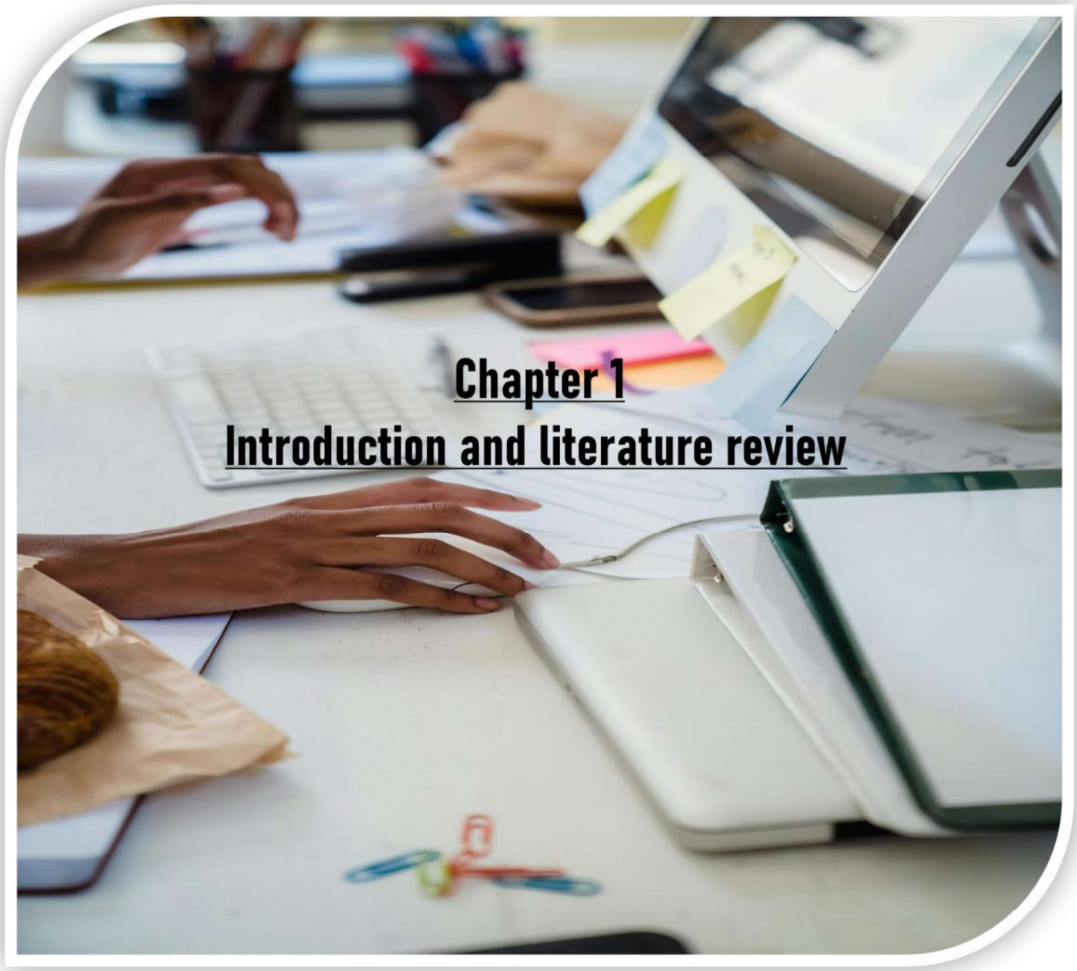

Chapter 1
Introduction and literature review

Chapter 1
Introduction and Literature Survey

1.1 Cancer

Normal cells develop through a very controlled process called the cell cycle, which involves a series of steps that set the cell up for division. This helps cells divide only as needed and maintains tissues and organs with proper structure and function. Cancer cells, however, ignore such regulatory signals. Their uncontrolled growth leads to multiplication. Almost every tissue in the body can develop cancer, and some can even give rise to multiple types of malignancies. Cancer is responsible for one in every six deaths worldwide. While effective treatments are still being sought, current approaches include conventional methods such as surgery, radiotherapy, and chemotherapy.

Traditional methods of killing cancer and their disadvantages

1.1.1.1 Surgery

Surgical removal has long been a cornerstone in the treatment and management of most solid cancers. While excising primary or metastatic tumors can save lives or extend survival, it is also well-established that surgery itself may inadvertently promote tumor recurrence. This concern was first brought about by Paget and Halsted[3] at the turn of the 20th century, who noted that patients treated with cancer resection seldom survived longer than those who were treated without surgery. Despite significant advances in surgical methods and the severe suffering of patients, still, to this day, about 30% of node-negative and 75% of node-positive patients eventually die of cancer from distant metastasis[4]. When these measures were found to be unsuccessful in providing long-term treatments, therapeutic philosophy began

changing. Fisher[5] proposed the idea that cancer possibly spreads early in the disease course before becoming clinically evident and therefore advocated less aggressive surgical therapy.

1.1.1.2 Radiotherapy

Radiotherapy, or radiation therapy, is a treatment of cancer in which high-energy radiation kills or damages cancer cells by injuring their DNA. This usually disrupts the cells' ability to reproduce and divide, thereby killing them. Epidemiological studies of the atomic bomb survivors[6] have revealed more about how radiation exposure might contribute to the onset of cancer. Radiotherapy is one of the treatments for cancer that unfortunately causes some destruction to the surrounding healthy tissues. Dosages usually fall between 56 and 66 Gy depending on whether the given radiation is of a type or target region[7]. In most cases, it causes difficulty in swallowing, soreness, hair loss, and tooth decay. The major long-term consequences of radiotherapy include xerostomia, or dry mouth, which leads to poor oral health, poor hygiene, altered sense of taste, nutritional deficiencies, sleep disturbances, and altered speech[8]. A dose of 35 Gy could permanently damage the salivary glands, causing chronic xerostomia[9].

1.1.1.3 Chemotherapy

Cancer chemotherapy is the use of cytotoxic drugs, which are agents that kill cells, to destroy tumors or reduce their size or relieve symptoms caused by a tumor, or even prolong the life of a patient. The origins of chemotherapy go back to 1942, when nitrogen mustard was discovered to have profound efficacy against malignant lymphoma[10]. The U.S. Food and Drug Administration (FDA) approved the first anticancer drug, nitrogen mustard, followed by the approval of 5-fluorouracil (5-FU) in 1962 for the treatment of multiple solid tumors, and has since been used as a very common anticancer agent in treating

gastric, breast, pancreatic, and ovarian cancers[11]. The cisplatin-induced growth inhibitory effects against E. coli were initially observed in 1965, and it was approved by the FDA in 1978. Anticancer drugs based on platinum, such as carboplatin, oxaliplatin, and nedaplatin, have found widespread use owing to their ability to cause DNA adducts and block DNA replication[12]. With the introduction of next-generation anticancer drugs like paclitaxel and docetaxel in the 1990s, there was a shift towards a new era in chemotherapy. The major mode of action of these traditional anticancer drugs is through the inhibition of DNA synthesis or cell division, which, as it turns out, also acts on normal cells, causing unwanted side effects. Chemotherapy has significant toxicity in cancer treatment, affecting several organ systems and impacting the patient's quality of life.

Intrinsic drug properties, which involve biodistribution and reaction kinetics determine which organs are affected. Other significant elements include internalization of the drug, excretion by active pumps, detoxification, and even when the treatment is administered. Most anticancer therapies operate at a subcellular level by producing different kinds of DNA damage depending on the class of chemotherapy agents. This DNA damage not only takes place in cancer cells but also within healthy tissue surrounding them, and also has systemic effects in the body. The downstream effects of DNA damage may be mutations that drive oncogenesis or deficiencies in DNA replication, RNA synthesis, cell-cycle progression, cellular senescence, or cell death, which may contribute to functional decline in cells and organs and accelerate aging. The exact result of DNA damage[13] may often depend on the specific organ or type of cell affected. For instance, chemotherapy can lead to cardiotoxic effects that range from dilated cardiomyopathy to arrhythmias and myocardial infarctions[14]. Cardiovascular disease stands among the top causes of long-term morbidity and mortality

among cancer survivors. Nephrotoxicity usually refers to alkylating agents like melphalan[15] and platinum drugs like carboplatin[16], leading to conditions like hyponatremia, glomerular dysfunction, and tubulointerstitial disease. Antimetabolites[17] such as pemetrexed can result in acute kidney injury, whereas nitrosoureas are associated with chronic kidney disease. Hepatotoxicity[18] is seen with agents such as mitomycin and lomustine, leading to hepatitis, whereas topoisomerase inhibitors such as irinotecan can result in fatty liver and VOD. Neurotoxicity[19] is quite significant with agents such as mitomycin, resulting in sensory neuropathy, and vinca alkaloids, which can cause peripheral neuropathy and acute encephalopathy. Cardiotoxicity[20] is seen with agents such as mitomycin and 5-fluorouracil, which can lead to heart failure, arrhythmias, and myocardial infarction. Hematologic toxicity, including bone marrow depression, is a characteristic of drugs like chlorambucil, nitrosoureas, and combination therapy, leading to anemia, neutropenia, and thrombocytopenia. These toxicities are significant in controlling side effects and optimizing the results of cancer therapy. In **Table 1.1.1.3a**, the toxicity details are listed below.

