International Journal of Pharmaceutics 495 (2015) 508–515

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Chitosan coated vancomycin hydrochloride liposomes: Characterizations and evaluation

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ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form 11 August 2015
Accepted 26 August 2015
Available online 29 August 2015

Chemical compounds studied in this article:
Vancomycin hydrochloride (PubChem CID: 6420023)
Phosphatidylcholine (PubChem CID: 45266626)
Cholesterol (PubChem CID: 5997)
Chitosan (PubChem CID: 21896651)

Keywords:
Vancomycin hydrochloride
Chitosan wrapped liposomes
Gram-positive bacterial infections
In vitro release
Pharmacokinetic
Tissue distribution

ABSTRACT

The present work evaluated the feasibility of chitosan coated liposomes (c-Lips) for the intravenous delivery of vancomycin hydrochloride (VANH), a water-soluble antibiotic for the treatment of gram-positive bacterial infections like osteomyelitis, arthritis, endocarditis, pneumonia, etc. The objective of this research was to develop a suitable drug delivery system in vivo which could improve therapeutic efficacy and decrease side effects especially nephrotoxicity. Firstly, the vancomycin hydrochloride liposomes (VANH-Lips) were prepared by modified reverse phase evaporation method, then the chitosan wrapped vancomycin hydrochloride liposomes (c-VANH-Lips) nanosuspension was formulated by the method of electrostatic deposition. Based on the optimized results of single-factor screening experiment, the c-VANH-Lips were found to be relatively uniform in size (220.40 ± 3.56 nm) with a narrow polydispersity index (PI) (0.21 ± 0.03) and a positive zeta potential (25.7 ± 1.12 mV). The average drug entrapment efficiency (EE) and drug loading (DL) were $32.65 \pm 0.59\%$ and $2.18 \pm 0.04\%$, respectively. The in vitro release profile of c-VANH-Lips possessed a sustained release Characterization and the release behavior was in accordance with the Weibull equation. Hemolysis experiments showed that its intravenous injection had preliminary safety. In vivo, after intravenous injection to mice, c-VANH-Lips showed a longer retention time and higher AUC values compared with the VANH injection (VANH-Inj) and VANH-Lips. In addition, biodistribution results clearly demonstrated that c-VANH-Lips preferentially decreased the drug distribution in kidney of mice after intravenous injection. These results revealed that injectable c-VANH-Lips may serve as a promising carrier for VANH to increase therapeutic efficacy on gram-positive bacterial infections and reduce nephrotoxicity, which provides significantly clinical value for long-term use of VANH.

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1. Introduction

Endocarditis, meningitis, osteomyelitis, pneumonia, sepsis or soft tissue infection, all can be caused by Gram-positive bacterium. Especially, the medical profession believe that chronic osteomyelitis has been the second biggest chronic disease following cancer, which is a bone destruction caused by microorganisms infection, often occurs in the long bones, diabetic foot or penetrating bone lesion due to trauma or surgery-induced (Walter et al., 2012; Mader and Calhoun, 2000). Gram-positive bacteria are the most common pathogens, and it's conventional clinical treatment that continuous high-dose antibiotics are applied after debridement (Darley and MacGowan, 2004; Lew and Waldvogel, 2004). As osteomyelitis, endocarditis, pneumonia and other having longer course, frequently sensitive antibiotics are given for long term which leads to the increase of drug resistance and high recurrence rate of osteomyelitis, endocarditis, pneumonia etc. Vancomycin hydrochloride is the first-generation glycopeptide antibiotics whose antibacterial mechanism is to inhibit the synthesis of bacterial cell wall by interfering poiesis of phospholipids and peptides to inhibit growth and reproduction of bacterium. Moreover, it has no cross-resistance to other antibiotics. So it rarely generates resistant strains and is effective for most gram-positive bacteria, especially Staphylococcus aureus (Mader et al., 1999; Kinik and Karaduman, 2008). Although it is specific for the bacterial cell wall peptidoglycan, more serious renal toxicity, ototoxicity, neuromuscular blockade and other side effects often appear in the early application (Reynolds, 1989; Yang et al., 2012; Alipsour et al., 2008). Poor Immunity in patients with osteomyelitis, endocarditis, pneumonia and other, the majority of vancomycin hydrochloride excretes from kidney in original form, which can

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http://dx.doi.org/10.1016/j.ijpharm.2015.08.085
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easily lead to acute kidney injury and chronic kidney disease (Rybak, 2006). Gene expression profiling of animals given high-dose vancomycin hydrochloride have shown that the accumulation of vancomycin hydrochloride in proximal tubular cells leads to cell necrosis which is mechanisms of renal toxicity (Dieterich et al., 2009). These side effects hinder the treatment of diseases, which put forward a new research topic for clinical pharmacy workers.

Liposome is a potential sustained-release system with good ability to encapsulate water-soluble drug. Its lipid bilayer is composed of phospholipids and cholesterol which are similar to the cell membrane. So it is easy to fuse with pathogenic bacteria. Therefore, liposome is considered to be non-toxic biodegradable slow-release drug delivery system (Huh and Kwon, 2011; Chun et al., 2013). However, due to the low affinity of water-soluble drug for phospholipid, high entrapment efficiency is hard to be achieved for hydrosoluble drug except for some special drugs. Ma et al. (2011) prepared the vancomycin hydrochloride cationic liposomes with a low encapsulation efficiency of 7.58% using a modified reverse phase evaporation method. Nevertheless, as cationic lipids, the stearamide has certain toxicity. Kadry et al. (2004) prepared octadecylamine modified cationic vancomycin liposomes whose encapsulation efficiency was only 5.2% by the method of film dispersion. Moreover, the octadecylamine has some toxicity on the body. Yang et al. (2013) prepared the cationic vancomycin hydrochloride liposomes with an encapsulation efficiency of 24.9% by the method of double emulsion. The encapsulation efficiency was still not so high. Besides the particle size of 3.3 μm is so large, which go against the retention in circulation.

