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Cytarabine-AOT catanionic vesicle-loaded biodegradable thermosensitive hydrogel as an efficient cytarabine delivery system

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ABSTRACT

Carrier with high drug loading content is one of the most important issues in drug delivery system. In the present work, an ion-pair amphiphilic molecule composed of anticancer drug cation and surfactant anion is used for straightforward fabricating vesicles for cancer therapy. Anticancer drug (cytarabine hydrochloride) and anionic surfactant (AOT) are selected for the fabrication of ion-pair amphiphilic molecule. One amphiphilic molecule contains one drug cation, thus the drug loading content is 50% (mol/mol) in theory. The in vitro drug release study shows that the release time of cytarabine is about 3 times of the pure cytarabine solution and the permeability of cytarabine has been improved about 160 times tested by parallel artificial membrane permeability assay model. However, the hemolytic toxicity is largely decreased in the studied concentration range. The in vitro cytotoxicity results show that cytarabine-AOT amphiphiles have a much lower IC_{50} (drug concentration resulting in 50% cell death) value and a higher cell inhibition rate comparing with their respective components, indicating its effective therapy for leukemic cells. To obtain a longer and a convenient drug release system, the prepared vesicles are further incorporated into the thermosensitive PLGA–PEG–PLGA hydrogel to prepare a subcutaneous administration. The in vivo drug release results indicate that cytarabine-AOT vesicle-loaded hydrogel is a good injectable delivery system forcontrolled release of cytarabine for cancer therapy.

1. Introduction

Vesicles are of technological interest for potential application in various areas, such as cosmetic industry, nanostructured system (Chen et al., 2010; Jiang et al., 2012a), bioseparations and sensing (Kaler et al., 1989; Consola et al., 2007), drug/gene delivery system (Wang et al., 2006; Bramer et al., 2007). Especially in drug delivery system, vesicles can simultaneously encapsulate hydrophilic drug molecules in the aqueous lumen of the vesicles and hydrophobic drugs in the hydrophobic membrane of the vesicles, which vastly improves the pharmacokinetics and biodistribution of drugs that suffer from poor solubility, poor stability and unwanted toxicity. Until now, the application of vesicles for drug delivery system is mainly concerning on the loading of drug in vesicles formed by the surfactants, which results in a low drug loading content with uncertainty. Therefore, it is of great interest to find a straightforward drug delivery system with higher drug loading content for application in the biomedical area. We prepared the "catanionic pharmacosome", a new type of amphiphilic prodrug molecules by proton transfer between a lipophilic drug antihypertensive agent and oleic acid molecules (Jiang et al., 2012b). To test the universality of this new drug carrier, in this paper we choose a hydrophilic antitumor drug, cytarabine, as model drug and AOT as anionic surfactant to prepare catanionic pharmacosome for cancer therapy by simple ion exchange process.

Cytarabine, a pyrimidine nucleoside antimetabolite, which is widely used in the treatment of acute leukaemia and lymphoma and as antiviral agent against human cytomegalovirus and herpes simplex virus (Pallavicini, 1984; Peters et al., 1987; Fiala et al., 1972). Several adverse effects such as leukopenia, thrombocytopenia, anemia, nausea, alopecia and liver damage can be produced (Wysocki et al., 1994; Vilpo et al., 1988) when it is employed in the treatment of meningeal leukaemia. Studies have shown that the toxicity of cytarabine can be reduced if it is able to maintain an effective therapeutic level for a long period of time. Therefore, it is of great importance to develop administrations in a

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controlled-release dosage form for cytarabine (Chen et al., 2010; Teijón et al., 1997; Giammona et al., 1996).

