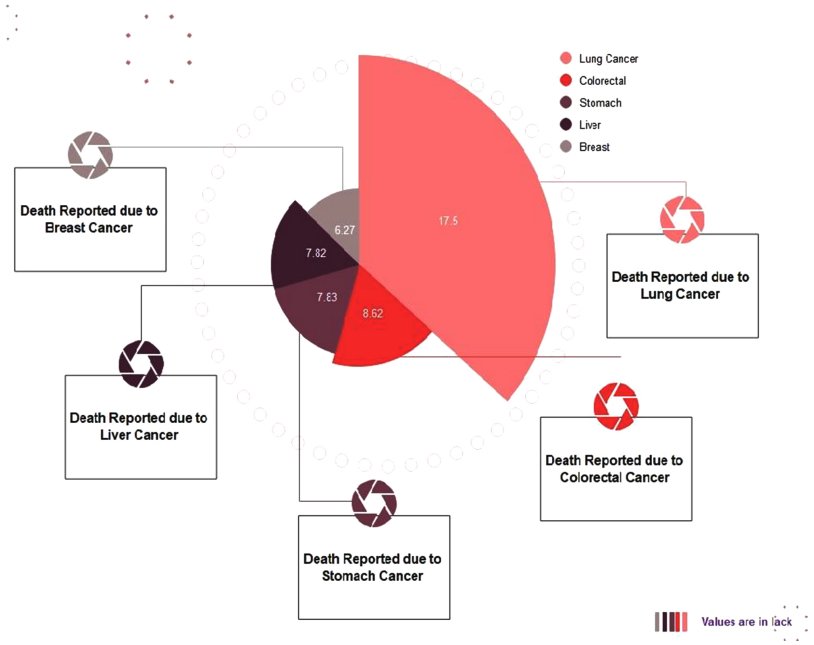

Fig. (3). Common causes of death due to different types of cancer according to WHO.

CHAPTER 8

Abridgment of Nanotechnology in Skin Cancer Treatment: Current Trends and Future Outlook

Chetna Modi[1,*], **Nikita Udhwnai**[1], **Pranav Shah**[2] and **Arjun Joshi**[1]

[1] *Department of Pharmaceutics, Anand Pharmacy College, Anand -388001, Gujarat, India*

[2] *Department of Pharmaceutics, Maliba Pharmacy College, Uka Tarsadia University, Bardoli-394620, India*

Abstract: This chapter focuses on skin cancer, which is represented by the accumulation of cells in one part of the skin. It enhances the form of the cells which line up along the membrane and separates the deep layer of the skin from the superficial layer. The recent skin cancer treatment includes surgical or excision biopsy, chemotherapy, targeted therapy, Mohs micrographic surgery, radiation therapy, photodynamic therapy, therapeutic hyperthermia, immunotherapy, *etc.* The drawback of skin cancer treatment with these therapies are skin irritation at the site of treatment and variation in the skin color or dark pigmentation after treatment, chances of cancer reoccurrence, longer treatment period and many more. Whereas, nanotechnology materials are used to deliver controlled and sustained drug dosage to skin cancer through the skin over a period of time without any skin irritation and other problems associated with recent treatments. The various kinds of nanotechnology products mentioned in this chapter offer numerous advantages for skin cancer, such as increased solubility, drug release in a sustained and controlled manner, better penetration through skin layers and precise site of action. This chapter discusses the various types and causes of skin cancer, current treatments and their limitations, as well as the role of nanotechnology and its products in skin cancer with its future outlook.

Keywords: Chemotherapy, Immunotherapy, Melanoma, Nanotechnology, Nanoparticles, Radiation Therapy, Skin Cancer.

INTRODUCTION TO CANCER

Cancer is the unrestrained growth of abnormal cells in the body. When normal cell growth control mechanism within the body stops functioning, cancer develops. Older cells do not dissolve; instead, they grow uncontrolled, developing newer abnormal cells. These newly formed cells form a mass of tissue, which is known as a tumor [1].

