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RECENT METHODS TO IMPROVE STABILITY PROFILE, PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES IN ANTICANCER DRUGS

Pravinkumar Darji[1]*, Jayendrakumar Patel[2], Binit Patel[3], Arpan Chudasama[4], Praneeth Ivan Joel Fnu[5] and Seshadri Nalla[6]

[1,2]Exemplify Biopharma Inc., Cranbury, New Jersey, USA – 08512.
[3]Hovione, East Windsor, New Jersey, USA-08520.
[4]Navinta LLC Formulation and Research and Development, Ewing, New Jersey, USA-08618.
[5]Exemplify Biopharma Inc., Cranbury, New Jersey, USA – 08512.
[6]Lamar University, 4400 S M king Jr PKWY, Beaumont, Texas, USA-77705.

***Corresponding Author: Pravinkumar Darji**

Exemplify Biopharma Inc., Cranbury, New Jersey, USA – 08512.

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ABSTRACT

Over the years, research on anticancer treatments has yielded impressive outcomes, although many of the drugs that have been approved still have significant systemic toxicity. This is primarily because these drugs lack selectivity for tumors and have pharmacokinetic limitations, such as low water solubility, which adversely impact their circulation time and bioavailability. The stability experiments conducted during the development of anticancer medications, either under benign settings or under exposure to high temperature, hydrolytic media, or light source, have revealed the susceptibility of these drugs to many factors. Therefore, the evaluation of degradation products is conducted in both pharmaceutical formulations and hospital waste in order to determine their production. So far, many formulations have been created to achieve drug targeting specific to certain tissues and to decrease harmful side effects, as well as to enhance drug stability. Prodrug development is a potential approach in targeted cancer therapy that aims to enhance the selectivity, effectiveness, and stability of active molecules. Recent research indicates that the inclusion of anticancer medications into vesicular systems, such as polymeric micelles or cyclodextrins, or the utilization of nanocarriers that contain chemotherapeutic agents conjugated to monoclonal antibodies, can enhance solubility, pharmacokinetics, cellular absorption, and stability. This paper provides a comprehensive overview of the most recent advancements in understanding the creation of potent and durable anticancer medications, which are designed as stable prodrugs or encapsulated in nanosystems.

KEYWORDS: Cancer therapy, Drug stability, Vesicular systems, Prodrugs, Nanoparticles, Trastuzumab.

1. INTRODUCTION

The GLOBOCAN is a web-based platform that offers cancer data, estimating the occurrence and death rates for 36 different forms of cancer and all cancer sites combined in 185 nations. Based on the data gathered in 2020, it is anticipated that approximately 20% of the global population will experience cancer at some point in their lives. Additionally, the mortality rate for cancer is higher among males, with one in eight succumbing to the disease, compared to one in eleven women. The rise in the number of elderly individuals, along with socio-economic conditions that pose a risk, may contribute to the observed increase in these estimated figures.[1,2]

Treatment options for cancer encompass surgical intervention, radiation therapy, chemotherapy, or a combination thereof. Chemotherapy is a systemic treatment that involves the administration of one or more drugs capable of causing harm to rapidly dividing cells, including cancer cells. Nevertheless, these compounds, due to their lack of selectivity, typically harm healthy cells and tissues that undergo fast turnover, resulting in significant toxic consequences. Chemotherapy is hindered by the quick development of drug resistance, the molecular instability, and the low water solubility, which prevent effective permeation across cell membranes. In order to surpass these constraints, it is customary to employ a combination of two or more chemotherapeutic agents. Alternative therapy approaches for several types of cancer involve the utilization of small molecules, such as genes, short RNAs, and plasmids. However, these methods have limitations due to their inadequate stability within living organisms.[1,3]

The drawbacks of traditional anticancer medications are the driving force behind the ongoing demand for the development of alternative treatments that offer decreased unpleasant side effects and greater therapeutic

efficacy. Prodrugs are a useful technique to enhance the selectivity of chemotherapeutics. The latter refers to chemicals that are not active themselves but are transformed into active drugs by chemical or enzymatic processes. This transformation helps to decrease the overall toxicity of traditional treatments. Moreover, prodrugs can be advantageous in mitigating drug toxicity. Despite the widespread recognition of the effectiveness of transition metals, their inherent toxicity often prevents their inclusion in pharmacological therapy. Designing transition-metal-based prodrugs can reduce their toxicity, enabling the medication to achieve therapeutically effective concentrations. Prodrug therapy offers an alternative strategy for developing medications that are less reactive and less toxic. The design of these novel molecules may also aid in overcoming obstacles related to pharmaceutical, pharmacokinetic, and pharmacodynamic factors. Indeed, they can be employed to enhance solubility and enhance chemical stability and organoleptic properties, such as the taste of the medications. Specifically, they can be engineered to enhance the uptake across the blood-brain barrier or to enhance the therapeutic index and selectivity of the site of action. Various prodrug formulations have been produced and successfully utilized for the treatment of different types of cancer, thanks to the numerous benefits offered by these agents. This information may be found in Table 1.[1]

Table 1: List of the anticancer Drugs and Prodrugs and The diseases in which they are most used.

