ADVANCEMENTS IN CANCER TREATMENT: A COMPREHENSIVE OVERVIEW OF DRUG DELIVERY METHODS

Abstract

Even though conventional chemotherapy has shown some degree of success, it has a number of important drawbacks. These include poor therapeutic indices and adverse effects, excessive dosage requirements, multiple drug resistance emerging, and non-specific targeting. The main goal of improving drug delivery systems is to efficiently address these drug administration difficulties and deliver drugs to the desired sites of therapeutic efficacy while minimising unfavourable side effects. This chapter attempts to investigate the many materials used as chemotherapeutic agent carriers, concentrating on their structural characteristics that improve the therapeutic efficacy of the medications. With a focus on the difficulties associated with treating cancer, recent scientific developments in the field of chemotherapy will also be covered.

Keywords: Advancements, cancer treatment, comprehensive, drug delivery methods

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I. INTRODUCTION

In modern medicine, drug delivery systems play a crucial role in revolutionizing the way medications are administered and enhancing the effectiveness of treatments for various medical conditions. These systems offer a range of benefits, from targeted drug delivery to improved patient compliance and controlled release of medications. By optimizing drug delivery, these advancements have paved the way for personalized medicine, tailoring treatments to individual patient needs and genetic profiles. Pharmacokinetics and pharmacodynamics are essential concepts in drug delivery, helping to understand how the body affects drugs and how drugs exert their effects on the body. Drug absorption, distribution, metabolism, and excretion are key aspects studied in pharmacokinetics to determine the appropriate drug dosage and dosing intervals for optimal therapeutic outcomes. Various routes of drug administration are utilized in medical practice, each offering unique advantages and implications. Oral, parenteral, topical, transdermal, and inhalation routes are some of the common methods used for drug delivery, each suited to specific medical conditions and patient needs. In the realm of cancer treatment, drug delivery systems have emerged as powerful tools to improve the efficacy of anticancer agents while minimizing side effects on healthy tissues.

Among the groundbreaking drug delivery methods are Radioactive Drug Delivery, Inhalable Drug Delivery, Gold Nanoparticle Drug Delivery, dendrimer drug delivery, folate receptor-targeted drug delivery, hyperthermia drug delivery, photodynamic therapy (PDT), ultrasound-mediated drug delivery, intra-arterial drug delivery, intralesional drug delivery, intrathecal drug delivery, nanorobots for drug delivery, magnetic drug delivery, viral vectors, drug-eluting devices, targeted therapies, antibody-drug conjugates (ADCs), polymer-based drug delivery, liposomes, and nanoparticle-based drug delivery.

Each of these methods harnesses cutting-edge technologies and scientific advancements to optimize drug delivery, making it more precise, effective, and patient-friendly. By understanding and utilizing the unique characteristics of these approaches, medical researchers and practitioners continue to pave the way for a new era of cancer treatment that holds the promise of improved therapeutic outcomes and a better quality of life for cancer patients.

In this comprehensive overview, we explore various drug delivery methods used in cancer treatment, including nanorobots, targeted therapies, antibody-drug conjugates, and more. Each approach holds the potential to revolutionize cancer treatment, offering new avenues for precision medicine and improved patient care.

II. SIGNIFICANCE OF DRUG DELIVERY SYSTEMS IN MODERN MEDICINE

Inmodern medicine, drug delivery systems have become indispensable due to their numerous advantages. One of the key benefits is enhanced therapeutic efficacy through targeted drug delivery, which enables medications to be directed to specific sites in the body, maximizing their effectiveness while minimizing adverse effects on healthy tissues. Additionally, these systems promote improved patient compliance by offering convenient and patient-friendly methods of drug administration, such as extended-release formulations, which reduce dosing frequency and enhance treatment adherence. Controlled-release drug

delivery systems further contribute to patient welfare by providing sustained therapeutic effects, decreasing the need for frequent dosing and maintaining stable drug levels. They also play a crucial role in protecting labile drugs from degradation, ensuring drug stability and activity until they reach their intended targets. Moreover, drug delivery advancements have ushered in the era of personalized medicine, allowing treatments to be tailored to individual patient needs and genetic profiles, thus optimizing therapeutic outcomes and providing more patient-centric healthcare solutions. These multifaceted advantages collectively underscore the significance of drug delivery systems in modern medical practice [1,2].

III. PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics form the foundation of drug delivery, governing how the body processes medications and how they interact with their targets. Pharmacokinetics involves drug absorption, distribution, metabolism, and excretion (ADME), guiding optimal dosing intervals and dosages for desired therapeutic effects. Drug absorption depends on factors like formulation, route of administration, and physicochemical properties. Following absorption, drugs are distributed throughout the body, influenced by blood flow, tissue binding, and solubility. Drug metabolism, primarily occurring in the liver, transforms drugs into metabolites, affecting their activity (Fig.1). Subsequently, drug excretion eliminates drugs and metabolites from the body, often through urine, feces, or breath. [3,4].

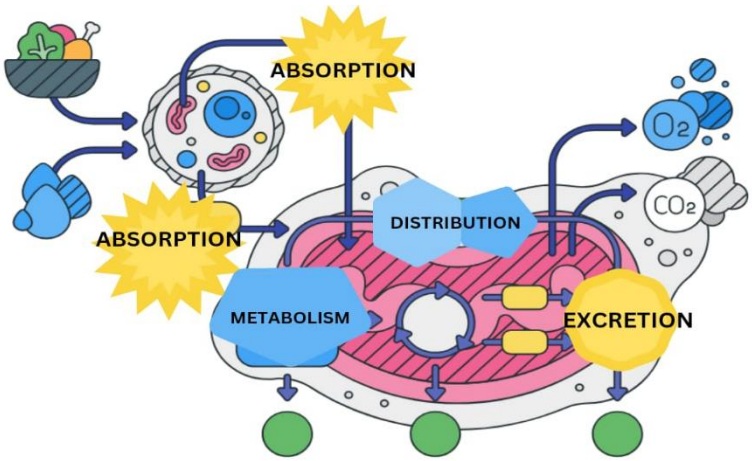

Figure 1: Pharmacokinetics of Drug Core

IV. ROUTES OF DRUG ADMINISTRATION

Various routes of drug administration including oral, parenteral, topical, transdermal, and inhalation routes, each of which has specific benefits and disadvantages. Effective medication delivery requires a variety of drug administration routes, each of which has its own benefits and drawbacks. The most popular and practical method of administration is taking pills, liquids, or tablets of medication orally. However, drug absorption can be influenced by factors such as gastrointestinal pH, enzymatic activity, and first-pass metabolism in the liver, affecting bioavailability. On the other hand, parenteral routes, which

include intravenous, intramuscular, and subcutaneous injections, deliver drugs directly into the body, bypassing the gastrointestinal tract and ensuring rapid absorption. This route is particularly useful for patients who cannot take medications orally or require immediate effects. Topical administration involves applying medications directly to the skin or mucous membranes, providing localized effects and minimizing systemic side effects. Transdermal drug delivery, through patches applied to the skin, offers the advantage of controlled and sustained drug release into the bloodstream over an extended period, making it suitable for drugs with poor oral bioavailability. Inhalation route, on the other hand, delivers drugs directly to the respiratory system, which is highly effective for treating respiratory conditions, and allows rapid absorption through the extensive capillary network in the lungs Each of these drug administration routes offers a valuable contribution to the arsenal of drug delivery methods, catering to diverse patient needs and therapeutic objectives [5].

