

Chapter 2

Biomaterials and Its Advances for Delivering Anticancer Drugs



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Abstract Most of the anticancer drugs affect both the cancerous cells and the normal cells. The most common treatment chemotherapy is always associated with the poor selection of the targeted cancer cells and also the drug resistance. Therefore, to enhance the therapeutic efficacy of anticancer drugs, nano-drug delivery systems have been designed and implemented. To limit the challenges associated with the conventional chemotherapy, there are strategies to combat it. The strategies are functionalising the material, functionalisation with multiple targets, in vivo imaging and dual/multiple drug delivery system. This chapter provides insights about the wide range of polymers which helps to engineer the anticancer molecules. It also emphasises the different mechanisms for releasing the anticancer drugs in an effective manner. The recent advances about the materials used for cancer therapy and commercially available products are also discussed. The effect of engineered biomaterials for treating the cancer patients is mostly expected to increase in the future.

Keywords Anticancer drugs · Biomaterials · Targeted delivery system · Release · Functionalisation · Chemotherapy

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1 Introduction

Cancer is the most major disease in the world with huge number of death due to exposure of carcinogenic substances, change in diet, age, suppression in the immune system and other factors [1]. In the recent years, a lot of progress has been taken place in developing a targeted delivery system. By these effective treatments, the survival rate of patients will be increased and still some of the disadvantages occurs. The chemotherapy treatment acts non-specifically in the cancerous cells and also in the normal cells because of the toxic side effects. Moreover, a high dose is required for some of the patients at regular intervals to improve the therapeutic efficacy in the targeted area [2, 3]. The recent advancements of the biomaterials incorporated delivery system provide the specific release of the anticancer agents only in the cancerous cells by subsequently improving the life of patients and its side effects are eliminated [4].

There have been a lot of developments in the recent years for the treatment of cancer are formulations of controlled delivery system, targeted delivery systems and nano-drug delivery system. Formulating a biomaterial with a controlled or targeted release is quite challenging task and needs a multidisciplinary approach [5, 6]. There are certain parameters to develop the formulation and they are incorporating the sufficient drug within the biomaterial for the controlled and prolonged release to achieve better efficacy. Secondly, to protect the drug in the human environment (in vivo) to increase the biological activity. Thirdly, formulating a drug by predicting its release behaviour to improve its therapeutic efficacy which ranges from weeks to years. Fourthly, the drug component and the biomaterials should be biocompatible and nontoxic within the system. Fifthly, the developing material should avoid the discomfort before and during administration. Finally, the drug-biomaterial formulation should be affordable to the patients which are most important factor to taken into account before designing the formulation [7, 8].

There is strong growth in developing biomaterials for the controlled/targeted release of anticancer drugs by imbibing different types of mechanisms which is not confined to diffusion, swelling, magnetic and chemical-based mechanisms [9–11]. There are formulations which consist of phospholipids with bilayer structures that lead to the preparation of liposomes and it is one of the nanocarrier delivery systems. This then expanded into many carriers such as micelles, nanospheres, nanomaterials, dendrimers and inorganic nanoparticles in the rapidly increasing field of nano-drug delivery system. The biomaterials and the drug can also be modified by microfabrication technology to formulate patches consisting of microneedles which pierce the skin without pain to deliver the drug. This transdermal delivery system allows the drug to improve the permeability in skin, it should dissolve, should be biodegradable and should not leave any waste. Very recently, there are smart and intelligent biomaterials have been developed which responds to the environmental factors (pH, enzymes, temperature and pressure) for releasing the drug. Likewise, there are biomaterials which can be triggered by UV-Vis light, NIR light, sound, electrical currents and by means of magnetic pulse for delivering the drugs in controllable pace [12–16].

In this chapter, the importance and the need for the incorporation of biomaterials in the drug delivery system are explained. An outline of the natural, synthetic and combination of both natural and synthetic materials used for the development of the targeted delivery system is also highlighted. The recent advancements in the design, development and preparation of hybrid materials are also described. Lastly, the significance of the polymeric materials incorporated in the targeted system and commercially available products are also presented.

2 Classes of Biomaterials for Anticancer Activity

There is a broad array of polymers used as carrier for the anticancer compounds and this includes natural, synthetic and hybrid classes (Fig. 1). In the synthetic class, organic and inorganic materials are used, and this section deals with the physical, chemical properties and mechanisms of drug delivery of individual class of carriers. The natural source of biomaterials comes from both the animals and the plants which includes collagen, alginates, hyaluronic acid, silk fibroin, chitosan and others. The synthetic classes of biomaterials include poly(ethylene glycol) (PEG), polylactides, polyglycolide and its derivatives. Then, the hybrid materials include PEG-alginates, PEG-proteins and others [17].

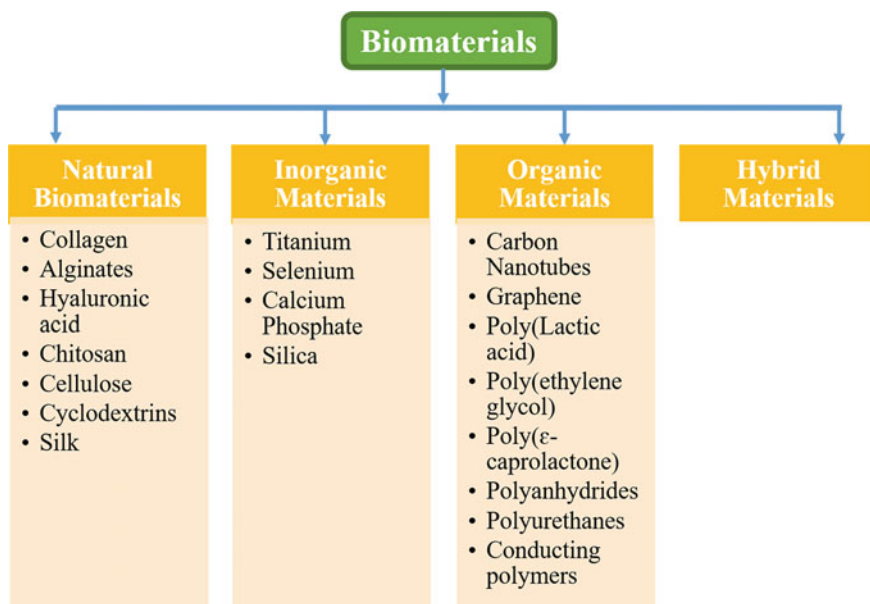


Fig. 1 Classification of biomaterials

3 Natural Biomaterials

In the tumour stroma, there are natural proteins which occur in the tumour stroma which increases the formation of tumour in the cancerous cell through interactions of physicochemical properties. Those proteins include fibrin, collagen and laminin, and to improve the biochemical nature of the extracellular matrix (ECM) proteins, these natural biomaterials are used and they are explained below;

