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# Controlled release of cephradine by biopolymers based target specific crosslinked hydrogels

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ABSTRACT

The novel silane crosslinked (TEOS) hydrogels based on eco-friendly biodegradable chitosan/guargum were prepared by blending with PEG to develop pH sensitive hydrogels (CGP) and achieved its hydrophilicity and target specificity for controlled release of drug. The crosslinker amount was varied to analyze its effect on the hydrogel properties and were characterized using FTIR, SEM, TGA, swelling studies (water, buffer and ionic solution) and in-vitro release of cephradine (CED). FTIR confirmed the presence of characteristic peaks and crosslinking between the components while SEM images showed the formation of clear micro- and macro-pores. The swelling behavior in water showed that compared to the controlled hydrogel, the crosslinked hydrogels revealed more swelling but a decrease in swelling with further increase in the amount of crosslinker was observed. The hydrogels showed low swelling at basic and neutral pH while maximum swelling was observed at acidic pH. This pH response made these hydrogels an ideal candidate for injectable controlled release. The CED was loaded on hydrogels and its release mechanism was studied in PBS, SGF and SIF which revealed that out of all hydrogels (CGP100, CGP150, CGP200 and CGP250), CGP100 has shown CED release of 85% in 130 min in PBS and 82.4% in SIF.



## 1. Introduction

Despite a remarkable advancement in the field of drug delivery, many of the drugs have uncontrolled side effects potentially due to the undesired interactions of the drug with the other organs that are not the desired target of the administered drug. The incorporated drug is to be efficient and effective subsequently it is introduced into the body. One of the major problems associated with the conventional drug dosage method is the dispersal of major drug throughout the body with only small portion reaching the desired target area [1]. The controlled release of drug should be fit in the therapeutic range and there must be no possibility of harmfulness and also the wastage of drug in contrast to the conventional intermittent drug release systems. For targeted delivery of the drug and intensification of therapeutic efficiency, a sophisticated drug delivery system is an urgent requirement where pH sensitive hydrogels serve as promising choice to be used as drug carriers. Certainly, there is an increasing concern in the development and usage of biopolymers and the advanced skills that can lessen the reliance on artifact energy and transfer to a viable resources. Generally, natural polymers such as chitosan (CS) are well suited for the controlled drug delivery with low cost, eco-friendly, nontoxicity, versatility, biocompatibility, biodegradability and antimicrobial characteristics which make it ideal to be used in biomedical applications [2]. It has established substantial consideration in the area of controlled drug delivery systems. CS is a linear polysaccharide mainly composed of β-(1–4) linked D-glucosamine and *N*-acetyl-D glucosamine small repeating units. It is the second most abundant natural biopolymer after cellulose usually obtained as a result of the alkaline deacetylation of chitin which is the prime component of the cuticles of the crustaceans like crabs, shrimps, lobsters and in the cell walls of some fungi [3–5]. Guar gum (Gg) is a cheap, greatly abundant, film forming via simple dissolution casting process and merely accessible among several biopolymers. It is a polysaccharide (water soluble) which consists of a linear chain of pyranosyl units joined by D, (1 → 4) linkage and (1 → 6) linkage. It is typically used as an assimilated ingredient in hydrogels and other biomaterials for medical applications [6–8].

A significant work has been dedicated to the natural polymers itself in addition to the fabrication of CS and Gg based hydrogels. The intrinsic limitations of natural polymers for instance their weak mechanical strength and unwanted obstacle properties can be overwhelmed by

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the chemical alteration enhanced via coupling it with synthetic polymers like polyethylene glycol (PEG) to have synergistic effect of natural and biocompatible synthetic polymer. PEG is hydrophilic and its affinity for water increases the solubility of drugs or carriers when combined with water which are otherwise hydrophobic in nature. Biocompatible PEG has attained an inordinate attention in current years and forms a good polymeric hydrogel network with CS and Gg. One of the most compelling area of research for PEG is its ability to conjugate with proteins, peptides and non-peptides where these conjugates exhibit stability towards degrading enzymes and are less immunogenic [9,10]. PEG have been widely designated as drug carriers due to its ability to increase the constancy and the therapeutic outcome of the drug, minimal toxicity, biocompability, good water solubility and the prevention of aggregation. They can be *co*-polymerized for use in drug delivery, tissue engineering and other biomedical fields enhancing the biocompatibility of polymers [11]. It is approved by Food and Drug Administration (FDA) for a wide range of biomedical applications.

A considerable interest has been anticipated in recent years in the synthesis of polymeric network from biodegradable natural and biocompatible polymers to attain a well-established coordination. CS and Gg have enormous essential potentials for chemical modification in order to produce novel characteristics using different crosslinking agents like formaldehyde, glutaraldehyde, epichlorohydrin, etc. [12,13]. Tetraethoxysilane (TEOS) is preferred mainly due to the general ability of the silane crosslinkers to undergo inorganic crosslinks in the polymers amorphous zones. It is the best possible way to develop covalent bonding between the polymeric chains and the inorganic part generally used in biomaterial applications. They can be easily crosslinked via condensation reactions while being non-toxic as compared to previously used crosslinkers (epichlorohydrine, borate and tripolyphosphate) [14].

