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Review Article

Biomaterial implants in the treatment of oncology: a review

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ABSTRACT

In globally, cancer is a second leading disease next to cardiovascular diseases in non-communicable diseases, which affect the all ages, sex, social status, ethnicity and primary cause of illness related death. Traditionally, systemic delivery drug systems like chemotherapy *via* oral capsule, injections of nanoparticles/micro particles, immunotherapy and others, which can inhibit or halt the progression of tumors. The short half-life of drugs which cannot achieve the targeted dose level to the tumor site and not able to target desired cell and commonly produces the organ toxicity. Recently, researchers have been attempting to direct delivery agents for cancer therapy. One of the best methods is a local therapy system, which deliver the drug directly via implantable procedure and it's achieved the maximum concentration of the desire drug at the tumor site, non-target systemic exposure and minimize the organ toxicity to the patients. Biomaterial implants are widely used in the local concurrent delivery of chemotherapy and anti-angiogenic agents, local delivery of poly-chemotherapy, gene therapy as an alternative to drug delivery, scaffolds for cancer immunotherapy and polymer-based composites of drug molecules. There are different types of polymers like poly anhydride poly [bis (p-carboxyphenoxy) propane-sebacic acid] copolymer [p(CPP:SA)], fatty acid dimer-sebacic acid copolymer (FAD-SA), poly (lactic-co-glycolic acid) copolymer (PLGA), poly (ϵ -caprolactone) (PCL), poly (glycerol monostearate-co-caprolactone), alginate and silica, used in successively cancer therapy. In order to minimize the risk of unwanted side effect of different types of biomaterials implants, it's biocompatible to reduce the ability to elicit the inflammatory effect to the implanted area or the site. Therefore, the key role of choosing the appropriate and biocompatible implants to particular therapy is an indispensable. This should be validated with respect to risk benefit ratio in case of cancers. Biomaterial based implant local delivery systems provide more versatile and tailorable approach to against treatment of different types of the cancer.

Keywords: Adverse reactions, Biomaterials, Cancer, Hazard, Implants, Alginate, Silica

INTRODUCTION

According to the National Cancer Registry Programme Report 2020 (NCRP) which was published by Indian

Council of Medical Research (ICMR) and National Centre for Disease Informatics and Research (NCDIR) about 13.9 lakhs of cancer cases was estimated and which would likely to increase to about 15.7 lakhs by 2025.¹ The various

treatment options available for cancer includes surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, stem cell transplant and precision medicine.² The difficulty in both diagnosis and treatment of cancer is due to the complex nature of the cancer like drug resistance developed by cancer cells, penetration of the drug being obstructed by the increasing levels of interstitial fluid pressure (IFP) etc., with the advancement of bioengineering tools and their incorporation in the cancer research paved the way for completely newer techniques for the treatment of cancer.^{3,4} In addition to it, these tools also promoted the efficacy of the classical treatment procedures like chemotherapy and surgery.^{5,6}

One of the important contributions of the bioengineering is the biomaterials in which various novel strategies are being applied for the treatment of cancer. Biomaterials can be of natural or synthetic origin which are used in various medical applications for supporting, enhance or replace damaged tissue or biological function and various fields of science like medicine, biology, physics, chemistry, tissue engineering and material science are also combined with the modern field of biomaterials.⁷ The different clinical applications of engineered materials include controlled drug delivery systems, gene therapies, development of scaffolds for tissue engineering, replacement and augmentation of body tissues, and surgical devices.⁸ Based on their utilization in different implant applications biomaterials are classified mainly into five types such as natural biomaterials, biopolymers, metals and their alloys, composites and bio-ceramics. When compared to the metals and ceramics polymers show versatility, which is the main reason for being widely used.⁹ The various examples for natural biodegradable polymeric materials are proteins such as silk, fibrin, collagen, gelatin and polysaccharides like as alginate, starch, hyaluronic acid derivatives and chitosan.^{10,11} Though natural polymers are potential candidates they have few limitations like difficulty to control their degradation rates and mechanical properties, ability to induce an immune response.¹² In case of synthetic polymers biocompatibility is considered to be a huge challenge and hence synthetic biodegradable polymers plays a significant role due to their ability of overcoming the effects of synthetic polymer like inflammation and scarring.¹³ Some of the examples of synthetic biodegradable polymers are poly (glycolic acid) (PGA), poly (lactic acid) (PLA) and their copolymers such as poly (lactic-co-glycolide) (PLGA) or poly (L-lactic acid) (PLLA), polydioxanone (PDO), poly (caprolactone) (PCL) and the copolymers of glycolide and trimethylenecarbonate.^{14,15} This review focuses on the various polymers which are used for making different group of biomaterial implants for the treatment of cancer.