Drug classes	Active compound	Prodrug	Diseases
Antimetabolites	Mercaptopurine	Azathioprine	Acute lymphoblastic leukemia
	5-Fluorouracil	Capecitabine	Breast cancer, esophageal cancer, laryngeal cancer, gastrointestinal and genitourinary tract cancer
	Deoxyadenosine	Cladribine	Hairy cell leukemia
	1-β-D-arabinofuranoside 5′-triphosphate	Cytarabine	Acute myeloid leukemia
	9-beta-D-arabinosyl-2-fluoroadenine	Fludarabine	Chronic lymphocytic leukemia
	5-Fluorouracil		Different types of neoplasms
	Gemcitabine diphosphate and triphosphate	Gemcitabine	Solid cancers
	6-Mercaptopurine		Acute lymphoblastic leukemia
	Methotrexate		Several kinds of cancer, such as colon cancer
	6-Thioguanosine	6-Thioguanine	leukemias, lymphomas,mesothelioma, melanoma, biliary tract cancer, glioblastoma, osteosarcoma, soft tissue sarcoma, neuroendocrine tumors and lung, pancreatic and squamous cell carcinomas
	5-Fluorouracil	Floxuridine	Liver cancer
	Methyl-tetrahydrofolate	Leucovorin	Acute lymphoblastic leukemia
Alkylating agents	Busulfan		Chronic myelogenous leukemia
	Carmustine		Glioblastoma multiforme
	Acrolein and phosphoramide mustard	Cyclophosphamide	Several kinds of cancer and autoimmune disorders
	5-aminoimidazole-4-carboxamide	Dacarbazine	Malignant melanoma or sarcoma
	Lomustine		Brain tumors
	Mechlorethamine		Mycosis fungoides
	Melphalan		Multiple myeloma
	Azo-Procarbazine	Procarbazine	Hodgkin’s lymphoma
	Triethylenethio-phosphoramide	Thiotepa	Ovarian cancer, breast cancer and superficial bladder cancer
	Semustine		Lewis lung carcinoma, leukemia, metastatic brain tumor, Hodgkin’s lymphoma, malignant melanoma and lung carcinoma
Anthracyclines	Daunorubicin		Leukemia
	Doxorubicin		Leukemia, breast cancer

	Epirubicin		Breast cancer
	Idarubicin		Acute leukemia
	Mitoxantrone		Breast and prostate cancers, lymphomas and leukemias
Antitumor antibiotic	Bleomycin		Hodgkin's and non-Hodgkin's lymphoma, renal, cervical, laryngeal, testicular, lung and others
	Dactinomicyn		Different solid cancer
	Mitomycin		Adenocarcinoma of the stomach
	Plicamycin		Testicular and germ cancers
Epipodophyllotoxins	Etoposide		Small-cell lung cancer, leukemia, lymphoma, breast and ovarian carcinomas, testicular cancer
	Teniposide		Small-cell lung cancer, leukemia
Taxanes	Cabazitaxel		Prostatic cancer
	Docetaxel		Metastatic prostate cancer
	Paclitaxel		Ovarian, breast and lung cancer, as well as Kaposi's sarcoma
Vinca alkaloids	Vinblastine	Vinblastine-N-Oxide	Pancreatic ductal adenocarcinoma
	Vincristine		Precursor B-cell acute lymphoblastic leukemia
	Vinorelbine		Non-small-cell lung cancer and metastatic breast cancer
Campotothecins	SN-38 (7-ethyl-10-hydroxy-camptothecin)	Irinotecan	Solid tumors, including colorectal, pancreatic and lung cancer
	Topotecan		Cervical cancer
Platinum analogs	Carboplatin		Ovarian cancer cells
	Cisplatin		Solid cancers, such as testicular, ovarian, head and neck, bladder, lung, cervical cancer, melanoma, lymphomas and several others
	Oxaliplatin		Colorectal cancer
Monoclonal antibody	Bevacizumab		Metastatic colorectal cancer, metastatic breast cancer, non-small-cell lung cancer, glioblastoma, renal-cell carcinoma, ovarian cancer and cervical cancer
	Cetuximab		Non-small-cell lung cancer
	Rituximab		Lymphoid malignancies, including aggressive forms of B-cell non-Hodgkin lymphoma, B-cell malignancies, follicular lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia and mantle cell lymphoma
	Trastuzumab		Breast and metastatic gastric cancer
Growth inhibitor	Axitinib		Renal-cell carcinoma
	Bortezomib		Multiple myeloma
	Bosutinib		Philadelphia chromosome-positive chronic myelogenous leukemia
	Crizotinib		Non-small-cell lung cancer
	Dabrafenib		BRAF-mutated melanoma
	Dasatinib		Chronic myeloid leukemia and Philadelphia chromosome-positive

			acute lymphoblastic leukemia
	Imatinib		Chronic myeloid leukemia (CML)
	Lapatinib		Breast and gastrointestinal cancer
	Nilotinib		Chronic myeloid leukemia (CML)
	Pazopanib		Metastatic renal-cell carcinoma
	Sorafenib		Hepatocellular carcinoma
	Sunitinib		Renal-cell carcinoma
	Trametinib		BRAF-mutated melanoma
	Vandetanib		Metastatic medullary tyroid cancer
	Vemurafenib		BRAF-mutated melanoma

Integrating anticancer medications into drug delivery systems (DDS) is a method to effectively overcome pharmacological and pharmacokinetic limits. This strategy allows drugs to be directly transported to the targeted site of action, while minimizing negative side effects. Innovative nanotechnologies have had a significant effect on clinical therapies, particularly in the field of anticancer medications. Of all the incorporation systems that have been extensively researched, vesicular matrices, such as niosomes, cubosomes, and polymeric systems, have demonstrated the most favorable outcomes. Nanocarriers with chemotherapeutics attached to molecules that can bind to overexpressed antigens provide innovative targeting techniques.

The stability of a medicine is assessed during all phases of development, utilizing research conducted on both the active ingredients and the final formulation. The analytical procedures often rely on the guidelines outlined in the ICH (International Conference on Harmonization) to guarantee the safety, effectiveness, and quality of the tested pharmaceuticals. As per this document, stability tests are conducted under various environmental conditions of preservation, including pH, temperature, light, air, and humidity. During the quality control process of a medicine, the analytical method is meticulously chosen depending on the drug's properties or formulation. This approach is used to accurately assess the amount of residual drug and any potential by-products that may be present over a period of time. Chromatographic methods are widely employed for both separating and quantifying analytes, making them the most regularly utilized technique.[2,3]

Moreover, researchers have investigated the durability of numerous antineoplastic medications in surface waters and wastewater treatment effluents. These substances, when present in the environment, can pose a threat to aquatic creatures due to their mutagenic, genotoxic, cytotoxic, carcinogenic, and teratogenic properties.

This book presents a comprehensive analysis of the latest research in the subject, with a specific focus on new methodologies that have proven beneficial in evaluating the stability profile of anticancer prodrugs and drugs, as well as enhancing their pharmacokinetic and technical characteristics.