Table 1.1.1.3a: Side effects of Chemotherapy observed directly or late in life

Toxicity	**Chemotherapy**		**Toxicity Details**
Nephrotoxicity	**Alkylating agents**	Platinum derivatives	
		Melphalan	Hyponatremia-SIADH[15], glomerular dysfunction[16]
		Carboplatin	Hypomagnesemia[15], Glomerular disease[16], Tubulointerstitial disease[16]
	Antimetabolites	Nitrosoureas	CKD[1517,21] (chronic interstitial nephritis, glomerulosclerosis)

		Pemetrexed	AKI (ATN)[15,22], AIN[17], renal tubular acidosis[15,1722], NDI[15,17,22], glomerular disease[16]
	Anti-cancer antibiotics	Mitomycin	HUS[16,22,23], prerenal azotemia[16], glomerular disease[16], TMA[23]
		Plicamycin	Glomerular disease[16]
Toxicity	**Chemotherapy**		**Toxicity Details**
Hepatotoxicity	**Alkylating agents**	Platinum derivatives	
		Carmustine	Hepatitis[18]
		Lomustine	Hepatitis[18]
	Topoisomerase inhibitors	Irinotecan	Fatty liver/steatosis[18,24,25,26,27], hepatitis[24,27], VOD[18]
		Etoposide	Hepatitis[18], cholestasis[18], hepatocellular injury[28], hyperbilirubinemia[28]
	Enzyme		
		Asparaginase	Steatosis[18,25], hepatitis[18,25]
		Cytarabine	Biliary stricture[18,25,27], cholestasis[18,25,27,28], fibrosis[27]
	Antimetabolites		
		5-Fluorouracil	Steatosis[24,25], hepatitis[18,25], VOD[25], hyperbilirubinemia[24], cirrhosis[29]
		Methotrexate	Hepatitis[18,25], cirrhosis[18,25,27,28], nodular hyperplasia[25], fibrosis[18,25,27,28]
	Anti-cancer antibiotics	Dactinomycin	Hepatitis[18], VOD[18]
		Mitomycin	Hepatitis[18], VOD[18]
		Vinca alkaloids	

	Mitotic inhibitors	Radiotherapy	RILD[30], VOD[28,30,31], combined modality-induced liver damage (CMILD)[30], SOS[30]
		Vinblastine	Hepatitis[27], VOD[18]
Toxicity	**Chemotherapy**		**Toxicity Details**
Neurotoxicity	**Alkylating agents**	Platinum derivatives	Distal symmetrical sensory impairment[19,32], ataxia[19,32], (peripheral) neurotoxicity[19,32], loss of deep tendon reflexes[32]
		Oxaliplatin	Posterior reversible (leuko) encephalopathy[33], acute (peripheral) neurotoxicity[19,34,35], chronic sensory neuropathy[34,35], acute cramps and fasciculations[35]
	Topoisomerase inhibitors	Etoposide	Acute encephalopathy[33], chronic leukoencephalopathy[33], seizures[33], transient cortical blindness[33]
	Antimetabolite		
		Gemcitabine	Acute encephalopathy[33], posterior reversible (leuko)encephalopathy[33], thrombotic microangiopathy[33], seizures[33]
		5-Fluorouracil	Acute encephalopathy[33], acute pancerebellar syndrome[33], stroke/arterial ischemia[33], extrapyramidal syndrome[33]
	Anti-cancer antibiotics		
		Mitomycin	Acute encephalopathy[33]
		Bleomycin	Cerebral and myocardial infarcts[34]
	Enzyme		
		Asparaginase	Acute encephalopathy[33], intracranial hemorrhage[33], sinus/cortical vein thrombosis[33]

	Mitotic inhibitors		
		Vinca alkaloids	
		Vincristine (and Vinblastine, Vindesine, Vinorelbine)	Acute encephalopathy[33,34], posterior reversible (leuko)encephalopathy[33], acute pancerebellar syndrome[33], seizures[33,34], SIADH[33,34], transient cortical blindness[33,34], sensory impairment[19,34,35], distal motor impairment[19,34], ataxia[19,34], autonomic neuropathy[19,34,35], muscle cramps[34,35], mild distal weakness[34,35], parkinsonism[34], athetosis[34]
		Taxanes	
		Docetaxel	Sensory impairment[35], myalgia[35], myopathy[35]
	Proteasome inhibitors		
		Bortezomib	Severe neuropathic pain[19,34,35], autonomic neuropathy[35], dizziness[34], aphasia[34]
		Radiotherapy (combined with chemotherapy)	Chronic leukoencephalopathy[33], myelopathy[33]
Toxicity	**Chemotherapy**		**Toxicity Details**
Cardiotoxicity	**Alkylating agents**	Mitomycin	CHF[36,37], HF[20], cardiomyopathy[20],
		Carmustine	Chest pain[36], hypotension[36], arrhythmia[36]
	Antimetabolites	Capecitabine, 5-fluorouracil, cytarabine	Ischemia[38], pericarditis[38], CHF[38], cardiogenic shock[38]
		Capecitabine, 5-fluorouracil	Angina-like chest pain[37], MI[37], arrhythmia[37], HF[37]
	Topoisomerase inhibitors		
		Etoposide	Hypotension[3620], MI[36]
		Teniposide	Arrhythmia[36], hypotension[36]

	Mitotic inhibitors		
		Vinca alkaloids	MI[3620], dyspnea[36], pulmonary edema[36], atrial fibrillation, angina pectoris[20]
		Docetaxel	Left ventricular dysfunction[20], ischemia[37,20], MI[20]
	Other		
		Tretinoin	Retinoic acid syndrome[36], arrhythmia[36], hypotension[36], hypertension[36], HF[36]
		Pentostatin	Angina pectoris[36], MI[36], CHF[36], arrhythmia[36]
Toxicity	**Chemotherapy**		**Toxicity Details**
Hematological Toxicity	**Alkylating agents**	Chlorambucil	Bone marrow suppression[39,40]
		Nitrosoureas	Bone marrow suppression[39], myelosuppression[41]
	Antimetabolites		
		6-Mercaptopurine	Bone marrow suppression[39]
		Anthracyclines	Myelosuppression[41]
	Anti-cancer antibiotics		
		Dactinomycin	Bone marrow suppression[39]
		Docetaxel-cyclophosphamide	Febrile neutropenia[42]
	Combination therapies		
		Cyclophosphamide-doxorubicin-5fluorouracil	Neutropenia[43]
		5-Fluorouracil-cisplatin	Neutropenia[43]

Since the late 1990s, fourth-generation anticancer agents, referred to as molecular targeted therapies[44], have been widely noted since significant progress was made in cancer molecular biology. The agents are developed to act against particular molecules that play a role in carcinogenesis and tumor growth, hence decreasing side effects relative to conventional chemotherapy. For instance, imatinib, which inhibits the BCR/ABL tyrosine kinase, has

shown an unexpectedly strong effect in treating chronic myelogenous leukemia (CML)[45]. Similarly, gefitinib is used for non-small cell lung carcinoma (NSCLC) by targeting the tyrosine kinase of the epidermal growth factor receptor (EGFR). Although gefitinib shows some efficacy, in some instances, it is inconsistent in its effectiveness. Moreover, response to gefitinib is enormously different between Japanese and United States clinical trials. This difference lies in genetic dissimilarities of Japanese and Caucasian populations in terms of their susceptibility to the drug.

In 2004, Lynch et al. and Paez et al. reported independently the molecular explanation for the responses to Gefitinib[46,47]. The patients of NSCLC who had responded well to gefitinib showed structurally altered EGFR, while such mutant EGFR was not found among the patients who did not respond to the drug. These studies indicate that the molecular target drug works effectively for some patients of 30%, but not for others because of the genetic difference. **Table 1.1.1.3b** below represents clinical trials of Molecularly Targeted Therapy in Malignant Glioma.

Table 1.1.1.3b: Summary of selected clinical trials of Molecularly Targeted Therapy in Malignant Glioma.

Targets	Agents	Phase	Results
Growth factor ligands **VEGF** **Growth factor receptors**	Bevacizumab + irinotecan	II	Recurrent MG 63% CR1PR; PFS-6 GBM 43%; AA 61%[48]
EGFR	Gefitinib	II	Recurrent GBM (1st relapse) no radiographic response; PFS-6: 17%[49]
		I/II	Recurrent MG 14% PR; PFS-6: 11%[50]

	Erlotinib (±Temozolomide) Erlotinib Erlotinib +RT Cetuximab	I/II	Recurrent MG 6–25% PR; PFS-6 10–20%[51,52]
		I	Newly diagnosed GBM MTD-not reached; median TTP: 26 wk[53]
		II	Recurrent GBM ongoing[54]
VEGFR	Vatalanib (±Temozolomide or lomustine)	I/II	Recurrent GBM 4% PR; 66% SD; TTP: 12–16 wk[55,56]
PDGFR	Imatinib mesylate	II	Recurrent GBM PFS-6: 3%; Recurrent AA PFS-6: 10%[57]
	Imatinib mesylate+hydroxyurea	II	Recurrent GBM 9% PR; 42% SD; PFS-6: 27%[58]
Intracellular effectors **RAS (Farnesyltransferase)**	Tipifarnib	I/II	Recurrent GBM PFS-6: 12%; Recurrent AA PFS-6: 9%[59]
	Lonafarnib (+temozolomide)	I	Recurrent GBM 27% PR; PFS-6: 33%[60]
mTOR	Sirolimus (+gefitinib)	I	Recurrent MG MTD identified; 6% PR; 38% SD[44]

Most targeted agents aimed at growth and survival pathways have not demonstrated significant survival benefits when used alone in unselected glioma patient populations. This suggests that targeting a single pathway may be insufficient due to the redundancy and complexity of signaling networks in cancer cells. Gliomas and other tumors are genetically diverse, and therefore, not all tumor cells will respond to a given targeted therapy. The tumors

can also become resistant to treatment with time by way of mutations, activation of alternate pathways, or adaptive responses, diminishing the long-term efficacy of targeted drugs.

Pharmacokinetic evaluation is necessary in early-phase studies to provide estimates of drug concentrations and drug-drug interactions. Antiepileptic medication (AED) can be administered to patients with glioma, some of which induce the cytochrome P450 enzyme, increasing the metabolism of agents of interest, reducing their therapeutic levels. Independent dose escalation and stratification within trials are now necessary, which complicates trial design.