* **Corresponding author Chetna Modi:** Department of Pharmaceutics, Anand Pharmacy College, Anand -388001, Gujarat, India; E-mail: chetnamodi306@gmail.com

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It is reported that carcinogenic tumors have a malignant property, and they have the ability to extent into or invade nearby body tissues. These tumor cells develop and expand; some of the sarcoma cells, upon breaking off, travel to distant places within the body *via* blood or the lymph system and develop newer tumor cells far from the original tumor [2].

Skin cancer can be detected by using the ABCD method:

A = a growth with an Asymmetrical shape;

B = a growth with an irregular Border;

C = a growth with a dark or irregular Color;

D = a growth with a Diameter larger than a pencil eraser.

There are five main categories of cancer:

1. Carcinomas initiate in the skin or tissues that line the internal organs.

2. Melanomas develop in the bone, cartilage, fat, muscle or other connective tissues.

3. Leukemia originates in the blood and bone marrow.

4. Lymphomas start in the immune system.

5. Central nervous system cancers develop in the brain and spinal cord.

Cause of Cancer Development

Cancer is a kind of genetic disease caused by changes in gene sequences or its alteration that control the cells function, specially their growth and division [3].

Cancer is caused by genetic alterations that occur as cells proliferate as a result of damage to DNA produced by dangerous substances, such as tobacco components, cigarette smoke and UV rays from the sun [3, 4].

INTRODUCTION TO SKIN

Skin is composed of 2 layers, the epidermis and the dermis, which remain parted by an asymmetrical boundary (Fig. **1**). Cone-shaped dermal papillae cover the ascendant into the epidermis forming peg-like rete ridges of the epidermis [5].

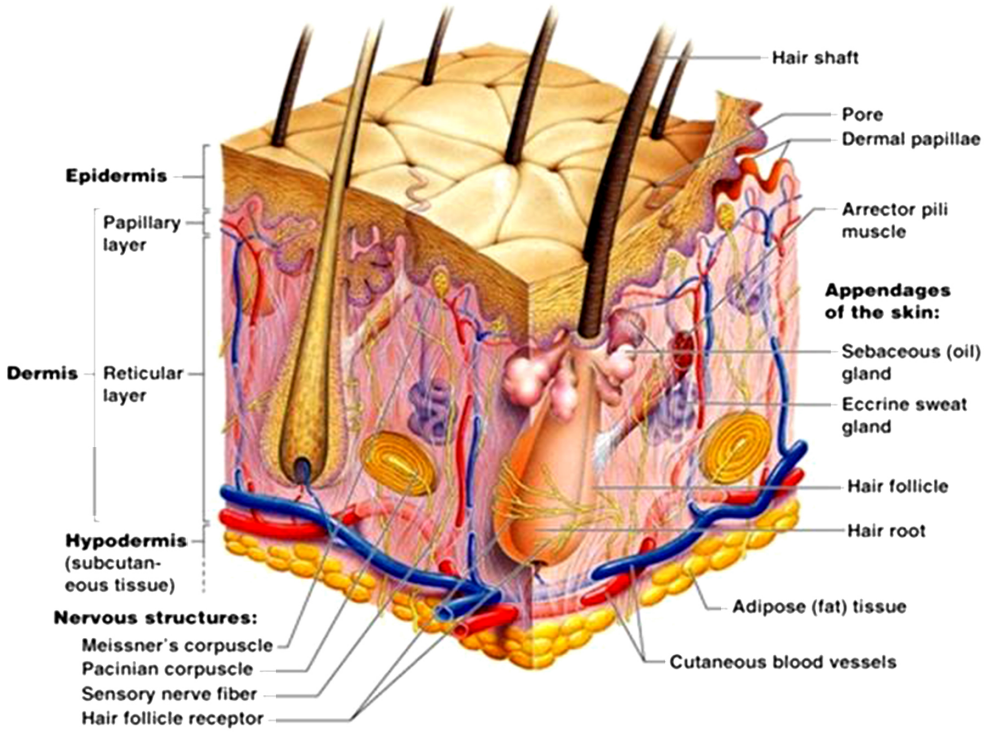

Fig. (1). Anatomy of Skin.

