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Research paper

A study on sustained release formulations for oral delivery of 5-fluorouracil based on alginate–chitosan/montmorillonite nanocomposite systems

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ABSTRACT

The objective of this study was to develop a sustained drug release system for 5-fluorouracil (5-FU), an anticancer drug, to improve its half-life. 5-Fluorouracil was loaded on montmorillonite (Mt) layers through the preparation of 5-FU/Mt nanocomposite by an intercalation method. In order to retard the drug release in the gastric environment, the prepared 5-FU/Mt nanocomposite was compounded with alginate (Alg), and further coated with chitosan (CS). This novel drug delivery system was characterized by Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), and scanning electron microscopy (SEM) analyses. By in vitro experiments the effects of Mt contents and pH of the release media on the release rate of the drug were investigated. According to the results, the Alg–CS/5-FU/Mt nanocomposite system containing 30 wt.% Mt in the release media with the pH of 7.4 effectively sustained the drug release and the time for 50% release, $T_{50\%}$, is about 8 h. The release profile of 5-FU from the Alg–CS/5-FU/Mt nanocomposite system was best fitted by the Korsmeyer–Peppas kinetic model suggesting the diffusion controlled release mechanism. The prepared Alg–CS/5-FU/Mt nanocomposite system is suitable for the delivery of 5-FU in the small intestine with a controlled manner.

1. Introduction

In recent years, the discovery of new drug delivery systems based on biomaterials has attracted much attention for the treatment of cancer diseases. The most important advantage of biomaterials is that they can be disappeared as implanted foreign materials from the body as a result of their biodegradation (Greco and Vicent, 2009; Nanda et al., 2011). Widely used biomaterials for the controlled release of anticancer drugs include natural polymers, such as alginate (Alg), chitosan (CS), and cellulose derivatives (Xing et al., 2010).

Alg is a linear, naturally occurring anionic polysaccharide, extracted from brown sea algae, containing D-mannuronic (M) and L-guluronic (G) acids. The distinctive properties of Alg, e.g. hydrophilicity, biocompatibility, mucoadhesiveness, nontoxicity, and inexpensiveness, make it a suitable drug delivery carrier. Also the capability of Alg to form gel in the presence of divalent cations has been exploited to incorporate numerous drugs, proteins, or enzymes (Tonnesen and Karlsen, 2002). The drug delivery from Alg hydrogels is a pH-dependent phenomenon which leads to site-specific delivery. Alg shrinks at low pH values (gastric environment) and the encapsulated drugs cannot be released in the stomach. Due to the increase of the pH as the encapsulated drugs pass down the intestinal tract, the degree of swelling increases which facilitates its rapid disintegration and drug releases at preferred sites (Shilpa et al., 2003). Chitosan, a cationic polysaccharide consisting of D-glucosamine and N-acetyl glucosamine, obtained from the chitin deacetylation process in an alkaline solution, has been extensively applied in drug delivery systems, because it is biodegradable, biocompatible, nontoxic, non-immunogenic, non-carcinogenic, anti-bacterial and mucoadhesive (Li et al., 2011). The use of polyelectrolyte complexes (PECs) between the anionic Alg and cationic CS has been widely studied for the controlled delivery of drugs (Sarmento et al., 2007; Rawat et al., 2008).

Among chemotherapeutic compounds in the treatment of cancer diseases, 5-fluorouracil (5-FU) is one of the most widely used antineoplastic drugs for the treatment of breast cancer (Longley et al., 2003), gastric cancer (Dickson and Cunningham, 2004), pancreatic cancer (Pasetto et al., 2004), brain tumor (Lesniak and Brem, 2004), liver cancer (Elias et al., 2004), and colorectal cancer (Glavas Dodov et al., 2009; Dev et al., 2011). 5-FU is a pyrimidine analog that inhibits the biosynthesis of deoxyribonucleotides for DNA replication by the inhibition of thymidylate synthase activity, leading to thymidine depletion, incorporation of deoxyuridine triphosphate into DNA and cell death. An additional mechanism of cytotoxicity of 5-FU is the incorporation of uridine triphosphate into RNA, which disrupts RNA synthesis and processing