V. INFLUENTIAL FACTORS IN DRUG DELIVERY AND BIOAVAILABILITY

Several factors exert significant influence on drug delivery and its bioavailability. One key determinant is the drug formulation, encompassing solubility, particle size, and stability. A well-designed formulation can enhance drug absorption and bioavailability, while poorly formulated drugs may have limited efficacy. Physicochemical properties of drugs, such as solubility, ionization, molecular weight, and lipophilicity, significantly influence drug absorption and distribution within the body. These characteristics affect how drugs interact with biological membranes and barriers, influencing their overall pharmacokinetic behavior. Moreover, gastrointestinal factors like pH and gastric emptying rate impact drug solubility, dissolution and absorption. Gastric emptying rate influences the time it takes for a drug to leave the stomach and enter the intestine for further absorption. Drug-drug interactions present another critical consideration, as concomitant administration of multiple medications can affect each drug's absorption, metabolism and excretion altering the drug bioavailability resulting in unexpected therapeutic outcomes. First-pass metabolism is a crucial aspect of drug delivery, especially for orally administered drugs**.** Before entering the systemic circulation, medications that are absorbed through the gastrointestinal tract first pass via the liver. During this first pass, the liver may metabolise a sizable percentage of the drug, lowering its bioavailability and diminishing its therapeutic potential.. Drug transporters located in various tissues govern the movement of drugs across cell membranes, affecting their overall fate in the body. Furthermore, the presence of specific disease states or medical conditions can significantly impact drug absorption, metabolism, and excretion, leading to alterations in drug bioavailability. Understanding these various factors is crucial in optimizing drug delivery strategies and designing effective therapeutic regimens [6]

VI. DRUG DELIVERY METHODS USED IN CANCER TREATMENT

Drug delivery methods used in cancer treatment refer to the various techniques and approaches employed to administer therapeutic drugs specifically to cancerous cells or tumors in a targeted and efficient manner. The primary goal of these methods is to enhance the drug's efficacy while minimizing damage to healthy tissues, reducing side effects, and improving overall patient outcomes. There are several drug delivery methods used in cancer treatment. (Figure 2)

1. **Radioactive Drug Delivery:** Radioactive drug delivery, also referred to as radiopharmaceutical drug delivery, is a specialized method for delivering targeted radiation therapy for the treatment of various diseases, including cancer. Radioactive isotopes are incorporated into pharmaceutical agents or carriers. This approach aims to deliver radiation precisely to the tumour location while minimizing damage to nearby healthy tissues, combining the therapeutic advantages of radiation treatment with the accuracy of targeted medication administration [8]. For instance, SIR-Spheres® (Yttrium-90 microspheres) is a type of selective internal radiation therapy (SIRT) used to treat colorectal cancer that has progressed to the liver and liver cancer (hepatocellular carcinoma) [9].

2. **Inhalable Drug Delivery:** Inhalable drug delivery systems typically involve the use of inhalers or nebulizers. Inhalers are portable medical devices that disperse a specific amount of medication into the lungs as an aerosol or fine mist. Nebulizers, on the other hand, are tools that turn liquid prescription drugs into a fine mist, enabling patients to inhale the drug more gradually over a period of time. For respiratory diseases, inhalable drug delivery can improve patients' overall quality of life by providing quick relief of symptoms and allowing them to better manage their condition. Additionally, inhalable drug delivery has also been explored for systemic drug delivery, where medications are delivered through the lungs and absorbed into the bloodstream for treating conditions beyond the respiratory system [10]. Example: Alecensa®(TABLE 1) (Alectinib)(Fig 3) is an oral medication for non-small cell lung cancer that is ALK positive. It comes in the form of capsules for oral administration [11].

3. **Gold Nanoparticle Drug Delivery:** Gold nanoparticle drug delivery is an innovative approach that utilizes gold nanoparticles as carriers to deliver therapeutic agents, such as drugs or biomolecules, to specific targets in the body. Gold nanoparticles are intriguing prospects for drug delivery applications due to their tiny size, biocompatibility, and capacity to be functionalized with diverse molecules. In this drug delivery system, drugs or therapeutic agents are attached or encapsulated onto the surface of gold nanoparticles. The functionalization of gold nanoparticles allows for specific targeting of the drug to certain cells or tissues, enhancing the drug's effectiveness and reducing potential side effects on healthy tissues. Gold nanoparticle drug delivery has been explored in various medical fields, including cancer treatment, Because of the enhanced permeability and retention effects (EPR effect), the nanoparticles can aggregate preferentially in tumour tissues. This passive targeting allows for improved drug delivery to the tumor site, increasing the drug concentration in cancer cells and minimizing damage to surrounding healthy tissues. Additionally, gold nanoparticles have unique optical properties that can be utilized for image-guided drug delivery and therapy. They can be combined with other imaging agents to monitor drug distribution and efficacy in real-time, providing valuable feedback for personalized treatment strategies [12]. Example: CYT-6091 (AuroShell™) is a gold nanoparticle-based drug used for targeting solid tumors, and it is currently being studied in clinical trials [13].