METHODS

Polyanhydride poly [bis (p-carboxy-phenoxy) propane-sebacic acid] copolymer (p(CPP:SA))

It is widely used for the delivering of anticancer drugs in the form of an implantable device and the biocompatibility was found to be non-toxic.¹⁶ By modifying the ratio of carboxy phenoxy propane (CPP) and sebacic acid (SA) the degradation rate can be controlled. An implantable device (Gliadel®) made of (p(CPP:SA)) is commercially available for the treatment of brain glioblastoma, which is approved by the U S Federal Food and Drug Administration (FDA, USA) for treating high grade malignant gliomas and recurrent glioma multiforme (GBM) in added to the surgical procedures.^{17,18} The heat of fusion value (ΔH) (p(CPP: SA)) found to be decreased from the value of 36.6 to 2.0 Cal/g when the CPP was added up to 40% whereas the ΔH value found to be increasing when the value is up to 26.5 Cal/g while CPP is further added. The p(CPP:SA) comprising of the ratio as 60:40 is found to have a low molecular weight of about 6400 but with high tensile strength of about 981 MPa. It is found to be one of the most successful polyanhydride copolymers which undergoes erosion at a constant rate.^{19,20} By increasing the concentration of CPP the erosion velocity of p(CPP:SA) gets decreased. The erosion zones of p(CPP:SA) are found to be separated by erosion fronts from the non-eroded polymer and these erosion fronts will move to the centre from the surface of matrix at a constant velocity.²¹

Poly (lactic-co-glycolic acid) copolymer (PLGA)

Poly - (lactic acid) (PLA) and poly - (glycolic acid) (PGA) are synthetic biodegradable polyesters are being used as monofilaments and absorbable sutures, since early 1970s.^{22,23} Drug delivery, surgical and medical devices, tissue engineering are some of the different applications of PLGA owing to its nature of non-toxic, bio-degradability and biocompatibility.^{24,25} USFDA has also approved PLGA for various purposes. Organic solvents are required for formulation with PLGA, because of its comparatively hydrophobic nature.^{26,27} PLGA has very good solubility in different kinds of solvents like ethyl acetate, acetone, tetrahydrofuran whereas the solubility is poor for the pure forms of polylactic and polyglycolic acid. Hence, encapsulation of water soluble or water-insoluble drugs can done using this polymer.²⁸ PLGA is obtained by different proportions of the lactic acid and glycolic acid and it is found to be a linear aliphatic copolymer. The synthesis of PLGA involves polymer having molecular weight ranging from 10,000 to 200,000 g/mol and diverse ratios of lactic acid and glycolic acid.²⁹ PLGA could be made either as an amorphous form or crystalline form. It was found that when the lactic acid is less than 70% the polymer is said to be in amorphous form.³⁰ An amorphous form provides uniform dispersion of the payload in the polymer matrix. Hence, it is very much suitable for the drug release and also it exhibits low mechanical strength.³¹