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(Kevadiya et al., 2012). However, it metabolizes so fast that the biological half-life is only 10–20 min (Sanoj Rejinold et al., 2011). Other limitations in the use of 5-FU are its non-uniform oral absorption due to metabolism by dihydropyrimidine dehydrogenase, toxic side effects on the bone marrow and gastrointestinal tract, and non-selective action against healthy cells (Kevadiya et al., 2012). So, to obtain an effective clinical blood drug concentration, people often choose to increase drug mass or to administer the drug to patients continually or repeatedly, which enhance the toxic side effects of 5-FU. Currently, only intravenous preparations of 5-FU are available in market for clinical use. Intravenous administration is associated with pain and formulations have to be sterile. Moreover, owing to skillfulness required for administration, it is time consuming for doctors and patients and therefore self-administration is not possible. Psychological distress, hypertrophy or atrophy of the subcutaneous fat at the site of injection, and occasional allergies are some of the additional factors responsible for non-conformity by the patient to the therapy using this route. Furthermore, intravenous administration of the drug has been reported to cause severe gastrointestinal, dermatological, hematological, cardiac and neural side effects (Diasio and Harris, 1989). Most of these side effects are due to the exposure of the drug to the unwanted sites. Severe systemic toxic effects along with a short plasma half life make it necessary that this drug to be delivered by a local delivery system capable of providing a continuous sustained release (Wei et al., 2008).

Delivery of drugs to the receptors at a particular site has the potential to reduce side effects and to increase pharmacological response. Among the different routes of targeting a drug, the oral route remains to be the choice of administration (Krishnaiah et al., 2002). Oral chemotherapy represents great challenges in drug delivery and its success could become a revolution in the history of chemotherapy. It can maintain an appropriate concentration of the drug in the circulation to achieve a prolonged exposure of cancerous cells to the drug. This will increase the efficacy and decrease the side effects of the anticancer drugs (Dong and Feng, 2005). Also, oral chemotherapy is an important step towards the patients' dream: “Chemotherapy at Home”, which will greatly improve their quality of life and give hope to those of late stage cancer, who have been too weak to accept any treatment at all (Feng et al., 2009). Until now, there is no dosage form of 5-FU for oral delivery, although this would be particularly useful in colon cancer therapy. Also conventional oral dosage forms are ineffective in delivering drugs to the colon due to the absorption or degradation of the active ingredient in the upper gastrointestinal tract (Dev et al., 2011).

Therefore, pharmaceutical technologists are working on ways to deliver the drug more effectively to the colon via the gastrointestinal (GI) tract, where it can target the tumor tissues. However compared to the protein drugs, the controlled release of anticancer drugs with low molecular weights through encapsulation into polysaccharides such as Alg and CS still suffers from certain limitations. Due to the high water content of the polysaccharide based release matrices, the release of low molecular weight drugs usually cannot be effectively controlled and the release rate is very fast with an obvious burst release (Yu et al., 2008). Recently, the application of polymer/layered silicate nanocomposites for drug delivery systems has attracted much attention (Kevadiya et al., 2010). These hybrid materials benefit from the combined properties of both components, such as swelling, water uptake, mechanical characteristics, thermal behavior, rheology and bioadhesion (Salcedo et al., 2012). Studies on the applications of clays to carry out specific functions such as delaying and/or targeting drug release, improving drug dissolution, increasing drug stability and modifying drug delivery patterns have been reviewed (Liu et al., 2011). Among layered silicate materials, montmorillonite (Mt) has attracted a great deal of attention due to its ability to release drugs in a controlled manner, mucoadhesiveness to the pharmaceutical formulations, ability to cross the gastrointestinal barrier and orally bioavailability. It also has a capability to adsorb dietary toxins, microbial toxins associated with gastrointestinal turbulences, hydrogen ions in acidosis and metabolic toxins such as steroidal metabolites associated with pregnancy. Mt has also been proved to be non-toxic by hematological, biochemical and histopathological studies in rat models (Kevadiya et al., 2012). The crystalline structure of Mt consists of multiple layers and each layer is made up of one octahedral alumina sheet (O) sandwiched between two tetrahedral silica sheets (T). It possesses a net negative charge, due to the imperfection of the crystal lattice and the isomorphous substitutions in the T–O–T structure. Owing to approximately 0.9 to 1.2 nm of interlayer spacing and the excellent cation exchange property of Mt, it can form many nanocomposites with different organic compounds. These inherent advantages make Mt suitable as both the excipient and carrier in controlled drug delivery systems (Lee et al., 2005; Liu et al., 2011).