While molecularly targeted agents bring promising developments in cancer care, their shortcomings underscore the importance of combination therapy, personalized medicine strategies, and novel trial designs to counteract these limitations and enhance patient benefit.

1.2 Biomaterials and its chronology

Biomaterials is a multidisciplinary field that blends biology, chemistry, materials science, and engineering, which is essential for the development of medical devices, implants, and regenerative medicine. Biomaterials have been used since ancient times; the Egyptians used linen threads to mend wounds, while Europeans used catgut for sutures during the Middle Ages. Carbon particles and spear tips were inserted into the human body during the prehistoric era. Nevertheless, the formal recognition and structured study of biomaterials began in the mid-20th century. The term biomaterials gained its form in early developments with biologically inert materials (in 1950s) that were produced for medical use, with an emphasis on biocompatibility to ensure that there was no adverse reaction because of the materials in the body. Year 1980s-1990s saw the rise of polymer science with synthetic

polymers (such as nylon and Teflon) in biomedical applications. A term coined tissue engineering in the 1980s, and, in the 1990s, it began to acquire momentum with the discovery of biodegradable polymers. This led to the preparation of temporary implants and scaffolds for tissue regeneration. Today, from the scenario of 2000 onwards, the arena has widened towards smart biomaterials, which possess properties in the form of self-healing and shape memory. Other 3D-printing technologies[61] are also explored by researchers as they extend toward making customized biomaterials with certain medical requirements. Recent advances in hydrogels, responsive polymers, and biopolymers now enable novel applications in regenerative medicine, controlled drug delivery, and tissue engineering. Biomaterials have been classified into various categories: -

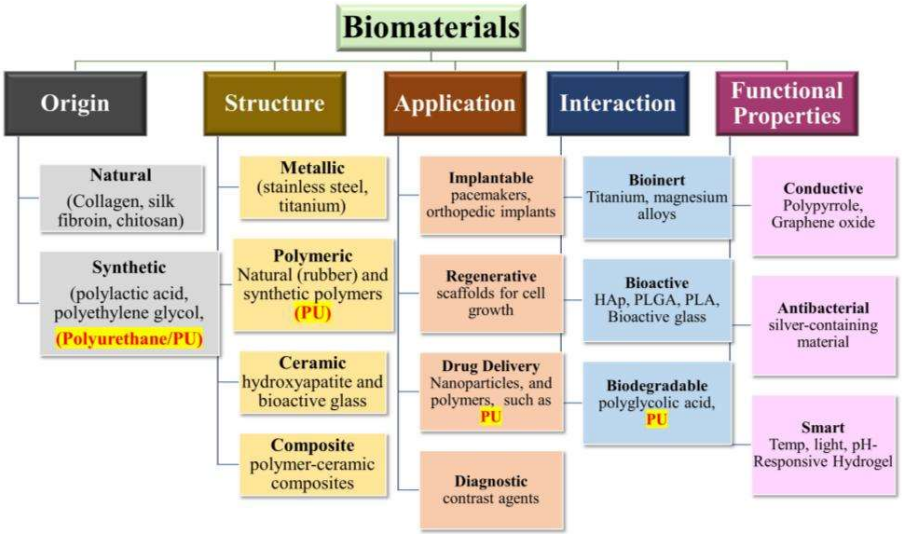

Figure 1.2: Classification of Biomaterials

Biomaterials development has continued to expand the possibilities of biomaterials, driving innovation evolution in polymer science and providing scientists with more complex and effective medical solutions. This is a very exciting area with lots of scope for more

innovations in the coming decades!

1.3 Importance of Controlled Drug Delivery Systems/Vehicles in Cancer

A drug delivery vehicle is a formulation or system designed to transport a therapeutic agent (such as a drug) to a specific site in the body to achieve a desired therapeutic effect. Essentially, drug delivery vehicles act in order to overcome the several limitations associated with conventional chemotherapy for cancer treatment. These vehicles can improve the solubility, stability, and bioavailability of drugs, enhance their targeting to specific tissues or cells, and control the release of the drug over time. The drug delivery vehicles may specifically target the cancerous cells, causing least damage to healthy tissues. This minimizes side effects and maximizes the therapeutic index by delivering drugs directly to the tumor site, thus, vehicles maximize the concentration of the drug where it's needed most, enhancing the anticancer activity. Because the drugs are delivered more precisely to the tumor, lower dosages can be used, minimizing systemic toxicity. Targeted delivery minimizes the possibility of adverse effects that are always coupled with traditional chemotherapy in most cases, including cardiotoxicity and hepatotoxicity[62]. Drug delivery vehicles enhance the bioavailability of chemotherapeutic agents so that a larger portion of the drug will reach the tumor. These vehicles can help overcome multi-drug resistance (MDR)[63] by achieving the delivery of drugs in a manner that bypasses resistance mechanisms. Use of biomaterials in drug delivery systems has been able to create vehicles that may effectively target cancer cells, providing high efficiency with low toxicity. Those carriers can respond to particular stimuli inside the body, releasing drugs at the right time and the right location. **Figure 1.3** shows time vs plasma drug concentration. The therapeutic window is indicated between the subtherapeutic level (minimum effective concentration) and

the toxic level (maximum safe concentration), showing the desired range for clinical effectiveness. The traditional release (or immediate release) profile reveals a sudden surge in drug concentration (usually with a burst effect), which temporarily can surpass the therapeutic window and cause side effects, and then drops steeply below the therapeutic level, which implies the need for multiple dosing. The burst release profile is not well controlled, shows a sudden peak in drug concentration shortly after injection, usually reaching toxic levels. Sustained release profiles have a slower rate of onset and longer duration of drug release, with drug levels being kept within the therapeutic range for a longer

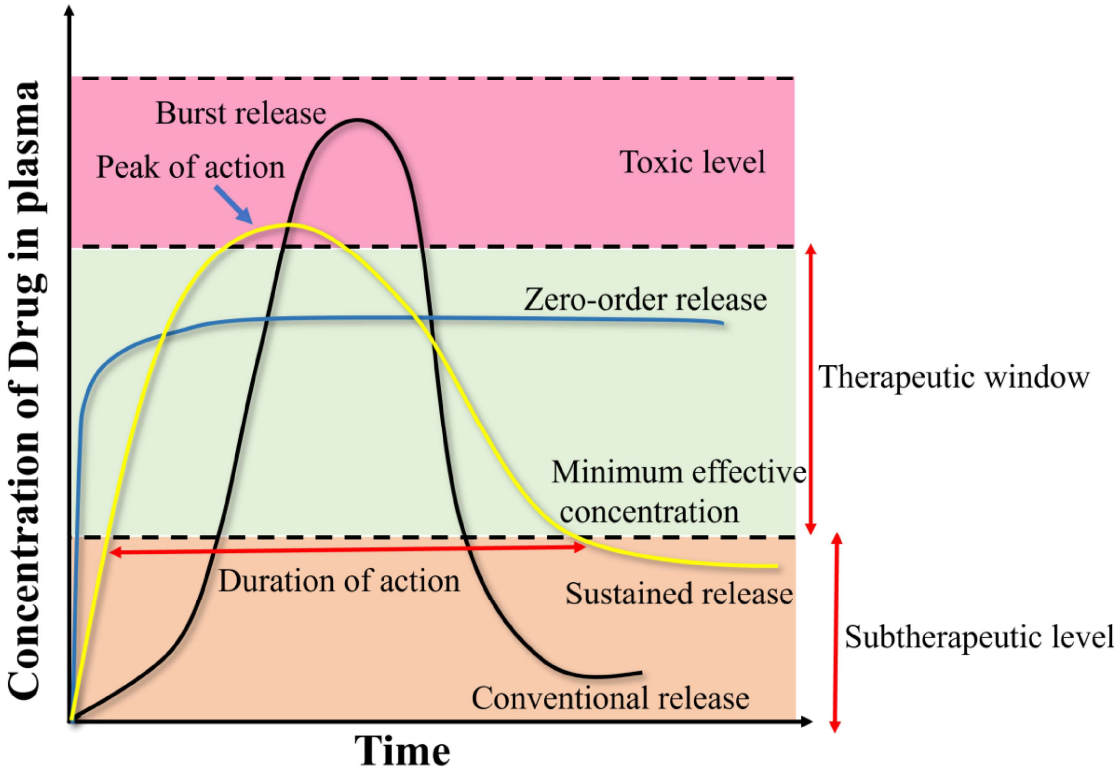

Figure 1.3: Schematic representation of controlled vs traditional drug release

period, but can still exhibit a peak-and-decline phenomenon. Zero-order release profile illustrates a theoretical controlled drug release system under which drug output is linear, the

plasma concentration remains within the curative levels all the time, except for short excursions above the toxicity level. Drug action duration is indicated by how long the concentration of the drug remains in the therapeutic range; higher in controlled as compared to simple release systems.