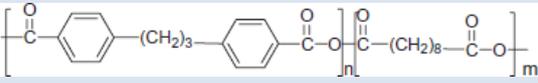
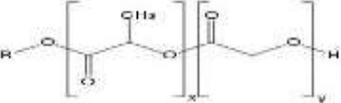
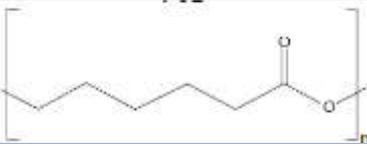
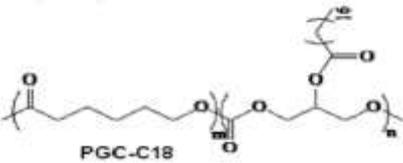
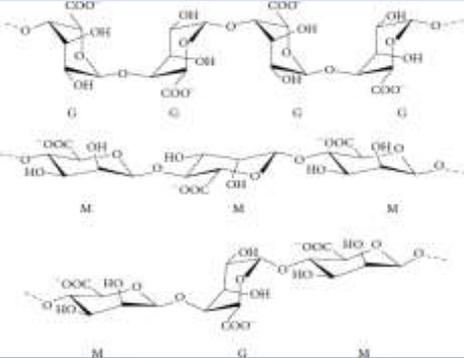
Poly (ϵ -caprolactone) (PCL)

PCL is found to be chemically comprising of repeating units of hexanoic acid (C₆H₁₀O₂)_n and it can be also

called as 6-caprolactone polymer or 2-oxepanone homopolymer.³² The melting temperature (T_m) of PCL ranges around 332-337 K and glass transition temperature

(T_g) of about 213 K, because of the relatively low melting point it allows to easily producing of drug delivery systems and scaffolds.³³

Table 1: Structure of the polymers.

Name of the polymers	Structure of the polymers	Reference
Polyanhydride poly [bis (p- carboxy- phenoxy) propane-sebacic acid] copolymer (p(CPP:SA))		67
Poly (lactic –co- glycolic acid) copolymer (PLGA)		68
Poly (ε-caprolactone) (PCL)		68
Poly (glycerol monostearate-co- caprolactone)		48
Alginate		49
Silica		69

The synthesis of PCL involves ring-opening polymerization of ε-caprolactone which proceeds by different mechanisms like anionic, cationic and radical or coordination and also one of the non-hazardous polymers.³⁴ The solubility of PCL is found to insoluble in petroleum ether, ethyl alcohol and water. Similarly, in solvents like acetone, acetonitrile, 2-butanone, dimethylformamide, ethyl acetate the solubility is low whereas in solvents like benzene, carbon tetrachloride,

chloroform, cyclohexanone, dichloromethane, toluene, and 2-nitropropane the solubility is high.³⁵⁻³⁹

The PCL chains will move freely at the body temperature, since the amorphous chains becomes rubbery at ambient conditions and this will ultimately result in the increase in permeability of the body metabolites being replaced into the body.⁴⁰ The PCL chain fragments will take longer time for degradation by the hydrolysis by enzymes because of the presence of ester bonds per monomer in a less

frequently manner and hence, it makes the polymer more stable in comparison to polylactides but biodegradable. It is found that in the biological media with the presence of a constantly changing interstitial fluid the complete degradation of the polymer generally takes about 2-3 years.⁴¹⁻⁴³ Hence, the degradation rate is influenced by the pH of the medium and when compared to the acidic environment the degradation rate is rapid in alkaline environment.⁴⁴ The polymer provides desirable interfacial characteristics and surfaces for the tissue because of its adaptability of surface roughness and hydrophilicity.⁴⁵ Since, the degradation rate of PCL is slow, it is found to be a polymer of choice in the long-term drug delivery and it also has another advantage of being compatible with different group of drugs particularly drugs which are lipophilic in nature.⁴⁶

Poly (glycerol monostearate-co-caprolactone)

The polymer has an advantage of attaching different functional groups which enables it to modify its ability for different healthcare applications like imaging, drug delivery systems, targeted delivery of drugs and also allows to being responsive to the stimulation from the environment (like change in pH). Different structures like 3D constructs, particles and fibres can be processed by employing this. It was found that, when the hydroxyl group of the glycerol is not free and being coupled with a group like benzyl alcohol then the poly (glycerol-co-caprolactone) copolymer backbone will not degrade significantly taking at least 6 months on exposing to a phosphate buffered solution maintained at 37°C.⁴⁷ Hence, in case of a functionalized polymer cast films the drug release kinetics is said to be diffusion controlled. When compared to the unmodified polymer functionalization of polymer by a lipophilic side chain prolonged the drug release kinetics promisingly from the solvent-cast polymer film.⁴⁸