The examples of using of Mt in drug delivery systems include ibuprofen release control by interaction with montmorillonite (Zheng et al., 2007), intercalation of donepezil, a well-known drug for Alzheimer's disease, in montmorillonite, saponite or laponite (Park et al., 2008), intercalation of 5-fluorouracil with Mt as a drug carrier (Lin et al., 2002), release of promethazine chloride and buformin hydrochloride from Mt (Fejer et al., 2001), and loading and delivery of sertraline using K10 (Nunes et al., 2007). Other example includes an intercalated system of montmorillonite by polylactic glycolic acid to obtain nanoparticles loaded with docetaxel (an anticancer drug) (Feng et al., 2009). Campbell et al. (2008) prepared composites of a modified montmorillonite with poly(ethylene glycol) by hot melt extrusion for controlled release of paracetamol. Sodium alginate and magnesium aluminum silicate were used to prepare films loaded with nicotine to be used in buccal release (Pongjanyakul and Suksri, 2009). Poly(D, L-lactide-co-glycolide)/Mt nanoparticles for targeted breast cancer chemotherapy of paclitaxel have been reported (Dong and Feng, 2005).

Although 5-FU has been investigated using alginate and chitosan as carriers, the use of layered silicate along with Alg and CS as carriers has not been investigated. The present work deals with the intercalation of 5-FU into the interlayers of Mt to sustain the drug release. In order to retard the delivery of 5-FU in the gastric environments, the prepared 5-Fu/Mt nanocomposite was compounded with Alg and CS. The in vitro drug release studies were performed using buffer solutions of pH 1.2, 7.4, and 10. Higuchi and Korsmeyer–Peppas kinetic models were applied to elucidate the drug release mechanism.

Table 1
Formulation composition and characterization of drug containing systems.

Sample	5-FU (mg)	Alg (g)	CS (g)	Mt (g)	EE (%)	DLC (%)
F_1	400	1.6	0.3	0	85.74	17.87
F_2	400	1.6	0.3	0.08	86.23	14.54
F_3	400	1.6	0.3	0.24	86.11	14.15
F_4	400	1.6	0.3	0.48	85.99	9.99
F_5	400	1.6	0.3	0.8	85.90	7.64
F_6	400	0	0	0.48	98.76	20.37
F_7	400	0	0	0	–	–

2. Experimental

2.1. Materials

Sodium alginate was supplied by Merck (Germany). Chitosan (medium molecular weight, degree of deacetylation 85%) was purchased from Sigma-Aldrich (USA). Calcium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, sodium carbonate, sodium hydrogen carbonate, hydrochloric acid, acetic acid and sodium hydroxide were all obtained from Merck (Germany). 5-Fluorouracil (5-FU) was purchased from Sigma-Aldrich (USA). Sodium montmorillonite KSF (specific surface area = 20–40 m^2/g, cation exchange capacity = 30 meq/100 g) was obtained from Sigma-Aldrich (USA). Dialysis membrane bag (with a molecular cut-off of 12400) was purchased from Sigma-Aldrich (USA). All other reagents were of analytical grade and used as received.