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Review Article

A review on carbohydrate embedded polyurethanes: An emerging area in the scope of biomedical applications

Archana Solanki[a,b,**], Manita Das[a], Sonal Thakore[a,*]

[a] Department of Chemistry, Faculty of Science The Maharaja Sayajirao University of Baroda, Vadodara 390 002, India
[b] Research and Development Centre, Gujarat Narmada Valley Fertilizers and Chemicals Ltd, Bharuch 392015, India

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ABSTRACT

Polyurethanes (PUs) are expanding to newer horizons in the field of biomedical sciences, particularly due to their exceptional set of properties that deem fit for applications in the said field. On the other hand, carbohydrates find increasing attention as components of biomedical devices due to their easy availability from renewable resources. The manipulation of PUs by carbohydrate has solved the major concern of biodegradability, biocompatibility and economy. This review summarizes the recent trends in PUs embedded with carbohydrates ranging from monosaccharide to polysaccharides, including supramolecular host such as cyclodextrin etc. Diverse approaches for embedding them in PUs in various forms have been listed. In recent decade, significant research has been carried out to employ such polymers in biomedical applications such as drug delivery devices, implants, scaffolds for tissue engineering etc. This knowledge could facilitate the selection of more efficient approach for synthesis of polymeric systems based on the biological macromolecules.

1. Introduction

Design and development of polymers adaptable for biomedical applications is a rapidly growing field. Amongst range of polymers, Polyurethanes (PUs) are being used for several biomedical applications such as tissue engineering, orthopedic implants, transdermal patches, catheters, and drug delivery carriers (Cherng, Hou, Shih, Talsma, & Hennink, 2013). PUs serve as effective carriers for the delivery of small molecules, proteins, genes, or peptides, aiding effective drug delivery (Cherng et al., 2013). This is due to fact that PUs can be fabricated to possess properties such as biocompatibility, biodegradability, ease of modifications, high drug loading efficiency and greater compatibility with drugs (Bazban-shotorbani, Hasani-sadrabadi, Karkhaneh, & Serpooshan, 2017). Any factor that leads to enhancement in such properties can be considered as effective solution for utilization in biomedical applications. For PUs, besides polyol and isocyanate being major raw materials, incorporation of additives has made large impact on their final properties. Looking at environmental concerns and structural compatibility, we have recently explored carbohydrates as additives in PUs (Desai, Thakore, Sarawade, & Devi, 2000; Lalwani and Desai, 2010; Solanki, Mehta, & Thakore, 2014; Solanki, Sanghvi, Devkar, & Thakore, 2016; Solanki, Kamath, & Thakore, 2015; Solanki and Thakore, 2015; Valodkar and Thakore, 2010, 2011). Based on our research, we have envisioned that there is vast scope for carbohydrate embedded PUs in this field.

This review describes a comprehensive outline of carbohydrate embedded PUs and their application to design and develop a variety of biomedical applications. It comprises of five sections; a brief introduction (Section 1) followed by Section 2 which will cover an overview of general chemistry of PUs. Section 3 describes logical reasoning for use of carbohydrates in PU backbone. Section 4 illustrates the variety of carbohydrates such as starch, cellulose, cyclodextrin, chitosan, alginate and their derivatives incorporated in to PU network for biomedical applications. This section describes the structure of each carbohydrate, its benefits in terms of drug delivery and variety of incorporation approaches such as fillers, crosslinkers, composite materials and IPNs. The review concludes in Section 5, highlighting the limitations and future directions.

2. General features and chemistry of PUs

The chemistry of PUs involves reactions between organic isocyanates and polyols (i.e. compounds containing active hydrogen) (Ionescu, 2007; Sonnenschein, 2014) in proper ratio in presence of suitable catalyst (Fig. 1). The reaction is exothermic and leads to the formation of prepolymer. If the initial concentration of isocyanate is

* Corresponding author at: Department of Chemistry, Faculty of Science,The Maharaja Sayajirao University of Baroda, Vadodara 390 002, India.
** Corresponding author at: Research and Development Centre,Gujarat Narmada Valley Fertilizers and Chemicals Ltd, Bharuch 392015, India.
E-mail addresses: archu.hrt@gmail.com (A. Solanki), chemistry2797@yahoo.com (S. Thakore).

