Investigation on Liposome-berberine Composites: Synthesis, Characterization and Absorption Characteristics

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Introduction:

Liposome is used as the carrier for berberine hydrochloride and berberine sulphate to produce a controlled release system. Berberine [$(C_{20}H_{18}NO_4)^+$, m = 336.37], an isoquinolin alkaloid, is one of the main constituents of the Chinese medicinal herbs *Rhizoma coptidis* (Huanglian) and *Cortex phellodendri* (Huangbai) (Fig. 1). Traditionally, it is used to treat diarrhea because of its antibacterial and anti-inflammatory properties. Recently many studies have demonstrated that this compound has other applications in pharmacology as for anti-tumor, anti-hyperlipidemia, anti-hyperglycemia, and for the treatment of cardiovascular diseases. However, its absorption by oral administration is poor, and intravenous injection is prohibited, which thus limits its applications. Berberine hydrochloride and sulphate are the two salt forms most frequently used. These two berberine forms have similar pharmacological effects but very different solubilities in water. The corresponding solubility of the hydrochloride ($C_{20}H_{18}ClNO_4$, m = 371.82) is 1:500, whereas the solubility of berberine sulphate ($C_{20}H_{18}NO_8S$, m = 432.43) is 1:30. With the similar structure to the cell membrane, liposome can increase the absorption of drug into blood; In addition, liposome has the advantages of the sustained release, targeting, and reducing drug toxicity. The objective of the present study is to design a drug delivery system which can not only extend the release time of both berberine forms, but also increase their absorption in blood.

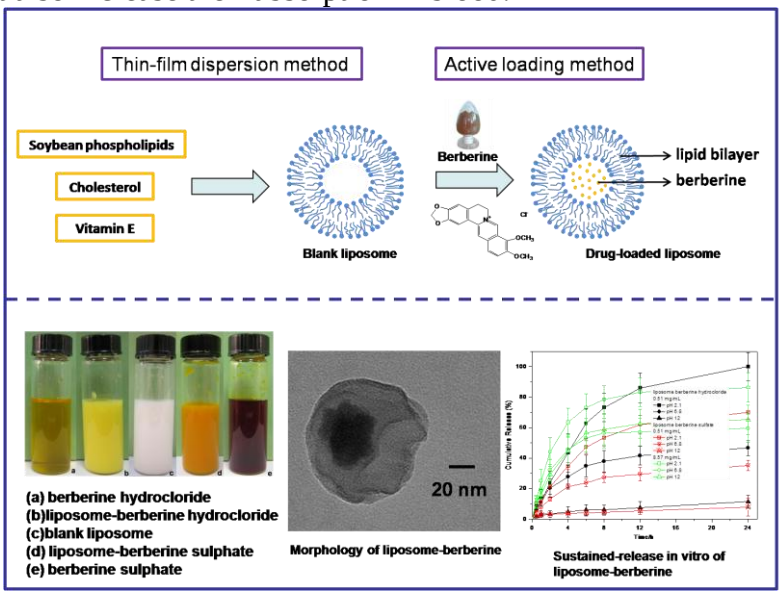

Fig. 1 Schematic representation of the experimental process and results of SEM and release studies in vitro.

Materials and Methods:

As shown in Figure 1, thin-film dispersion method and active loading method were used to prepare the drug-loaded liposome. Its size, zeta potencial, morphology and encapsulation efficiency etc. were characterized by particle size analyzer, SEM and ion exchange column. Release studies were carried in vitro and in vivo, respectively. Following Chinese Pharmacopoeia 2005 procedure,

drug release profiles were obtained using the basket method (putting liposomes into the dialysis bags) in an automatic dissolution apparatus at 100 rpm. The dissolution medium volume was 900 mL SGF (HCl solution, pH 2.1), H_2SO_4 solution (pH 2.1), SIF (phosphate buffer, pH 6.8), or NaOH solution (pH 12) kept at 37.0±0.5 ℃. Samples of 10 mL were withdrawn after 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h, and immediately replaced with 10 mL fresh pre-thermostated medium. The concentration of drug was measured spectrophotometrically at 263 nm (for berberine hydrochloride) or 346 nm (for berberine sulphate). For animal experiment, after intraperitoneal injection, blood samples were taken from the ear vein at predetermined time points. Through pretreatment, blood samples were analyzed by HPLC method, and the parameters of C_{max}, T_{max}, $T_{1/2}$, AUC, V_d etc. were calculated to describe the pharmacokinetics of berberine.

Results:

Figure 1 shows the obvious sustained-release of drug-loaded liposome. Liposome released the drug at the lowest rate in SIF, at a faster rate under basic conditions, and most rapidly in SGF. The release rates of berberine sulphate were slower than the hydrochloride. The mean diameters, PdI, zeta potential and encapsulation efficiency of blank liposome, liposome-berberine hydrochloride and sulphate are 79.10±8.97 nm, 112.18±9.62 nm and 152.20±8.20nm; 0.43±0.07, 0.37±0.14 and 0.476±0.01; -0.70±0.77, -6.09±0.87 and -5.04±1.41; 96.27±0.02 % and 81.31±7.34 %, respectively. SEM shows the outer layer of the liposome membrane and the center of drugs. The results of animal experiment showed that compared with berberine solution, liposome could notable increase the concentration of berberine in blood.

Discussion:

Among several kinetics models, all the drug delivery systems fit best to Ritger-Peppas model. According to the Ritger-Peppas model, $n > 0.85$, the drug release process is swelling-controlled, which is also called case-II transport. The acid can greatly undermine the liposomes, so the drug was released quickly. Strangely, the drug was released very slowly under alkaline conditions, this is because the ionic state of the drug can freely go through dialysis bags, but the molecular state of it cannot. Berberine ionizes in the neutral and acidic conditions, whereas it maintains the molecular state under alkaline conditions; Consequently the illusion of slow release occurred. The concentration of berberine in blood increased which encapsulated by liposoluble liposome.

References:

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