3.1 Collagen

The most important biomaterial is hydrogels and they occur in the crosslinked chains of collagen with a high amount of absorption of water and also it facilitates the exchange of nutrients. This is one of the natural proteins found in abundance in the ECM protein which occurs in the tumour stroma and it provides mechanical strength to the tissue [18]. Moreover, the biochemical and mechanical properties of the hydrogels are improved by changing the crosslinking behaviour or the individual polymer chains. The bioactive components, growth factors and metalloproteases are incorporated in the hydrogel matrix for the encapsulation of the drugs. Therefore, these hydrogels are formulated by mechanical, chemical and structural means in particular to change the behaviour of the cells and to provide targeted delivery [19]. The hydrogels were prepared with the collagen which are formed through a physical crosslinking and they are used for the encapsulation of the anticancer drugs. Through enzymatic crosslinking the collagen-based gels have been prepared with the enzyme transglutaminase. These hydrogels are used against the MDA-MB-231 metastatic cells which are breast cancer cells and it forms tissue hypoxia and necrosis. In the case of MCF-7, a non-metastatic breast cancer cells it exhibits epithelial–mesenchymal transition (EMT) markers. Owing to its fibril nature, they have been widely used to study the migration of bioactive moieties through the diameter of fibril, pores and crosslinking density. The elastic modulus and the alignment of the fibres in the collagen matrix are responsible for the release behaviour [20]. For example, an increase in the collagen density leads to mechanical stiffness which leads to invasion of malignant cells. This kind of collagen hydrogels is used against the epithelial organoids and tumour spheroids which invades through adhesion by integrin [21].

3.2 Alginates

They are natural biomaterial which are derived from the seaweeds and it has been used as gel for the controlled delivery of anticancer drugs. They have α -L-guluronic and β -D-mannuronic acid in the structure and it involves in the ion-exchange

reaction for the release of the bioactive components. The advantages of using alginates and agarose as carrier are they have high porosity and high water holding capacity [22]. Agarose is also similar to alginates which has D-galactose and 3, 6-anhydro-L-galactopyranose in its structure. The physicochemical properties of these biopolymers such as molecular weight, pH, ionic strength, mechanical strength, porosity can be tuned by modifying the concentration of the two structural units. These two polymeric gel can be used as encapsulating agent for the cancer drugs because of its thermal stability. Alginates incorporated bioactive moieties are used against breast cancer cells, leukaemic cells and squamous cell carcinoma. The alginates have very good mechanical stiffness which ranges from 21 kPa to 105 kPa and this characteristic property destroys the tumourigenic potential of hepatocellular carcinoma. Agarose is used against the renal carcinoma cells and MCF-7 cancer cells [23–25].

3.3 *Hyaluronic Acid (HA)*

It is a high molecular weight biopolymer and it consists of the repeating units of D-glucuronic acid and D-N-acetyl glucosamine. Because of its presence in the ECM matrix, this HA have been widely used as carrier for the anticancer moieties. The molecular weight of hyaluronic acid (0.5–2 MDa) and its interaction with the tissues are the main determining factors for the release of the active moieties in the cells. In a study, the ultra-high molecular weight (6–12 MDa) of HA leads to an invasion of cancer cells due to the decrease in activity of degrading enzymes of HA. The molecular weight of HA is reliant on the comparative activity of HA synthases and they are denoted as HAS1, HAS2 and HAS3 which specifically synthesis HA of different molecular weights [26]. The hyaluronidase activity (HYAL1, HYAL2) is the one in which it breaks the HA high molecular weight into small chains HA in the ECM matrix. In an another study, they have found that the higher levels of HA low molecular weight along with the higher levels of HAS1, HAS2, HYAL1, HYAL2 exhibited an invasion of breast cancer cells [27].

Anticancer drugs encapsulated HA hydrogels (0.5–1.3 MDa) forms a cluster formation by the hyaluronidase enzyme which involves in destroying the cancer cells. HA with the molecular weight of 500 kDa along with the thiol and acrylate groups forms the hydrogel bilayer constructs which were used to invade the prostate cancer cells. HA with molecular weight >1 MDa forms a reticulated hydrogels which is combined with the adipic dihydrazide were used to destroy the primary tumours based on its secretion of hyaluronidase. HA hydrogel with molecular weight ~1.5 MDa along with the tyramine were used to attack CD44 and CD133 of U87 astrocytoma cells. Therefore, for choosing HA, the physicochemical and biological properties should be optimised cautiously to study the cell reaction through tissue-matrix interactions [28–30].

3.4 *Chitosan*

This is obtained from the polymer chitin and they are used for many biomedical applications starting from sutures to implants [31]. The chitosan films were impregnated with the paclitaxel and it is implanted in the tumour site to obtain the sustained release behaviour. The release profile shows an initial burst effect and this chitosan offers a high loading capacity of about 31% W/W. The further release behaviour shows the sustained delivery of paclitaxel and the film lost its integrity by the biodegradation mechanism. There is no inflammatory response of this biopolymer films and its biodegradation behaviour helps in the delivery of implantable anticancer drugs [32]. Chitosan is used in many anticancer treatments and the examples include chitosan-doxorubicin for chemo-immunotherapy [33], chitosan-cisplatin used for pleural mesothelioma [34] and chitosan-letrozole for the breast cancer treatments [35].

3.5 *Cellulose*

This is another kind of biocompatible biopolymer used as carrier for biomedical applications [36]. In a clinical study, cisplatin was administered for treatment of glioblastoma multiforme. For this, they have used biodegradable carbomethylcellulose biopolymer is incorporated with the cisplatin drug and they have administered as chemotherapy (polymer-drug) for 17 patients. After the removal of the tumour cells, the polymer-drug plates were implanted into the tumour area and they have found that the total survival rate of patients increased (427.5 days), whereas for patients from the control group is 211 days [37]. In another study, cellulose sulphate is encapsulated in the genetically modified cells and they were implanted in the tumour site for the treatment of pancreatic cancer. The cytochrome P450 2B1 enzyme modified the cells and it could able to modify the cancer drug ifosfamide to its toxic metabolites. By this method, the tumour cells were ablated completely and it shows an example of in situ mechanism [38].

3.6 *Cyclodextrins (CD)*

It consists of 6–8 glucopyranoside unit which are interconnected and they are used as carriers for many bioactive molecules [39, 40]. It contains a hydrophilic part in the outer region and the hydrophobic part in the inner region and this type of shape creates an inclusion complex between the CD and the hydrophobic anticancer drugs. β -CD are covalently linked with the amino acid poly-L-lysine and anticancer

drug risedronate which is used for the treatment of bone cancer [41, 42]. Manchun et al. demonstrated about the dextrin nanogels incorporated doxorubicin and they have formulated by an emulsion method. Using a cross-linker glyoxal and formaldehyde, the doxorubicin was bonded (acid labile bond) to the CDs. They have also found that the release of doxorubicin is a pH responsive and it delivers the drug at pH-5 which is the pH of the cancer cells. The obtained nanogels were effective for destroying the colorectal cancer cells nuclei and the side effects were reduced [43, 44].