4. **Dendrimer Drug Delivery:** There are two ways to use dendrimers for drug delivery: formulation and nanoconstruction. pharmaceuticals are covalently bonded on dendrimers in the nanoconstruct approach, whereas in the formulation approach, pharmaceuticals are physically entrapped in a dendrimer utilising non-covalent interactions. It is possible to

construct dendrimer platforms to attach imaging molecules and targeting ligands to create nanodevices, which could lead to the development of next-generation nanodevices. [14]. Example: A dendrimer-based drug delivery system called Genexol-PM® (TABLE 1) (Paclitaxel-loaded Polymeric Micelle) (Fig 3) is used to treat breast cancer and other solid tumours. [15].

5. **Folate Receptor-Targeted Drug Delivery**: More than 90% of ovarian carcinomas have an overexpression of the folate receptor, which is a highly selective tumour marker. For the targeted delivery of medications to tumour cells that express the folate receptor, two broad approaches have been developed: coupling to a monoclonal antibody against the receptor and coupling to folic acid, a high affinity ligand [16]. Example: A medicine called Vynfinit® (Vintafolide) (Fig. 3) that targets the folate receptor is used with the chemotherapy agent docetaxel to treat several advanced cancers, including non-small cell lung cancer [17].

6. **Hyperthermia Drug Delivery:** The basic concept of hyperthermia drug delivery involves raising the temperature of the tumor region or cancer cells using various methods, such as radiofrequency, microwaves, or ultrasound. The increased temperature can improve the blood flow to the tumor site and alter the tumor's physiology, making it more susceptible to the effects of certain drugs [18]. Example: Thermodox® (Lyso-thermosensitive liposomal doxorubicin) is designed to release doxorubicin under hyperthermic conditions. It is being investigated for the treatment of hepatocellular carcinoma [19].

7. **Photodynamic Therapy (PDT):** A photosensitizing chemical, light, and oxygen are used in conjunction with photodynamic therapy (PDT) to target and harm specific aberrant cells, such as cancer cells or some microbial infections. It is a focused, minimally invasive therapy that has found use in a number of medical specialties, including ophthalmology, dermatology, and cancer [20]. Example: An intravenous photosensitizing agent called photofrin (porfimer sodium) builds up in cancer cells. When Photofrin is activated by light of a particular wavelength, it produces reactive oxygen species that cause cancer cells to die. PDT is used to treat a number of cancers, including lung cancer, some forms of skin cancer, and esophageal cancer [21].

8. **Ultrasound-Mediated Drug Delivery:** Ultrasound-mediated drug delivery is a non-invasive and innovative technique that uses ultrasound waves to enhance the delivery and penetration of therapeutic agents into targeted tissues or cells. This approach has gained considerable interest in recent years as it offers a promising means to improve the efficiency and effectiveness of drug delivery while minimizing side effects [22]. Example: Sonodynamic therapy (SDT) is a developing technique that uses ultrasound in combination with certain drugs, known as sonosensitizers, to enhance their anticancer effects. Ultrasound activates the sonosensitizers, leading to the production of reactive oxygen species and encourages the death of cancer cells. SDT is being investigated as a potential treatment for various types of cancer [23].

9. **Intra-Arterial Drug Delivery:** Intra-arterial drug delivery is a specialized method of administering medications or therapeutic agents directly into a specific artery that supplies blood to a targeted area of the body. This approach allows for targeted treatment

of diseases or conditions affecting specific organs or regions while minimizing the exposure of the rest of the body to the drug. Intra-arterial drug delivery is commonly used in interventional radiology and interventional oncology to treat various conditions, including cancer, stroke, peripheral artery disease, and certain liver diseases [24].Example: Intra-arterial chemotherapy involves delivering anticancer drugs directly into the artery that supplies blood to the tumor. This technique allows for higher drug concentrations at the tumor site while reducing systemic side effects. It is commonly used for the treatment of liver cancer (hepatocellular carcinoma) and retinoblastoma[25].