One important factor that we need to know is that, clinically, single-factor delivery has not proved sufficient for curing most diseases and pathological states thus far. With the complexity of many illness states, this comes as little surprise. For example, the response to normal wound healing, for instance, involves an inflammatory stage, a stage of proliferation, and a stage of remodeling. All phases of wound healing become dysregulated if there is improper wound healing, as seen in diabetic patients. However, it is certain that an effective approach must be multifaceted in order to take care of the pathological condition. This holds true for diabetes as well as for some other diseases, such as myocardial infarction (MI) and critical limb ischemia (CLI). But because events such as inflammation and angiogenesis are so interconnected that they have extremely dissimilar time-courses, administrating several agents with differing functions simultaneously may complicate matters. To be able to support transitions from one phase of the diseased state to another, it is thus not only necessary to provide different variables, but it must also be controlled in a temporal fashion. Due to this, biomaterials that can control when different elements are delivered relative to each other have therapeutic value. Biomaterials capable of temporal control of release of multiple components are valuable for biology as well as for being medicinal delivery systems. Cross-talk of multiple factors can be studied by the use of biomaterials, which can be employed for control over the temporal release of factors. For example, the development of mature and stable vessels in all four

dimensions can be researched by investigating the interaction between various angiogenic agents with scaffolds having this multi-modal release[64,65] property. The processes of complex procedures might be explained, and more relevant and efficient treatments could be developed by systematically utilizing these resources. [66]Day et al. encapsulate two drugs, Palbociclib against T cells, and Resiquimod against macrophages, on two types of silicone particles that are dispersed in the hydrogel. They demonstrated that the crosslink density of particles, independent of the bulk property of the hydrogel, governs drug release. The hydrogels can adhere to skin explants for several days without being toxic, the process can be used to polarize macrophages in an anti-tumor fashion, both *in-vitro* and *ex-vivo*, sustainably. The drug carrying capacity of poly (propylene fumarate)/PPF scaffolds was demonstrated by [67]Choi et al., who also studied the kinetics of release of doxorubicin and measured the results using optical and magnetic resonance imaging (MRI). MRI and optical imaging were utilized to quantify the release of iron oxide (IONP) or manganese oxide nanoparticles (MONP) loaded with the anti-cancer drug doxorubicin into solution under physiological conditions after absorption or mixing with the scaffold. Protamine sulfate, a chemical exchange saturation transfer (CEST) MR contrast agent, was attached to the scaffold to examine the release behavior of proteins and polypeptides. During the first 24 hours, the release rate of protamine sulfate remained constant.

Drug delivery vehicles can be individualized for every patient, using the specific characteristics of their tumors and overall health. They can be used in combination with other therapeutic procedures, such as immunotherapy, to enhance overall treatment outcomes.

In summary, drug delivery vehicles are an important component that could be used to improve the precision, efficacy, and safety of cancer treatments, thus a significant element in modern oncology.

1.3.1 Polymeric Drug Delivery Vehicles

Polymeric drug delivery vehicles revolutionized cancer treatment with targeted, controlled, and sustained delivery of therapeutic agents. They are usually prepared from polymers—large molecules of repeating subunits—for several reasons: their versatility, biocompatibility, and ease of modification. Polymers can be used to improve drug efficacy, reduce side effects, and enhance compliance from the patient's side. Polymers have the potential to design controlled release of the drug, which will reduce the dosing frequency and can improve the compliance of patients, as well as lead to better therapeutic outcomes. Polymeric carriers can be functionalized with targeting ligands (such as antibodies, peptides, or aptamers) to preferentially deliver a therapeutic to specific cells or tissues, thereby reducing off-target effects. A good number of poorly water-soluble drugs can be encapsulated within polymeric systems, thereby improving their solubility and bioavailability, particularly for oral delivery. By controlling the release profile, polymeric systems can reduce the peak drug concentration, thereby decreasing systemic toxicity and side effects. The structure of the polymers could be designed in such a way as to dictate certain properties like degradation rate, release profile, and targeting ability for specific use in therapy. Polyurethane/PU, PLGA, PEG, and PLA are widely used very extensively because of their biodegradability (does its job and excretes out of the system without requiring surgical removal), biocompatibility, and prolonged circulation time. There are

various types of polymeric drug delivery vehicles (shown in **Figure 1.3.1**) which are described below: -

1.3.1.1 Dendrimers

Dendrimers are hyperbranched tree-like molecules with significant interest in drug delivery systems because of their distinctive properties. The internal cavities and surface functional groups present a possibility for encapsulation or conjugation of therapeutic agents, including drugs, genes, and imaging agents. Typically, nanoscopic in size, the dendrimers reveal monodispersity. Drugs can interact with dendrimers through three main mechanisms: physical encapsulation, electrostatic interactions, and covalent conjugation. For example, dendrimers of poly (propylene imine) dendrimers (PPI G5.0)[68] have been synthesized by conjugating ethylenediamine and acrylonitrile with lipoproteins to facilitate the targeted delivery of the drug docetaxel. Experiments have shown that such lipoprotein-conjugated dendrimeric nano-architectures display enhanced uptake by cancer cells and increased biodistribution of docetaxel into the liver and spleen. Furthermore, folate-conjugated poly-L-lysine dendrimers (FPLL)[69] have been proven to be an effective carrier of the anticancer drug doxorubicin hydrochloride (Dox). These dendrimer-based nanoconjugates entail pH-sensitive drug release, selective targeting to cancer cells, and improvement in anticancer and antiangiogenic activities. Dox was released rapidly at first, followed by a slower, sustained release, which had a pH-dependent rate, with more found at lower pH in the drug release studies *in-vitro*.

1.3.1.2 Transdermal Patches

Transdermal patches are a form of drug administration in which the drug crosses the skin layers to enter the systemic circulation. The beauty of transdermal patches is that they avoid

several disadvantages of other parenteral routes of administration (oral or injectable routes). It is a very non-invasive route as drugs can be administered through absorption directly into the bloodstream via the skin, bypassing the digestive system and liver (first-pass metabolism). Generally, transdermal patches contain a backing layer for protection and support, a drug reservoir or matrix containing the active pharmaceutical ingredient, an adhesive layer to attach the patch to the skin, and sometimes a rate-controlling membrane. Some of the benefits of transdermal patches include consistent levels of drugs in the blood, increased compliance in the use of medication due to ease of use, and decreased risk of gastrointestinal adverse effects. Such transdermal patches have been utilized in the management of certain therapeutic applications, such as pain therapy (like fentanyl for chronic pain)[70,71], hormone replacement therapy (estrogen and testosterone replacement), and smoking cessation (nicotine patches).

1.3.1.3 Micelles

Amphiphilic molecules, which have both hydrophobic and hydrophilic regions, are the starting materials for spherical structures that form via self-assembly in aqueous solutions. These include structures with hydrophobic cores and shells of hydrophilic outer shells, enabling them to encapsulate and deliver hydrophobic drugs very effectively. Micelles improve the poor solubility of hydrophobic drugs, thus increasing their bioavailability. They can also passively accumulate in tumor tissues via the so-called Enhanced Permeability and Retention effect[72], where the abnormal, leaky blood vessels in tumors allow micelles to concentrate more in tumor sites than in normal tissues. A stimuli-responsive paclitaxel (PTX)-loaded polymeric micelle formulation with poly (ethylene glycol) (PEG) and poly (d,

l-lactide) (PLA)[73] block copolymer has been developed and has shown promise in the treatment of ovarian, breast, lung, cervical, and pancreatic cancers.

1.3.1.4 Liposomes

Liposomes are spherical vesicles consisting of a bilayer of phospholipids that enclose an aqueous core. They can encapsulate both hydrophilic drugs and hydrophobic drugs, thus, they are very versatile for delivering drugs. The bilayer configuration of the liposome closely

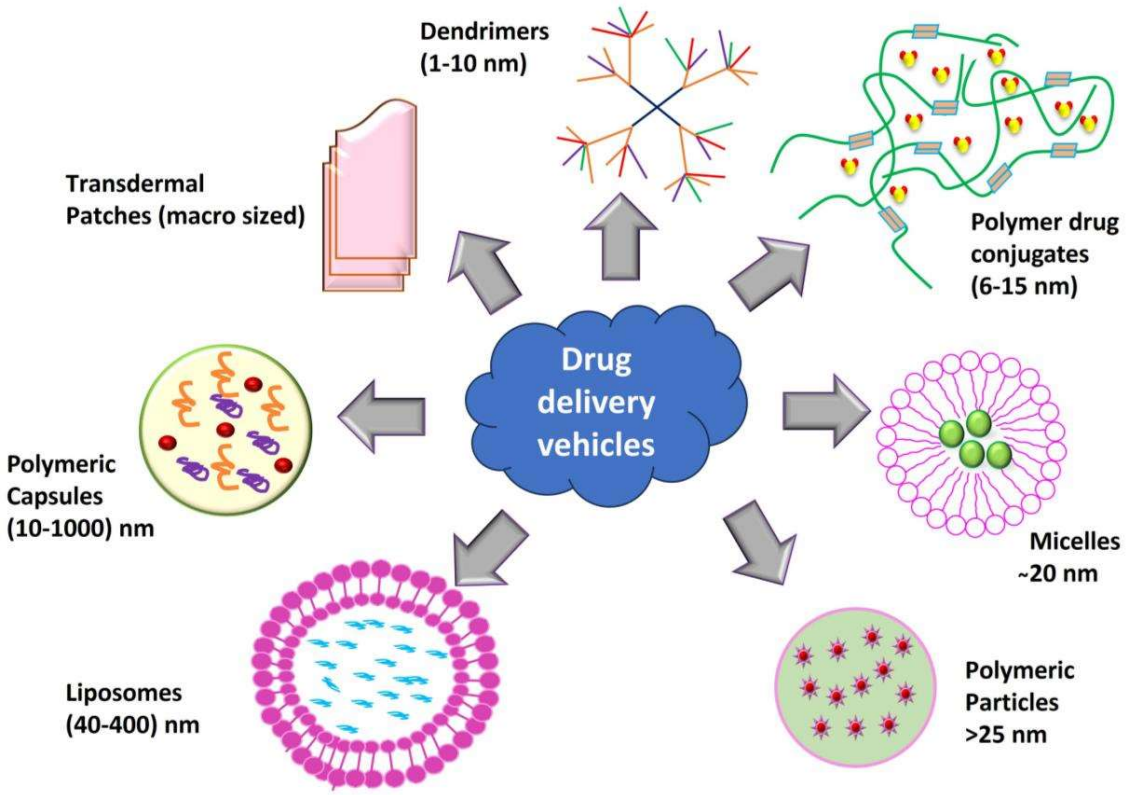

Figure 1.3.1: Various types of Polymeric drug delivery vehicles

resembles the cell membrane; thus, it fuses well with the cell membrane to effectively deliver the encapsulated contents. The modified PEG-lipid derivatives liposomes are also known to increase circulation times, which thus improves the usefulness of *in-vivo* drug delivery.