3.7 *Silk*

Silk fibroin is used as a suitable biomaterial since long time for biomedical applications [45, 46]. There are a lot of advantages and some of them are it has extremely good mechanical and elastic properties, good immune behaviour, biocompatible, biodegradable and very low adherence to bacterial cells. These proteins can be developed into films without any difficulty, and the films act as a carrier for the anticancer moieties. In a study, they have prepared silk fibroin hydrogels and doxorubicin was incorporated into it and they observed a good loading efficiency. The self-assembling nature of the silk showed extraordinary anticancer activity [47, 48]. One of the reported works suggests that the cell-specific and site-specific delivery of doxorubicin was achieved by the silk-doxorubicin matrix films. These films are used for the treatment of advanced stage of breast cancer and their results of the in vivo studies proves that it showed an exceptional improvement in inhibiting the cell growth when compared to the control. In addition, they have also identified huge reduction in the tumour cells weight and the tumour spread was also reduced with no toxic effects in the normal cells [49–51]. For treating the not resectable neuroblastoma cells, the silk fibroin films were loaded with doxorubicin and crizotinib. It forms a crosslinking between the drug and the film which showed an outstanding results in treating the unresectable neuroblastoma cells. It is also reported that it exhibited an excellent activity in the in vitro and in vivo studies when compared to the intravenous dose of drugs. Moreover, it also displayed a good release profile with desirable kinetics and can be directly placed over the tumour surface [52–54]. It was also reported in a study that they have combined the surgery along with the drug loaded silk films to treat the neuroblastoma cancer cells. It was stated that the drug release was observed in the sustained manner, and thereby during shrinkage of cells, it was removed surgically. Recently, silk fibroin nanospheres were fabricated along with the incorporation of floxuridine for the prevention and treatment of cancer cells. Nanogels silk elastin was loaded with floxuridine for the treatment of hepatocellular carcinoma [55, 56].

4 Inorganic Biomaterials

4.1 Titanium and Selenium

The titanium is one of the most used metals in the development of implants owing to its many advantages like good mechanical strength [57], resistant to corrosion properties, biocompatible and time-dependent biodegradable behaviour [58]. The implant consists of a layers of titanium oxide and it is implanted over the surface of the cancerous bone. The orthopaedic implant will replace the cancerous bone cells and it is the common method adopted to treat bone cancer. The titanium alone cannot able to prevent the cancer cells, and hence the anticancer drugs are incorporated in the titanium dioxide layers by surface modification technique [59–61]. For supporting the above-said statement, Perla et al. found two strategies to develop the new type of bone implants. The first one is modifying the surface of the implants by using nanosize range of particles particularly to improve the adhesion and growth rate. The second one modifying the surface through chemical means by using metal particles exhibiting anticancer properties. The one such inorganic material which has anticarcinogenic potential is selenium. They observed improved adhesion of osteoblasts cells in the surface modified selenium and nanoparticles matrix. It was reported that selenium nanoparticles found to be a promising material for the anticancer orthopaedic implants [62].

Tran et al. used nanoselenium along with the titanium and found that it inhibits the growth of cancerous cells from recurrence simultaneously improving the growth of bone. In the *in vivo* experimentation, the Se-coated Ti nanoparticles were observed to be a promising material for the tumourous bone cells and also for the healthy cells [63–65]. Chen et al. came up with a new modification in the surface of the titanium. They have formulated a chitosan coated over the surface of nano-titania tubes and deposited selenium on the surface of nanotubes. They have studied its efficacy by implanting this material and observed that it prevents the growth of cancerous cells and improves the proliferation of healthy cells. In addition, they have also shown that selenium exhibits sustained release behaviour of about twenty-one days. Titanium nanowires and titanium nanotubes are incorporated with doxorubicin drug for treatment of brain cancer (doxorubicin implants) [66]. Gulati et al. demonstrated that this novel nano-metal-drug conjugates were successful in the prevention of brain tumour. The loading efficiency and the release profile of the doxorubicin showed better characteristics. The added advantage of this method was it could able to bypass the blood-brain barrier which actually prevents the release of doxorubicin from the blood and thereby releases the drug in the brain [67].

4.2 Calcium Phosphate

The calcium phosphate biomaterial is very similar to the bone mineral in its composition and this biomaterial itself acts as an anticancer agent. This biomineral also offers several advantages and they are osteoconductive, biocompatible and biodegradable based on its porosity, bioactive, nontoxic and stable. The most commonly used calcium phosphate-based biomaterials are tricalcium phosphate, hydroxyapatite and amorphous calcium phosphate [68–72]. Cisplatin is incorporated in the bone mineral and studied its release behaviour. The release pattern followed the sustained release behaviour and it was observed for nearly 12 week period under in vitro conditions. The in vivo behaviour of this implanted material of about 3 months shows good compatibility and better release profile [73]. Then, in another study, they have used hydroxyapatite material which is incorporated with adriamycin and it was found that hydroxyapatite (2 mm diameter) can load about 0.08 of adriamycin. The in vivo studies revealed that the implanted composites exhibited sustained release behaviour and used in the treatment of early stage hepatic cancer whereas for the late stage it was unresectable. After resection of tumour, the bone mineral containing high concentration of anticancer drug was placed in the tumour site for improving the cells present in the site. Likewise, the calcium phosphate mineral loaded with *cis*-diaminedichloroplatinum and the release profile was observed to be 0.1 mg/day. After implantation of over six weeks, the platinum release was 3200 $\mu\text{g/g}$ tissue which was found accumulated in bone marrow whereas it was not present in other organs. When the platinum is administered intravenously, the concentration of platinum is very low in bone marrow 0.2 $\mu\text{g/g}$ tissue and it was lower than that of liver 3.5 $\mu\text{g/g}$ tissue and kidneys 3.5 $\mu\text{g/g}$ tissue [74]. The composites showed that the concentration of platinum at the tumour site is higher than that of other tissues and organs. This idea was taken by Tanzwa et al. prepared a composite containing calcium phosphate loaded with caffeine and the cisplatin. Here, the cisplatin release was improved in the tumour site because of the presence of caffeine which holds the cisplatin in the tumour site [75]. Recently, Chen et al. developed a polycaprolactone scaffold along with chitosan, nanoclay and β -tricalcium phosphate loaded with doxorubicin for the controlled delivery of the drug in the tumour site [76].

4.3 Silica

This biomaterial is related with the breast implants and they are also used for drug delivery applications. They are hydrophobic material which are used as membrane-based reservoir systems [77]. The first work on silicone-based anticancer drug delivery was introduced by Ueno. The selected anticancer drug 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) is incorporated in the different types of

silica, silicone and silicone-nylon refillable systems. In this work, they have selected silicone balloons as a reservoir for the drug and it is used for the treatment of ocular malignancies [78].

Nanoporous silica was developed by Bell et al. and he reported that because of its solubility, biocompatibility, biodegradability and low toxicity, and it has very wide range of biomedical applications [79]. The applications include biosensors [80], chemical sensors [81], radiotherapy [82], drug delivery and biotechnological applications [83–86]. The porous silica nanoparticles are used for delivering anticancer drugs like doxorubicin [87, 88], cisplatin [89], celastrol [90] and camptothecin [91]. Therefore, the biodegradation pathway of nanosilica particles paves the way to remove safely from the body [92]. Tzur et al. investigated the porous nanosilica films loaded with the anticancer agent mitoxantrone dihydrochloride for the local drug delivery. The drug was loaded into the nanostructured silica by means of alkylation and thermal hydrosilylation using undecylenic acid and dodecene. And the drug was adsorbed and covalently linked to the porous nanosilica scaffold. The release pattern exhibited no burst effect initially followed by the sustained delivery of mitoxantrone in the breast cancer site. They have also denoted that it can be further developed either into injectable nanosilica particles or implantable material [93, 94].

