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Commentary

Injectable hydrogel of biopolymers as controlled drug-delivery vehicle for melanoma treatment: A commentary

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Abstract

Melanoma is a strongly incursive cancer situated in the skin with narrow consecutive therapies. The goal of this article is to reveal some of the latest advances in using hydrogel for cancer especially melanoma therapy. Biocompatible brush biopolymer (linear dextrin) graft with polyurethane is developed for monitoring the hydrophilic and hydrophobic equipoise for regulating the delivery of drug to the target region. Drug incorporated brush copolymers upon embedded in gelating agent (methyl cellulose) develop an injectable hydrogel with potential melanoma compression without any side effects with better control of drug release at a constant rate for an extended period of time as contrary to intense noxious effects noticed in conventional chemotherapy. The aim of this commentary is to highlight the recent advancements made to the understanding of the particular implementation technique of drug-loaded injectable hydrogel just under the tumor site forming this system especially successful through internment in the paper "Injectable hydrogel of newly designed brush biopolymers as sustained drug-delivery vehicle for melanoma treatment" by Shukla et al.

Introduction

Recently, cancer spread like a dreaded disease with an elevated fatality rate across the globe which needs a strong attention especially since last few decades. To improve the cancer therapy there are several approaches such as surgery, chemotherapy, radiotherapy etc. which have their own intriguing limitations. Melanoma, a malignant tumor developed from melanocytes, is the highest incursive form among the different cancers with more than 80% of the deaths related to skin cancers [1]. For the primary period of melanoma, the prosperity rate of surgery is the key cause for the high success rate, but the anointment rate has noticeably been reduced after metastasis. Now, the current treatments are primarily focused on the molecularly targeted therapy, chemotherapy and systemic immunotherapy. The above mentioned therapy has very restricted effectiveness for the treatment of melanoma due to their severe side effects. Recent analyses have been observed with limited chemotherapeutic drugs such as dexamethasone, oxaliplatin, doxorubicin, cyclophosphamide, mitoxantrone, epirubicin, cyclophosphamide and idarubicin, resulting induced immunogenic death of cancer cells during therapy for various tumors. In this report, drug loaded brush embedded in methylcellulose (gelating agent) forming an injectable hydrogel system is discussed, which released dexamethasone drug to pursue the anti-cancer efficiency. In an effort to improve controlled delivery for drug and pinpoint for melanoma treatment, Shukla et al. investigated the role of an injectable hydrogel of newly designed brush biopolymers in their paper titled "Injectable hydrogel of newly designed brush biopolymers as sustained drug-delivery vehicle for melanoma treatment" [2].

Design of Brush Biopolymers and Injectable Hydrogel

The model of dextrin graft polyurethane has been developed to maintain the extent of hydrophobicity and look into the achievability of these novel materials as a new vehicle for anti-cancerous dexamethasone drug for controlled delivery. To understand the architecture with the extent of interaction of drug embedded brush, different spectroscopic methodologies has been performed.

These dextrin graft polyurethanes are mechanically and thermally stable and hence, this stability enhances the grafted brush copolymers more effective along with their uses. Injectable hydrogel has been developed by embedding the dextrin graft polyurethane in gelating agent such as methyl cellulose (MC) with selective concentration for maintaining the suitable gelation time, therefore gel can easily be placed for *in vivo* study.

Drug Release Kinetics of Brush Copolymer and Hydrogel

Developed brush copolymers, which are mechanically and thermally stable with nanostructurally prefabricated, are suitable biomaterials for delivery of anti-cancer drug and other biomedical applications. When drug release kinetics is controlled i.e. sustained in nature, then availability of drug in the blood stream has been found for a larger period of time. The release kinetics study shows that in the case of dextrin and prepolymer i.e. polyurethane, most of the drugs are released within 2 h that indicates burst release pattern. On the other hand, release of ~50% drug takes place from brush copolymers which reflect the controlled release nature to deliver the drug into the target site. Brush copolymers embedded in gel system deliver the drug in a sustained manner without any burst kinetics. The sustained drug release nature of brush embedded in gelatin system, for injectable gel system, enhances the availability of drug in the tumor sites for a longer period of time which suggest its potential applicability for melanoma treatment. From the Korsmeyer-Peppas model, the release kinetics can be explained smoothly having higher linear correlation coefficient values around one while the exponent value indicates non-Fickian diffusion kinetics of drug molecules from the polymer matrix. Researchers worked on polymeric micelles as vehicle for the treatment of melanoma but maximum of the polymeric micelles can carry only lipophilic drugs having a low loading capacity and depends on the critical micellar concentration.