The epidermis is composed of 5 layers from base to the surface:

a. Basal cell layer (stratum germinatum)

b. Prickle cell layer (Stratum spinosum)

c. Granular cell layer (stratum granulosum)

d. Stratum lucidum.

e. Horny layer (Stratum corneum).

The dermis comprises 2 portions—the superficial pars papillaris or papillary dermis, and the deeper pars reticularis or reticular dermis.

INTRODUCTION TO SKIN CANCER

The greatest distortion in Western countries is skin cancer, and melanoma accounts for most of skin cancer-related deaths globally. Skin cancer is the uncontrolled proliferation of abnormal cells in the epidermis, the outermost layer

CHAPTER 9

Nanofibers Approach for Gastro Retentive Cancer

Anand J. Patel[1,*], **Bhavin R. Patel**[1] and **Pranav Shah**[2]

[1] *Tarsadia Institute of Chemical Science, Uka Tarsadia University, Bardoli-394620 Surat, Gujarat, India*

[2] *Department of Pharmaceutics, Maliba Pharmacy College, Uka Tarsadia University, Bardoli-394620, Surat, Gujarat, India*

Abstract: Gastric cancer is the world's second leading cause of cancer-related death. Due to inadequate drug release and limited residence time at the absorption site, traditional oral dose forms have poor/low bioavailability. GRDDS is particularly useful for increasing the bioavailability of medications with a narrow absorption window in the gastrointestinal tract and for treating local diseases. Polymeric nanofibers have sparked a lot of attention among the numerous nanomaterials used in high-tech applications because of their simplicity of production, controlled size/shape, and characteristics. Filtration, barrier fabrics, wipes, personal care, and biological and pharmaceutical applications have been intensively researched with polymeric nanofibers. Electrospun polymeric nanofibers have recently been demonstrated to be a promising approach for drug delivery systems. The nanofiber method allows for stomach-specific drug release for a more extended period and improves local drug action due to the drug's extended contact time with the gastric mucosa. As a result, nanofiber technology appears to be a promising strategy for gastric retention drug delivery systems.

Keywords: Bio-adhesive System, Drug Delivery System, Electrospun Technology, Floating System, Gastroretentive Cancer, GIT, GRDDS, Nanofibers, Non-floating System, Stomach, Swelling System.

INTRODUCTION

Both hereditary and environmental factors influence the development of cancer. Environmental factors, namely eating habits and social behavior, are responsible for about half of all cancer cases [1]. Tumor growth and progression is a multi-year, multi-stage procedure. Cancer usually develops after 20–30 years of exposure to carcinogenic chemicals. Modern medicine's capabilities allow for improved detection of most tumors in their advanced stages, where radical

* **Corresponding author Anand J. Patel:** Tarsadia Institute of Chemical Science, Uka Tarsadia University, Bardoli-394620 Surat, Gujarat, India; Tel: +919998579879; E-mail: anand.patel@utu.ac.in

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resection in 50% of cases allows for recovery [1]. Gastric cancer (GC) is a complex disease in which environmental and genetic factors can influence its progression [2]. According to current statistics, GC is the fourth most prominent cause of cancer deaths globally, with a median survival rate of fewer than 12 months for advanced-stage patients [3]. Gastric carcinoma is high-aggressive cancer with a heterogeneous nature that continues to be a global health issue [4]. As a result, alternative preventive measures, such as a healthy diet, early diagnosis, and effective follow-up therapies, decreased reported incidences [5]. GC is uncommon and unfamiliar in the young population (under 45), with only about 10% of individuals seeing disease progression [6 - 10].

