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Ternary system of dihydroartemisinin with hydroxypropyl-β-cyclodextrin and lecithin: Simultaneous enhancement of drug solubility and stability in aqueous solutions☆

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ABSTRACT

The purpose of this study was to simultaneously improve the solubility and stability of dihydroartemisinin (DHA) in aqueous solutions by a ternary cyclodextrin system comprised of DHA, hydroxypropyl-β-cyclodextrin (HP-β-CD) and a third auxiliary substance. Solubility and phase solubility studies were carried out to evaluate the solubilizing efficiency of HP-β-CD in association with various auxiliary substances. Then, the solid binary (DHA–HP-β-CD or DHA–lecithin) and ternary systems were prepared and characterized by Fourier transform infrared (FT-IR), differential scanning calorimetry (DSC) and power X-ray diffraction (PXRD). The effect of the ternary system on the solubility, dissolution and stability of DHA in aqueous solutions was also investigated. As a result, the soybean lecithin was found to be the most promising third component in terms of solubility enhancement. For the solid characterization, the disappearance of the drug crystallinity indicated the formation of new solid phases, implicating the formation of the ternary system. The dissolution rate of the solid ternary system was much faster than that of the drug alone and binary systems. Importantly, compared with binary systems, the ternary system showed a significant improvement in the stability of DHA in Hank's balanced salt solutions (pH 7.4). The solubility and stability of DHA in aqueous solutions were simultaneously enhanced by the ternary system, which might be attributed to the possible formation of a ternary complex. For the ternary interactions, results of molecular docking studies further indicated that the lecithin covered the top of the wide rim of HP-β-CD and surrounded around the peroxide bridging of DHA, providing the possibility for the ternary complex formation. In summary, the ternary system prepared in our study, with simultaneous enhancement of DHA solubility and stability in aqueous solutions, might have an important pharmaceutical potential in the development of a better oral formulation of DHA.

1. Introduction

The combination of dihydroartemisinin (DHA)-piperaquine is recommended to cure plasmodium infections by World Health Organization (WHO) in 2010. However, an increased treatment failure with DHA has been reported in the western Cambodia from 8.1% to 27.6% in 2010 [1]. The major reason is the Plasmodium resistance to antimalarial medicines, which makes the transmission of malaria gain momentum in turn and brings new challenges to the malaria prevention. The long term use of drugs with relative low solubility, stability and bioavailability is possibly a negatively important factor to malaria drug resistance. The use of effective drugs with relative high solubility, stability and bioavailability will be of great benefit to reduce the incidence of malaria drug resistance.

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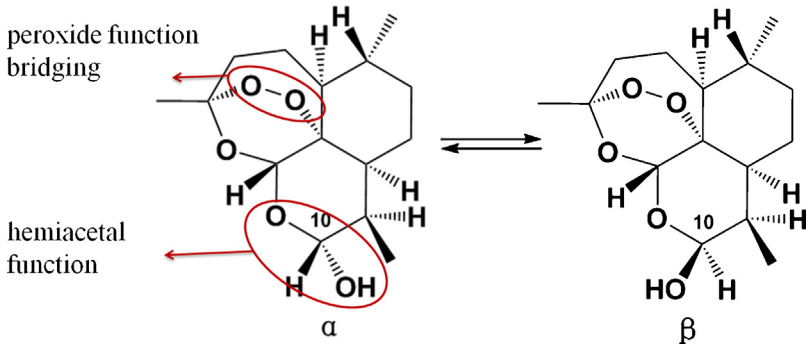

Fig. 1. Structure of dihydroartemisinin.

Among artemisinin derivatives, DHA provides improved antimalarial potency in vitro and in vivo compared to other artemisinin analogues. However, the aqueous solubility of DHA is very low due to the glucopyranose rings in its chemical structure [2,3]. It contains peroxide bridging over the seven-membered ring, which is known to be rather unstable. The hemiacetal functional group, which is more susceptible to acidic situations and moisture, is another contributor to its low stability [4,5]. DHA is also physically unstable due to the conversion of the lactone carbonyl group at C-10 (Fig. 1).