In vitro Cell Killing Efficiency and Controlled Cellular Uptake

In vitro cell killing efficiency has been performed using HeLa and B16F10 cell lines. Designed brush biopolymers in this article and prepared hydrogels are biocompatible in nature which acts as vehicles for controlled drug delivery for biomedical applications with accessing through *in vitro* cell proliferation over the surface of the materials. Biocompatibility of these materials has been studied using 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay technique with time variation. MTT assay reclines on cellular metabolic activity of Nicotinamide adenine dinucleotide phosphate (NADPH) enzyme which reduces MTT reagent to purple color formazan crystals that indicates viable cells in different wells with and without the treatment of materials. Brush copolymers show higher cell viability in MTT assay experiment that indicates the biocompatible nature of the materials. To understand the cancer cell killing effect, controlled drug release from brush copolymers are important phenomena in *in vitro* study. Interestingly, in the case of HeLa cell line, ~70% cell killing has been observed in three days for drug loaded brush copolymers but for pure drug only ~25% cell killing effect has been found. On the other hand, melanoma cell line, B16-F10 exhibit ~72% killing from the drug loaded brush copolymers as opposed to very few cell killing (~30%) is observed using pure drug. In both the cases, time duration and dosage remain same. Therefore, these results clearly indicate that the sustained behavior of drug release from novel brush copolymers is effective for killing tumor cells. The cellular uptake efficiency of the drug with its vehicles strongly influences the therapeutic potential of an anticancer drug. To understand the cellular uptake of the anticancer drug, dexamethasone is chemically attached with the contrasting reagent, rhodamine B. Rhodamine tagged drug can penetrate through cell membrane, therefore, can be delivered smoothly to the cytoplasm of the cell that can easily be marked by the fluorescence photograph of the cells. In case of rhodamine tagged drug, no fluorescence is observed after 5 hr. and meagre fluorescence is found after 24 hr. This indicates very few drug molecules can penetrate to the cell even after 24 h. In contrary, interestingly in case of rhodamine tagged drug embedded in brush system, enough fluorescence has been noticed at 1 h and with increasing time their higher intensity reflects the homogeneity of the drug into the entire cell cytoplasm. Their fluorescence photographs clearly differentiate the rhodamine tagged drug and rhodamine tagged drug embedded in brush and significantly higher intense fluorescence from embedded system indicates higher cellular uptake of drug using the brush copolymer as the vehicle as compared to pure drug. Therefore, in case of *in vitro* and cellular uptake analysis, brush copolymers are highly effective as compared to the pure drug.

Melanoma Treatment Using Injectable Hydrogel of Brush Biopolymers

Current treatment analysis for melanoma cancer primarily encircles systemic therapy, adjuvant therapy, radiotherapy, photodynamic therapy, surgical treatment, and transmits to mucosal melanoma treatment. Common surgical treatments are biopsy, enlarged resection, sentinel lymph, node biopsy, lymph node dissection, and in-transit metastasis [3,4]. Most of the mentioned therapies for melanoma are mainly based on the clinical stage and risk grade of patients which are attached with poor prediction and a deficiency of efficient treatments, systemic treatment based on internal medicine. In recent years, breakthrough in individual targeted therapy with controlled drug release and immunotherapy are being conducted to enhance the outcome in patients with advanced stage of melanoma.

This article mainly focuses on the potentiality of controlled drug release on mice melanoma tumor through injectable hydrogel of newly designed brush biopolymer. Apparent tumors of volume ~20 ± 5 mm^3 are generated in mice with B16-F10 cell line which subsequently reduced heavily after treatment. One literature reports a tumor suppression of 20.6 mm^3 against 96.4 mm^3 in control using MPEG-PCL based diblock copolymer loaded with paclitaxel as intra tumoral drug depot [5]. To eliminate some limitations, the idea of injectable hydrogel has been prepared to understand when gel, applied subcutaneously near contact to the tumor site, will be in touch with the tumor sites for longer period of time. For *in vivo* study, five groups are categorized by using melanoma bearing mice with a subcutaneous injection of saline (control), brush embedded in gelatin, drug (5 mg/kg), drug in gel, and brush embedded in gel with drug. In all of the cases same amount of drug has been applied for such study. In the case of control, tumor volume gradually increases with time but in the case of brush embedded in gel with drug system, the tumor volume reduces effectively such as 40% reduction after 30 days. This is mainly due to controlled drug release from brush embedded in gel with drug and, therefore, the availability of drug reaches exclusively to the tumor sites while maintaining therapeutic