5 Synthetic Biomaterials

5.1 Carbon Nanotubes (CNTs)

There has been extensive research in using the carbon nanotubes structures as a nanocarrier for numerous biomedical applications. The CNTs are said to be a universal carrier for a large number of bioactive molecules [95]. The CNTs containing immobilised drug can be combined with the nanoparticles containing magnetic properties and this hybrid structures releases the drug via the external magnetic field for targeting the cancer cells [96]. Functionalising the CNTs and surface modifications are another way of releasing the drug in the target site. The oxidised CNTs are difunctionalised using folic acid and iron nanoparticles which are useful in dual targeting [97, 98]. Doxorubicin drug is incorporated into the dual targeted nanocarrier CNTs and found the controlled release behaviour. The *in vitro* studies prove that the difunctionalised CNTs-doxorubicin act against the HeLa cells. It was also reported that CNTs exhibit improved doxorubicin loading capacity and it provides 6 times better release profile than the free drug. When the CNTs functionalised with folic acid and it is particularly useful in targeting the lymphatic systems through the external stimuli magnetic field. The externally placed magnet will target the lymph nodes and releases the drug cisplatin and 5-fluorouracil in a controlled fashion [99, 100]. The natural bioactive compound quercetin is incorporated in the CNTs nanocarrier and they are formulated by polymerisation of methacrylic acid around CNTs. Then, the quercetin drug was found to be covalently

conjugated which showed a better release profile. The in vitro studies proved that it acts against the HeLa cells effectively than the free quercetin. The quercetin was particularly loaded in nanocarrier CNTs particularly to improve the stability and release profile [101].

5.2 Graphene

An interesting nanomaterial which provides many advantages since its inception and they are graphene-based materials (GBMs) and in particular graphene oxide (GO) and reduced graphene oxide (rGO) [102]. The GO and rGO attracted much interest in the last few years for the development of drug delivery systems and in many biomedical applications [103]. There are lot of studies reported that it has toxic potential based on its size and amount used. But the side effects produced from GBMs are very low compared to the chemical molecules. Huge number of reports studied that GBMs was used as nanocarrier for many anticancer drugs [104–107]. Zhang et al. study reported that GO functionalised with folic acid in particular to target the MCF-7 cells. Doxorubicin and camptothecin are loaded in the GO through hydrophobic and π - π interactions. The effects showed that it targets specifically to the cancer cells with higher loading and better release properties [108]. Wu et al. studied the effects of doxorubicin-GO-Adramycin complex and found a good loading capacity of about 93.6%. They revealed that doxorubicin undergoes a pH mediated release in a controlled fashion and found effective in killing breast cancer cells. The pH mediated release is that the hydrogen bonding between the GO and doxorubicin is dissociated and protonated $-\text{NH}_2$ groups in the doxorubicin molecule [109].

5.3 Poly(Lactic Acid) (PLA)

PLA has a lot of advantages and they are biocompatible, biodegradable, easily processable and nontoxic. PLA and its product poly(D,L-lactide-coglycolide) (PLGA) have been used since its inception in many pharmaceutical products for biomedical applications and these polymers are approved by FDA [110]. Zhao et al. used recombinant drug interleukin-2 and it is conjugated with PLA/PLGA microspheres along with dextran. The microspheres were prepared with a core/shell morphology with the loaded drug and this was used for the treatment of paracrine cancer. When the interleukin-2 was administered multiple injections, it has been proved that the rate of growth inhibition of the cancer cells was higher. The L-lactide and g-lactide with the dextran molecules form the stereocomplex which undergoes gelation and releases the drug in controlled fashion [111]. PLA nanofibres along with sodium dichloroacetane and diisopropylamine dichloroacetate loaded with the oxaliplatin and studied its release profile. It was reported that it

has good loading efficiency and release profile. The *in vivo* studies showed that prolonged release behaviour of oxaliplatin in tumour site and it also completely inhibit the growth and limits the recurrence of tumour in the liver. The suppression rate of the tumour was observed to be 95% and its asymmetric structure enables in diffusion of oxaliplatin in normal cells and other tissues [112, 113].

5.4 *Poly(Ethylene Glycol) (PEG)*

Mostly, the anticancer drugs are incorporated in the PEG as hydrogel formulation [114–116]. Hydrogels are powerful structures and are widely used in smart drug delivery systems because its delivers the drug inside the system through the changes in the pH, light, temperature and sound. They also have all the advantages in which the carrier molecules should possess and they biocompatible, biodegradable and nontoxic. When the drug is incorporated in the system, it changes from the liquid state to gel state by means of chemical interactions such as hydrogen bonding, crosslinking, hydrophobic–hydrophilic, charge, stereocomplexation, photopolymerisation and molecular recognition. When the drug loaded hydrogels are implanted in the tumour site, it releases the drug via diffusion coefficient mechanism. PEG are formulated into a hydrogel delivery system for many biomedical applications [117–120]. 5-fluorouracil is loaded into the PEG hydrogels which are used to prevent the growth the malignant tumours. The *in vivo* studies shows that when the drug was administered via bolus injection, the release rate was very poor and leads to short half-life. Whereas the hydrogel formulation showed that it increases the drug residence time and half-life of the drug was observed to be satisfactory [121]. In order to increase the desired properties of PEG, it is to be copolymerised with the other molecules such as poly(methyl methacrylate) (PMMA) [122], poly(vinyl ether) [123], poly(styrene) [124]. In a study, they have incorporated polycaprolactone (PCL), PLGA into the PEG system and it undergoes crosslinking through gelation process. The crosslinking takes place when the temperature is increased and resulted in aggregation of the hydrophobic portion of the molecule [120]. In a study by Cheng et al., they have formulated hydrogels composed of triblock copolymers consists of poly(γ -ethyl-L-glutamate)–poly(ethylene glycol)–poly(γ -ethyl-L-glutamate) and incorporated the drug paclitaxel. The *in vivo* studies demonstrated that within 3 weeks of time, it completely prevents the growth of tumour without damaging the other tissues and cells [125]. In another study, PEG was formulated in the micellar structures along with the 2,2-bis(methylo)propionic acid loaded with the drug paclitaxel. The *in vivo* experimentation showed that it inhibits the growth of tumour cells. Nanoparticle delivery system was developed by combining PEG and poly(propylene succinate). Then, it is loaded with the drug cisplatin and it was found to be controlled delivery of drug in the tumour site and thereby preventing the growth of malignant cells [126].