The majority of evaluations in the literature primarily address the limitations of anticancer medications or the utilization of nanocarriers as drug delivery systems (DDS). This review compiles all the currently available findings on the approaches employed to address the pharmacokinetic and pharmacodynamic limitations of these medications, as well as to ensure enhancements in their stability profile. The study extensively analyzed the benefits of utilizing prodrugs and/or integrating drugs or prodrugs into vesicular systems. These methods prioritize the delivery of the therapeutic substance to the target location at optimal concentrations, while minimizing harmful side effects. The advantages and disadvantages of utilizing monoclonal antibodies (mAb) or other experimental approaches to surpass the limitations of traditional medications have also been deliberated.[4,5,6]

2. Stability of anticancer drugs[1,7,8]

Various experimental circumstances have been employed to assess the stability of the majority of anticancer drugs. Due to the high levels of certain antineoplastic agents or their breakdown products detected in hospital sewer drains or wastewater, numerous studies have been conducted to assess their presence in the environment. All stability investigations in this particular context have been carried out by subjecting the medications to gentle settings, such as ambient temperature and the inherent pH of the water utilized as a solvent. Several cytostatic drugs, such as daunorubicin, doxorubicin, vinblastine, chlorambucil, vincristine, irinotecan, and melphalan, have been discovered to be extremely unstable in milli-Q water (pH 6.3) due to the existence of reactive groups in their chemical structures that promote hydrolytic reactions. Specifically, daunorubicin, doxorubicin, irinotecan, and vincristine have seen fast degradation, with just 10% of the original concentration remaining after 5 minutes of exposure. However, vinblastine, chlorambucil, and melphalan experienced degradation during the initial 240 minutes. The stability of the substance has been assessed in an aqueous setting by altering factors such as pH and/or temperature. Mitoxantrone undergoes degradation in water, resulting in the formation of four distinct and stable breakdown products. These compounds were identified through the use of liquid chromatography combined with mass spectrometry (LC-MS). The medicine underwent a swift alteration in its structure, leading to the creation of

harmful byproducts that remained unchanged and stable in water for a maximum of two days. Busulfan, an alkylating drug commonly used to treat chronic myeloid leukemia, has demonstrated significant instability in aqueous formulations. The deterioration caused by precipitation events seems to be influenced by temperature: as the storage temperature increases, the stability of the diluted solutions diminishes. Busulfan is administered intravenously, although its manufactured formulation from a concentrate has a limited duration of storage. The solution's stability exhibits only a marginal increase when held at temperatures ranging from 2 to 8 °C, irrespective of the type of container employed.

Inductively coupled plasma mass spectrometry (ICP-MS) was employed to evaluate the stability profile and detect the presence of cytostatic derivatives of platinum (CPC) in hospital wastewater. CPC refers to antineoplastic drugs that are commonly utilized in clinical applications. The substances excreted by patients undergoing treatment are discharged into aqueducts and sewers, resulting in harmful impacts on the local ecosystem, even at low levels of concentration. Although all chemicals in the CPCs class, including oxaliplatin, carboplatin, and cisplatin, share a similar chemical structure, their environmental behavior varies significantly. These compounds in the environment experience several processes such as hydrolysis, photolysis, dilution, adsorption, sedimentation of suspended solids, and biodegradation. These processes result in the formation of either unchanged compounds or degradation products. Cisplatin products have higher soil surface absorption rates compared to carboplatin and oxaliplatin derivatives. This is attributed to the establishment of hydrogen bonds or electrostatic interactions with aqueous soil groups. The stability of carboplatin in a water-based solution is primarily influenced by the concentrations of nucleophiles and the pH of the solution. In comparison to cisplatin, the activation process of carboplatin is consistently slower. Oxaliplatin generates reactive species that can contaminate groundwater, the extent of which depends on the nature of the aqueous solution.

Other studies have examined the stability of anticancer drugs by analyzing their degradation profile and the formation of transformation products immediately after being exposed to stressful conditions. One such drug is imatinib, a powerful tyrosine kinase inhibitor commonly used as a first-line treatment for chronic myeloid leukemia. The breakdown kinetics of this molecule have been investigated using heterogeneous photocatalysis in the presence of radicals. The degradation mechanism has been determined using LC-MS analysis. A total of 12 transformation products have been identified, and in silico toxicity experiments revealed that certain compounds among them had structural patterns that have the ability to cause DNA damage. High-performance liquid chromatography and infrared spectroscopy were employed to investigate the stability of 5-fluorouracil, a commonly utilized chemotherapeutic drug for many cancer types, under various stressful situations. The drug has demonstrated excellent stability under UV radiation, with only slight degradation observed at 275°C and greater degradation at 285°C. It undergoes approximately 22% degradation under acid hydrolysis conditions and around 97% degradation under alkaline conditions. Additionally, when exposed to oxidative conditions, the drug experiences degradation ranging from 26% to 41%.

3. Stability of anticancer prodrugs[1,9,10]

Prodrugs are often inert precursors of medicinal substances that undergo chemical or enzymatic conversion within the body to produce one or more active metabolites. The well-established knowledge is that a prodrug has the capability to enhance the pharmacokinetic characteristics or stability of a drug. Various methodologies, such as the utilization of vector- or bio-precursor-linked prodrugs, have been devised to guarantee the precise delivery of a medication to its intended destination at an appropriate concentration. This approach enables the resolution of various limitations, such as low water solubility, chemical instability, insufficient oral or local absorption, short half-life, and formulation or administration challenges. It facilitates the concentration of a drug at the intended site of action, thereby enhancing its selectivity and safety. Given that a prodrug undergoes transformation into the active metabolite within the body, it is necessary to conduct stability studies on both the prodrug and the active metabolite.