One of the most difficult challenges for academics and industry is the development of novel medicine candidates [11]. Pharmaceutical companies are predicted to have spent 179 billion dollars on the research and development of new drugs in 2018 [12]. However, only about 11% of fresh candidates have a chance of making it to the job market [13]. The most typical failure occurs during phase II clinical trials when most medication candidates exhibit previously undiscovered harmful side effects or insufficient efficacy to cure the medical condition under investigation [14]. Still, medications that make it to the market are not without potential side effects; for example, anticancer chemotherapeutics are a source of concern for both therapists and patients due to their inherent toxicity. Although their efficacy and target selectivity have increased over time, serious side effects such as infections, vomiting, exhaustion, loss of taste, anemia, and immune system destruction remain [15]. Drug delivery systems, in general, are nanostructures that can be loaded with small molecules or macromolecules and employed as carriers for specific substances in the pharmacological administration process. They are currently one of the most promising problems in advancing biomedical research [16]. Such materials can transport a chemotherapeutic molecule to a specific location, boosting the drug concentration and delivering it in a regulated manner. Polymeric nanoparticles have been extensively described as drug delivery systems for use in, for example, the chemotherapeutic treatment of solid tumors, among many nanoformulations [17]. However, in recent years, polymeric nanofibers (NFs) have been reported as a scaffold capable of encapsulating anticancer medicines for biomedical research, including drug delivery and cancer treatments, in addition to colloidal structures [18, 19]. Electrospinning is a simple technique for producing NFs with high interconnected pores in the nano-scale range [20], as well as a large surface-are--to-volume ratio, high interfiber porosity, low mass transfer hindrance, flexible handling, adjustable morphology, and high mechanical strength, making NFs useful as therapeutic patches or mats for biomedical applications [21, 22]. Polymeric drug delivery systems have been the subject of the greatest research. Polymeric delivery vehicles have been developed using a variety of conventional

and custom-designed polymers [23]. The creation of new ways for drug delivery systems became a new promising technique in the pharmaceutical sector as nanotechnologies, such as nanoparticles, nanofibers, nanogels, micelles and microspheres, were discovered [24]. Furthermore, a wide range of polymers is available to fabricate nanofibers. By using passive or active targeting strategies based on the final formulation, nanocarriers can be employed to wrap and distribute medications that are too poisonous, insoluble, rapidly removed, or unstable as free molecules [25, 26]. Loading active medicinal components using the electrospinning technology, which produces ultra-fine fibers (from micro- to nanometers in diameter) with controlled surface shape, is an alternate option for various release forms. These fibers are made by applying a high electrical field to a desirable polymer solution or by melting the polymer and exposing it to the electrical field if the polymer does not have a good solvent. When the diameters of polymer fiber materials are reduced to micrometers or nanometers, interesting properties emerge, such as a higher surface area to volume ratio, flexibility in surface functionalities, and superior mechanical performance (*e.g.*, stiffness and traction resistance) when compared to any other known form of the material. Polymer nanofibers are ideal options for various biomedical applications due to their remarkable characteristics [27, 28]. A wide range of medications with various bioactivities, such as anti-inflammatory, anti-microbial, anticancer, cardiovascular, miscellaneous, anti-histamine, gastrointestinal, palliative, and contraceptive treatments, have been developed as a result of these amazing nanofibers features. As well as the polymers used for this application such as poly(vinyl alcohol) (PVAL), poly(ethylene oxide) (PEO), poly(-caprolactone) (PCL), chitosan (CHS), poly(acrylic acid) (PAA), ethyl cellulose (EC), cellulose acetate (CA), hydroxypropylmethylcellulose (HPMC), poly(L- lactic acid) (PLLA), poly(lactic-co-glycolic acid) (PLGA), poly(acrylonitrile) (PAN), cellulose acetate phthalate (CAP), and poly(urethane) (PU), among others, unfolding the advantages of electrospun polymeric nanofibers over other drug delivery systems. In addition, focused *in-situ* application of nanofibrous scaffolds could reduce the drawbacks of systemic perfusion with free drugs or alternative drug delivery systems while increasing drug action pharmaceutically through a regulated and sustained release directly at the site of action [29].