Examples of successful utilization of PEGylated liposomes loaded with doxorubicin and targeted specifically to KLN-205 squamous cell carcinoma of the lung with the help of specific antibodies on the liposome surface have resulted in a reduced tumor burden[74].

1.3.1.5 Polymeric Capsules

Over 90% of patients with metastatic cancer experience treatment failure as a result of developing multidrug resistance (MDR) to chemotherapeutic drugs, which is a significant obstacle to effective cancer treatment. The overexpression of the ATP-binding cassette (ABC) transporters, especially P-glycoprotein (Pgp), has been linked to the most prevalent underlying mechanism of MDR. This results in the efflux of numerous anticancer medications and, subsequently, drug insensitivity. A lot of work has gone into creating medications that either avoid efflux or inhibit Pgp's function in order to reverse MDR and make resistant cancer cells more sensitive to various anticancer medications. In this aspect, polymeric capsules play a significant role in modern drug delivery systems. These are hollow structures made from polymers that can encapsulate drugs, typically designed for oral delivery. The first study on the use of layer-by-layer (LbL)[75] assembled biodegradable microcapsules to overcome Pgp-mediated multidrug resistance (MDR) in colorectal cancer cells showed that loading the microcapsules with either doxorubicin (DOX) or paclitaxel (PTX) effectively restored drug sensitivity in MDR cells. This indicates that the Lbl microcapsule system could be a broadly applicable strategy for bypassing Pgp-mediated MDR. FA-HPCs[76], lately, have been fabricated with hollow porosities and specific targeting ability. These capsules showed a high efficiency in drug encapsulation, up to 86%, and controlled release of the drug up to 50% over 30 hours under acidic conditions. In vitro

studies suggested that FA-HPCs, compared to bare HPCs, exhibited increased cellular uptake and intracellular doxorubicin release efficiencies.

1.3.1.6 Polymeric Particles

Polymeric nanoparticles (PNPs) are small, discrete particles made from polymers that can encapsulate or adsorb drugs. They may be of the nanoparticle or microparticle type. For example, PLGA-PEG-PLGA nanoparticles[77] are reported to co-encapsulate both 5-fluorouracil (5-FU) and Chrysin with encapsulation efficiencies of 81.3% for 5-FU and 97.5% for Chrysin. Strong synergy was confirmed for synergistic anticancer effects of the drugs when loaded into NPs, given the CI value of 0.35. For free drugs given at the same concentrations of 5-FU and Chrysin, the CI value was found to be 0.73, which indicated their weaker synergistic effects in free forms compared to their co-loaded forms into NPs. Other researchers have focused on designing PNPs made from PCL-SS-PEG, PCL-PEI, and PCL-PEI-Fol to enhance delivery[78]. In these formulations, the PEG will render steric stabilization and stealth properties, whereas PCL-PEI and the disulfide linkages in PCL-SS-PEG respond to the tumor microenvironment, and the folate (Fol) group allows for targeted delivery to cancer cells.

1.3.1.7 Polymer Drug Conjugates

This thesis focuses mainly on polymer-drug conjugates, or PDCs, which constitute complexes produced by joining drug molecules to a polymer backbone through covalent interactions. The PDC approach has been one of the most promising drug delivery technologies in the last ten years because it exhibits many advantages, including prevention of premature drug release, simplification of controlled and targeted delivery, and enhancement of the stability, safety, and pharmacokinetics of conjugated drugs. PEG, PVA,

and PU are some of the most used polymers. Phase I/II clinical trials of the first copolymer-drug conjugates, including the N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-doxorubicin,[79] revealed an unexpected decrease in anthracycline toxicity by four to five times. Even with a cumulative dose reaching 1680 mg/m², which is equivalent to doxorubicin, cardiotoxicity was absent. Another example includes Ce6-PPE-TK-DOX nanoparticles[80], which are based on the co-self-coassembly of PPE-TK-DOX with the photosensitizer Ce6; these were capable of preventing premature drug leakage. Once this reaches the tumor site, the 660 nm red light, guided by fluorescence and magnetic resonance (MR) dual-model imaging, initiates localized ROS generation. Rapid scission of the thioketal (tk) bond occurs through ROS generation, thereby initiating site-specific release and activation of the DOX prodrug, achieving precise and controllable tumor-targeted drug delivery via light.

In summary, polymeric drug delivery vehicles offer a versatile and promising platform for improving the efficacy, targeting, and safety of pharmaceutical treatments, with ongoing research is likely to expand their applications across a range of diseases and therapies.

1.4 Mechanism of drug release via polymers

The mechanism of drug release from polymers can be quite complex and is influenced by several factors. Here are the primary mechanisms:

1.4.1 Degradation

Dissolution/degradation-controlled drug release relies on the dissolution or degradation of a polymer membrane that encapsulates the drug reservoir or a drug-containing polymer matrix[81]. Since most water-soluble polymers dissolve too quickly, they are generally not

suitable for developing drug-eluting stents (DESs). Though biodegradable polymers like poly (glycolic acid)[82], poly (lactic acid), and poly (ε-caprolactone) are hydrophobic, degradation due to hydrolysis can be achieved over weeks or months. In this case, materials will degrade slowly and are therefore applicable to any drug delivery formulation that needs a prolonged release over time, such as in stents. The rate of degradation of the polymer is dependent on various parameters, which include the molecular weight and functional groups of the polymer and the monomers, as well as its crystalline structure, which could influence the release kinetics. When cleaved by enzymes[83], the polymer-drug bond triggers drug release, and the rate of these cleavages determines the release behavior. This can be targeted towards the site of interest if the enzyme is concentrated there.

1.4.2 Diffusion

In diffusion-controlled release systems, drugs are diffused into a polymer under the motion of either the drug and often that of the degrading polymer. A simple example of diffusion-controlled release is where the drug can be encapsulated in a core or reservoir from which it gradually diffuses. These systems can be classified into two types: reservoir devices and matrix devices[84]. In reservoir systems, the drug is contained within a hollow inner core, surrounded by a polymer membrane. The overall drug release is primarily determined by the diffusion of the drug through the membrane, which is the rate-limiting step. In this case, the drug is either dispersed or dissolved in the polymer reservoir, and its release is driven by the concentration gradient across the membrane. In matrix systems, there is no distinct membrane or barrier. The drug is uniformly distributed within the polymer matrix, and the release occurs as the drug diffuses through the matrix. Initially, the drug is released rapidly, but as the release progresses, the rate slows down due to the increasing diffusion distance.

1.4.3 Swelling

The transport of solvent into a drug carrier can significantly affect the drug release behavior from the carrier. Solvent-controlled release mechanisms include osmosis-controlled and swelling-controlled release. Osmosis-controlled release occurs when a drug carrier is encased in a semi-permeable polymeric membrane, allowing water to flow from an area of low drug concentration (outside the carrier) to a high drug concentration (inside the drug-loaded core). This mechanism results in a zero-order release profile as long as a constant concentration gradient is maintained across the membrane. In swelling-controlled release, when glassy hydrophilic polymeric systems are exposed to aqueous solutions, such as body fluids, water diffuses into the system, causing the polymeric particles to swell. This swelling process leads to drug release. The release rate in this case depends on both the rate of water diffusion and the chain relaxation of the polymers. Swelling-controlled systems often use polymeric materials with three-dimensional crosslinked networks, like hydrogels, where the mesh size is crucial in regulating the drug release behavior. The drug release from hydrogels can be analyzed using the semi-empirical Peppas model[85].

1.4.4 Stimuli-responsive release

Responsive polymer-based materials are designed to modify their chemical and/or physical properties as a response to external stimuli. They can adapt to their environment, control the transport of ions and molecules, change wettability and adhesion, and convert chemical and biochemical signals into optical, electrical, thermal, and mechanical signals, or vice versa. Some polymers, including poly[N-[2-(diethylamino) ethyl acrylamide]][86] (PDEAEAM), poly (N, N-dimethylaminoethyl methacrylate) (PDMAEMA), poly (N, N-diethylaminoethyl methacrylate) (PDEAEMA), poly(2-(N-morpholine) ethyl methacrylate) (PMEMA), poly

[oligo (ethylene glycol) methacrylate], and poly (N, N-diethylacrylamide) (PDEAAM), have LCSTs (low critical solution temperature)[87]. Multi-responsive polymers can also be prepared by introducing functional groups responsive to more than one stimulus. For example, pH-responsive groups with ionizable functional groups, such as acrylic acid (AAc) and N, N-dimethylaminoethyl methacrylate (DMAEMA), can be used. Light-sensitive monomers, including azobenzene, can be incorporated to make materials that are responsive to temperature and light as well. Responsive nanoparticles that release payloads of drugs in response to pH changes or oxidative stress are particularly promising in the clinic, where they are offering targeted drug delivery to specific loci or states of disease. Polymer systems can exploit the ionization of functional groups at different pH values. Thus, carboxylic acids are charged as a negatively charged species at near-neutral pH but protonate at lower pH and become uncharged. The pK of the carboxylic acid group can be modified to control when this transition occurs within the physiological environment. Likewise, tertiary amines act in the opposite manner. They are unprotonated, neutral, and lipophilic in neutral and basic solutions but become protonated, positively charged, and hydrophilic in weakly acidic environments[88].

1.5 Modes of drug delivery in Cancer treatment

1.5.1 Intravenous

An IV injection is the direct administration of a drug into a vein, with rapid entry of that drug into the bloodstream. It is commonly used in emergencies when speed is essential or precise dosing is required. Peripheral lines are administered into an arm, while central lines are given for longer infusions. Since chemotherapeutic agent is delivered through the bloodstream, the drugs will affect not just the cancer cells but also healthy cells, leading to side effects such

as nausea, fatigue, hair loss, and many more. Some drugs even have long-term effects of toxicity to an organ in an individual, like the heart, kidneys, and liver[89].

