Editorial

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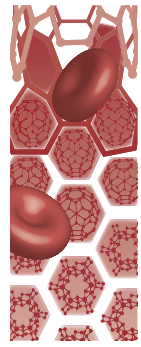

Targeted bioadhesive nanomedicine: an effective approach for synergistic drug delivery to cancers

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"In a recent work, Deng *et al.* described a new form of bioadhesive nanosystem that can stay for prolonged period in the peritoneal space by interacting with mesothelial cells lining the abdominal cavity."

First draft submitted: 10 April 2018; Accepted for publication: 17 April 2018; Published online: 4 July 2018

Keywords: biolabels • cancer nanotechnology • drug targeting • molecular biomaterials • molecular imaging • nanoprobes • theranostics

Current drawbacks of conventional cancer chemotherapy are largely addressed by the innovative anti-cancer nanomedicine platforms of biodegradable and biocompatible materials that can target the cancer site accurately [1–4]. The nanomedicine can passively reach the intended target by enhanced permeability and retention effect or actively targets the receptor over expressing cancer-cell surface using appropriate ligand conjugated on the nanocarrier surface [5,6]. Chitosan is a biocompatible, biodegradable and nontoxic polymer which is extensively studied as a bioadhesive material in fabricating advanced drug delivery systems, such as micelles, liposomes, hydrogels and microparticles [7]. In fact, it is a mucopolysaccharide closely related to cellulose, and commonly obtained by deacetylation of chitin by boiling it in sodium hydroxide. Chitin is the principal component of exoskeletons in crustaceans such as crab and shrimp shells [8,9]. In general, if the N-acetyl-glucosamine units are less than 50%; it is termed as 'chitosan'. The presence of primary amine at the C-2 position of the chitosan molecule confers it with a strong positive charge, which strongly attracts and binds it to a negatively charged molecule. The degree of deacetylation of chitosan plays a major role in solubility, hydrophobicity and the extent of electrostatic interaction with anionic molecule. Also, natural aminopolysaccharide with such high content of primary amines is very rare, and these amines impart unique functional properties to chitosan which can be further manipulated for nano- and bio-fabrication [10,11].

Chitosan, also popular for its nontoxic nature, has a lethal dose 50 (LD50) as similar to sugar and table salt. Indeed, safety and efficacy of the chitosan obtained from fungal origin was also successfully assessed up to Phase IV of clinical trials. Besides its biodegradability, the solubility of chitosan portrays a key role in the use of chitosan and its derivatives in the design and development of bioadhesive nanocarriers. The amino as well as carboxyl groups of the chitosan molecule usually form a hydrogen bond by lipoprotein interaction with the cell membrane, bringing out an ideal adhesive effect [6]. Moreover, some of the other factors that may contribute to the bioadhesive character are its chain flexibility, strong electrostatic interaction and surface energy properties. Most of the epithelial cell adenocarcinomas, nonepithelial cancers and other hematological cancers, such as B-cell non-Hodgkin lymphoma and multiple myeloma also exhibit overexpression of mucin-1 which became phenomenal in preparing nanocarriers of anti-cancer agents [12–15]. Additionally, chitosan has a bioadhesive property with epithelial barriers, tumors and associated mucous membranes, and thus can produce synergistic effect whenever combined with targeting ligands [16]. Indeed, to improve drug bioavailability, bioadhesive systems were designed that facilitate prolonged contact and residence time with cellular surfaces, thereby improving drug absorption. Furthermore, targeted site

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accumulation of nanocarriers was achieved by loading chitosan nanomedicines with theranostic moieties which produced the synergistic therapeutic effect with simultaneous diagnosis [17]. In a recent work, Deng *et al.* described a new form of bioadhesive nanosystem that can stay for prolonged period in the peritoneal space by interacting with mesothelial cells lining the abdominal cavity. They also showed that adhesiveness of nanoparticles has indeed made them stay on the skin for an extended time after topical delivery. These new materials were actually based on the polylactic acid and polyglycerol copolymers that resulted in invisible or 'stealthy' non-adhesive nanoparticles that persisted for long times in circulation after intravenous injection. The oxidation of the nonadhesive nanoparticles has resulted in the formation of bioadhesive nanoparticles, owing to the conversion of vicinal diols into aldehydes present on their surface. The aldehydes may instantly form a variety of bonds such as Schiff-base by reacting with proteins; therefore, leading to particle adhesion on protein-rich surfaces [18]. In another study, Saltzman *et al.* evaluated the bioadhesive polymeric nanoparticles loaded with antiretroviral elvitegravir after intravaginal administration. The results suggested that bioadhesiveness of nanoparticles has much improved and prolonged the delivery of the therapeutic agent due to Schiff-base interaction [19].