10. **Intralesional Drug Delivery:** Intralesional drug delivery is a therapeutic approach that involves directly administering medications or therapeutic agents into a localized lesion or specific area of disease. This method allows for targeted treatment of the affected tissues, bypassing systemic circulation and minimizing potential side effects on healthy tissues.Intralesional drug delivery is commonly used in various medical fields, including dermatology, oncology, orthopedics, and rheumatology, to treat conditions such as skin disorders, cancers, joint diseases, and inflammatory conditions [26]. Example: Intralesional drug delivery involves injecting anticancer drugs directly into tumor lesions. This approach is commonly used for certain skin cancers, melanoma, and other localized tumors [27].

11. **Intrathecal Drug Delivery:** Intrathecal (IT) drug delivery systems (IDDS) are well-established as a successful therapeutic approach for patients with chronic malignant or benign pain, as a tool for managing patients with severe spasticity, and to deliver therapeutics that address a variety of spinal pathologies directly to the site of action while avoiding first pass metabolism [28]. Using a catheter or reservoir device, intrathecal drug administration entails injecting anticancer medications directly into the cerebrospinal fluid. Brain metastases and malignancies of the central nervous system are both treated with this technique [29].

Figure 2: Mind Map for Drug Delivery Methods Employed In Cancer Treatment

12. **Nanorobots for Drug Delivery:** Nanorobots for drug delivery, also known as nanomedicine or nanorobotics, refers to the use of nanoscale robots or nanodevices for targeted and precise delivery of therapeutic agents, such as drugs or other bioactive molecules, to specific sites within the body. These nanorobots are engineered with precision at the nanoscale level to navigate through biological environments and deliver drugs with high specificity to the intended targets, such as cancer cells or diseased tissues [30]. Example: Nanorobots are miniature devices designed to deliver drugs precisely to cancer cells. Although they are still in the early phases of research, they show promise for the future of tailored medication delivery [31].

13. **Magnetic Drug Delivery**: A targeted medication delivery method called magnetic drug delivery employs magnetic fields to direct and concentrate therapeutic medicines to certain body parts or target areas. This method utilizes magnetic nanoparticles as carriers for drugs or therapeutic agents and external magnetic fields to control their movement and accumulation at the desired location [32]. Example: MagForce's Nano Therm therapy uses magnetic nanoparticles to heat tumor cells and is being investigated for the treatment of brain tumors [33].

14. **Viral Vectors**: Modified viruses called viral vectors are used to introduce genetic material (DNA or RNA) into cells for research or therapeutic reasons. These vectors are extensively utilized in research to understand how genes work and regulate as well as in gene therapy and gene editing applications to treat genetic abnormalities, malignancies, and other illnesses. Viral vectors are engineered in a way that removes the viral genes responsible for replication and pathogenicity while retaining the necessary components for efficient gene transfer. The genetic material of interest, such as a therapeutic gene or a gene-editing tool like CRISPR/Cas9, is then inserted into the viral vector [34]. Example: An oncolytic viral therapy called T-VEC (talimogene laherparepvec) is used to treat metastatic melanoma. Direct injection of it causes it to proliferate and kill cancer cells in tumours [35].

15. **Drug-Eluting Devices:** Medical equipment that has been coated or impregnated with medications or therapeutic substances is referred to as a drug-eluting device. These tools are used to localise medication delivery to certain bodily tissues or locations, enabling tailored therapy and minimising systemic adverse effects. Drug-eluting implants, catheters, balloons, and stents are examples of common drug-eluting medical equipment. To provide the intended therapeutic effect, each type of device is created to release therapeutic substances in a regulated manner over time [36]. An example is the implanted Gliadel Wafer (TABLE 1) (carmustine implant) (Fig 3), which, following glioblastoma multiforme surgical resection, distributes carmustine to the tumour site.[37].

