Saudi Pharmaceutical Journal (2016) **24**, 250–253

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Study on fluorouracil–chitosan nanoparticle preparation and its antitumor effect

Gaimin Chen [a], **Rudong Gong** [b,*]

[a] *Pharmacy Department, Nanyang Medical College, Nanyang 473061, China*
[b] *Public Teaching Department, Nanyang Medical College, Nanyang 473061, China*

Available online 23 April 2016

KEYWORDS

Fluorouracil;
Chitosan;
Nanoparticles;
Preparation method;
Antitumor effect

Abstract To successfully prepare fluorouracil–chitosan nanoparticles, and further analyze its anti-tumor activity mechanism, this paper makes a comprehensive study of existing preparation prescription and makes a detailed analysis of fluorouracil–chitosan in vitro release and pharmacodynamic behavior of animals. Two-step synthesis method is adopted to prepare 5-FU–CS–mPEG prodrugs, and infrared, ^{1}H NMR and differential thermal analysis are adopted to analyze characterization synthetic products of prepared drugs. To ensure clinical efficacy of prepared drugs, UV spectrophotometry is adopted for determination of drug loading capacity of prepared drugs, transmission electron microscopy is adopted to observe the appearance, dynamic dialysis method is used to observe in vitro drug release of prepared drugs and fitting of various release models is done. Anti-tumor effect is studied via level of animal pharmacodynamics. After the end of the experiment, tumor inhibition rate, spleen index and thymus index of drugs are calculated. Experimental results show that the prepared drugs are qualified in terms of regular shape, dispersion, drug content, etc. Animal pharmacodynamics experiments have shown that concentration level of drug loading capacity of prepared drugs has a direct impact on anti-tumor rate. The higher the concentration, the higher the anti-tumor rate. Results of pathological tissue sections of mice show that the prepared drugs cause varying degrees of damage to receptor cells, resulting in cell necrosis or apoptosis problem. It can thus be concluded that ion gel method is an effective method to prepare drug-loading nanoparticles, with prepared nanoparticles evenly distributed in regular shape which demonstrate good slow-release characteristics in receptor vitro and vivo. At the same time, after completion of drug preparation, relatively strong anti-tumor activity can be generated for the receptor, so this mode of preparation enjoys broad prospects for development.
© 2016 Production and Hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

In recent years, constant social and economic development results in people's accelerating pace of life. Meanwhile, environmental problems deteriorate (He et al., 2008). As a result, global cancer incidence and mortality rates stay a high level, posing a serious threat to people's health, wherein, liver

* Corresponding author.
E-mail address: gongrdong@sina.com (R. Gong).
Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2016.04.008
1319-0164 © 2016 Production and Hosting by Elsevier B.V. on behalf of King Saud University.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

cancer, stomach cancer, esophageal cancer and colorectal cancer and other gastrointestinal cancers have a high incidence (Chao and Zhang, 2012). Currently, chemotherapy is one of the primary means for treatment of cancer, but its treatment effect is subject to drug side effects and drug resistance. In recent years, with the blend of molecular biology, molecular pharmacology, polymer materials, thermal chemistry and other subjects, the researchers have developed controlled release preparations and targeting preparation which can be intelligently controlled according to tumor site characteristics (Wang et al., 2010; Li et al., 2012a,b; He et al., 2011). Chitosan (shown as Fig. 1) (CS), the product of deacetylation of chitin, is the only alkaline polysaccharide in nature. With broad range of sources, good biodegradability, biocompatibility and low toxicity, it is widely used in such aspects as pharmaceutical, textile, environmental monitoring and tissue repair. But intermolecular and intramolecular hydrogen-bond interaction reduces its solubility, only partially soluble in acid, such as acetic acid, hydrochloric acid, methane sulfonic acid. In order to make excellent the properties of chitosan that are benefit for more cancer patients, chitosan must be modified. 5-Fluorouracil (shown as Fig. 2) (5-Fu) is an anticancer drug of DNA synthesis cycle. As its cells enjoy relatively strong destruction characteristics, it is widely used in the treatment of a variety of solid tumors such as colorectal cancer, stomach cancer, breast cancer in clinics. However, metabolic rate of the drug is relatively fast, which easily leads to problems such as gastrointestinal reactions and poor selectivity, so these drugs are not very widespread in practice. To enhance anti-cancer effect and reduce toxicity, over the years, people have done a lot of chemical modification work on 5-FU, to effectively reduce side effects of these drugs (Xu et al., 2014). Nanoparticles (NP) is ultra fine particle decentralized administration system formed by aggregate, poly charge of natural or synthetic polymer materials, which belongs to colloid administration system; its shape is mostly solid colloidal particles with diameter of 10–1000 nm (Li et al., 2012a,b). Nanoparticles have significant medicinal property transport advantages, so preparation of nanoparticles has always been the focus of research questions. With constant progress and development of chemical preparation level, preparation mode of nanoparticles demonstrates significant diversification characteristics. In this paper, preparation effect of fluorouracil–chitosan nanoparticles with ion gel method is deeply analyzed, and its inhibitory effect for cancer tumors is explored.