Chitosan-based bioadhesive nanomedicine

There are two primary strategies for the targeted endocytic drug delivery such as receptor-mediated transcytosis and absorptive mediated transcytosis. Receptor-mediated transcytosis relies upon selective uptake mediated by the specific binding to the receptor. Absorptive mediated transcytosis is initiated through electrostatic interaction between the negatively charged cell membrane and a positively charged material. These endocytosis processes are the outcomes of interaction between the nanomedicine systems and cell surface binding sites [2]. In a study, Agrawal *et al.* prepared synergistic transferrin receptor-targeted bioadhesive d-α tocopheryl polyethylene glycol 1000 succinate (TPGS) conjugated chitosan micelles loaded with docetaxel which specifically reached the transferrin receptors overexpressed on glioma cells for brain glioma treatment. The considerable decrease in the IC_{50} values explained that the synergistic effect shown by transferrin receptor-targeted TPGS-chitosan micelles was actually due to two reasons: first, chitosan produced bioadhesion and transferrin facilitated the receptor-mediated endocytosis. Second, chitosan also rendered a pH-dependent drug release to the micelles. The drug release was initiated by pH 5.5 which was correlated to pH of tumor cells that triggered the release of anticancer drugs as the micelles entered the cancer cell via transferrin receptor-mediated endocytosis where pH falls to 4.0–6.0 in endosomes and lysosomes. The *in vivo* pharmacokinetic studies explained that when compared with Docel™, the nontargeted and targeted chitosan micelles exhibited prolonged circulation times in blood and there was a significant improvement in bioavailability [20]. These micelles were exploited as a platform for nanomedicines used in cancer therapies as they extend drug release, provide pH-triggered drug release, bioadhesion and receptor-targeted delivery. In another work, Agrawal *et al.* prepared TPGS conjugated-chitosan nanoparticles with or without transferrin attachment. The cellular uptake and cytotoxicity studies showed that nontargeted and targeted nanoparticles demonstrated significantly higher IC_{50} values than Docel. The relative bioavailability values from *in vivo* pharmacokinetic studies were also found to be higher for nontargeted and transferrin receptor-targeted nanoparticles than Docel. It was evident from the results that the combination of chitosan with transferrin decorations had markedly improved the cytotoxicity of nanoformulations. It was also clear from the results that targeting transferrin receptor could improve the cellular internalization of nanoparticles and in turn, improve pharmacokinetics with enhanced cytotoxicity of docetaxel which will be beneficial for clinical applications [2]. Moreover, such targeted nanoformulations prepared with natural polymers in combination with therapeutics like taxanes could further assist in the development of a treatment protocol for transferrin receptor overexpressing cancer cells. The bioadhesive nanomedicines are also considered as a promising strategy to prolong residence time at the disease site with improved bioavailability. The conjugation with various targeting moieties that can actively target the desired location can further improve the therapy by minimizing nonspecific distribution to healthy tissues so that undesirable side effects will be decreased. Due to its unique properties, chitosan can provide bioadhesion, especially in the cancer cells due to their low pH compared with physiological pH. Numerous research works have already been performed on bioadhesive nanosystems based on chitosan and attained preclinical success which proved them beneficial in achieving desired therapeutic effects. From these facts, we also believe that these targeted bioadhesives or sticky nanomedicines can improve delivery of any drug to its respective targets using receptor targeting ligands which will be the promising synergistic strategy in fighting all cancers. After regulatory compliance, these nanomedicines may be considered for viable clinical applications.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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