Water sorption is the main reason for the degradation of capecitabine. The degradation of this process is expedited when exposed to higher temperatures and humidity. Specifically, it is enhanced when subjected to 40°C at 75% relative humidity. Thermoanalytical methods and HPLC studies have demonstrated that capecitabine remains stable after being stored for 6 months at a temperature of 25 °C and a relative humidity of 60%. The degradation of irinotecan hydrochloride has been examined using liquid chromatography-mass spectrometry under various stress conditions specified by the International Council for Harmonisation (ICH). This analysis revealed the presence of seven degradation products in pharmaceutical dosage forms. The prodrug underwent deterioration when subjected to oxidative, acid, base, hydrolytic, thermal, and photolytic conditions, with notable degradation occurring under oxidative, base hydrolysis, and photolytic conditions. Various concentrations and temperature settings were used to investigate the stability of floxuridine and leucovorin calcium in combination therapy. Both compounds exhibited stability after 48 hours under all testing conditions. Leucovorin calcium experienced deterioration, which was more pronounced at low concentrations, when exposed to near-physiological body temperature as opposed to temperatures of 4–8°C and 20°C.

The chemical properties of each component can influence the degradation of a medication in combination therapy. The physical compatibility and chemical stability of irinotecan, when diluted in a solution of 5% dextrose in water and mixed with the racemic form of leucovorin, were evaluated after the formulation was stored at 23°C without protection from light. The solutions maintained their clarity and lack of color consistently during the whole 24-hour testing period, regardless of the concentrations of the medications being evaluated. However, when the formulation was created with a low quantity of irinotecan (0.30 mg/mL) and a high concentration of leucovorin (3.60 mg/mL), there was a rapid degradation of irinotecan. This is likely because the high dose of leucovorin led the solution to have a higher pH.

Anticancer medicines often undergo light degradation, leading to the creation of transformation products that are also responsible for harmful effects. The study examined the breakdown of cyclophosphamide and iphosphamide using ruthenium-doped titanate nanowires in both distilled water and wastewater when exposed to UV–vis radiation. The results demonstrated that ruthenium displayed photocatalytic activity for both medicines, resulting in the production of four photodegradation products for cyclophosphamide and six for isophosphamide. The identification of these compounds was achieved by the use of high resolution mass spectrometry, which confirmed a greater concentration in wastewater compared to pure water. The results have shown that environmental matrices can generate distinct transformation products. It is crucial for the experimental circumstances in photodegradation investigations to closely resemble those of environmental systems. Dacarbazine, an alkylating agent frequently administered in conjunction with other chemotherapeutic drugs to treat metastatic malignant melanomas, Hodgkin's lymphoma, and pheochromocytomas, undergoes a photochemical conversion to 4-diazoimidazole-5-carboxamide. This photo-transforming substance frequently causes the pain sensations reported when peripheral intravenous infusion is administered in a clinical setting. The medication solutions' photodegradation profile was determined using High-Performance Liquid Chromatography (HPLC) coupled with Ultraviolet (UV) detection. The study showed that the synthesis of photoproducts rises over time, up to 4 hours, at both 4 and 25 °C, even when the sample is protected from light. This suggests that light protection is not necessary during sample preparation.

4. Stability of anticancer monoclonal antibody[1,11,12]

Currently, there have been notable advancements in cancer treatment through the use of mAb-based immunotherapy. This approach involves the use of antibodies that may specifically target cancer cells and also stimulate the immune system to generate durable responses against these cells. Nevertheless, despite the demonstrated efficacy of this technique in treating many types of cancer, there are still several challenges that need to be addressed. The main obstacles that persist are medication resistance and limited stability caused by the glycoprotein characteristics of monoclonal antibodies (mAb).

The causes of its instability might be attributed to either chemical or physical factors. Various factors, such as protein structure, temperature, and light exposure, influence the stability of monoclonal antibodies (mAbs). Oxidation is the primary process involved in chemical deterioration. It can happen either spontaneously or in the presence of oxidizing agents like peroxides or metals. Amino acid residues, such as methionine and cysteine, exhibit high susceptibility to oxidation. Furthermore, asparagine residues have the ability to undergo acid-base deamidation, leading to the formation of a succinimide intermediate which then spontaneously hydrolyzes into aspartic or isoaspartic acid.

Fluctuations in temperature or pH can trigger the denaturation of proteins, resulting in a direct impairment of mAb activities and promoting their aggregation, which is the primary factor for their physical instability. Protein aggregation occurs when misfolded proteins come together to form larger structures, such as oligomers and insoluble aggregates. This happens through the formation of weak bonds, including Van der Waals interactions, hydrogen bonds, hydrophobic and electrostatic interactions. Importantly, these interactions do not alter the primary structure of the proteins. Moreover, in formulations with high concentration, the viscosity rise causes the creation of aggregates that cannot be reversed, resulting in difficulties during the manufacture or administration of the medicine. Typically, formulations include chemicals like salts, amino acids, sugars, polyols, or surfactants to counteract these occurrences. In this particular situation, bis-acetyl-lysine and propionyl serine have been recognized as superior substances in comparison to the typically employed additives for reducing the viscosity of the antibody solution and preventing interactions between proteins.

The main structure of monoclonal antibodies (mAb) contains several aromatic amino acid residues, which renders them very susceptible to light-induced degradation. This degradation process involves the generation of oxygenation radicals, as well as fragmentation and cross-linking. An investigation should be conducted to examine the impact of light on the aggregation of monoclonal antibodies (mAb) in both the initial medication samples and the diluted formulations. Although light does not appear to directly change the secondary and tertiary structures of the mAb, studies have shown that exposure to light causes the monomeric and dimeric portions of an IgG1 monoclonal antibody to aggregate. Specifically, mass spectrometry research has revealed that controlled irradiation of the monoclonal antibody (mAb) leads to increased flexibility in some

segments of the CH2 and CH3 domains in both dimensional fractions. Additionally, reduced flexibility has been seen in certain segments of the Fab and CH1 domains in the dimer fraction.

