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Review

The implications of recent advances in carboxymethyl chitosan based targeted drug delivery and tissue engineering applications

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ABSTRACT

Over the last decade carboxymethyl chitosan (CMCS) has emerged as a promising biopolymer for the development of new drug delivery systems and improved scaffolds along with other tissue engineering devices for regenerative medicine that is currently one of the most rapidly growing fields in the life sciences. CMCS is amphiprotic ether, derived from chitosan, exhibiting enhanced aqueous solubility, excellent biocompatibility, controllable biodegradability, osteogenesis ability and numerous other outstanding physicochemical and biological properties. More strikingly, it can load hydrophobic drugs and displays strong bioactivity which highlight its suitability and extensive usage for preparing different drug delivery and tissue engineering formulations respectively. This review provides a comprehensive introduction to various types of CMCS based formulations for delivery of therapeutic agents and tissue regeneration and further describes their preparation procedures and applications in different tissues/organs. Detailed information of CMCS based nano/micro systems for targeted delivery of drugs with emphasis on cancer specific and organ specific drug delivery have been described. Further, we have discussed various CMCS based tissue engineering biomaterials along with their preparation procedures and applications in different tissues/organs. The article then, gives a brief account of therapy combining drug delivery and tissue engineering. Finally, identification of major challenges and opportunities for current and ongoing application of CMCS based systems in the field are summarised.

Contents

Abbreviations: ADR, adriamycin; AQCOM, alginate-Q-CMCS-organic montmorillonite; bFGF, basic fibroblast growth gactor; BSA, bovine serum albumin; BMSCs, bone marrow stromal cells; CPT, camptothecin; CMC, critical micelle concentration; CMCS, carboxymethyl chitosan; O-CMCS, O-carboxymethyl chitosans; N-CMCS, N-carboxymethyl chitosans; N,O-CMCS, N,O-carboxymethyl chitosans; N,N-di-CMCS, N,N-di-carboxymethyl chitosans; CMHC, carboxymethylhexanoyl chitosan; CMCPEG, methoxy poly(ethylene glycol)-grafted carboxymethyl chitosan; CMCS-g-D-GA, CMCS-graft-D-glucuronic acid; CD, cyclodextrin; DD, degree of deacetylation; DS, degree of substitution; DA, deoxycholic acid; DOX, doxorubicin; EPR, enhanced permeability and retention; EDC, 1-ethyl-3(3-dimethylaminopropyl) carbodiimide hydrochloride; FA, folic acid; 5-FU, 5-fluorouracil; GA, glutaraldehyde; GL, glycyrrhizin; GFLX, gatifloxacin; HAP, hydroxyapatite; IPN, interpenetrating; iPSCs, induced pluripotent stem cells; LA, linoleic acid; mPEG-g-CMC, methoxy poly (ethylene glycol) grafted carboxymethyl chitosan; MW, molecular weight; MTA, mineral trioxide aggregate; MIC, minimum inhibitory concentration; MMA, methyl methacrylate; N-CECS/nano-HAP, N-carboxyethyl chitosan/nanohydroxyapatite; OCT, octreotide; OCC, N-octyl-O,N-carboxymethyl chitosan; OD, ornidazole; OMMT, organic montmorillonite; PTA, Cis-3-(9H-purin-6-ylthio)-acrylic acid; PTX, paclitaxel; PNIPAM, poly(N-isopropylmethacrylamide); PBS, phosphate buffer saline; PEG, polyethylene glycol; PAMAM, poly(amidoamine); PVA, poly-vinyl alcohol; QCMCS, quaternised carboxymethyl chitosan; SA, stearic acid; SMCs, smooth muscle cells; TLAC, thiolated lactosaminated; VEGF, vascular endothelial growth factor.

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1. Introduction

Natural polysaccharides, due to their non-toxicity, biocompatibility and biodegradability, are widely being studied as biomaterial for drug delivery and tissue engineering applications. Among them, chitosan, which is known to be biocompatible, biodegradable, non-toxic, mucoadhesive and antimicrobial, has been exhaustively exploited for developing different formulations for controlled delivery of biotherapeutics and in regenerative medicine. But limited solubility of chitosan in water and other organic solvents has prevented its full exploitation in drug delivery and tissue repair and reconstruction [1,2]. In addition to this, the limited colloidal stability of chitosan based particulate drug delivery systems are known to exhibit immunogenicity [3] and degradability of chitosan based formulations in tissue regeneration and drug delivery is uncontrollable [4]. Therefore derivatisation of chitosan seems a promising way to get rid of these limitations of chitosan and widening range of drug delivery and tissue engineering applications. In fact, life sciences and bio-technologies is the realm where chitosan and chitosan derivatives have raised greater scientific interest because of their remarkable structural and functional properties. Among them, carboxymethyl chitosan (CMCS), a water soluble derivative of chitosan, has attracted booming interests in several fields such as *in vitro* diagnostics [5–7], theranostics [8] bioimaging [9], biosensors [10,11], wound healing [12], gene therapy [13–16] and food technology [17,18] but its greatest impact has been in the area of drug delivery and tissue engineering. CMCS is potentially biologically compatible material that is chemically versatile ($-NH_2$ and –COOH) groups and various molecular weight, (MW). The positive facets of increased water solubility, excellent biocompatibility [19], admirable biodegradability, high moisture retention ability [20], improved antioxidant property [21], enhanced antibacterial [22] and antifungal [23] activity and non-toxicity as compared to chitosan has provided ample opportunities to the drug delivery and tissue engineering scientists to create a plethora of formulations and scaffolds. In addition, it is also known to be more bioactive [24], promotes osteogenesis [25] and its safety evaluation on compounds [26], *in vitro* models, blood systems [27] and tumor application [28] has been well established. All these favorable physical, chemical and biological properties of CMCS make it a promising biomedical material for drug delivery and tissue engineering applications in several formulations. Recently numerous experimental results have been reported on the potential therapeutic applications of CMCS in reduction in post surgical adhesion formation [29], antibacterial biomaterial [30] and accelerated wound healing [31]. The most exhaustively investigated CMCS based drug delivery formulations include hydrogels [32], microspheres [26], beads [33], micelles [34], aggregates [35], nanoparticles [36,37], films [38] and membranes [39]. Similarly, repairing and reconstruction of tissues like bone, cartilage, and nerve by CMCS based tissue engineering devices like scaffolds [40], injectable gels [2], and biocomposites has been reported by various researchers in recent years.

2. Scope of the present review

In consideration of the above, the scope of the present review is to identify the lines of applied research that are now consolidating major advances made with the CMCS during the last decade in the field of drug delivery and tissue engineering. The novelty of these facts is underlined by the fact that a previous attempt to review the literature on CMCS has focused primarily on the general biomedical applications of CMCS with only a minor part dealing with drug delivery and tissue engineering applications [41]. While another review article authored by Mourya et al. [42] mainly covers literature regarding the synthesis and characterisation of CMCS along with its pharmaceutical applications. CMCS being inherently bestowed with astonishing physical, chemical and biological features, emerging trends show that it is highly suitable for the delivery of numerous bioactive and therapeutic compounds and for the repair and reconstruction of damaged and/or diseases tissues. Excellent biocompatibility, improved biodegradability, enhanced antimicrobial activity, better chelating ability, moisture