The main deficiency in the conventional drug release system is their lack of site specificity and inability to release the drug in a controlled manner and not to maintain its concentration effectively. As a consequence of which only a diminutive amount of the administered drug is consumed by the body while the rest is excreted out and cause unavoidable side effects. To attenuate this damage, the need is to devise substitute method to derogate the damage and to maintain the actual drug dosage range effectively. Keeping this prospect, the injectable hydrogels are more appropriate to facilitate the drug release in a controlled way for the desired delivery period. They are more advisable to be used owing to their ability to minimize the patient discomfort while effectively fulfilling the ultimate benefit of the administered dose [15]. The widely used polymers for the synthesis of injectable hydrogels are carboxymethylcellulose, cellulose, Polyvinyl alcohol, polyvinylpyrollidone, chitosan, polyethylene glycol, etc. [16,17]. The utilization of the injectable hydrogels compared to the formerly prepared hydrogels seems to be more appealing as it can minimize the potential risk of infection and cost of the operative procedures [18]. Consequently, for localized and controlled release of drugs, the injectable hydrogels hold a substantial place whereas the ingredients must be nontoxic and have the ability to degrade after the desired target is achieved.

CED is a first generation antibiotic drug which is acid stable and is absorbed rapidly after oral administration. The in-vitro studies by ultracentrifugation technique shows that mainly at the therapeutic antibiotic concentrations, CED is marginally bound to the (8–17%) normal serum protein. Overall, 90% of the administered drug is excreted unaltered in the urine within few hours.

The main aim of the present study is to fabricate silane crosslinked (TEOS) pH sensitive injectable hydrogels using biodegradable and biocompatible natural and synthetic polymers; chitosan, guargum and PEG for controlled drug release. The novel characteristics and combined properties of two different polysaccharides (CS and Gg) have essential abilities for chemical modification and crosslinked by TEOS used for the controlled release of CED. To the best of our knowledge, no work has been reported using CS/Gg/PEG/TEOS for the injectable release of CED. The main reason for opting TEOS was its nontoxic nature and its widely accepted use in the biomedical applications [19]. The effects of variation in the amount of the crosslinker on the properties of the synthesized hydrogels were studied. The swelling response of hydrogels was evaluated in water, buffer (varying pH) and ionic solutions. The hydrogel samples were analysed for controlled drug release of CED which was selected as a model drug and release mechanism was examined in phosphate buffer saline (PBS), simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) using UV–vis spectroscopy.

## 2. Materials and methods

### 2.1. Materials

Chitosan (Mw = 406,039.4 g/mol; degree of deacetylation; DDA = 85%; viscosity = 800 cps) was purchased from Biolog (GmbH) TM, Germany. Guar gum (food grade extra refine; viscosity 5000 cps) was supplied from Dabur India Ltd. Poly (ethylene glycol) (Mw = 600 g/mol), absolute ethanol and formic acid were obtained from Merck, Germany. TEOS (98.5%) was purchased from DAEJUNG chemical and metals Co. Ltd., Korea. Hydrochloric acid was received from Labscan Asia, Co. Ltd., Thailand. NaCl, $CaCl_2$, $NaH_2PO_4$, $KH_2PO_4$, KCl, HCl, NaOH, Acetic acid, NaOAc and $H_3BO_3$ were purchased from Sigma Aldrich. CED used as a drug and was obtained locally. *E. coli* DH5α strain, tryptone and yeast extract were also used for antimicrobial analysis.

### 2.2. Synthesis of designed hydrogels

Chitosan (0.50 g) was dispersed in 45 mL of 1% formic acid solution at 50 °C with continuous stirring until complete dissolution. Guar gum (0.20 g) was dissolved in 25 mL of distilled water with stirring at 50 °C. The two prepared solutions were blended, stirred for 1 h and PEG (0.3 mL) was added into this chitosan-guar gum blend and finally stirred for another hour. This blend was referred to as CGP blend and then crosslinking was established via addition of crosslinker. The varying amount (100, 150, 200 and 250 μL) of crosslinker (TEOS in 5 mL ethanol) was added dropwise to the previously prepared CGP blend under continuous stirring at 60 °C for 2 h. The drying oven (LVO-2040, Lab Tech, Korea) was used to dry blended hydrogel at 60 °C and fabricated hydrogels were stored in a desiccator. The controlled hydrogel sample was prepared using above procedure without adding crosslinker. The codes on the basis of crosslinker concentration were CGP (controlled), CGP 100, CGP 150, CGP 200 and CGP 250, respectively. The synthesis of the hydrogel have been done three times to obtain hydrogels with reproducible properties.

## 3. Analyses and characterization

### 3.1. Functional group analysis

Fourier transform infrared analysis (FTIR) spectra for CGP hydrogels were obtained on Brukeralph-P, equipped with attenuated total reflectance technique. The hydrogels spectra were collected at 4 $cm^{-1}$ resolution with scanning range of 4000–400 $cm^{-1}$. According to the FTIR protocol, the hydrogels were washed gently with distilled water to remove any acid as an impurity present on the hydrogels prior to analysis.

### 3.2. Thermal stability analysis

Thermogravimetric analysis (TGA) of the prepared hydrogels was performed at the heating rate was 20 °C/min with nitrogen flow of 15 mL/min from ambient room temperature to 600 °C.