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# Synthesis of chitosan-based nanohydrogels for loading and release of 5-fluorouracil

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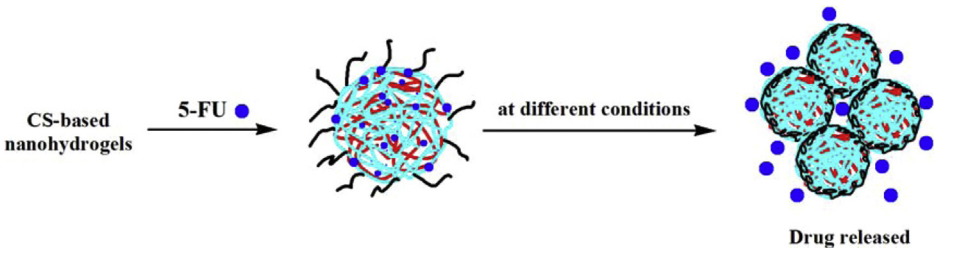
## HIGHLIGHTS

- Several novel functionalized chitosan-based nanohydrogels were synthesized.
- These nanohydrogels show different soluble property at a wide range of pH.
- 5-Fluorouracil (5-FU), a chemotherapy drug, was loaded into the nanohydrogels.
- These nanohydrogels showed a consecutive release of 5-FU at different conditions.
- Possible mechanisms of CS-based nanohydrogels and 5-FU loading were investigated.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Several functionalized copolymer nanohydrogels consisting of chitosan (CS) and the monomer acrylic acid (AA), methyl methacrylate (MMA) and *N*-isopropylacrylamide (NIPAM), which were used to adjust the limited solubility of CS under alkaline condition, have been synthesized by free radical polymerization method. They exhibited favorable solubility behavior in a broader pH range as well as thermal-sensitive properties at 37 °C. The nanohydrogels were analyzed by particle size, zeta potential, FT-IR and SEM. Results showed that the nanohydrogels possessed of a uniform spherical morphology with 140–190 nm in size and carried obvious positive surface charges. 5-Fluorouracil (5-FU) loaded nanohydrogels were prepared and the loading efficiencies of 5-FU with different concentrations of nanohydrogels were investigated. The maximal loading efficiency was 99.5%. And these nanohydrogels could provide a consecutive release of 5-FU at different conditions. Furthermore, the possible synthesis mechanisms of CS-based nanohydrogels and 5-FU loading were studied in this paper.



## 1. Introduction

Polymer-based nanohydrogel as effective delivery carriers of anticancer drugs has received considerable attention in recent years [1–4]. It has been proven that nanohydrogels have excellent physicochemical and biological properties [5]. Up to now, various methods have been applied to fabricate polymer-based

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nanohydrogel including microemulsion polymerization, free radical polymerization, emulsification-diffusion method [6–8] and so on. Pérez et al. [9] prepared bioresponsive nano gels using microemulsion polymerization method and it had many good properties in drug loading capacity, encapsulation efficiency and in vitro release. Lee et al. [10] reported the preparation of alginate nanohydrogels using emulsification-diffusion method and the nanohydrogels size could be controlled from 49.2 nm to 1.9 μm. Jaiswal et al. [11] synthesized poly(NIPAAm)-CS based nanohydrogels using free radical polymerization method, and the prepared materials showed a moderate and excellent cytocompatibility. Compared with other methods, free radical polymerization could easily form nanohydrogels through intra/interchain collapse, which worked as a moderate method to fabricate well-defined, biocompatible materials.

CS is the most abundant organic polysaccharide on earth. It is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and *N*-acetyl-D-glucosamine (acetylated unit). Due to its excellent biological property including biocompatibility, biodegradability, nontoxicity, CS is extensively used in the field of medicine [12–14]. Dyondi et al. [15] prepared CS nanohydrogel by the ionic gelation method which showed good biocompatibility and release behaviors for protein. However, CS nanohydrogels have a limit of lacking good solubility under alkaline condition. And it will lose surface charge when the pH was above 7, which will affect the absorptive property in physiological environment [15].

5-FU, a pyrimidine analog, has been extensively used for the therapy of solid tumors. However, as the important clinical chemotherapy drug in tumors, it has serious damage to normal body cells and often produces side effects [16–18] while inhibiting or killing tumors cells simultaneously. According to relevant investigation [19], CS-based nanoparticles could prevent the side effects caused by 5-FU.

In order to overcome the limited solubility of CS under alkaline condition, MMA and AA were grafted on CS to adjust the suitable pH range in the present study. Poly(*N*-isopropylacrylamide) (PNIPAM) as the thermal-sensitive material was also grafted to CS basing on free radical polymerization. 5-FU was loaded on the nanohydrogels through hydrogen bonding and van der Waals interactions. Simultaneously, the loading efficiencies and release behaviors of 5-FU-loaded nanohydrogels were investigated at pH 7.4. Moreover, the release behaviors of 5-FU from CS-based nanohydrogels in the artificial gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) environment were also evaluated.