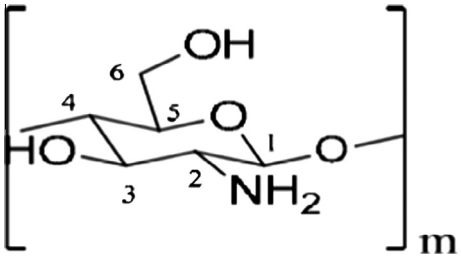

Figure 1 Chemical structure of chitosan.

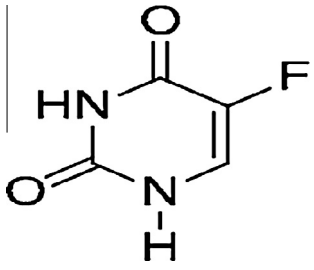

Figure 2 Chemical structure of 5-fluorouracil.

2. Materials and methods

2.1. Fluorouracil–chitosan preparation

Chitosan (molecular weight 5.0 × 104), 5-fluorouracil, polyethylene glycol monomethyl ether 5000 (mPEG), 1-ethyl-3-(3 -dimethylaminopropylamine) carbodiimide salt, silicate (EDC ś HCl), N-hydroxysuccinimide (NHS), succinic anhydride, 4-dimethylaminopyridine (DMAP), N,N-dimethylformamide (DMF), anhydrous ether, chloroacetic acid, methyl orange/phenolphthalein, dialysis bags, and deuterated reagent.

Acid/ alkaline buret, 8LGJ-18A freeze-drying machine, WQF-410 Fourier transform spectrometer, 500 MHz fully digital superconducting NMR spectrometer, UV-1700 UV spectrophotometer, DF-101S heat collection constant temperature magnetic stirrer, constant temperature magnetic stirrer, differential scanning calorimeter.

Determination of degree of deacetylation of chitosan: (1) Determine degree of deacetylation of chitosan; (2) demarcate acid or alkaline solution with primary standard substance anhydrous Na_2CO_3; and (3) Calculate the degree of deacetylation: formula is as follows:

$$(\text{–NH}_2)\% = \{[(C_1V_1 - C_2V_2) \times 0.016]/G\}100\%$$

$$\text{DD} = [(\text{–NH}_2)\%/9.94\%]100\%$$

wherein C_1 represents concentration of HCl, V_1 represents HCl volume needed, G represents mass of chitosan, C_2 represents concentration of NaOH standard solution, and V_2 represents volume of NaOH.

Preparation of polyethylene glycol monomethyl ether chitosan, with synthetic method is shown in Fig. 3 below (Yan et al., 2011a,b).

Structural characterization of polyethylene glycol monomethyl ether chitosan of 5-fluorouridine conjugate: (1) Weigh 1–2 mg sample after drying treatment with infrared spectrophotometry (FT-IR), after mixed compression with KBr, measure on infrared instrument, with scan range at 4000–400 cm^{-1}; (2) nuclear magnetic resonance spectroscopy (^{1}H NMR), measure ^{1}H NMR of substance with AVANCE III 500 MHz NMR instrument, measuring solvent of 5-FUA is DMSO-d6, measuring solvent of mPEG is D_2O, and measuring solvent of other substances is mixed solution of deuterated water and deuterated hydrochloric acid (D_2O/DCl) (Yan et al., 2012). Degree of substitution of mPEG on chitosan is calculated with integration of characteristic peaks in ^{1}H NMR. (3) Differential thermal analysis method employs Perkin ElmerDSC4000 for determination: Weigh 5 mg substance for die determination, nitrogen flow rate: 20 ml/min, measuring range: 20–300 °C.

Download English Version:

https://daneshyari.com/en/article/2509230

Download Persian Version:

https://daneshyari.com/article/2509230

Daneshyari.com