An investigation should be conducted to examine the impact of light on the aggregation of monoclonal antibodies (mAbs) in both the original formulation and the diluted preparation used in clinical practice. Hernández-Jiménez et al. conducted accelerated photodegradation experiments on both the commercial medication and the routinely diluted formulation of five monoclonal antibodies (bevacizumab, cetuximab, infliximab, rituximab, and trastuzumab). The photodegradation profile was assessed using size exclusion chromatography, revealing the production of aggregates as a result of light exposure in each experiment. The procedure led to the fragmentation of monoclonal antibodies (mAb) and subsequent aggregation, which was more commonly observed in diluted solutions rather than concentrated ones. The aggregation phenomenon is associated with the concentration and characteristics of monoclonal antibodies (mAb) in both light-exposed formulations and other stressful situations, such as freeze/thaw cycles, for all the medicines examined. The monoclonal antibodies (mAbs) experienced deterioration, resulting in the aggregation and/or disruption of the protein chains. This degradation is likely caused by the breakdown of the cystines that connect the two heavy chains. Although bevacizumab and rituximab had a similar IgG1 structure, they remained stable when held at 4 °C and subjected to freeze/thaw cycles, with only a little amount of aggregation formation. In contrast, infliximab and cetuximab deteriorated even under mild conditions. Due to the unique three-dimensional structure that is stabilized in the final formulation of Herceptin®, trastuzumab is shown to be the antibody with the least sensitivity to light, even though it is not the most concentrated.

Furthermore, the inclusion of surfactants in formulations has the potential to cause secondary structural alterations. An investigation was conducted to examine the impact of various concentrations of a non-ionic surfactant, sodium dodecyl sulfate, on bevacizumab formulations. The results revealed that the development of aggregates followed the traditional pattern, but only occurred at medium concentrations (0.5-2 mM) of the surfactant. In contrast, when the concentrations were low (0-0.2 mM), alterations in the structure were seen in both the β sheet and the α helix, resulting in a disorganized configuration. The presence of high amounts of surfactant (3–5 mM) led to an increase in the production of disordered structures.

Overall, monoclonal antibodies (mAbs) are highly significant biotechnological drugs used to treat diseases that are becoming more prevalent in the population, including cancer, autoimmune, inflammatory, infectious, and degenerative diseases. Additionally, they have been investigated as potential therapeutic options since the onset of the COVID-19 pandemic. Consequently, stability studies play a vital role in the development of therapeutic proteins to guarantee the quality and safety of the ultimate medication. A more profound understanding of the mechanisms involved in a protein can prevent the occurrence of conformational and colloidal alterations that diminish its therapeutic effectiveness.

5. Anticancer drugs in nanoparticle systems[1,13,14,15,16]

The utilization of vesicular systems that can effectively deliver anticancer medications to the targeted region of therapeutic action in precise amounts to exert their effects is on the rise. These systems enhance the effectiveness of therapy while minimizing adverse effects, offering several benefits such as improved pharmacodynamic and pharmacokinetic properties. This leads to a longer duration of action and improved stability of the medication, protecting it against chemical or physical breakdown. Given the sensitivity of most antineoplastic agents to various conditions, enhancing the stability profile of these drugs can streamline the tasks of pharmacists in formulating different preparations and healthcare professionals in administering them in hospital settings. Moreover, enhancing the stability of anticancer medications could enable the use of home therapy, where the pharmaceuticals can be delivered to patients through portable elastomeric pumps without the risk of their modification and subsequent treatment ineffectiveness.

The nanocarriers now accessible for anticancer medications exhibit diverse shapes, sizes, and physicochemical features. These systems can be either natural, composed of simple structures generated from phospholipids like lecithin, or manufactured, characterized by more complicated structures consisting of polymers that are occasionally complexed with metals. Niosomes, which are vesicles formed by non-ionic surfactants, are frequently used as carriers for anticancer medicines. These vesicles are formed through the hydration process of a non-ionic surfactant with cholesterol. The surfactants create a closed bilayer vesicle in water due to their amphiphilic properties. Within this arrangement, the molecules of the surfactant are positioned in a manner where they face away from the solvent. This causes the hydrophilic portions of the non-ionic surfactant to extend outward, while the hydrophobic portions come together to create a bilayer. Meanwhile, the hydrophilic heads of the surfactant remain in touch with the watery solvent. The characteristics of niosomes, such as their composition, size, lamellarity, tapping volume, surface charge, and concentration, determine the qualities of natural liposomes. Contrary to niosomes, liposomes are costly and their constituents, such as phospholipids, are prone to oxidative destruction. Liposomes pose difficulties in handling due to their requirement for certain storage

conditions. These structures have both watery compartments for the inclusion of water-loving molecules and lipid layers for the movement of fat-loving molecules.

In recent decades, the utilization of nanoparticle (NP)-based drug delivery systems (DDS) has demonstrated several benefits in the treatment of cancer. These advantages include the capacity to overcome drug resistance induced by the overexpression of drug efflux transporters, faulty apoptotic pathways, and a hypoxic environment. As an illustration, nanoparticles (NPs) can prevent the anticancer medications from being exposed to efflux transporters since they largely enter the cell by endocytosis instead of diffusion. Typically, the selection of NPs for cancer therapy (organic, inorganic, or hybrid) is determined by their size, features, and the pathophysiology of the tumors. Organic nanoparticles (NPs) encompass liposome- and polymer-based NPs, such as micelles and dendrimers. Inorganic NPs consist of gold NPs (Au-NPs), carbon nanotubes, silica NPs, magnetic NPs, and quantum dots. Lastly, hybrid NPs combine the benefits of different types, including lipid-polymer, organic-inorganic hybrid NPs, and cell-membrane-coated NPs.

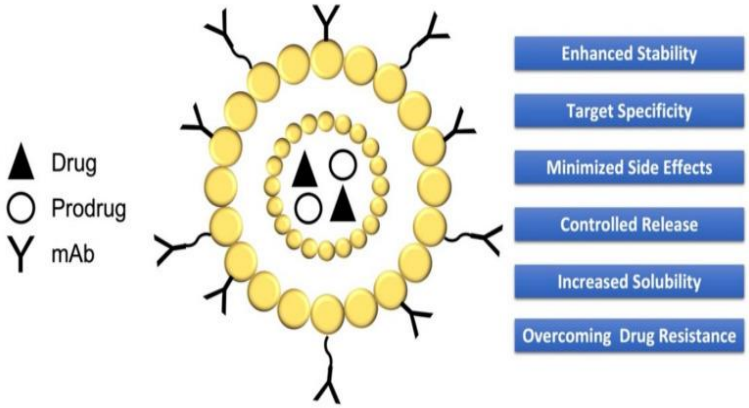

Figure 1: NP entrapping Drugs and Prodrugs coated with mAbs. List of advantages in the use of NPs.