1.5.2 Subcutaneous

A subcutaneous (sub-Q) injection is administered into the tissue layer between the skin and the muscle. This method is generally used for medications that require slow, sustained absorption into the bloodstream. Medications are injected subcutaneously in common sites in the abdomen, thigh, or upper arm. Subcutaneous injections are usually faster and less painful than IV treatments, which cause vein irritation or require long infusion times. For example, where some sub-Q anticancer drugs might cause a mere, minimal localized reaction at the site of injection, such reactions tend to be milder than those produced by more invasive interventions. Other sub-Q anticancer drugs may achieve lower systemic exposure overall, with a proportionally diminished risk for many toxic effects on organs like the liver, kidneys, or heart from such drugs compared with systemic forms of chemotherapy with IV administration. It can increase the drug's efficacy while limiting systemic exposure.

1.5.3 Intraperitoneal

An intraperitoneal (IP) injection involves injecting a substance directly into the peritoneal cavity, the area that contains the abdominal organs. It is commonly employed in research work on animals and sometimes administered to people for specific types of chemotherapy for ovarian cancer. The catheter or port used for the administration of chemotherapy may become infected, leading to peritonitis or any other infection in the abdominal cavity.

1.6 Strategies for polymer modification

1.6.1 Grafting

Graft copolymers consist of polymer branches covalently attached to a primary polymer chain. When a graft copolymer has only a single branch, it is referred to as a miktoarm star copolymer. Both the backbone and branches can be homopolymers or copolymers with varying chemical structures or compositions. However, when the polymer is a homopolymer, the process of forming the branches is known as polymer branching. In contrast, polymer grafting typically refers to a chemical method for creating materials where the branches are chemically distinct from the backbone or primary polymer chain. These branches are

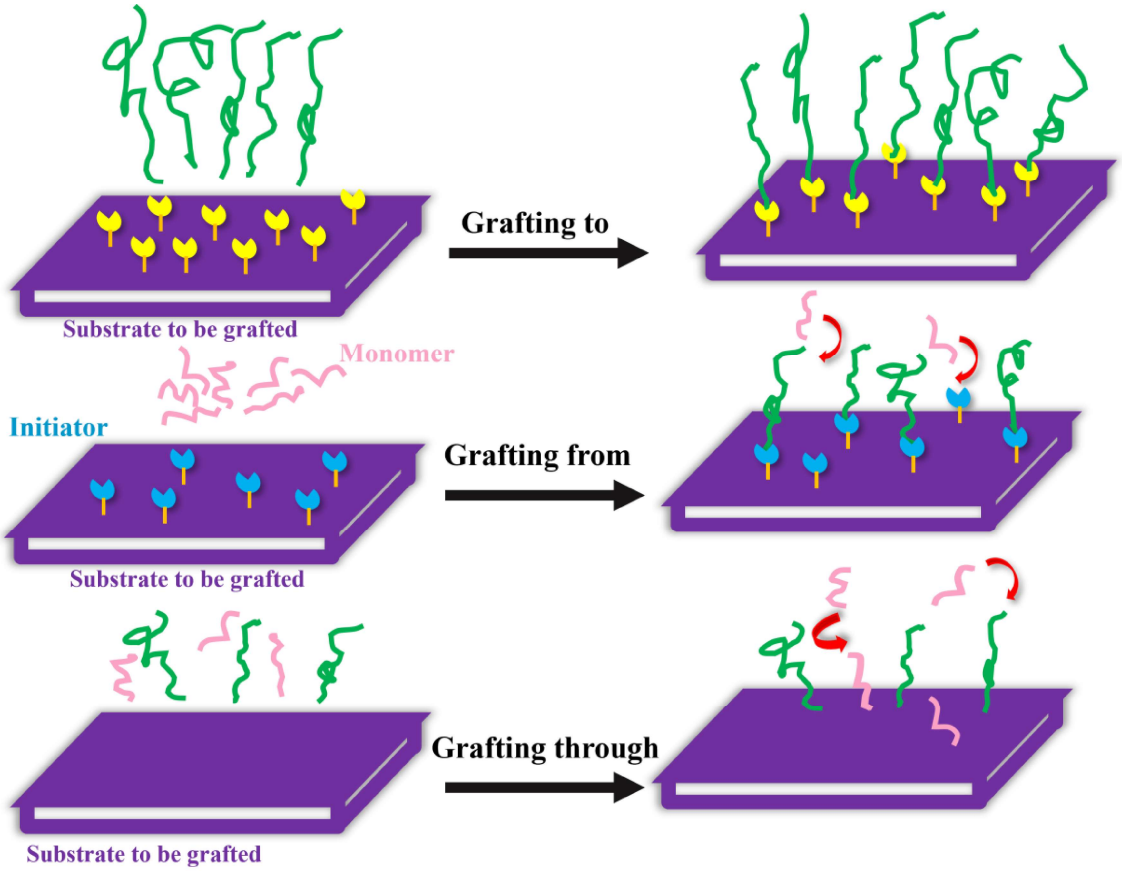

Figure 1.6.1: Mechanism of Grafting Polymerization

generally uniform in size, although they have a random distribution along the backbone as a result of the method of synthesis. There are three principal methods by which polymer grafting can be achieved: "grafting to," in which a functionalized polymer with a reactive end group reacts with functional groups on the backbone; "grafting from," in which chains of polymer grow out from initiating sites within the backbone; and "grafting through," in which a macromolecule, itself having a reactive end group, copolymerizes with a low-molecular-weight monomer. These grafting methods are represented schematically in **Figure 1.6.1.** Among these, “grafting to” and “grafting from” are the most widely used techniques. The "grafting to" method typically produces more well-defined graft segments, as the polymerization process is separate from the bonding between the backbone and the grafts[90].

1.6.2 Atom transfer radical polymerization

A general mechanism for ATRP is outlined in **Figure 1.6.2.** In this process, active species, or radicals, are generated through a reversible redox reaction facilitated by a transition metal complex ($M_t^m L_p$/Ligand, where L may be another ligand or the counterion). This complex undergoes one-electron oxidation, which leads to the abstraction of a (pseudo) halogen atom, X, from a dormant species, R−X. The activation occurs at a rate constant, k_a, while the deactivation occurs at k_d. Polymer chains grow as the intermediate radicals add to monomers, similar to conventional radical polymerization, with a propagation rate constant, k_p. Termination reactions (k_t) also occur in ATRP, mainly via radical coupling and disproportionation. However, in well-controlled ATRP, only a very small percentage of polymer chains end up undergoing termination. Under the conditions of the nonstationary initial short stage of polymerization, no more than 5% of the growing chains undergo

termination. In this case, products are oxidized metal complexes, $M_t^{m+1}L_pX$, that act as persistent radicals, reducing the number of growing radicals and termination.

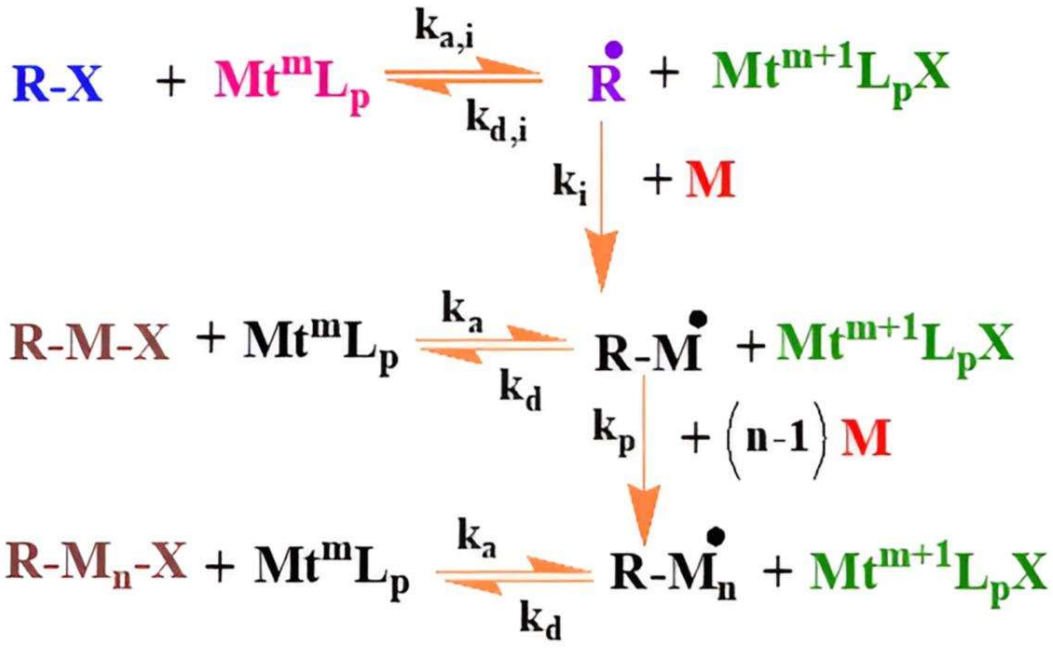

Figure 1.6.2 Mechanism of ATRP Polymerization

A successful ATRP limits the termination of chains but also ensures uniform growth across all chains by rapid initiation as well as fast reversible deactivation[90,91].

1.6.3 Reversible addition-fragmentation chain transfer polymerization

Reversible addition-fragmentation chain transfer (RAFT) is a highly robust and versatile technique for controlling radical polymerization. By carefully choosing the appropriate RAFT agent based on the monomers and reaction conditions, this method can be applied to most monomers that undergo radical polymerization. This allows for the synthesis of well-defined homopolymers, gradient polymers, diblock copolymers, triblock copolymers, and star polymers, as well as much more complicated structures, including microgels and polymer brushes. The activation/deactivation process of RAFT polymerization occurs

through degenerate chain transfer, **Figure 1.6.3.** This chain-transfer process is termed "degenerate" because it only involves a functional group interchange, with the only distinction between the two species in the equilibrium being its degree of polymerization[91,92]. The creation of a radical (step 1) is the initial stage of polymerization, known as the initiation phase. Thermal auto initiation of monomers like styrene, direct photochemical stimulation of the chain transfer agent/CTA by ultraviolet light, γ radiation, and pulsed laser irradiation are only a few of the several forms of initiation that have been documented for RAFT polymerization. However, because these chemicals are commercially available, the most popular initiation technique is the thermal breakdown of radical initiators.