5.5 *Poly(ϵ -Caprolactone) (PCL)*

This polymer also possesses many advantages like biocompatible, biodegradable, nontoxic and no side effects [127, 128]. This is widely used in situ forming drug delivery system and this polymer along with its copolymer poly(ϵ -caprolactone fumarate) loaded with tamoxifen is formulated into injectable preparation. The in vitro studies show that it shows a higher loading efficiency, excellent release rate and it prevents the growth of breast cancer cells against MCF-7 cells. They have also reported that the composites do not display no toxicity, no cytotoxicity in normal cells and tissues [129]. PCL was also formulated into implants together with its copolymers such as derivative poly(ethylene glycol)-block-poly(ϵ -caprolactone). This PCL and copolymer nanoparticles were loaded with hydroxypropyl- β -cyclodextrin and docetaxel drugs. These implants were placed over the patients having breast adenocarcinoma and found outstanding anticancer activity. Therefore, these PCL-based nanoparticle implants were proven to be suitable for the anticancer therapy [130]. Pereira et al. developed PCL incorporated methotrexate and found it effective for the treatment of Ehrlich solid tumour cells [131]. PCL was formulated into nanofibres and the natural bioactive compound curcumin was incorporated into it. This curcumin loaded PCL fibres were tested against MCF-7 and A459 cells and found better entrapment efficiency which leads to be effective in killing the breast cancer cells and lung cancer cells [132]. PCL along with curcumin was developed into micellar formulation and both the in vitro and in vivo studies displays that they are very effective in treating colon cancer cells [133]. Recently, Wong et al. developed a formulation containing dual functions in which it serves in treating the cancer cells and as well as in tissue regeneration. In this study, PCL was loaded with doxorubicin where it acts in dual functions such as locally delivering the drug in the tumour site and cells get attached for generating new tissues. They have suggested that this kind of drug loaded nanofibres formulation will be very useful in post-surgery of the limb salvage process for repairing the tissues [134].

5.6 *Polyanhydrides*

This polymer is one perfect example in the category of surface eroding polymers owing to its high water content of the anhydride bonds over the surface and highly hydrophobic in the bulk of the polymer [135]. In this type of polymers, the release of the drug is directly proportional to the erosion rate of the polymer. So, to achieve the control in release of a drug is possible only when the surface of the biomaterial starts degrading. The in vivo experiments suggest that polyanhydride can be easily excreted from the body via urine and faeces as CO₂ [136]. This biomaterial was together mixed with its copolymer poly[bis(pcarboxyphenoxy) propanesebacic acid] for the local delivery of cancer drugs which was also approved by the FDA. In this matrix, the drug camptothecin was incorporated to study the effects in treating

gliosarcoma. The results showed that the release rate was prolonged for about 1000 h [137]. Poly(ester anhydride) along with oligomers of poly(sebacic acid) and ricinoleic acid was studied for its possibility of selecting as drug carrier. To the above polymers, the cisplatin drug was loaded and studied that it was very effecting in inhibiting the growth of cancer cells. The above-said polymers are incorporated with 5-fluorouracil, paclitaxel and methotrexate to find out the release rate. The release profile was found to be very effecting and showed prolonged release [138–140]. Recently, curcumin was loaded in the poly(anhydrides) for the prevention of growth against breast cancer cells, osteoblasts cells and HeLa cells. This polymer has also been used for improving the immune response inside the body by the vaccine delivery formulation [141].

5.7 *Polyurethanes (PU)*

This is one of the synthetic polymers which also has good biocompatibility, biodegradability, good mechanical strength and nontoxic [142, 143]. Chen et al. developed polyurethanes nanocomposite implants loaded with the drug paclitaxel. It releases the drug with tunable on and off switching mechanism for delivering to the tumour site. The temperature-responsive PU nanocomposite membrane releases the drug by heating at 44 °C (switching on) and drops at 37 °C (switching off) results in temperature-responsive release [144]. Another work reported about the solvent casted PU along with paclitaxel drug to make stent-based delivery system for the treatment of tumours in the gastrointestinal area. The PU-paclitaxel stent could able to inhibit the growth of tumour in a better way and its release was inversely proportional to the paclitaxel loading. The major threat to a patient who underwent tumour removal surgery is that it increases the growth in other normal cells [145]. To cure this problem, Manabe et al. came with a new device, i.e. infusion pump with elastomeric tube which delivers the drug gemcitabine directly into the resected tumour site and the tube is used for reloading the drug. The controlled delivery of the gemcitabine drug inhibits the growth, slows down the growth and also prevents regrowth of the tumour [146].

5.8 *Conducting Polymers*

Mostly, these kinds of polymers are used in electronics, but these kinds of polymers also used as fascinating materials for the drug delivery system [147, 148]. The conducting polymers are not biodegradable and its degradability is increased by chemical modification. So that the polymers become biodegradable with the in vivo enzymes reaction. These polymers are biocompatible, which allows ion-exchange

reactions, electrically conductive which undergoes charging and discharging process [149, 150]. With the help of electric potential, the drugs with anionic charge get immobilised during the process of oxidation and the drugs get released during reduction process which is called as charging-discharging potential of polymer [151]. There are many reported works of this kind of polymer as reservoir for many drugs (ibuprofen [150], salicylate [152], dexamethasone [153] and ciprofloxacin [154, 155]) where they get released inside the system with the help of electrical stimuli. Few years back, scientists have started using this type of polymers as reservoirs for delivering anticancer drugs. They have used a conducting polymer polypyrrole loaded with methotrexate along with oleanolic acid making the system electrochemically active. The kinetic analysis exhibited that methotrexate release was sustained by means of both temperature and electrical stimuli [4]. In another study, authors have used a different type of conducting polymer poly(3,4-ethylenedioxythiophene) as reservoir for releasing methotrexate drug. The *in vitro* experimentation proved that it acts against the A-549, HeLa and KB cell lines and it showed a controlled release profile. Therefore, these kinds of polymers are used as promising material for the development of formulation containing anticancer drugs [156].

6 Hybrid Materials

By combining two polymers HA and methylcellulose, it forms injectable gel-like structures. This mixed polymers go through the process of gelation technique through hydrogen bonding interactions [157]. Another example is that mixing of sodium carboxymethyl cellulose along with chitosan to encapsulate doxorubicin which can be formulated into microspheres or hydrogels. Because of the porous nature of carboxymethyl chitosan (oxidised hydrogel) shows no cytotoxicity in the umbilical endothelial cells, compatible in the blood and degraded by the lysozyme. This behaviour enables the doxorubicin delivery as an advantageous method for broad spectrum of vascular embolisation. In the microsphere formulation, owing to its porous nature doxorubicin were easily loaded. The *in vitro* and the *in vivo* studies proved that doxorubicin was delivered by enzyme degradation [158].

Haupt et al. studied the treatment for colorectal cancer using chitosan and guar gum. Celecoxib as an individual component delivers with the increased side effects with most majorly complications in the gastrointestinal tract (GIT). Along with the hybrid polymers, the celecoxib delivery results in the decrease in the growth of tumour cells and simultaneously reduces the toxic reactions [159, 160].

The CD complexes were combined with the polyelectrolytes in a multilayer fashion for the effective covering of bone implants and this is said to be an *in situ* prevention of bone tumour. The CD is combined with hydroxyapatite (HA) for the prolonged delivery of chemotherapeutic agent for the treatment of bone reformation. Chai et al. also revealed that there is improvement in the loading of cisplatin

and it is due to the presence of CDs over the surface of HA. It is also noted that it undergoes a prolonged release of cisplatin in the bone defects to reconstruct the bone structure which also exhibits good biocompatibility [42].