Figure Credit: *Ioele G, Chieffallo M, Occhiuzzi MA, De Luca M, Garofalo A, Ragno G, Grande F. Anticancer Drugs: Recent Strategies to Improve Stability Profile, Pharmacokinetic and Pharmacodynamic Properties. Molecules. 2022 Aug 25;27(17):5436*.

Table 2 lists most of the applied inclusion systems for anticancer drugs and prodrugs and the advantages obtained from the proposed formulation.

Table 2: Inclusion systems and their advantages in protecting the anticancer drugs.

Drug	Inclusion Systems	Advantages
Capecitabine	Smart pH-responsive co-polymeric hydrogels	Protection from chemical and enzymatic hydrolysis and improvement in the stability in the gastric media
Cladribine	Nanostabilized polyacrylamide matrix	Better operational stability and mechanical properties
Cytarabine	Liposomal formulation in hydrogel system	Improvement in stability
Fludarabina	Co-encapsulation with mitoxantrone in liposomes	Improvement in long-term stability
5-Fluorouracil	Co-encapsulation with leucovorin in NPs	Improvement in long-term stability
Gemcitabine	Temperature-sensitive liposomes	Improvement in long-term stability
6-Mercaptopurine	NPs	Improvement in thermal stability
	Gold NPs	Improvement in stability in diluted aqueous solutions
	Magnetite NPs	Improvement in thermal stability
Methotrexate	Gellan gum microparticles	Higher thermal stability
	Amphiphilic PEO–PPO–PEO tri-block co-polymeric nanomicelles	Improvement in thermodynamic stability
6-Thioguanine	Inclusion in βcyclodextrin and subsequent interaction with gold NPs	Increase in solubility and improvement in stability
Floxuridine	Boron nitride nanotube encapsulation	Improvement in long-term stability
Leucovorin	Co-encapsulation in NPs with of 5-fluorouracil	Improvement in long-term stability

Busulfan	Encapsulation within water-soluble pillae[5]arene	Reduction in hydrolytic degradation
Carmustine	Adsorption on the surface of the γ-Fe_2O_3 NPs	Improvement in long-term stability
	Cationic core-shell NPs	Improvement in long-term stability
Lomustine	Thermosensitive liposomes	Improvement in long-term stability
Mechlorethamine	Addition of free radical inhibitor for topical use	Improvement in long-term stability
Melphalan	Liposomal formulation based on a fluid lipid bilayer of natural phospholipids in the form of dioleoylglyceride ester	Improvement in stability in human serum
Daunorubicin	Liposomes	Improvement in long-term stability
Doxorubicin	Poly(lactide-co-glycolide) NPs with poloxamer 188	Improvement in long-term stability
	Peptide-based hydrogels and nanogels	Improvement in long-term stability
	Chitosan-coated nanodiamonds	Improvement in long-term stability
	PEGylated liposomal nanodrugs	Improvement in long-term stability
Epirubicin	Drug-eluting beads	Improvement in long-term stability
	Bifunctional drug-loaded micelles	Improvement in long-term stability
Idarubicin	Drug-eluting beads	Improvement in long-term stability
	Drug-eluting embolics beads	Improvement in long-term stability
Mitoxantrone	Estrone-targeted liposomes	Improvement in long-term stability
	Hyaluronan magnetic NPs	Improvement in long-term stability
	Liposomes in PLGA NPs	Improvement in long-term stability
Bleomycin	Biodegradable chitosan nanogel	Improvement in thermal stability
Mitomycin	PEGylated liposomes	Improvement in long-term stability
Etoposide	PLGA NPs	Improvement in long-term stability
	Nanostructured lipid carriers	Improvement in long-term stability
Teniposide	Aqueous mixtures of detergent-phospholipid	Improvement in long-term stability
	Nanosuspensions	Improvement in long-term stability
Docetaxel	Nanocrystal-loaded micelles	Enhancement in blood circulation
	Chondroitin sulphate-hybridized zein NPs	Improvement in long-term stability
Cabazitaxel	Surfactant-stripped micelles	Improvement in long-term stability
	Albumin NPs	Improvement in long-term stability
Paclitaxel	Natural exosome	Improvement in stability profile
	Polymeric micellar system	Increased solubility, greater stability
	Merocyanine conjugates	Favorable biological stability
	17-fluorinated ethanol-modified drug in NPs	Robust colloidal stability
Vinblastine	PEGylated niosomes	Increased solubility in water, reduction in side effects
Vincristine	Artificial low-density lipoproteins	Improvement in diffusion capacity in tumor tissue and lower toxicity
	Liposomes	Improvement in efficacy stability
Vinorelbine	Liposomes prepared with ammonium salts of several anionic agents	Improvement in efficacy and stability
	Nanomicelles	Reduction in side effects and increase in drug efficacy
	Liposome encapsulating polymeric micelles. Co-encapsulation with cis-diamminedichloroplatinum (II)	Reduction in toxicity and increase in plasma half-life
	Intravenous lipid emulsion	Improvement in lipophilicity, and fewer toxic effects
Irinotecan	Superparamagnetic chitosan nanocomplex	Improvement in effectiveness and biodistribution
Topotecan	Thiolated chitosan NPs	Improvement in stability and increase in absorption