In recent decades, there has been a surge in interest in developing innovative gastro-retentive drug delivery systems (GRDDS) [30, 31]. GRDDS are particularly useful for medications with a small absorption window, are readily absorbed from the gastrointestinal tract (G.I.T.), have short half-lives, and are intended for local application [32]. In these circumstances, administering a traditional dosage form may necessitate regular dosing to obtain the desired therapeutic effect. To get over this constraint, oral sustained controlled-release formulations are being developed in an attempt to gently release the medicine into

CHAPTER 10

Regulatory Aspects of Nanomaterials: Current and Future Perspective

Mihir Raval[1,*], **Pratibha Chavda**[2] and **Priya Patel**[2]

[1] *Department of Pharmaceutical Sciences, Sardar Patel University, Vallabh Vidyanagar-388 120, Gujarat, India*

[2] *Department of Pharmaceutical Sciences, Saurashtra University, Rajkot – 360005, Gujarat, India*

Abstract: Nanotechnology and its applications have been a rapidly growing area of research in the previous two decades. In the domain of pharmaceutical research, nanotechnology is applied in the study and preparation of nano-size range materials ranging from 1-100nm. Nanoparticulate medications or nano drug delivery systems are not a novel concept, but they are a rapidly evolving nanoscience. In nanomedicine, nanoscale materials are used to develop diagnostic tools or to deliver active substances to a particular place in a consistent and controlled manner. Nanoparticles have groveled in many different forms, including liposomes, niosomes, solid lipid nanoparticles, emulsions, suspension nanocrystals, micelles, and dendrimers. When compared to pure drugs or other conventional formulations, these all have improved medication efficacy or therapeutic effect. Nanoparticles are being employed in a variety of fields, including cosmetics. However, as nanotechnology progressed, numerous controversies arise concerning nanoparticles. Consumer safety, as well as environmental repercussions, must be regulated. Nanotechnology has life-changing applications, yet nanoparticle regulation has been inconsistent and insufficient. Failure in biotechnology regulation in recent years has resulted in several negative consequences for the environment and human health. This article aims to raise knowledge about the importance of regulatory frameworks for nanotechnology and nanoparticles.

Keywords: Challenges, Nanotechnology, Regulatory Aspects.

INTRODUCTION

Nanotechnology is defined as the utilization of materials with dimensions in the nanoscale range. This extremely narrow range has various applications, including electronics, sunscreens, cosmetics, energy storage, and drug delivery [1]. When these particles are Nanoscale, they often have uniqueand desirable characteristics, such as chemical, physical, and biological capabilities, which may make them

* **Corresponding author Mihir Raval:** Department of Pharmaceutical Sciences, Sardar Patel University, Vallabh Vidyanagar-388 120, Gujarat, India; E-mail: rmihir@yahoo.com

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more useful than their larger counterparts. Nano-scale drugs can be particularly advantageous because many biologically significant molecules, such as water, antibodies, proteins, carbohydrates, enzymes, hemoglobin, and receptors, all fall within this range [1, 2] . Despite this, expectations have not lived up to the initial excitement, according to most experts in the field, this is the fact that nano medicine is still in its infancy, and a lack of clarity on regulatory difficulties for clinical use is preventing its implementation [1 - 4]. Even though we know little about the pharmacokinetics, pharmacodynamics and toxicity of many nanomaterials in humans, there are many potential benefits to employing this technology. Nanomedicine and its implications for the pharmaceutical industry continue to raise interest; however, regulatory advice in this sector is urgently needed to provide legal certainty to producers, legislators, healthcare professionals, and the general public [2, 3].

Potential Benefits Of Nanomaterials

Nanotechnology is a new and fast-developing subject that combines biological and pharmaceutical sciences to generate nanomedicine. Nano-pharmaceuticals, nano-imaging agents, and theranostics are all examples of nano medicine [5]. Compared to conventional drugs, nano medicine formulations can provide many physical and biological benefits, including improved solubility and pharmacokinetics, higher efficacy, reduced toxicity, and increased tissue selectivity [6]. The FDA considers nanotechnology to be present in the products it regulates if they contain or are made with nanoparticles ranging in size from 1 to 100 nanometers (nm), which, due to their small size and large surface area, demonstrate significant variations from bulk materials. Nanoparticles can alter a drug formulation's biochemical, electrical, magnetic, and/or optical properties, allowing it to be used for therapeutic purposes [7]. Liposomes, polymers, micelles, nanocrystals, metal oxides and other inorganic materials, and proteins are now employed in nano drug formulations. The particle shape, size, and surface chemistry of NPs are significant in determining important Pharmacokinetic criteria, such as adsorption, cellular uptake, accumulation and bio-distribution patterns, and clearance mechanisms [7]. When formulating nanodrugs, diverse strategies can be applied to improve drug efficacy. These include Nanoparticles that can entrap drug molecules to protect them from physiologically hostile environments; and use surface conjugation to target drugs to specific tissues, allowing for higher therapeutic levels at a target site even with the use of lower doses. Nanomaterials also have immunomodulatory effects that might potentially promote or influence the adaptive immune response [6 - 8]. Polymeric NPs, liposomes, nanoemulsions, and virus-like particles can enter antigen-presenting cells. As nano drugs may be tailored to give timed, targeted signals to enhance a coordinated immune response against specific cells, they may help improve the