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β-cyclodextrin based dual-responsive multifunctional nanotheranostics for cancer cell targeting and dual drug delivery

Manita Das[a], Archana Solanki[a], Apeksha Joshi[b], Ranjitsinh Devkar[b], Sriram Seshadri[c], Sonal Thakore[a,*]

[a] Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara 390 002, India
[b] Department of Zoology, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara 390 002, India
[c] Institute of Science, Nirma University, Ahmedabad 382 481, India

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ABSTRACT

Multifunctional nanoconjugates possessing an assortment of key functionalities such as magnetism, florescence, cell-targeting, pH and thermo-responsive features were developed for dual drug delivery. The novelty lies in careful conjugation of each of the functionality with magnetic Fe_3O_4 nanoparticles by virtue of urethane linkages instead of silica in a simple one pot synthesis. Further β-cyclodextrin (CD) was utilized to carry hydrophobic as well as hydrophilic drug. Superlative release of DOX could be obtained under acidic pH conditions and elevated temperature, which coincides with the tumor microenvironment. Mathematical modelling studies revealed that the drug release kinetics followed diffusion mechanism for both hydrophobic drug and hydrophilic drug. A number of fluorophores onto a single nanoparticle produced a strong fluorescence signal to optically track the nanoconjugates. Enhanced internalization due to folate specificity could be observed by fluorescence imaging. Further their accumulation driven by magnet near tumor site led to magnetic hyperthermia.

in vitro studies confirmed the nontoxicity and hemocompatibility of the nanoconjugates. Remarkable cell death was observed with drug-loaded nanoconjugates at very low concentrations in cancer cells. The internalization and cellular uptake of poor bioavailable anticancer agent curcumin were found to be remarkably enhanced on dosing the drug loaded nanoconjugates as compared to free curcumin. Site specific drug delivery due to folate conjugation and subsequent significant suppression in tumor growth was demonstrated by in vivo studies.

1. Introduction

Chemotherapy, the main stray in the treatment of malignancies, employs chemical agents to destroy cancer cells. Due to lack of selectivity, such chemical agents destroy healthy cells along with cancerous cells, inviting a serious drawback of adverse side effects and lowered therapeutic effect (Ang, Zhao, & Tan, 2014). Additionally over the course of therapy drug resistance may occur either due to lack to targeted drug delivery to tumor site or due to genetic alterations of the cancer cells(Cohen, Emmanuel, Kisin-finfer, Shabat, & Peer, 2014). Targeted delivery of chemotherapeutic drugs specifically towards cancer cells is one of the apparent solutions to overcome the limitations of selectivity. On the other hand drug resistance and mutations induced by drugs may be overcome with the help of combination chemotherapy wherein combination of two or more drugs is employed which disrupts different stages of the cell and enhances the apoptosis of cancer cells (Shen, Liu, Li, Lin, & Mo, 2017).

The design of an efficient drug delivery system, which targets drugs specifically to tumor site with improved therapeutic efficacy and minimal side effects, is a challenge for cancer therapy. Bearing this fact in mind, the concept of engineering multifunctional materials possessing more than one useful property in the same system, have been proposed for the evolution of targeted drug delivery system. Further, the amalgamation of imaging and therapeutic capabilities on a single nanoplatform, resulting in an approach termed "theranostics", has been recently realized and has gained increasing attention for drug delivery monitoring, image-guided therapy and therapy response observation (Lu et al., 2016). Stimuli-responsive polymers that upon exposure to specific environmental stimuli, such as changes in temperature, pH value, light, ionic strength, or magnetic field, undergo reversible changes in microstructure are often employed.

In the light of this approach in the past few years, efforts have been

* Corresponding author.
E-mail addresses: chemistry2797@yahoo.com, drsonalit@gmail.com (S. Thakore).