The recent studies showed that the nanosilica material can be used as implantable electronic delivery systems. Li et al. fabricated silica wafers incorporated with anticancer moieties cisplatin, carboplatin and platinum. The silica wafers consist of hydroxyapatite, silica and calcium phosphate impregnated with anticancer moiety for the treatment of bone cancer. The implanted material in the tumour site reveals that it delivers the drug via pulsatile delivery with the application of external stimuli involving electric current/radiation [161].

Kakran et al. developed a system containing GO combined with other polymers such as Tween 80, Pluronic F38, maltodextrin. They are loaded with the natural bioactive component ellagic acid via π - π stacking and identified its release kinetics. The cytotoxicity of the formulation is tested against MCF-7 and HT-29 cells and found good anticancer activity because of the antioxidant nature of drug ellagic acid [162]. In a study by Zhang et al., GO was conjugated with the dextran and the anticancer drug was incorporated into the system. They have proved that the GO-drug conjugates exhibited a reduction in the tumour site against cervical cancer cells. And also found that the GO was gradually cleared from the system without causing toxicity [108]. Liu et al. found that GO when combined with polymer polyethylene glycol (PEG) proves to be a promising material for delivering anti-cancer drugs. GO-PEG conjugates provide very good stability under physiological conditions and the drug molecule camptothecin along with SN38 were attached via π - π stacking. They have reported that this conjugate PEG-GO-SN38-Camptothecin is highly efficient than the FDA approved water soluble pro-drug used for the treatment of colon cancer [163].

Hydrogels were prepared using PLGA, PLA and PEG which is loaded with the anticancer drug topotecan. There are hydrophobic interactions between the polymer and the drug was observed which increases the pKa value of carboxylate group present in the topotecan. Because of this property, the loading percentage of drug was increased and its efficacy is also increased. The in vivo studies proved that when the hydrogels placed as implants in the tumour site it completely inhibits the growth and recurrence [164].

PCL along with chitosan was prepared in the form of core-shell nanoparticles to load the drug. The drug loaded in this formulation was mitomycin-C and they were very effective in treating bladder tumours. PCL along with the PEG diacrylate microneedles loaded with the drug were useful in obtaining the membranes with different structural surface design. They found that the drug release was very slow and delivered in controlled manner for about 112 days. The in vitro studies were studied against the human dermal fibroblasts cells and observed that scaffolds served as platform for attachment of cells [165].

7 Triggerable Biomaterials

There are biomaterials which are responsive to the different triggers and release the drugs effectively (Fig. 2). The triggers can respond to the stimulus such as physical, chemical and biological agents in which the biological and chemical stimuli are present within the body, whereas the physical ones present externally. By this way, the delivery of drugs can be controlled effectively and targeted to the particular site [17]. The following part briefs about the different classes of responsive biomaterials and its use in anticancer drug delivery.

7.1 Magnetic Responsive Biomaterials

The magnetic properties of the material act as a triggering agent for the controlled delivery of drugs. This idea has been extended to design a system for releasing the active moieties to specific organs by combining two techniques [166]. The magnetic resonance imaging techniques and the drug loaded polymers were paired together for the therapeutic treatment and active targeting. In a study, the doxorubicin loaded alginates were taken and incorporated magnetic beads into the material for targeting the diseased organ. This triggering agent can be combined with pH-responsive materials to offer double benefits in delivering the drugs. In a work, they have combined the magnetic particles in the polymeric matrix which

Triggerable Biomaterials	Magnetic responsive biomaterials
	pH responsive biomaterials
	Temperature responsive biomaterials
	Redox responsive biomaterials
	Enzymes responsive biomaterials
	Light responsive biomaterials
	Electrically responsive biomaterials
	Sound responsive biomaterials
	Light responsive biomaterials
	Swelling and shrinking biomaterials

Fig. 2 Triggerable biomaterials

contains drug molecules. Then, they have used MRI imaging to correctly identify the exact location in which the drug was delivered [167–169].

The advantage of including a magnetic material within polymer-drug matrix will be more beneficial because of its easy recovery. When an implant is inserted in a patient, it is necessary to determine the response of the implant. If there is any weak immune response or undesired rejection, to remove the implant from the patient/living system becomes critical. In such a case, this magnetic pulsing technique could be helpful in removing the material from the organ or from the blood circulation. Therefore, drug-polymer with the magnetic particles in the system expands the scope to develop a value-added formulation. It is important to note that some of the magnetic responsive polymer systems have been approved by FDA [170, 171].

7.2 *pH-Responsive Biomaterials*

There are pH values that exist within the human body and they are different for tissues, organelles and fluids. For example, acidic pH exists in stomach and vaginal areas ($\text{pH} < 7$). The neutral pH occurs in the ocular surface ($\text{pH} 7.1$) and in the blood ($\text{pH} 7.4$). In addition, pH values will differ in disease environment and in the barriers of organ. Therefore, a good approach to increase the efficacy of cancer drugs which involves in the polymeric delivery system which can react at particular pH [172]. To develop a pH sensitive product, functional groups to be included which can protonate or deprotonate in the polymeric matrix. Mostly, amine containing polymers which are derived from dimethyl aminoethylmethacrylate will be protonated to yield a cationic group of materials. Another example in this case is carboxylate containing polymers which includes poly(acrylic acid) will be deprotonated to yield anionic materials under basic environment. Therefore, the charge of these polymers could be easily changed and these materials can react to changes in the pH in the form of swelling, shrinkage, dissociated or degraded. By these strategies, these type of polymeric materials can release the drug moieties in the target organs and tissues [9, 173]. There are various pH-responsive polymers which are used for masking the taste, delivery nucleic acid and doxorubicin delivery (Fig. 3). Most commonly this pH-responsive materials have been used for targeting the tumour environment because they exist at lower pH (5.7). And the surrounding environment occurs at pH of 6.8–7 because of acidosis in the area. Hence, polymeric multifunctional nanocomposites (acid sensitive) were used for the controlled delivery of anticancer drugs. In the cancer environments, the folic acid receptors will be overexpressed and it can be used for functionalising the molecule for improved targeting. The acid-responsive polymer diaminoketal with the drug increases the cellular uptake compared to the free drug alone. A well-known example poly(ethylene glycol) has been used for the controlled delivery of drugs for tumour targeting. These pH-responsive polymeric materials continue to be an area of interest for delivering the anticancer drugs [174, 175].