efficacy of cancer immunotherapies. For the treatment of cancer, many nano drugs are being developed [8]. In most cases, the NPs utilized in these formulations either target a tumor site passively or actively, or they use a combination of both modes. The inclusion of pharmaceuticals into long-circulating NPs remain active for an extended period, since nano-pharmaceutical formulations can assist in cancer treatment [9]. Consequently, tumor sites are exposed to the drugs for a longer period due to the slow rate of drug release from the NP and the retention of the drug-loaded NPs in the vascular compartment. Potential Safety Benefits, the enhanced drug accumulation in diseased tissue may allow the nanoformulations with the effective dose of a drug as well as diminishing side effects. Better accumulation, and tailored release, may allow dose reduction and decrease side effects [9, 10]. The FDA approved the first nano drugs based on their lower toxicity when compared to their conventional formulation counterparts. Nano-formulations can also help manage the dose-limiting toxicities associated with conventional chemotherapeutic agents. For parenteral administration, they frequently require toxic solubilizing agents, that's why these medications frequently require dose reduction to minimize systemic toxicity, reducing efficacy [11]. Nano formulation is seen as a feasible solution to the challenges associated with poorly water-soluble drugs, and there has been a long interest in developing delivery systems for these therapies that do not require harmful solubilizing chemicals. For these reasons, nanoformulations of many chemotherapies have been approved, and more are in clinical development [9 - 11]

Potential Hazardousness Of Nanomaterials

Although handling nano- and bulk-sized materials as the same is harmful, the majority of nanoparticles are created through synthesis and high-scale novel procedures, which is not only harmful but also costly. Although nanoparticles like titanium dioxide are commonly used as food preservatives and may not be poisonous, multiple studies have proven that their nanoscale size makes them dangerous [11]. Nano-sized titanium dioxide causes significant growth retardation, death, and reproductive abnormalities in daphnia, according to experiments. Nano-sized Titanium Dioxide has been shown in some studies to damage the lung wall and produce pulmonary tumors when inhaled. Furthermore, Titanium Dioxide particles could be harmful to the environment [12]. Bacillus licheniformis, a common soil bacterium, has cell membranes damaged by titanium dioxide nanoparticles due to oxidative stress [10]. Other nanoparticles, such as copper and zinc nanoparticles, can disrupt DNA in plants and stop root elongation, which is essential for plant survival. As a result, criteria must be established to determine, measure, and control the safety of nanoparticles as needed [13].

CHAPTER 11

Recent Development and Advancement in Microneedle-Assisted Drug Delivery System Used in the Treatment of Cancer

Vaishali Thakkar[1,*] and **Saloni Dalwadi**[1]

[1] *Department of Pharmaceutics, Anand Pharmacy College, Anand, 388001, Gujarat, India*

Abstract: Cancer is one of the most common and distressing diseases. Cancer-related mortality and prevalence have both grown in the last 50 years. Due to its intricacy and progressive nature, cancer remains one of the most debilitating diseases in humans, and clinical care for this lethal disease remains a challenge in the twenty-first century. New and better cancer medicines are constantly needed. Due to the rising global incidence of cancer, the development of novel alternatives to traditional medicines is unavoidable to overcome constraints, such as limited efficacy, comorbidities and high cost. Microneedle arrays (MNs) have just been introduced as an innovative, low-cost, and minimally invasive technique. MNs can safely and precisely deliver micromolecular and macromolecular pharmaceuticals, as well as nanoparticles (NPs), to tumor tissue. However, only a few lipophilic pharmacological compounds with low molecular weight and a rational Log P value were able to pass the skin barrier. Microneedles (MNs) can circumvent these constraints by piercing the body's outermost skin layer and delivering a variety of medications into the dermal layer. MN patches have been made with a variety of materials and application methods. Recently, three-dimensional (3D) printing "A touch button approach" gives the prototyping and manufacturing methods the flexibility to produce the MN patches in a one-step manner with high levels of shape complexity and duplicability.