## 2. Experimental

### 2.1. Materials

CS (deacetylation degree of 95%, 1000 kDa) was purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). MMA and AA were obtained from Fuchen Chemical Reagents Factory (Tianjin, China). Potassium persulfate and *N*,*N*-methylenebisacrylamide (MBA) were purchased from Beijing Chemical Reagents Company (Beijing, China). NIPAM was obtained from TCI Development Co., Ltd. (Shanghai, China). 5-FU was provided from Shanghai Macklin Biochemical Co., Ltd. (Shanghai, China). Phosphate buffer solution (PBS, pH 7.4) was prepared using potassium dihydrogen phosphate (1.36 g) and NaOH solution (0.1 mol/L, 79.0 mL), followed by diluting the solution to 200 mL with ultrapure water. All the other regents were of analytical grade and were used without further purification.

The artificial gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) were prepared according to the previous report [20]. In general, 500 mL of artificial gastric fluid was obtained by dissolving hydrochloric acid (3.5 mL, 37 wt%) and sodium chloride (1.0 g) in 500 mL ultrapure water. The artificial intestinal fluid was prepared by dissolving potassium dihydrogen phosphate (3.4 g) in 125 mL ultrapure water, and then the pH was adjust to 6.8 by NaOH solution (0.2 mol/L, 59.0 mL), followed by diluting the solution to 500 mL with ultrapure water.

### 2.2. Preparation of nanohydrogels

Chitosan-methyl methacrylate (CM) was prepared by free radical polymerization of chitosan and MMA. Briefly, 0.5 g of CS was dissolved in 50 mL of acetic acid solution (2.0%, w/v) in a flask

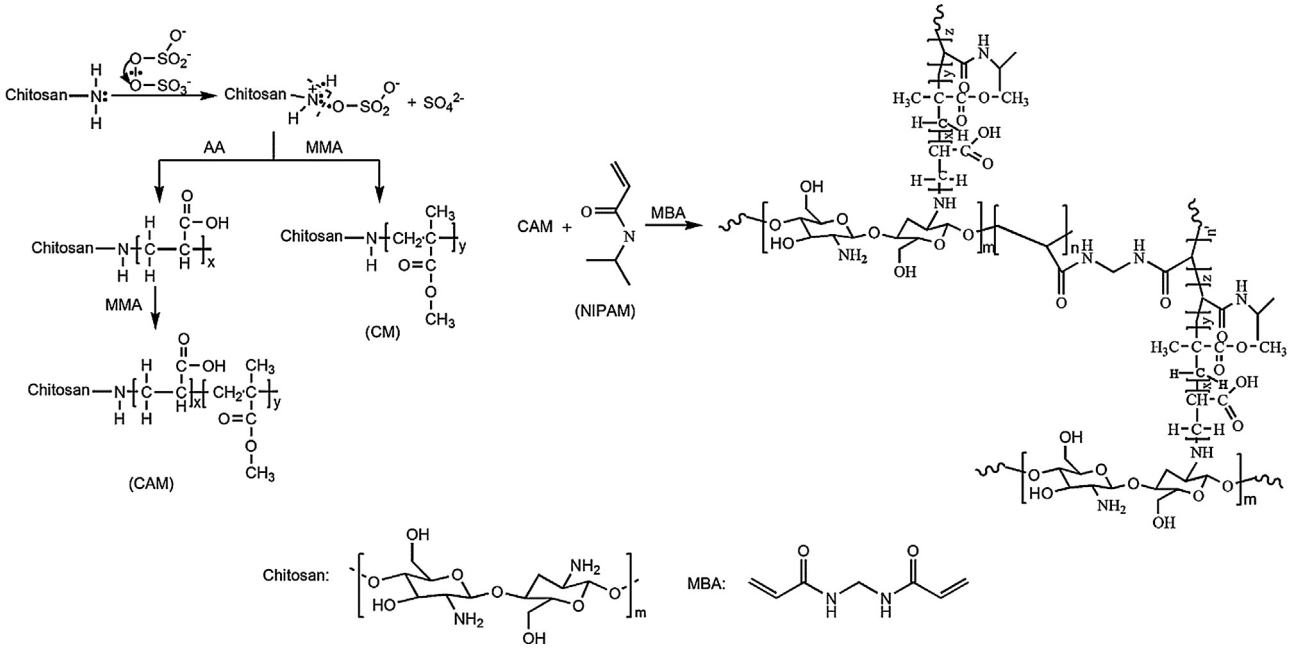


**Fig. 1.** Synthesis schematic of CS-based nanohydrogels.