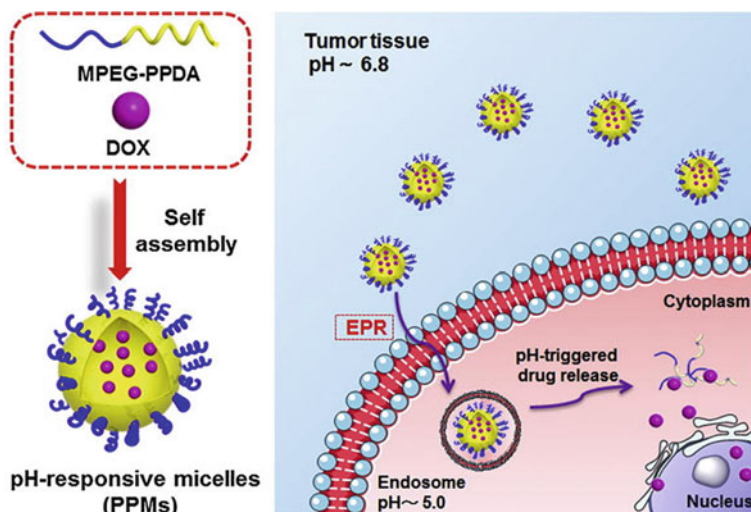


Fig. 3 pH-responsive biomaterials. Copyright permission obtained from Journal of Colloid and Interface Science

7.3 Temperature-Responsive Biomaterials

These kinds of polymers can be used for delivering and targeting the tissues and organs. Our human body exists in a temperature of 37 °C, and the room temperature is 25 °C [176]. This difference is advantageous in case of temperature-responsive polymers because these materials flow at ambient temperature and it gels at body temperature. These kinds of polymeric materials were developed by sol-gel techniques for the improved targeting. Examples of these type of polymers are cellulose, chitosan, poly(*N*-vinylcaprolactam), poly(*N*-alkyl acrylamides), poloxamers and xyloglucan. The strategies for formulating this type of materials are modifying the end group molecules, varying the post polymerisation process and changing the concentration of monomers. These strategies could be useful for the controlled delivery and for improved targeting [177–179].

7.4 Redox Responsive Biomaterials

The human body consists of reducing and oxidising agent which differs in organs, cells and tissues. Glutathione, a reducing agent found at higher concentration in cells than the surroundings. Hydrogen peroxide, oxidising agent found in the inflamed and injured tissues. The differences in these redox reactions between the cells/tissues and the surrounding environment develop a diseased state. Therefore,

it is important to formulate a materials which should balance the redox potential of the body [180].

The materials obtained from disulphides are used to stabilise the reduction trigger in the body. Inside the cells, it is mediated by glutathione molecule in which the disulphide bridges are reduced to form analogues of dithiol (Fig. 4). This interchange of dithiol and disulphide is a reversible reaction which is best suited for anticancer activity. Another example of this kind is that the sulphur-based materials have been used to balance the oxidation triggers. Sulphur exists in many oxidation states and in particular the sulphur-based block copolymers are used for cancer drug delivery, protein and gene delivery [181, 182].

Interestingly, materials with dual activation capacity can balance both of the oxidation and reduction triggers have been explored. The common functional group used are diselenides in which it has the similar chemical structure as that of disulphides. These diselenides can be incorporated into the bioresponsive polymeric system which prevents the triggers caused by the oxidation and reduction process [183].

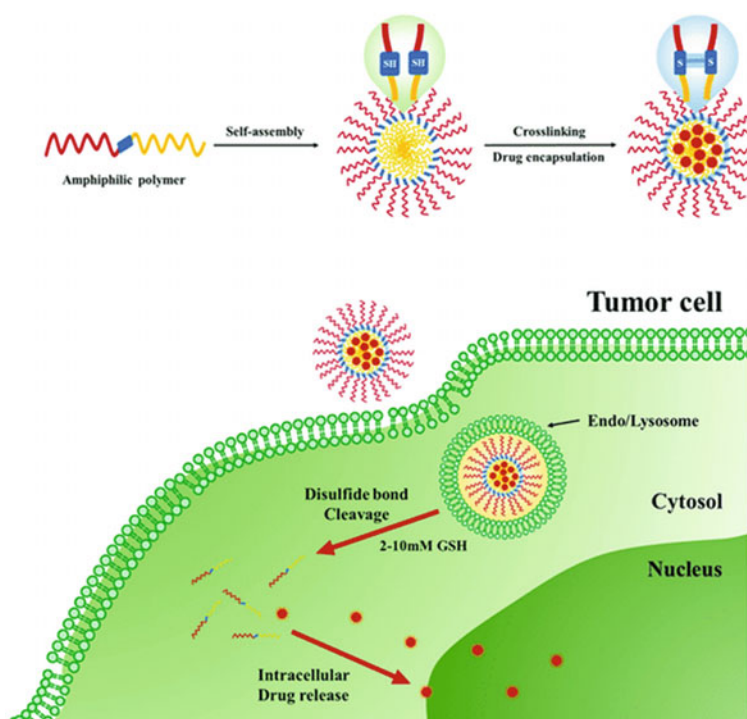


Fig. 4 Redox responsive biomaterials. Copyright permission obtained from Frontiers in Bioengineering and Biotechnology

7.5 Enzymes and Hydrolysis Sensitive Polymers

The enzymatic and hydrolytically responsive polymers have been designed and formulated for cancer drug delivery. Hydrolytic susceptible materials are the ones which are degraded by water. The degradation process happens by the nucleophilic addition of water into the functional group (electrophile) of the polymer [184]. The most commonly used electrophilic functional group of the polymers are esters and anhydrides. An example for such kinds of bioresponsive formulation available in the market is Gliadel wafer. This product consists of chemotherapeutic drug carmustine impregnated on the polymer polyanhydride. The Gliadel wafer shows the influence of hydrolysis responsive materials. This chemotherapeutic formulation could also be implanted into brain for the controlled delivery of carmustine to the tumours. Gliadel wafer can also be used in patients with glioblastoma multiforme and it improves the survival rate for about six months [7].

Enzyme sensitive polymers have been developed for tumour imaging and delivering the drugs (Fig. 5). With the disease pathology, some of the enzymes differ from the normal values and they are hyaluronidases, phospholipases, matrix metalloproteins, etc. For the colon tumour treatment, the enzyme responsive polymer along with the drug doxorubicin was developed. It was also found that it minimises the inflammation in the colon than any other systems developed [173, 185].

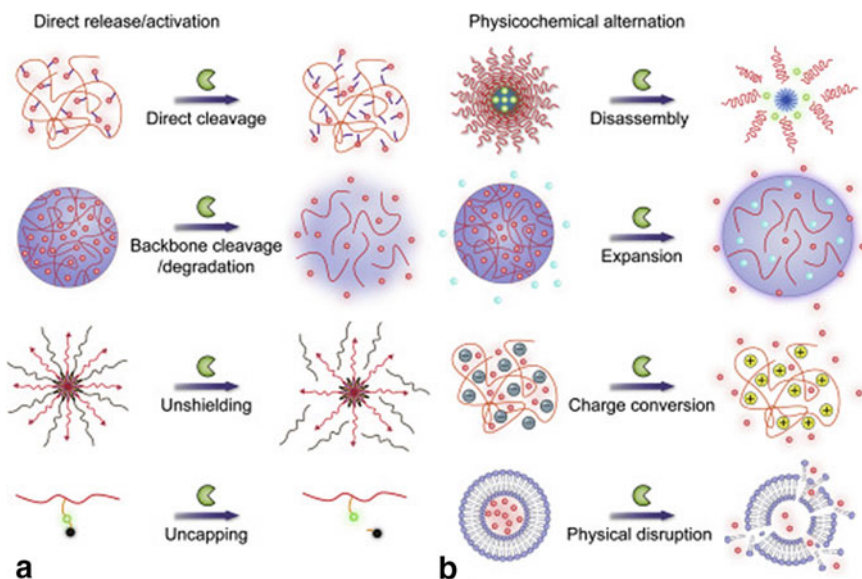


Fig. 5 Enzyme responsive biomaterials. **a** Direct release/activation, **b** indirect release/activation via physicochemical alternation. Copyright permission obtained from Elsevier

7.6 *Light Responsive Biomaterials*

Light-induced drug delivery has been used to target the cancerous cells by releasing the drugs through the source of light. This is one of the painless and non-invasive technique act as an external stimulus for delivering the cancer drugs [186]. This light stimulation system tuned into a non-invasive trigger for controlling the temporal and spatial delivery of drugs. UV-Visible light irradiation at a particular wavelength will release the drug in the targeted site and this acts as a remote activated system. There are some of the challenges to control the light activation system and they are drug degradation of during light exposure, distance of the light from the polymer-drug system and the thickness of the tissue and the penetration of the light [187]. The important mechanism for the light stimulated delivery is that it undergoes either a ring opening reaction or *cis-trans* isomerisation through the light source. In one of the study, they have used a light sensitive modified azobenzene block copolymer for targeting the melanoma cells. During irradiation, it undergoes a molecular conformation in the azobenzene molecule and by this means it alters the structure to release the drug [188, 189].