Keywords: Additive Manufacturing, Anticancer Therapy, Cancer, Dosage Form, Evaluation Parameters, Structure of Skin, Fabrication, Material, Method, Microneedle Arrays, Microneedle Drug Delivery System, Novel Drug Delivery, On-demand Manufacturing, Three-dimensional Technology, Transdermal Drug Delivery System, Transdermal Enhancement Techniques, Patient-centric Formulation, Personalized Medicine, Pharmaceutical Printing, Target Therapy.

[*] **Corresponding author Vaishali Thakkar:** Department of Pharmaceutics, Anand Pharmacy College, Anand, 388001, Gujarat, India; E-mail: vtthakkar@rediffmail.com

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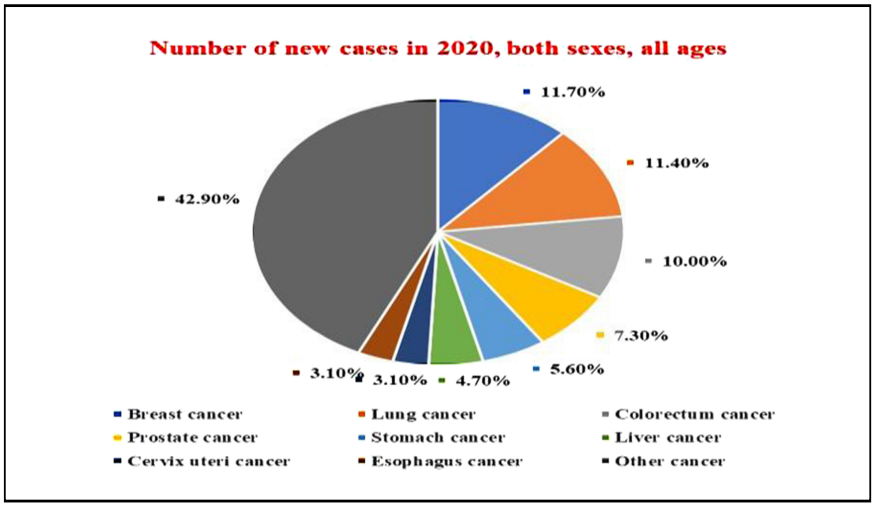
INTRODUCTION

Cancer is a group of diseases characterized by abnormal cell proliferation that can infiltrate or spread to other parts of the body [1]. In the cancer patient, old or damaged cells survive when they should die, and new cells form when they are not needed as cells become increasingly abnormal.These additional cells can divide indefinitely, resulting in tumors that do not spread to other organs and do not involve blood cancer [2]. Physical carcinogens and physical inactivity, such as ultraviolet and ionizing radiation; chemical carcinogens, such as tobacco smoke components, asbestos, aflatoxin (a food contaminant), and arsenic (a drinking water contaminant), air pollution, and various occupational chemical exposures; and biological carcinogens, such as infections from certain viruses, can all contribute to the rising cancer burden [3]. Tobacco use, alcohol usage, an unhealthy diet, excess body weight, aging, population expansion, genetic factors, and other non-communicable diseases are all other potential cancer risk factors [4, 5]. 30 to 50% of malignancies can be avoided by avoiding risk factors and using evidence-based preventative measures. Early identification of cancer, as well as appropriate treatment and care for people who have cancer, can help to lower the cancer burden. Many cancers have a good possibility of being cured if caught early and treated properly.