It is reported that artemisinin products in the market have hardly met the criteria of WHO, especially in Africa. The active pharmaceutical ingredient content is below the criterion of 90% at the end of shelf life [2]. In addition, the huge demand of artemisinins has created a global shortage of artemisinins. Therefore, it is urgently needed to develop DHA products with high solubility, stability and bioavailability. Several studies have been carried out to enhance the solubility and stability of DHA by preparing solid dispersions [6], nanosuspensions [7], micronization with supercritical solutions [8], and cyclodextrin complexes [9,10]. Among them, cyclodextrin inclusion is one of the most efficient ways to improve the solubility and stability of DHA. It has been reported that the aqueous solubility of DHA increased 77 folds after complexation with HP-β-CD. The hydrolysis rate constant of DHA in solid complexes of HP-β-CD (275.1 mM) decreased 29 folds compared with DHA alone at 50 °C after 3 months [5], and the degradation rate constant of DHA in aqueous solutions decreased approximately 10 folds in the presence of HP-β-CD (57 mM) at 60 °C [11].

However, due to the relatively high molecular weight of HP-β-CD, a large amount of cyclodextrins used in the formulation limits its application into a convenient and cost-effective dosage form. Moreover, high dose of cyclodextrins may lead to potential toxicity and other related side effects, which also impedes its application [12]. It is of importance to improve the complexation of DHA and cyclodextrins. Recently, it is reported that ternary system with drug, cyclodextrin and the third auxiliary substance can reduce the dose of cyclodextrins and increase the complexation efficiency (Table 1) [13–28].

To our literature research, there is no report available about the ternary system of DHA with HP-β-CD and auxiliary substances up to now. In this study, the simultaneous enhancement of solubility and stability of DHA through ternary system was investigated. The auxiliary substance added in the ternary system was screened through solubility studies. Then, the binary and the ternary systems for DHA constituted with HP-β-CD and the optimal auxiliary substance were prepared by the solvent evaporation method. Finally, the properties of DHA in the binary system, the ternary system and their physical mixtures were characterized by FT-IR, DSC and PXRD techniques in solid state, whilst their solubility, stability and dissolution behaviours in aqueous state were evaluated. Finally, combined with the solid state characterization, the possible molecular formation mechanism of the ternary complex was investigated by the molecular docking study.

2. Experimental methods

2.1. Materials

Dihydroartemisinin (DHA, 99% purity) was obtained from Chongqing Huali Wulingshan Medicine Co., Ltd. (Chongqing, China). 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD, degree of substitution = 4.5) was obtained from China Shijiazhuang Pharmaceutical Group Co., Ltd. (Shijiazhuang, Hebei, China). Soybean lecithin (phosphatidyl choline, 94% purity) was supplied by Lipoid GmbH (Ludwigshafen, Germany). Polyethylene glycol 4000 (PEG4000), polyethylene glycol 6000 (PEG6000), polyvinyl pyrrolidone K30 (PVP) and lactose were obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Polyethylenglycol 660-12-hydroxystearate (Solutol HS15) was procured from BASF (Germany). Lauroyl polyoxylglycerides (Gelucire 44/14) was purchased from Gattefosse (France). Hydroxypropyl methylcellulose (HPMC K4M) was obtained from Dow Chemical Company (USA). Acetonitrile and methanol were high performance liquid chromatography grade from Merck Co., Ltd. (Germany). Hank's balanced salts were purchased from Sigma-Aldrich Co. LLC. (USA). Water was prepared by ultra pure water system (Milli-Q). Other reagents were of analytical grade.

2.2. Methods

2.2.1. HPLC analysis

Quantitative analysis of DHA was performed using HPLC method listed in Chinese Pharmacopoeia (2010 edition). The HPLC instruments consisted of a binary pump, G1311C; autosampler, G1329B; and a diode-array detector G4212B (Agilent, Palo Alto, USA). The separation was achieved on a Diamonsil C18 analytical column (150 × 4.6 mm ID, 5 μm, Dikma, Beijing, China) equipped with an Easyguard ii C18 guard column (Dikma, Beijing, China) maintained at 20 °C. The mobile phase consisted of acetonitrile: ultra pure water (65:35, v/v) and the flow rate was set to 1 mL min^{-1}. The detection wavelength of the detector was set to 210 nm.

2.2.2. Stability studies

The stability tests of pure DHA in water or Hank's balanced salt solutions were carried out at 37 °C indicating the dissolution test temperature. The Hank's balanced salt solution was prepared with 8.00 g L^{-1} NaCl, 0.40 g L^{-1} KCl, 0.35 g L^{-1} $NaHCO_3$, 0.06 g L^{-1} KH_2PO_4, 0.05 g L^{-1} Na_2HPO_4, 0.19 g L^{-1} $CaCl_2{\cdot}2H_2O$, 0.09 g L^{-1} $MgSO_4$, and 1.00 g L^{-1} glucose and the pH values were adjusted to 6.8, 7.0, 7.2 and 7.4 with $NaHCO_3$ (3.8 mM, pH11.2) solution.