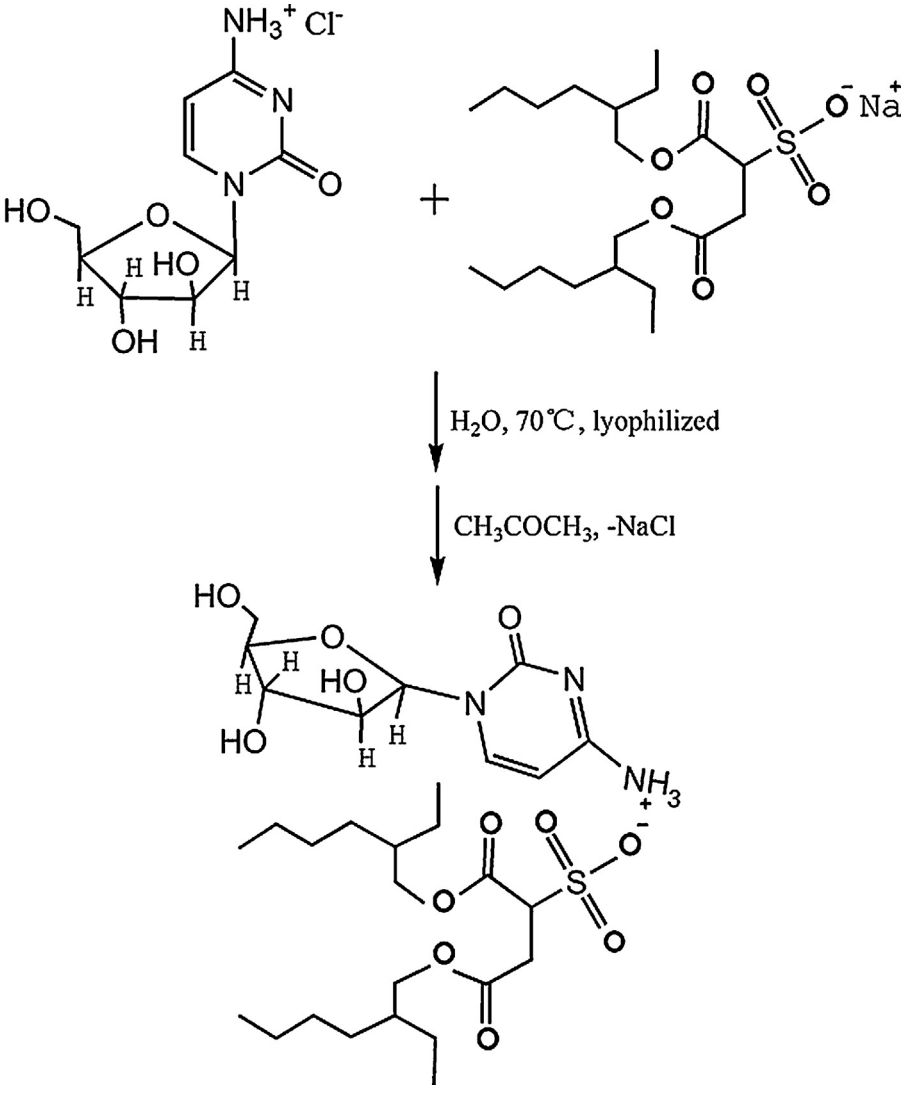
Hydrogels are three dimensional cross-linked polymer networks caused by chemical or physical cross-links and/or chain entanglements and they could absorb a considerable amount of water (more than 70% water). In the past decades, polymer hydrogels gain much attention in controlled drug release due to their biocompatible and biodegradable properties (Contri et al., 2014; Cigognini et al., 2014). Specially, the thermosensitive hydrogels have become the most attractive carriers in the injectable drug delivery systems because it has ability to release drugs in a controlled manner (Fang et al., 2009; Gong et al., 2012; Wang et al., 2013; Jeong et al., 1999). Among the reported copolymers, poly(lactic-co-glycolicacid)–poly(ethyleneglycol)–poly(lactic-co-glycolicacid) (PLGA–PEG–PLGA) is one of the most widely used polymers as controlled drug release carrier. It is a triblock copolymer composed of PLGA and PEG blocks and was firstly synthesised by Zentner et al. (Zentner et al., 2001). PLGA–PEG–PLGA is a biodegradable, temperature-responsive copolymer which has been widely used in subcutaneous injection (Jeong et al., 1999), intramuscular injection (Sridhar et al., 2005) and ocular drug (Gao et al., 2010) delivery systems. It could deliver drugs following simple hypodermic or intramuscular injection without the need for implant removal.

In the present study, PLGA–PEG–PLGA has been chosen as carrier material of subcutaneous injection and its solution has a good fluidity at or below room temperature but becomes hydrogels in body temperature (37 °C), forming drug depots at the injection site (Qiao et al., 2005). We firstly synthesized cytarabine-based amphiphile by the combination of anionic surfactant sodium bis(2-ethylhexyl) sulfosuccinate (AOT) and cationic drug cytarabine hydrochloride. The cytarabine-AOT amphiphiles can self-assemble into vesicles in the aqueous solution. In order to better control the release of cytarabine, the prepared cytarabine-AOT vesicles are incorporated in PLGA–PEG–PLGA copolymer hydrogel. The in vitro and in vivo release results indicate that the as-prepared cytarabine-AOT vesicle-loaded hydrogel could control the delivery of cytarabine for long time and reduce the burst effect. Thus, the present studies proved that cytarabine-AOT vesicle-loaded hydrogel is a very prospective candidate of injectable delivery system for controlled release of cytarabine.

2. Materials and methods

2.1. Materials

Cytarabine hydrochloride was purchased from Huameihua Technology Group Corporation, Wuhan, China. Sodium bis(2-



Scheme 1. The reaction scheme between cytarabine hydrochloride and AOT.