level for a long period of time. Pure drug and drug in gel systems shows burst release that indicates within short period of time the therapeutic level exceeds and very less or no drug is available in the site. Therefore, effectiveness of tumor suppression has been observed for brush embedded in gel with drug as compared to other systems. The body weight and degree of survival are comparatively better for brush embedded in gel with drug system and again the Kaplan-Meier survival plot also justifies the better survival percentage for such novel system. Plan of this study is to verify whether brush embedded in gel with drug system can release drug in a controlled way while maintaining the concentration of the drug in blood plasma within therapeutic region over a long time period. To evaluate the *in vivo* performance of drug and brush embedded in gel with drug, the drug concentration in blood is measured after applied the dose of 5 mg/kg of dexamethasone drug in two different sets for detailed study. For drug system, concentration of drug in blood stream rises suddenly (C_{max} = 1 μg/ml) within 1 h, then touching below the Minimal inhibitory concentration (MIC) within 8 h after application. On the other hand, steady rise of concentration of drug has been noticed for brush embedded in gel with drug system with maintaining the higher value that cross the MIC level after one day which reflects controlled release behavior of drug from such novel system. Half life time for brush embedded in gel with drug system is four times higher as compared to the pure drug system indicating the controlled behavior of drug release from such system therefore, increase the presence and elimination time of drug in blood considerably. Further, through this study one can conclude that brush embedded in gel with drug is a potential vehicle for controlled release of drug for melanoma treatment.

Histopathological analyses are carried out to understand the toxicity on vital organs. The stained images of melanoma, applied with brush embedded in gel with drug system shows effective tumor cell death reflecting large necrotic areas with nuclear shrinkages as compared to pure drug and drug in gel treated mice groups. After the treatment of drug and drug in gel systems, kidney of mice damage to some extent while normal kidney architecture has been observed in mice treated with brush embedded in gel with drug. In case of spleen most of systems shows no considerable damage and normal morphology of the organ is observed. Therefore, drug and drug in gel systems is found to damage the most of the important organs due to burst kinetics of drug release behavior like a conventional chemotherapy for cancer treatment resulting severe side effects. On the other hand, brush embedded in gel with drug system, which are injectable gel, does not show any side effect for most of the body organs arising from slow and steady release kinetics *i.e.* controlled nature for a longer period of time. The results of liver and kidney function tests are in good agreement and prepared novel gel system exhibit much better performance as compared to the drug and drug in gel systems. To understand the renal health, blood urea nitrogen and creatinine levels have also been performed and increased level of those are observed in mice treated with drug in gel or pure drug systems, while the normal range has been found for mice treated with brush embedded in gel with drug system. The immunohistochemistry of tumor tissues is performed after staining with melanoma inhibitory activity (MIA) detecting tumor suppression level. MIA is initial indicator of tumor progression relapse and metastasis [6]. In case of brush embedded in gel with drug system shows exceptionally lower expression of protein (as compared with the other groups) indicating lower proliferation rate of melanoma resulting efficient system for melanoma treatment. Effectiveness and homogenous MIA protein expression is directly related with severity of melanoma [7]. To develop an effective vehicle for drug by enfolding of hydrophobic layers over the hydrophilic chains through grafting synchronizes the hydrophilic–hydrophobic balance with changing the degree of grafting to incorporate sufficient dexamethasone drug. Good biocompatibility with its non-toxic nature helps to monitor the tumor progression without any detectable side effects. Therefore, brush biopolymer vehicle acts as a potential drug delivery carrier especially for cancer treatment.

Conclusion and Future Development

This article compiles the developed injectable hydrogel with novel designed brush biopolymers which exhibits controlled drug release for cellular and animal studies of melanoma treatment. The effectiveness of novel gel system has been revealed the potentiality for *in vitro* and also for uptake analysis. For animal study, developed novel injectable hydrogel using gelating agent can be applied near contact to the tumor site which can deliver the drug in a controlled way particularly to the tumor site and observed the good health and function of most of the body organs as contrary to huge damage of liver and kidney noticed for pure drug and drug in gel system, just similar with the conventional cancer chemotherapy. MIA study also reflects exclusively lower protein expression for novel brush embedded in gel with drug system that indicates the strong potential for melanoma treatment reflecting efficient targeted therapy for cancer treatment. Treatment of melanoma is still a prime challenge and material's biology is required to solve the challenges for better understanding of melanoma associated with existing therapies. Therapeutic vaccines, adoptive T-cell therapy, and chimerical antigen receptor T-cell therapy are some of the novel plan of action presently being analyzed in clinical trials [8].

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