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Carbon nanotube embedded cyclodextrin polymer derived injectable nanocarrier: A multiple faceted platform for stimulation of multi-drug resistance reversal

Manita Das[a], Pratik Nariya[a], Apeksha Joshi[c], Aliasgar Vohra[c], Ranjitsinh Devkar[c,**], Sriram Seshadri[d], Sonal Thakore[a,b,*]

[a] Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, 390 002, India
[b] Institute of Interdisciplinary Studies, The Maharaja Sayajirao University of Baroda, Vadodara, 390 002, India
[c] Department of Zoology, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, 390 002, India
[d] Institute of Science, Nirma University, Ahmedabad, 382 481, India

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ABSTRACT

A combination of cocktail chemotherapy (CCT), photothermal therapy (PTT) and inhibition of angiogenesis was investigated as an effective approach to combat major challenges of multidrug resistance and non-targeted drug delivery encountered in conventional cancer therapy. An injectable nanocarrier was developed through functionalization of carbon nanotubes (CNTs) with rationally modified carbohydrate (β-Cyclodextrin-CD) derived pH and thermo responsive polymer. Embedding CNT to CD polymer offers a nanocarrier which effectively demonstrated CCT, high NIR triggered photothermal efficiency, anti-angiogenic potential for selective tumor homing as well as enhanced multi-drug resistance (MDR) reversal with minimal toxic effects on normal cells. The simultaneously loading with curcumin and doxorubicin hydrochloride exhibited synergistic effect for triggering antitumor effect in vitro and demonstrated down regulation of growth factors associated with angiogenesis ex-ovo. *In-vivo* studies ascertained that the nanocarrier synthesized with the rational for MDR reversal can lead to enhanced cancer cell death via multiple approaches.

1. Introduction

Cancer therapy has shown a significant improvement over past decades with more effective drugs and better safety profiles. Despite these improvements unwanted side effects arising due to dearth of selectivity in conventional chemotherapy is an enigma which needs to be addressed (Liu et al., 2019; Penny & Wallace, 2015). Deploying nano-sized drug loaded cargos for cancer management provides an upper hand by improving stability and solubility of drug molecules (Wang, Zhao, Wang, Liu, & Tang, 2016), eluded drug release at normal tissues by their interaction with desired functional groups (Zhang et al., 2014) and most importantly targeting tumors by response to cancer specific stimulus (Das et al., 2019). Recent treatment strategies involve combining different modalities like single/multiple drug based chemotherapy, radiotherapy, hyperthermia by modulating substrates like gold (Fabbro et al., 2012), mesoporous silica (Wang et al., 2018), polymer nanoparticles (Yao et al., 2019), graphene (de Sousa, Visani de Luna, Fonseca, Giorgio, & Alves, 2018), carbon nanotubes (Bafkary & Khoee, 2016a) etc. to design drug carriers for more efficacious cancer management (Shi, Kantoff, Wooster, & Farokhzad, 2017). However there are several repercussions associated with these modalities including severe systemic toxicity, low specificity and drug resistance limiting multidrug resistance (MDR) their clinical applications (Lee et al., 2017). Tables 1–3 (SI) give the state of art in materials developed for cancer therapy

Certain systems developed for simultaneously aiding chemo and photothermal therapy are concomitant with implications of metastasis and cancer recurrence (Dong, Sun, Wang, & Leng, 2017; Dramou et al., 2018; Shao et al., 2017; Wang & Wu, 2016). To overcome these defies, the strategy of administering more than one drug (CCT), was adopted over single drug therapy (Du, Ding, Qian, Zhang, & Dong, 2019). Carbon Nanotubes (CNTs) are strong photothermal converters and have the potential of chemo-thermal combination therapy. They assist intracellular drug delivery and generate heat upon irradiation with NIR

* Corresponding author at: Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, 390 002, India.
** Corresponding author.
E-mail addresses: rv.devkar-zoo@msubaroda.ac.in (R. Devkar), chemistry2797@yahoo.com, drsonalit@gmail.com (S. Thakore).

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Emerging hybrid biomaterials for oxidative stress induced photodynamic therapy

Manita Das [a], Archana Solanki [c], Ashwini Ganesh [d], Sonal Thakore [a,b,*]

[a] Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, 3960002, India
[b] Institute of Interdisciplinary Studies, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, 3960002, India
[c] Research and Development Centre, Gujarat Narmada Valley Fertilizers and Chemicals Ltd, Bharuch, 392015, India
[d] Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara, 3960002, India

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ABSTRACT

Cancer therapy has undergone tremendous advancements in the past few years. The drawbacks of most of these therapies have encouraged researchers to obtain further insight into the complex chemical, biochemical and biological processes ongoing in the evolving cancer cells. These studies have led to an advent of reactive oxygen species mediated therapies to target and disrupt the cancer pathology. Photodynamic therapy (PDT) has emerged as a potent candidate for oxidative stress mediated non-invasive technique for rapid diagnosis and treatment of cancer. Towards this, biomacromolecules derived hybrid nanomaterials have contributed largely in the development of various therapeutics and theranostics for efficacious cancer management that can assist PDT. This review summarizes various hybrid biomaterials and advanced techniques that have been explored widely in the past few years for PDT application. The article also mentions some of the important in-vitro and in-vivo developments and observations explored by employing these materials for PDT application. The article also describes the interactions of these materials at the biological interface and the probable mechanism that assist in generation of oxidative stress and subsequent cell death.