Chitosan is positively charged polysaccharide obtained by the deacetylation of chitin. It's hydrophilic, bioadhesive, biocompatible, biodegradable and has a low toxicity. The natural polysaccharide chitosan wraps on the surface of liposomes by electrostatic deposition method, which makes the liposomes positively charged to form chitosan–liposomes complex (Banakar, 1997; Muzzarelli and Muzzarelli, 2005). The encapsulation of chitosan increases the stability and targeting of liposomes (Laye et al., 2008; Sandri et al., 2004; Janes et al., 2001; Aspden et al., 1997). Chitosan coated liposomes will Interact with negatively charged cell membrane, opening the tight junctions between epithelial cells, promoting the transport of macromolecules across epithelial tissue. Thereby, it can increase the paracellular permeability of hydrophilic macromolecules, promoting the absorption of hydrophilic macromolecules drug.

In this research, the design idea is as follows: Firstly, we prepare the VANH-Lips with soy lecithin for injection and cholesterol as carrier material using the method of modified reverse phase evaporation. Moreover, our research group has accomplished the preparation of VANH-Lips in previous research (Liu et al., 2015). Then, the c-VANH-Lips are prepared by electrostatic deposition method. Subsequently, physicochemical properties, release and preliminary safety in vitro are studied; Finally, with VANH-Inj and VANH-Lips as control groups, respectively. The pharmacokinetics and tissue distribution of c-VANH-Lips in mice are studied to evaluate the property of slow release and targeting, which provides clinical value for the long-term application of VANH.

2. Materials and methods

2.1. Materials

VANH was purchased from Shanghai Ziyi Reagent Co., Ltd. (China). Soybean lecithin (injection grade, phosphatidylcholine accounts for 95% pH 5.0–7.0) was provided by Shanghai Taiwei Pharmaceutical Co., Ltd., Shanghai, China. Cholesterol was purchased from Shanghai Medical Chemical Reagent Co., Ltd. (China). VANH-Inj (produced by Hisun in Zhejiang province, production batch: 5150302). Chitosan was purchased from Sigma USA. The other chemicals were of analytical reagent grade or higher.

2.2. Methods

2.2.1. Preparation of c-VANH-Lips

VANH-Lips were prepared as the methods described in previous literature (Liu et al., 2015). The lipid and aqueous phases were prepared separately. 65 mg soybean lecithin, 10 mg Cholesterol were weighted precisely and co-dissolved in 2 mL chloroform to form lipid phase. As aqueous phase, VANH solution(10 mg/mL) was dispersed dropwise with a microinjector (Kd Scientific 781100, Fabrique' Auxetats-Units Co., Ltd., USA) into the lipid phase. And the mixture was sonicated to form a primary emulsion at room temperature in an ultrasonic bath (Kun Shan Ultrasonic Instruments Co., Ltd.). Then the organic solvent was removed in a 45 °C water bath under reduced pressure by the rotary evaporator. 7.5 mL distilled water was added to hydrate for an additional 5 min under control temperature. Then, the liposomal suspension was uniformly dispersed by ultrasound.

The c-VANH-Lips were prepared by the method of electrostatic deposition. Chitosan was dissolved in acetic acid (1%, v/v) to form chitosan solution. Chitosan solution diluted with sodium acetate buffer (pH 4.5) was added dropwise to the liposomes suspension prepared previously under magnetic stirring for 30 min, then the c -VANH-Lips were formed.

2.2.2. Single-factor research of prescription

On basis of the optimal formulation and technology of VANH-Lips in reference (Liu et al., 2015), the formulation of c -VANH-Lips was examined by single factor research with influence on zeta potential and appearance as index.

2.2.2.1. Molecular weight of chitosan. The volume ratio of chitosan solution to liposomes suspension was 1:1. Concentration of chitosan solution was 2 mg/mL, but chitosan of different molecular weights (2, 50, 60–120 kDa and medium molecular weight) was chosen. Then c-VANH-Lips were prepared by method mentioned previously. Zeta potential and exterior were examined subsequently.

2.2.2.2. Concentration of chitosan solution. The volume ratio of chitosan solution to liposomes suspension was 1:1. molecular weight of chitosan was selected according to the results of the previous single-factor research, but different concentration of chitosan (1, 2, 4, 10 mg/mL) was chosen. Then c-VANH-Lips were prepared by method mentioned previously. Zeta potential and exterior were examined subsequently.

2.2.2.3. Volume ratio of chitosan and liposomal suspension. The concentration and molecular weight of chitosan was selected according to the results of the previous single-factor research, but different volume ratio of chitosan solution to liposomes suspension (1:1, 1:2, 1:4 and 1:7) was chosen. Then c-VANH-Lips were prepared by method mentioned previously. Zeta potential and exterior were examined subsequently.

2.2.3. Freeze-drying of c-VANH-Lips

In the freeze-drying process, mannitol was used as a cryoprotectant. Firstly, the c-VANH-Lips fresh prepared with mannitol (5%, w/v) were pre-frozen in an ultra-cold freezer (MDF-382E, Sanyo Electric Co., Ltd., Osaka, Japan) for 24 h at −80 °C. Then, the resultant samples were transferred to the lyophilizer (FD5-2.5, GOLD SIM, Issaquah, WA) at −50 °C for 48 h. The lyophilized powder was collected for further experiments.

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