16. **Targeted Therapies:** Targeted therapies refer to a class of medical treatments that specifically target certain molecules or cellular components involved in the growth, progression, or survival of diseased cells, while sparing healthy cells to a greater extent than traditional, non-targeted therapies. These therapies are designed to be more precise and selective, aiming to improve treatment efficacy while reducing adverse effects. The targets of these therapies can be various molecules, receptors, enzymes, or signaling pathways that are over expressed or mutated in diseased cells, such as cancer cells. By understanding the specific molecular alterations driving the disease, researchers and

medical professionals can develop drugs that directly inhibit or modulate these targets [38]. Example: Herceptin (trastuzumab) is a targeted therapy that specifically targets the HER2 protein and is used in the treatment of HER2-positive breast cancer [39].

17. **Antibody-Drug Conjugates (ADCs):** Antibody-drug conjugates ADCs are a family of targeted cancer medicines that combine the cytotoxicity of strong anti-cancer medications with the specificity of monoclonal antibodies. ADCs are made to deliver the deadly drug payload only to cancer cells that express certain surface antigens, which lowers systemic toxicity and increases therapeutic effectiveness [40]. Example: Adcetris (brentuximab vedotin) is an ADC used to treat Hodgkin lymphoma and systemic anaplastic large-cell lymphoma by targeting the CD30 antigen on cancer cells [41].

18. **Polymer-Based Drug Delivery**: Polymer-based drug delivery is a strategy that utilizes synthetic or natural polymers to create drug carriers for targeted and controlled release of therapeutic agents. These polymers can be designed to form nanoparticles, microparticles, hydrogels, or other structures that can encapsulate or conjugate drugs. The selection of polymers depends on factors such as biocompatibility, biodegradability, and the desired drug release profile [42]. Example: Abraxane (TABLE 1)(albumin-bound paclitaxel)(Fig 3) uses albumin nanoparticles to deliver paclitaxel and is used to treat breast cancer, pancreatic cancer, and other solid tumors [43]

19. **Liposomes**: Liposomes are a type of nanoparticle-based drug delivery system that consists of spherical vesicles made up of lipid bilayers. These lipid bilayers mimic the structure of cell membranes, making liposomes biocompatible and well-suited for drug delivery applications.To create liposomes, lipids (fatty molecules) are dispersed in an aqueous solution, and under certain conditions, they spontaneously self-assemble into closed vesicles with an aqueous core. The hydrophilic (water-loving) drug molecules can be encapsulated within the core, while hydrophobic (water-repellent) drugs can be incorporated into the lipid bilayers [44]. Example: DaunoXome (liposomal daunorubicin) is a liposomal formulation of daunorubicin used to treat Kaposi's sarcoma, a cancer commonly seen in HIV/AIDS patients [45].

20. **Nanoparticle-Based Drug Delivery:** To transport therapeutic agents, such as medications or genes, to certain target locations in the body, a method known as nanoparticle-based drug delivery is used. These nanoparticles are designed to enclose or adhere to the therapeutic payload, shielding it from deterioration, enhancing its stability, and permitting controlled release at the targeted site. These carriers are perfect for targeted and effective medication administration because of their nanoscale size (often between 1 and 100 nanometers), which enables them to interact with cells and tissues at the molecular level. Drug delivery nanoparticles can be made of a variety of components, including as lipids, polymers, metals, or inorganic compounds. Materials should be chosen based on their biocompatibility, stability, and desired drug release profile [46]. Example: Doxil (liposomal doxorubicin) is a nanoparticle-based medication that is used to treat a variety of malignancies, such as breast cancer and ovarian cancer, by delivering doxorubicin to cancer cells. [47]