1. Introduction

Generation of oxidative stress in a cell is a condition wherein there is an excess of reactive oxygen species (ROS) as compared to the antioxidants. The cell bears various complex biochemical mechanisms to establish a harmony between the two species. However an imbalance is associated with certain physiological anomalies. The same is true for cancer wherein ROS is associated with tumorigenesis and ample amounts of ROS generated within the tumor microenvironment that turns lethal for the cancer cells [1]. There are various ways to generate an oxidative stress within tumor and Photodynamic therapy (PDT) has evolved as an effective and practical theranostic strategy for the same. The treatment regimen is non-invasive in nature and depends on the administration of a light sensitive singlet oxygen species generating molecule called photosensitizer (PS). The PS accumulates within the tumor tissues and is only activated to release ROS in presence of endogenous molecular oxygen when irradiated with light source of appropriate wavelength. The light source is assorted as per the type of PS involved, the dosage of light required and the site of tumor. A variety of ROS are generated in the process, for instance singlet oxygen ($_1O^2$), superoxide anion ($O^{2\cdot-}$) and hydroxyl radicals ($^{\cdot}OH$). The ROS thus produced is highly toxic causing tumor cell death via oxidative stress. The phenomenon can be simply understood with the help of a Jablonski diagram as shown in Fig. 1c.

It is noteworthy that the cytotoxic species are released only upon irradiation by light otherwise the PSs are minimally toxic and hence are not a threat to normal cells [2]. Thus PDT is a modality that is comparatively specific poses lower side effects as compared to other light based modalities like radiotherapy.

Despite the potential of PDT for inducing an effective oxidative stress for efficient cancer cell death, the treatment regimen faces some clinical interventions due to certain limitations. The commonly faced hindrances include the challenges in formulating an ideal PS, choosing the perfect light dosage for an effective treatment and difficulties in administration of the treatment [3]. The development of hybrid nanomaterials as therapeutic and theranostic devices for PDT applications has been an effective solution towards overcoming many of these obstacles. This paper attempts to summarize some of the hybrid

* Corresponding author at: Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, 3960002, India.
E-mail address: chemistry2797@yahoo.com (S. Thakore).

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CHAPTER

Exploring potential of polymers in cancer management

4

Sonal I. Thakore, Archana Solanki and Manita Das

Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, India

4.1 Introduction

By the end of the past century, cancer had become the second most–likely cause of death of millions of people worldwide every year. Cancer is difficult to diagnose and treat due to its unpredictable growth, and the fact that immune system does not recognise cancer cells as foreign body. Since cancer is the uncontrolled growth and spread of cells, it often invades surrounding tissue and can metastasize to distant sites and affect any part of the body. The chance of being cured of cancer increases with early detection and treatment of the disease. Cancer biomarkers can be used for screening the presence of cancer, making a diagnosis of a specific type of cancer, determining the prognosis for a patient, and monitoring the course of cancer in a patient in remission or while receiving surgery, radiation, or chemotherapy. A biomarker is a molecule with biologically important intra- or intercellular functions. The expression or activity of biomarker gets specifically altered in response to corresponding pathological conditions. Biomarkers of cancer that facilitate diagnosis include proteins overexpressed in blood and serum or at the surface of cancer cells. However, cancer biomarkers are present at very low concentrations during the first stages of cancer and are difficult to detect. Therefore it is necessary to develop devices that can detect such low concentrations of biomarkers, which can be achieved with the help of nanoparticles (NPs).

Polymers are multiple assemblies of simple structural units that form a three-dimensional (3D) construct. Polymers gained high attraction for medical applications for various reasons, one being that different physical and chemical properties can be achieved based on the monomer units, polymerization reaction, and formation of copolymers. Polymers can be functionalized because of the presence of reactive groups anchored to them. Surface modification allows modifying the bulk properties and improving the biocompatibility to make them suitable for

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