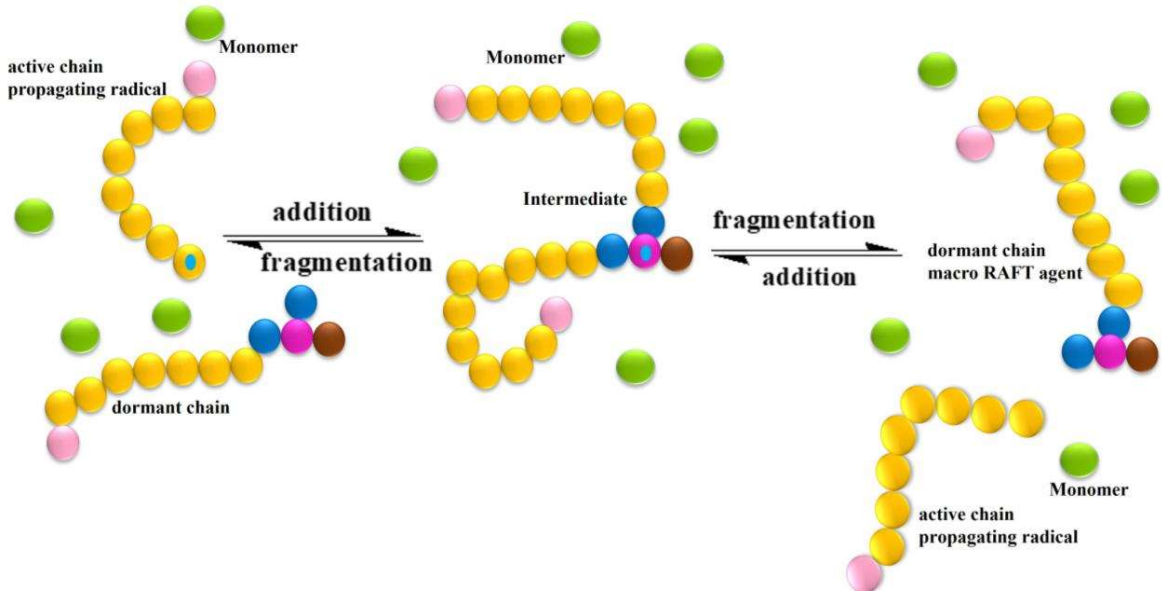

Figure 1.6.3 Mechanism of RAFT Polymerization

1.7 Polyurethane and its structural parts

Otto Bayer (German industrial chemist) unpredictably transformed the world of materials and engineering (in 1937) when he discovered polyurethane/PU, or rather as he named it, "Das “Dilsocganat-Poluadditionsverfahren”[93]. It is a highly desired polymer because it has

an easy synthesis mechanism and has adaptable qualities, which are determined by its structure. The name PUs points to the resulting urethane linkage,[94]a strong and versatile member of polymers that can be easily processed through polycondensation in the presence of the OH (hydroxyl) groups of a polyol and the NCO (isocyanate functional group) groups of an isocyanate in lenient conditions. Since polyurethanes are neither polymers with a preponderance of urethane groups nor polymers made by polymerizing a methane monomer, the word is more convenient than accurate. Polymers containing several urethane groups within the molecular backbone are considered polyurethanes regardless of the chemical nature of the remainder of the chain[95]. Urethane groups result from this exothermic reaction as seen in **Figure 1.7a**.

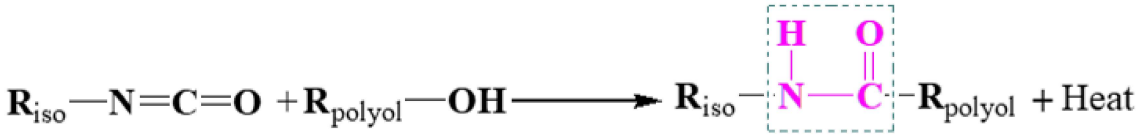

Figure 1.7a Generalized reaction scheme of Polyurethane synthesis.

While polyols[96,97] make up the majority of soft segments (SS), diisocyanates and chain extenders are essential ingredients in the formulation of hard segments (HS). The thermodynamic incompatibility between the hard and the soft segments of the polymer leads to microphase separation, responsible for the excellent elastomeric properties of PUs. The high glass transition temperature (Tg) of HS helps PUs have the solvent resistance, thermal stability, and mechanical qualities that are desired[98]. Conversely, SS, which has a low Tg, gives polyurethane (PU)[99,100]exceptional flexibility and elasticity. The selection of diisocyanate and chain extender substantially impacts the final properties of the polymer. PU-based biocompatible materials, which are increasingly complex and multifunctional,

have been developed to regulate drug release through a range of mechanisms. Biodegradable polymers,[101] in particular, are of great interest because they can degrade, be excreted, or reabsorbed naturally, eliminating the need for repair, removal, or surgical intervention. Aliphatic PUs have long been regarded as one of the most significant groups of biomedical and biodegradable polymers. Typically, biodegradable polymeric nanoparticles tend to release drugs slowly and insufficiently, which can limit their therapeutic effectiveness. To overcome this challenge, various stimuli-responsive polymeric nanoparticles have been developed[102]. Anti-cancer PU-DDSs are an area of active research interest within the fields of materials and pharmacology. These systems supply stable formulations, improved pharmacokinetics, and a degree of physiological or passive targeting to tumor tissues. As depicted in **Figure 1.7b,** the extensive use of PU in medicine, pharmacy, and biomaterial engineering proves its importance.

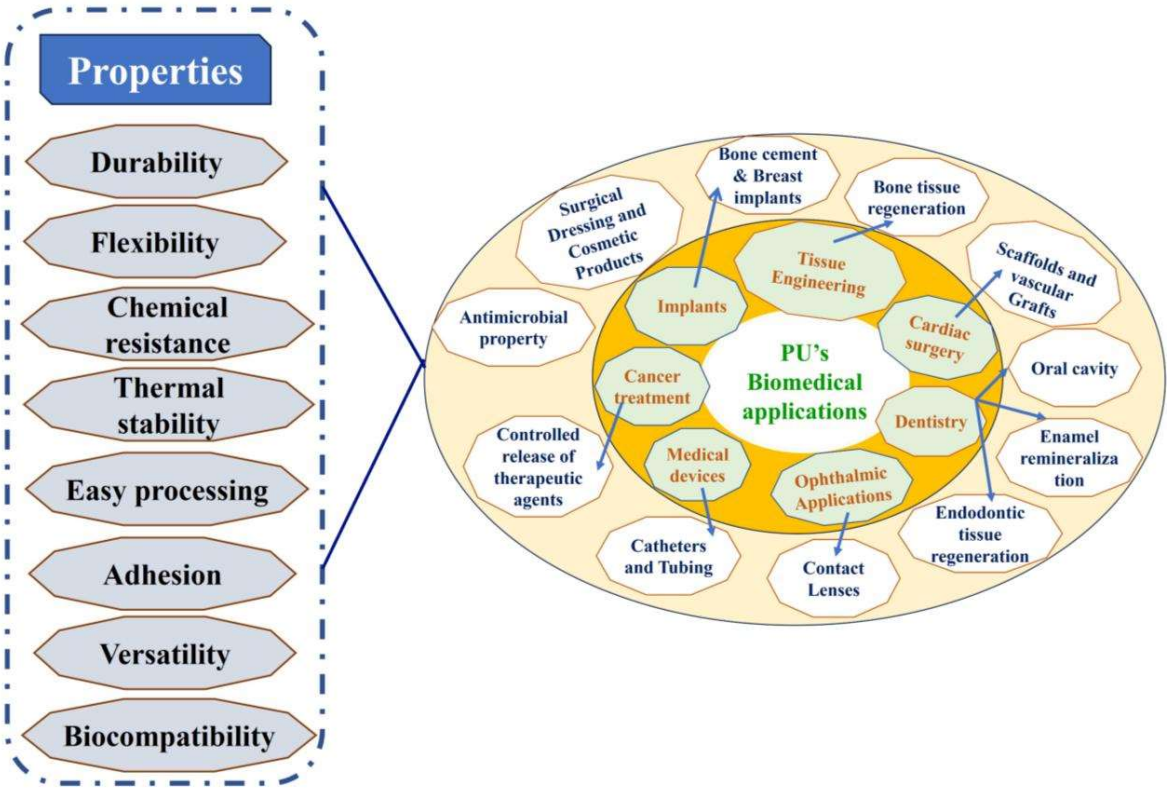

Figure 1.7b Biomedical applications of Polyurethane with various properties.

1.7.1 Chain Extenders

Typically, a chain extender is a low molecular weight compound that reacts with isocyanate groups in polyurethane to extend the polymer chain and modify its physical properties. The mechanical properties of PU elastomers significantly depend on the hard-to-soft segment ratio and the structure or the length of the chain extenders[98,103]. For biomedical applications, one desires good biocompatibility coupled with a low susceptibility to hydrolytic and enzymatic degradation. Inter-urethane hydrogen bonding between carbonyl and N–H groups, as well as in the composition of microphases, are the most critical factors in designing biodegradable materials. Hydrogen bonds' distribution can be broken by the presence of branched structures in the chain extender or chemical cross-links that prevent the free movement of macromolecular chains[104]. Biocompatible chain extenders, such as those from natural or bio-based sources, including polyethylene glycol (PEG), lactic acid derivatives, polyols, amino acids, peptides, cellulose, or dextrin, enhance polyurethane biotolerance. As such, components themselves have less chance of immune reactions or toxicity when exposed to body fluids or tissues. The system is more suitable for medical implants, drug delivery systems, wound dressings, and other biomedical uses. The surface properties of PU can be tailored through the type of chain extender used. For example, PEG-based chain extenders[105] provide anti-fouling or anti-bacterial properties, which are critical for preventing infections and promoting wound healing. Cell attachment, growth, and tissue integration are promoted by a more hydrophilic surface, whereas biocompatible hydrophobic chain extenders could decrease water absorption and hence stabilize the material in moisturizing environments.