7.7 *Electrically Responsive Biomaterials*

There are various types of electrically sensitive polymers were developed and they have been used for many biomedical applications in particular for targeted delivery of anticancer drugs [190]. Our body is supplied with electrical stimulus, whereas the neurons act as a neurotransmitters for transmitting the information through electrical signals. The electrically responsive polymers are highly conjugated aromatic materials and they will directly form a boundary with the cells when the electrical stimulus is applied. One such example is polypyrrole and they are widely used for electronic applications, bioimaging and targeting the cells. The polypyrrole nanoparticles have also been developed and they have studied its biocompatibility in mice. This kind of electrically sensitive polymers has also been combined with temperature sensitive polymers for the dual responsive systems [191, 192].

7.8 *Sound Responsive Biomaterials*

This is another way to release the drug in the targeted site via auditory stimuli. The challenges associated with this system to release the drug are tuning the properties of materials and functionalising the materials to optimise the release [193]. A study shows that to optimise the release, they have incorporated growth promoting molecules in the ultrasound responsive scaffolds through acoustic responsive polymer. In another study, the drug is impregnated in the fibrin scaffolds and to control the

release, and they have prepared a double layer emulsion using a microfluidiser. Through this microfluidic device, the multilayer delivery systems were created which includes microbubbles and an array of nanoparticle designs [171].

7.9 Swelling and Shrinking Biomaterials

Some of the polymers or biopolymers undergo swelling and contraction with respect to the exterior stimulus. Most common example of biopolymer releasing the anticancer drug is alginates. The anticancer drugs are encapsulated using the alginates by controlling the release profile. Alginates also functionalised by vascular endothelial growth factor (VEGF) to target the specific site in the body. These materials also used for sensing the specific region and the injectable was also prepared using alginates. Many applications are there for using alginates as biopolymer for delivering the drugs [194].

8 Commercially Available Products

There are many products which have been transferred from clinic, approved by FDA and they are commercially available in the market. Most of the formulations are available as ideas in the literature and not executed in commercial market for medical applications (Table 1). **Lupron Depot** is a commercially available drug which contains PLGA microsphere loaded with leuprolide which is used for the treatment of prostate cancer. PLA and PLGA are used in many products because of its versatility, biocompatibility and biodegradability nature which will be degraded into lactides and glycolides [195]. **Doxil** which contains PEGylated (PEG) liposomal formulation encapsulated with doxorubicin was approved by FDA for the treatment and prevention of regrowth of ovarian cancer and Kaposi's sarcoma [196]. **Marqibo** is a recently approved nanoparticle liposomal formulation containing vincristine for the treatment of leukaemia [197]. **Abraxane**, a nanoparticle formulation useful for the treatment of breast cancer [198]. **Zoladex**, a product containing PLGA and drug goserelin acetate for treating prostate and breast cancer cells. This implants duration of action was found to be 3 months and they are in 10 mm length and 1 mm in diameter [199]. **Eligard**, it is an injectable implant containing leuprolide acetate used for the treatment of prostate and breast cancer cells. This implant consists of 2 syringes one is filled with PLGA along with methyl pyrrolidone and the other with the drug. Before injecting at the site, it should be mixed together and injected into the tumour site and it forms implants [200]. **InGell Delta**, PLGA containing dextran and interleukin-2 and it forms a stereocomplex which preserves its three-dimensional structure. They exhibit very low initial burst release with good biocompatibility and useful for the treatment of lymphoma [201]. **Oncogel** is a product containing PLGA, PEG loaded with paclitaxel drug and it

Table 1 Commercially available products (anticancer drugs)

Brand name	Drug	Manufacturer	Biomaterial (reservoir)	Application
Lupron depot	Leuprolide	Torrent	PLGA	Prostate cancer, breast cancer
Doxil	Doxorubicin	Boehringer Ingelheim GmbH of Germany	PEG	Ovarian cancer and Kaposi's sarcoma
Marqibo	Vincristine	Eli Lilly and Company	PEG	Leukaemia
Abraxane	Paclitaxel	Abraxis BioScience	PLA	Breast cancer
Zoladex	Goserelin acetate	AstraZeneca	PLGA	Prostate cancer, breast cancer
Eligard	Leuprolide acetate	TAP Pharmaceuticals	PLGA	Prostate cancer, breast cancer
InGell Delta	Interleukin-2	InGell	Dextran and PLGA	Lymphoma
OncoGel	Paclitaxel	Macromed, Inc., Sandy	PLGA and PEG	Brain tumour
Viadur	Leuprorelin	Tolmar	PU	Endometriosis, prostate cancer, breast cancer
Gliadel wafer	Carmustine	Emcure Pharmaceuticals	Poly (carboxyphenoxy-propane/sebacic acid)	Brain tumour, Glioblastoma multiforme

turns into gel form at body temperature. It delivers the drug paclitaxel directly into the brain tumour cells through intralesional injection into the tumour cavity [202]. **Viadur**, osmotic implant which is made up of titanium, PU, elastomeric piston and polyethylene (PE) moderator which provides sustained delivery of drug for about one year in the implant site [203]. **Gliadel wafer** consists of wafers with dime shape and it contains poly(carboxyphenoxy-propane/sebacic acid) loaded with the drug carmustine. They are useful during the post-surgery of the brain tumour, glioblastoma multiforme and release is driven by two types of mechanisms one is surface erosion of biomaterial and drug releases by diffusion [204].

9 Conclusions

The biomaterials (natural, inorganic, organic and hybrid) act as reservoir for delivering the anticancer drugs is the most promising approach to improve the delivery of drugs to the tumour site and thereby reducing its side effects. This approach is advantageous in treating all types of tumour and it can be called as regional chemotherapy. With the expanding research on cancer treatment, the

biomaterials have the potential to deliver the drugs to the targeted site through functionalisation, surface modification, combined delivery and controlled release mechanisms. Hence, the biomaterials mediated drug delivery operate in these three mechanisms such as it inhibits the growth, slows down the growth and also prevents regrowth of the tumour. Moreover, it minimises the harm caused by traditional methods of delivery and it owns the broad spectrum of advantages in the biomedical field. In the last few years, a responsive drug delivery system has been widely considered for the improved permeability, treatment and prevention of cancer growth.

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