Alginate

Some of the brown seaweeds like *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica* are the sources for alginate which can be isolated by the extraction of these seaweeds.⁴⁹ Hence, they contain lot of impurities like heavy metals, endotoxins and other ingredients, which needs to be removed before their use. The composition of alginate involves a sequence of β -D-mannuronic acid (M) and α -L-guluronic acid (G) which are linked by a 1 \rightarrow 4 linkage.⁴⁹ The choice of sea weed and also their age which is used as a source determines the relative proportion of α -L-guluronate (G) and β -D-mannuronate (M) and the molecular weight ranges from 32 to 400 kg/mol.^{50,51} The ratio of M and G affects different factors like visco-elasticity, swelling and transmittancy of the alginate gel membranes.^{52,53}

The toxicity of alginate is found to be very low and is also biocompatible.⁵⁴ Alginates are widely used because of their ability of being soluble at alkaline and neutral

conditions by the presence of carboxyl groups which becomes charged when the pH increases more than 3-4. Alginate is found to be one of the preferable polymers especially in the conditions of modified drug release or protecting the drug from getting degraded in the stomach pH and get absorbed in the intestinal tract. Alginate is made as a satisfying biomaterial for drug delivery systems with these advantages.⁵⁵ The alginate gels will become harder and brittle when the α -L-guluronic acid (G) content is very high. Hence, the physical and mechanical stability is determined based on the α -L-guluronic acid (G) content. However, ethylene diamine tetraacetic acid (EDTA) or sodium citrate can be used in order to revert back the above process.⁵⁶

Silica

Silica also called as silicon dioxide (SiO₂) consists of a structure involving repeating units of SiO₄ in the form of tetrahedrons. The partial ionic character in silica is created by the larger covalent radii of the silica and oxygen atom than the bond length of 0.162 nm between Si-O atoms.⁵⁷ The important properties of silica with respect to *in vivo* drug delivery includes the in the presence of aqueous environment its nature of degrading into silicic acid exactly like *in vivo* conditions, membranes and micro-nano particles can be easily processed using silica, can be used for biosensing (photonic properties) and surface area being very huge such as up to 800 m²/g.⁵⁸⁻⁶⁴ The various forms in which silica can be used are synthetic silica (prepared by modification of sol-gel chemistry), freshly synthesized silica also. Bioactive glass monoliths and xerogels can be created by processing of the Sol-gel produced silica. The release kinetics of silica xerogel solids can be modified by altering the parameters such as temperature or gelation time which makes xerogels prominent for drug delivery.⁶⁵ Bioactive glass has the ability of promoting the bonding to both soft and hard tissue by forming a carbonate hydroxyapatite layer once there is a contact with the physiological fluids.⁶⁶ The structure of the polymers was tabulated in Table 1.

CONCLUSION

The perfect solution for the successful treatment of cancer lies on the developing of efficacious drugs and proper drug delivery system, which provides delivering of drugs selectively on the particular target cancer cells. This can be achieved through biomaterials – based implants, which help to overcome the obstacles which are faced by the systemic delivery of the drugs and ultimately resulting in better therapeutic outcomes. The drugs which are failed to provide successful outcome can be repurposed with the recent advancement of the local delivery devices. The important point to be considered in the local delivery of drugs are more desirable for localized lesions, however, the case of tumors which are spread and poorly localized, then the most appropriate approach will be a combination comprising of both systemic and local delivery. In future, novel strategies and methods in biomaterial implants

should be developed in such a way that instead of existing technology like delivery of drugs using only one method combinational therapy should be adopted.

In summary, the biomaterial implants are playing a crucial role in the treatment of cancer and will also act as an indispensable device for all the new generation therapeutics.

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Conflict of interest: None declared

Ethical approval: Not required

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