1.7.1.1 Amino-acid as chain extender

Amino acids are organic compounds, joined together to form proteins needed for many biological processes. Each amino acid has a different molecular structure, but they all have a common backbone in the form of an amino group (-NH_2), a carboxyl group (-COOH), and a side chain (R-group) that differs between the various amino acids. Hydrophilic amino acids-for example, glycine or serine-may improve the water solubility of the polyurethane and make it more flexible. Hydrophobic amino acids, including phenylalanine and leucine, can enhance the material's rigidity and hydrophobicity[106]. The size and type of amino acid used affect the molecular weight of the polymer and thus the hardness, flexibility, and tensile strength of the polyurethane[107]. Polyurethanes prepared using amino acids have enhanced biocompatibility, which allows their application in medicine in scaffolds for tissue engineering, drug delivery systems, and biomedical coatings. The amino acid can act as a crosslinking agent, especially if the molecule carries more than one functional group like in the case of those that contain an amino and a carboxyl group. This would increase the density of the polymer network, thermal stability, and mechanical strength.

1.7.1.2 Peptide as chain extender

Peptides, short chains of amino acids linked by peptide bonds, are naturally broken down by proteolytic enzymes, which makes polyurethanes containing peptide sequences more biodegradable and environmentally sustainable. This feature is especially valuable in medical and environmental applications where controlled, time-dependent degradation is needed. For example, collagen-mimetic peptides, which mimic collagen—a key protein in connective tissue—can be used as chain extenders in polyurethanes. These peptides, in fact, enhance cell recognition and adhesion; thus, the resultant polymer is suitable for tissue

engineering[108]. Similarly, the RGD[109] sequence, a known cell adhesion motif, has been known to enhance cell attachment in polyurethanes, making them ideal for biomedical applications such as wound healing and implantable devices. Peptides that mimic elastin[110], a highly elastic protein in connective tissue, can be used to increase the elasticity and stretchability of polyurethanes, making them more suitable for flexible biomedical materials. By utilizing the distinctive properties of peptides, polyurethanes can be engineered for a variety of applications in biomedicine, environmental sustainability, and smart materials.

Table 1.7: Polyurethane-based DDSs in the Cancer Treatment

Material	**Anti-cancer Drug**	**Advantage**	**Reference**
MPEG-PU(SS)-MPEG triblock copolymers	DOX	In vitro, DOX-loaded CCL-PUMs exhibit less cytotoxicity than either free DOX or DOX-loaded uncross-linked polyurethane micelles; *in-vivo*, however, the drug-loaded CCL-PUMs exhibit the greatest anti-tumor activity with the least amount of toxicity.	(2014)[111]
Polyurethane was synthesized from PEG, PCL, IPDI, Cys, and DMPA	DOX	*In-vitro,* cytotoxicity studies demonstrated that the DOX-loaded PU-CCL displays lower cytotoxicity *in vitro* compared to either free DOX or DOX-loaded uncross-linked PU micelles.	(2017)[112]
PCL-diol and PEG-diisocyanate	DOX	pH-sensitive drug delivery carriers demonstrated significant toward different tumor cells. Besides, the dual-fluorescence emission of this system can be practical for tracking and monitoring their intracellular drug release in real-time.	(2017)[113]
PEG and HDI-based PU with lysine, glutamine, and	Imatinib	These Pus have been loaded with drugs at 94% loading efficiency	(2018)[114]

arginine as chain extenders			
A 3D scaffold designed for local drug release is prepared by blending PTX-loaded phospholipid liposomes with waterborne PU.	PTX	The results of the cell experiment showed that the dual-encapsulated scaffold not only inhibited the breast cancer MCF7 cells at a higher rate but also caused less harm to normal tissue cells.	(2020)[115]
Disulfide with a cystamine-functionalized PEG as the hydrophilic block and polycaprolactone diol as the hydrophobic block	DOX	In a reductive setting, the micelles could quantitatively release almost 80% DOX in 5 hours. When DOX-loaded SS-PU-SS-PEG micelles were incubated with Saos-2 cells in vitro, their intracellular drug release increased.	(2020)[116]
PEG, PCL with L-lysine diisocyanate along with chain extenders 1,3-propanediol	RGD-decorated paclitaxel	The dual-targeting PTX-PDCs from scaffolds were shown to be able to specifically kill GBM cells while shielding healthy cells in an *in-vitro* cytotoxicity test.	(2022)[117]
A commercially available diisocyanate, with PEG-O as the chain stopper, results in the formation of an ABA-type amphiphilic block copolymer	Cisplatin	Polymer–prodrug conjugate nanocapsules demonstrated cellular uptake and the intracellular release of the active drug in a reducing environment.	(2023)[118]

1.8 Objective

The introduction above highlights the extensive research on DDSs using polymer formulations, particularly for bioactive small molecules, due to their numerous advantages. Additional benefits from polyurethane-based polymers have been derived apart from biocompatibility, these include host-guest inclusion complexes formation with various small molecules. In addition, grafting of amino acids as well as peptides onto different PUs makes it possible for targeted and theranostic approaches. The effect of graft density and length on

drug release through PU grafted with amino acids and peptides has not been fully explored in the literature. Second, controlled drug release via AA-PU hydrogels/films and peptide-PU systems for cancer therapy is yet to be addressed. Hence, the main objective of this work is to develop and prepare various polymeric architectures containing TRP, CYS, GLY, and their homopeptides, which could be altered chemically in order to modulate the release of drugs. The study would focus further on the sustained release efficacy in cellular and *in-vivo* studies, aimed towards the further improvement of cancer treatment. For this purpose, the specific objectives have been outlined as follows:

1.9 Plan of Presentation

To achieve the aforementioned goals, the following plan has been implemented.

a) Modulation of Drug Release: Exploring the Influence of Diisocyanate Variants on Polyurethane Matrix

- ✓ Four different types of PU have been synthesized by varying the diisocyanate units.
- ✓ To confirm the grafting spectroscopic characterization has been done, followed by mechanical and thermal properties investigation.
- ✓ *In-vitro* drug release kinetics have been explored by embedding Paclitaxel/PTX in the grafted polymer matrix, and hydrophilicity with the help of contact angle has been measured.
- ✓ Biocompatibility of the four PUs has been assayed using MTT, along with the cancer cell-killing efficacy of all the drug-loaded PUs, has been checked and compared with pure drug.

b) Tryptophan-based biocompatible Polyurethane, a theranostic approach for tumor killing and *in-vivo* toxicity study to check localized treatment efficacy

- ✓ PU has been modified by grafting with Tryptophan/TRP, and the grafting percentage has been calculated using NMR spectroscopy.
- ✓ FTIR and UV-VIS spectroscopy have been performed along with XRD to check crystallinity, followed by morphological and thermal property investigation.
- ✓ A fluorescence study has been performed by varying the concentration of the polymers to calculate the MFI.
- ✓ *In-vitro* drug release kinetics have been explored by embedding Paclitaxel/PTX in the grafted polymer matrix.
- ✓ Drug-polymer interaction has been explored theoretically by molecular docking study.
- ✓ Biocompatibility of all the PUs has been assayed using MTT on both cancer and healthy cell lines, along with the cancer cell-killing efficacy of all the drug-loaded PUs has been checked and compared with pure drug.
- ✓ Fluorescence images in the cancer cells are also taken to check the theranostics approach.
- ✓ To check the localized tumor treatment efficacy, subcutaneous injection of methyl cellulose/MC loaded PU-TRP-PTX hydrogel is given to mice, and H& E staining along with TNFα has been done.
- ✓ *In-vivo* drug release kinetics have been explored by embedding Paclitaxel/PTX in the grafted polymer matrix by incorporating with MC-gel in both IV and IP mode, and compared with pure drug.

c) L-cystine-based polyurethane as a drug delivery vehicle in targeted cancer therapy and biomedical applications

- ✓ PU has been modified by grafting with Cystine/CYS, and the grafting percentage has been calculated using NMR spectroscopy.
- ✓ FTIR and UV-VIS spectroscopy have been performed along with XRD to check crystallinity, followed by morphological, mechanical, and thermal property investigations.
- ✓ *In-vitro* drug release kinetics have been explored by embedding Paclitaxel/PTX in the grafted polymer matrix.
- ✓ Swelling properties of the matrix, as well as biodegradation studies, have also been performed.
- ✓ Biocompatibility of all the PUs has been assayed using the MTT assay on both cancer and healthy cell lines, along with the cancer cell-killing efficacy of all the drug-loaded PUs has been checked and compared with pure drug.
- ✓ Anti-bacterial properties of CYS-modified PU, along with ROS-assay, have also been performed.

d) Engineered Polyurethane with Glycine and its homopeptides: A biomimetic approach for targeted drug delivery in cancer therapy

- ✓ Three different types of PU have been synthesized by varying Glycine and its homo-dipeptides and tripeptides.
- ✓ To confirm the grafting spectroscopic characterization has been done, followed by thermal property investigation.
- ✓ *In-vitro* drug release kinetics have been explored by embedding Paclitaxel/PTX in the grafted polymer matrix.

- ✓ Drug-polymer interaction has been explored theoretically by molecular docking study.
- ✓ Biocompatibility of all the PUs has been assayed using the MTT assay on both cancer and healthy cell lines, along with the cancer cell-killing efficacy of all the drug-loaded PUs has been checked and compared with pure drug.