	Lipid NPs	Protection from hydrolysis
Cisplatin	Liposome encapsulating polymeric micelles. Co-encapsulation with vinorelbine	Reduction in toxicity and increase in plasma half-life
	NPs	Improvement in stability
Carboplatin	Niosomal nanoplatform	Improvement in stability
	Conjugation with an arginine-rich triple-helical peptide	Improvement in pharmacokinetic profile
	NPs	Outstanding plasma stability
Oxaliplatin	Conjugation with PEGylated-nanobody	Prolonged circulation in vivo
Bevacizumab	Excipient in dilute solutions	Stabilization in unfavorable conditions, such as low concentration or body temperature. Prevention of aggregation.
	Lipid NPs	Biochemical and biophysical stabilization. Prevention of aggregation.
	Nanoincapsulation into PLGA NPs	Improvement in long-term stability. Prevention of aggregation.
Cetuximab	Silica NPs	Improvement in stability and bioavailability. Prevention of aggregation.
	Chitosan NPs with and without drug conjugation	Improvement in stability and bioavailability. Prevention of aggregation.
	Polymersome–mertansine nanodrug	Improvement in stability and bioavailability. Prevention of aggregation.
Rituximab	Iron oxide NPs	Colloidal stability in buffer solution. Prevention of aggregation.
Trastuzumab	Coated NPs with docetaxel	Prevention of aggregation and improvement in stability and pharmacokinetics profile
	Stealth immunoliposome coated with docetaxel	Prevention of aggregation and improvement in stability and pharmacokinetics profile
	Choline ionic liquid vesicles	Prevention of aggregation and improvement in stability and pharmacokinetics profile
	Drug conjugated with SCN-Bn-NOTA and radiolabeled with ^{64}Cu	Prevention of aggregation and improvement in stability and pharmacokinetics profile
Axitinib	Nanofibrous membranes prepared with poly(ε-caprolactone)/collagen	Improvement in long-term stability
Bortezomib	Polymeric NPs	Improvement in water solubility chemical stability
Crizotinib	Thermosensitive liposome	Improvement in targeting efficacy
Dasatinib	Biodegradable NPs	Improvement in long-term stability
	H-sensitive targeted micelle system. Co-encapsulation with curcumin	Improvement in long-term stability
Imatinib	Nanostructured lipid carriers	Improvement in long-term stability at 25 °C
	Nanocrystal delivery system	Improvement in long-term stability
Lapatinib	Nanocrystals stabilized with a PEG coating	Improvement in stability for at least 4 days in plasma-containing buffers
	Polymeric micelles	Improvement in stability
	Human serum albumin NPs	Improvement in stability
	Incorporation in lipoprotein-like NPs	Improvement in solubility in water and organic solvents
Sorafenib	Solid lipid NPs	Increase in homogeneity and

		improvement in physical stability
	Nucleoside-lipid-based nanocarriers	Increase in homogeneity and improvement in physical stability
Sunitinib	Self-nanoemulsifying system	Improvement in long-term stability
	Paclitaxel-loaded micelles	Improvement in long-term stability
	Self-nanoemulsifying system	Improvement in long-term stability
Vandetanib	Nanocarrier based on apoferritin	Improvement in drug delivery
Vemurafenib	Peptide-modified loaded liposomes	Improvement in long-term stability

So far, numerous studies have been published on the integration of anticancer medications into supramolecular systems. In all of these investigations, an enhancement in the chemical-physical stability of the drug has been seen, leading to improved therapeutic effectiveness. Below are a few instances. The targeting of paclitaxel has been enhanced through its incorporation into exosomes generated from natural milk. This molecule exhibits limited solubility in water, however its incorporation into exosomes enables a sustained release for up to 48 hours, providing an optimal stability profile suitable for clinical applications. The thermal stability of methotrexate has been increased by encapsulating it in new targeting systems. Dhanka et al. have suggested putting the medication into gellan gum microparticles using a straightforward water-in-oil emulsion solvent diffusion technique. Mishra et al. achieved an enhancement in thermodynamic stability by incorporating methotrexate into novel-targeted Pluronic (PEOPPO- PEO tri-block co-polymer) F127 polymeric micelles, which were suggested for intravenous treatment in MCF7 cancer cells. Polymeric nanoparticles synthesized using N-(2-hydroxypropyl)methacrylamide have been utilized to encapsulate bortezomib, thereby enhancing its stability and bioavailability. In vitro, the effectiveness of nanostructured lipid carriers containing imatinib has been evaluated in MCF-7 breast cancer cells. In this instance, vesicles have been created by the hot homogenization technique utilizing fat and oil. To stabilize the system, sodium lauryl sulphate (SLS) and T80 have been employed as surfactants. Because of their diminutive size (about 100 nm) and lipid composition, these particles have the ability to provide sufficient drug penetration through membrane barriers, resulting in a notable enhancement in the effectiveness of the treatment.[17,18,19,20]

The impact of temperature on the stability of lipid nanocarriers has been confirmed. Temperature had an impact on many characteristics of the produced formulations, such as particle size, polydispersion index, encapsulation effectiveness, and zeta potential, during a three-month storage period. Specifically, there has been an apparent enlargement of the particles, likely caused by the swelling or adsorption of surfactants on their surfaces. However, these particles nonetheless stayed within the colloidal nanometer range (<550 nm), indicating that aggregation did not occur.[21,22,23]

5.1. Anticancer prodrugs in nanoparticles systems

As stated in Section 3, the clinical application of numerous anticancer prodrugs with high anticancer potential is restricted due to their vulnerability to acid and enzymatic hydrolysis. In order to address these restrictions, prodrugs have been integrated into various controlled delivery systems. For instance, capecitabine has been developed in a co-polymeric hydrogel as a pH-responsive network to make it easier to take orally and decrease its susceptibility to stomach acidity. A potential solution to address certain therapeutic limitations of 6-thioguanine involves a supramolecular ternary system. This system includes the medication being enclosed within β-cyclodextrins (βCD) and then interacting with gold nanoparticles (NPs). This approach enhanced the ability of the prodrug to dissolve in a solution and made it more resistant to degradation. As a result, it offered several benefits, including targeted delivery to specific sites, thanks to its small size in the nanometer range. Chitosan-based polyelectrolyte complexes, utilizing aligned superparamagnetic nanoparticles, have been created for the purpose of delivering irinotecan directly to the tumor location through the influence of a magnetic field. The complexes were synthesized by utilizing chitosan and polyglutamate through an all-in-water method, eliminating the need for any potentially harmful substances. This approach resulted in increased stability and improved effectiveness of the inclusion complex against colon cancer cells compared to the free drug.[24,25,26,27]