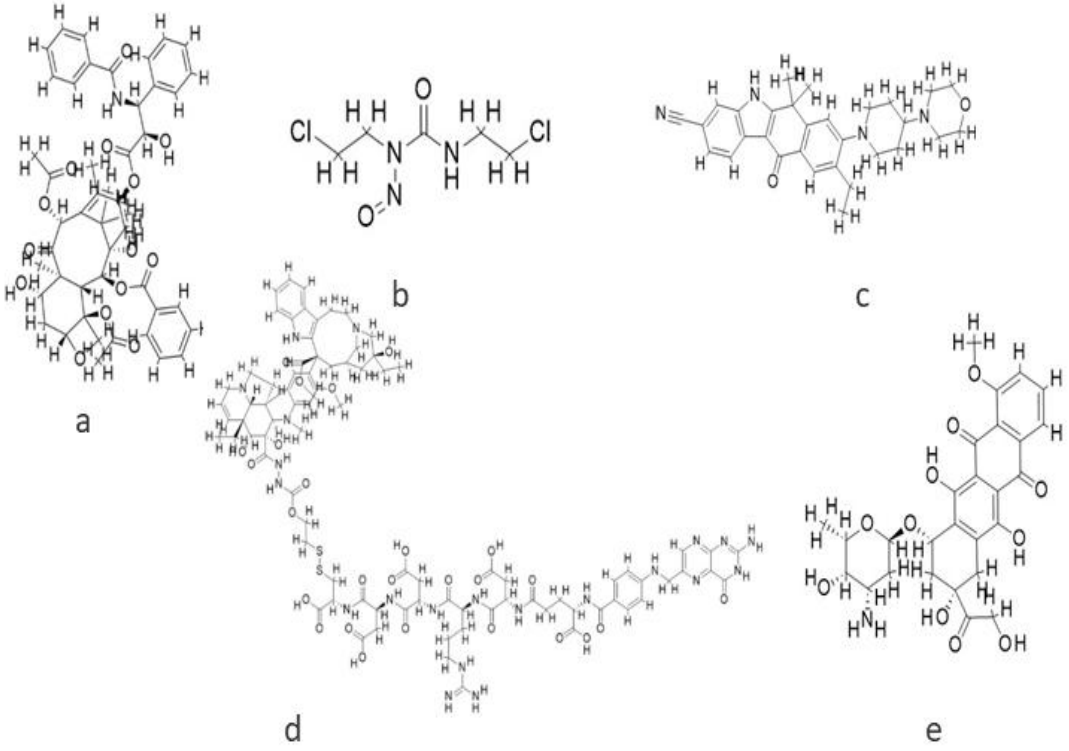

Figure 2: a) Genexol, b) Gliadel wafer, c) Alectinib, d) Vintafolide, e)Abraxane

Table 1: Physicochemical Properties of Anti-Cancer Drug involved in various Drug Delivery System.

Drugs	Formula	Molecular weight (g/mol)	Number of rotatable bonds	Number of H-bond acceptors	Number of H-bond donors	Molar refractivity
Genexol	$C_{47}H_{51}NO_{14}$	853.91	15	14	4	218.96
Gliadel wafer	$C_5H_9CL_2N_3O_2$	214.05	7	3	1	46.77
Alectinib	$C_{30}H_{34}N_4O_2$	482.62	3	4	1	149.63
Abraxane	$C_{47}H_{51}NO_{14}$	853.91	15	14	4	218.96

VII. CONCLUSION

In the context of cancer therapy, the chapter offers a thorough discussion of a number of materials that are now being used or have the potential to be used as drug delivery systems. The use of medication delivery systems has significantly advanced the area of cancer therapy as well as contemporary medicine as a whole. The application of cutting-edge methods, such as radioactive drug delivery, inhalable drug administration, gold nanoparticle drug delivery,

dendrimer drug delivery, and other cutting-edge strategies, has profoundly changed the area of cancer. These technologies have revolutionized the field by improving the accuracy and effectiveness of drug administration, as well as enhancing patient adherence to treatment protocols. These methodologies, in conjunction with focused therapies, antibody-drug conjugates, and nanorobots for pharmaceutical administration, present customised therapy alternatives that are specifically designed to align with the unique patient profiles and genetic attributes of individuals. The distinctive characteristics of these entities have enabled medical practitioners to present them as novel therapeutic options, either as standalone treatments (monotherapy) or as supplementary components to current treatments (combined therapy), with the aim of enhancing therapeutic efficacy. While several materials have not achieved success in their clinical translation, there are several emerging materials that are currently being developed and exhibit significant potential. These resources provide promising opportunities for the creation of fresh treatment options in the near future.

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