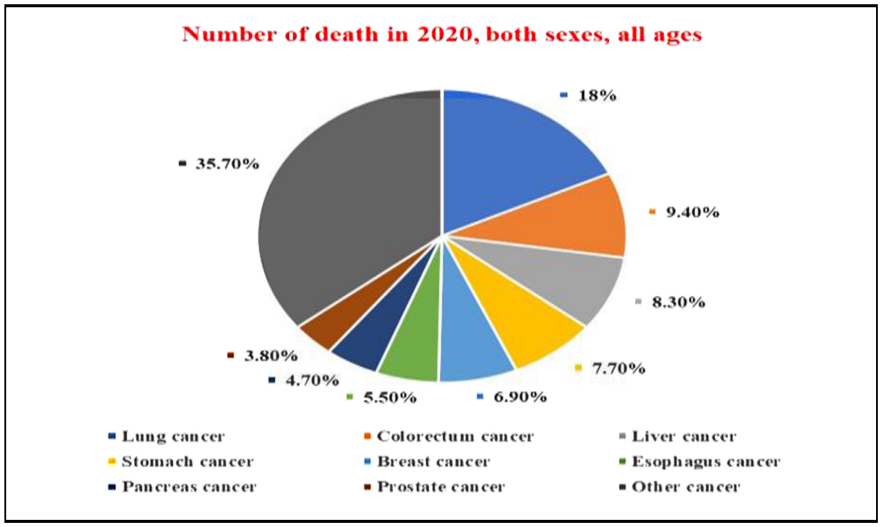
Cancer has become one of the leading causes of death around the world. There were 18.1 million new cancer cases and 9.5 million cancer-related deaths globally in 2018 [4]. By 2040, the annual number of new cancer cases are predicted to reach 29.5 million, with 16.4 million cancer-related deaths [6]. Cancer rates are generally highest in countries with the highest life expectancy, educational attainment, and way of living. However, for some cancers, such as cervical cancer, the opposite is true, and the incidence rate is greater in countries with low population growth [6]. Globally, new cancer cases and death due to cancer have been shown in Fig. (**1A**) and (**1B**), respectively, in all ages and all sexes. For the year 2020, the expected incidence of cancer patients in India was 679,421 (94.1 per 100,000) for males and 712,758 (103.6 per 100,000) for females. Cancer affects one in every 68 men (lung cancer), one in every 29 women (breast cancer), and one in every nine Indians. Males' cancers (lung, mouth, prostate, tongue, and stomach) accounted for 50% of all cancers in 2020, while female cancers (breast, cervix uteri, ovary, corpus uteri, and lung) accounted for 53% of all cancers [7].

Stages of Cancer

Stages of cancer can be classified in two ways which are mentioned here: Number system and TNM system.



(A)



(B)

Fig. (1). (**A**) Number of new cases of cancer in 2020, both sexes, all ages (**B**) Number of death due to cancer in 2020, both sexes, all ages.

1. Number system

- Cancer in Stage 1 is generally small and localized within the body organ.
- Stage 2 tumors are frequently larger than Stage 1 tumors, but the malignancy has

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Priya Patel

Dr. Priya Patel is working as an Assistant Professor in the Department of Pharmaceutical Sciences, Saurashtra University, Rajkot. She has more than 11 years of Teaching & Research Experience. She obtained B.Pharm and M.Pharm degrees from Anand Pharmacy College, Anand, Gujarat under Sardar Patel University, V.V.Nagar and Gujarat Technological University, Ahmedabad respectively. Her research interests include Nanoparticulate Drug Delivery System, Pulmonary targeted Multiparticulate drug delivery system, Cancer Nanotechnology, and Novel drug delivery system. She has guided 26 master's students for their research work and has published more than 30 papers in various International and National Journals. Besides, she has 04 books and 05 book chapters to her credit. She has delivered 10 Invited talks in various Seminars, Conferences and workshops. She served as a reviewer in many reputed journals. She received a Young Researcher award from the 23rd International Conference on Nanomaterials and Nanotechnology held in London, UK. She has received a Research grant worth Rs 11 Lakh from GUJCOST, SSIP, Saurashtra University, Rajkot. She has filed 3 final patents on the area of nanoparticulate drug delivery system and novel drug delivery system.