5.2. Combination therapy in nanoparticles systems

In modern times, combination therapy has become a generally accepted approach for treating cancer. This is because targeting numerous factors simultaneously enables the use of lower doses for each individual medicine and helps delay the development of drug resistance. Recently, there has been a development of vesicular systems that are meant to encapsulate combination medications in order to enhance their effectiveness. The combination therapy of fludarabine and mitoxantrone has proven to be effective in treating various forms of lymphoma and chronic leukemia. The effectiveness of this combined treatment has been improved by encapsulating both chemicals in liposomes: fludarabine has been enclosed within the liposomes during their synthesis, while the loading of mitoxantrone has been facilitated by a pH gradient across the liposome membrane. This formulation has the potential to be an effective and efficient treatment approach. Additionally, it could enhance the durability of both medications over

time, as demonstrated by a recent study that monitored their effectiveness for three months.

Liposomes containing polymeric micelles that contain vinorelbine and cis-diamminedichloroplatinum (II) (cisplatin) have been developed for the treatment of non-small-cell lung cancer, a highly lethal and unfavorable malignancy. The formulation's stability was assessed in PBS (pH 7.4) solvent and 10% plasma. The results revealed no notable alteration in particle size, but a slight rise in the polydispersity index. This suggests that if the particles are stored for more than 72 hours, they may accumulate. Consequently, the co-delivered drugs are shielded from metabolism and rapid elimination.[1,28,29,30]

5.3. Monoclonal antibody in nanoparticles systems[1,31,32]

Although monoclonal antibodies (mAbs) have been shown to be effective in treating cancer, their practical application is greatly hindered by their low chemical and enzymatic stability, which leads to the formation of aggregates. An effective approach to overcome these obstacles and achieve a sufficient release of non-aggregated antibodies inside the intended location involves encapsulating the monoclonal antibody (mAb) within polymeric or lipid nanoparticles (NPs). Due to their resistance to many chemical and physical conditions, such as body temperature, these systems can effectively safeguard the antibody while it remains in the bloodstream. In addition, when the nanoparticles (NPs) are taken up by the tumor cells by endocytosis, they release the antibody molecules within the cytoplasmic compartment. This process allows the antibodies to avoid being broken down by lysosomes and prevents enzymatic destruction. The Bevacizumab-loaded nanoparticles exhibited excellent performance as a controlled release method, effectively retarding enzymatic breakdown. Bevacizumab lipid nanoparticles have been created as a novel method of delivering drugs through intravitreal injection, effectively maintaining the drug's stability. Moreover, this formulation enhanced the bioavailability of the medicine within the eye and increased patient adherence by eliminating the need for multiple injections into the vitreous. The inclusion of choline dihydrogen phosphate, a highly compatible ionic liquid, in the formulation of monoclonal antibodies (mAb) led to a notable enhancement in the effectiveness of the treatment. This improvement can be attributed to the prevention of the unfolding and clumping together of trastuzumab, a specific mAb. Consequently, the use of choline dihydrogen phosphate is justified for the creation of stable formulations of therapeutic antibodies.

The combination of docetaxel and trastuzumab is an effective treatment strategy for breast cancer. Docetaxel, typically dissolved in Tween 80 surfactant for its therapeutic formulations, often leads to significant hypersensitivity and other unfavorable effects. The utilization of nanoparticles (NPs) that carry many medications can be advantageous in addressing the limitations of individual drugs, while also enhancing the effectiveness of the combined treatment. For this aim, lipid-polymer hybrid nanoparticles have been created by mixing poly (D, L-lactide-co-glycolide), polyethylenimine, and lipids to form a hydrophobic core. Trastuzumab has been attached to the surface of these nanoparticles using electrostatic adsorption as a ligand that targets breast cancer cells that have the human epidermal growth factor receptor 2 (HER2) protein. Meanwhile, Docetaxel is confined inside the core of the nanoparticles. The stability of the proposed formulation has been assessed at physiological (37 °C) and storage conditions (4 °C). The impact of dilution has been examined at a concentration of 1.0 mg/mL using PBS (0.02 mol/L, pH 7.4) and PBS with 10% fetal bovine serum (vol/vol). The results demonstrate excellent stability throughout storage, transportation, and usage. The effectiveness of the identical drug combination has been evaluated by the preparation of stealth liposomal docetaxel with trastuzumab attached to its surface. Two types of liposomes with different engraftment procedures have been examined: a neutral formulation utilizing phosphatidylcholine (antibody nanoconjugate-1) or a positive formulation utilizing 1,2-dioleoyl-3-trimethylammonium-propane. Stability studies have verified that the light-protecting system exhibits excellent performance at temperatures of 4 °C or 25 °C for a duration of up to 1 week.[33,38,39,40]

6. CONCLUSIONS

Although conventional chemotherapy drugs have made significant contributions to cancer treatment, they have several disadvantages. These include quick elimination from the body, limited ability to reach the target site, low release within the tumor, non-specific toxicity, and subsequent systemic side effects. Additionally, the development of drug resistance often occurs. In the past ten years, many drug delivery methods have been created to address these restrictions. This has led to a notable enhancement in the effectiveness and safety of medications, as well as their stability. Polymeric or lipid nanoparticles are frequently employed to include anticancer medicines and prevent aggregation in monoclonal antibody production. Cyclodextrin matrices are commonly used to enhance the solubility of various substances by including many prodrugs into them.

The effectiveness of anticancer drugs incorporated in nanosystems has been extensively demonstrated. These nanosystems enable a controlled release of the drug at the intended site of action and minimize the drug's susceptibility to physicochemical factors during the preparation, handling, and storage stages. The potential to include many medications into a single vehicle has further benefits by enabling a decrease in the dosage of each drug and, thus, reducing toxicity. For these situations, liposomes and other bigger vesicles are employed. Ongoing research is being conducted on the creation of novel formulations. These systems, including some that have already received approval and others in

various phases of clinical or preclinical development, hold promise for the adoption of safer and more efficient solutions for cancer therapy in the near future.

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