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Solid lipid nanoparticles modified with amphipathic chitosan derivatives for improved stability in the gastrointestinal tract

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ABSTRACT

In order to reduce enzymatic degradation and thereby improve the stability of solid lipid nanoparticles (SLNs) in the gastrointestinal tract (GIT), two comb-shaped amphiphilic macromolecular materials of N-stearyl-N-trimethyl chitosan (STMC) and N-linoleoyl-N-trimethyl chitosan (LTMC) were fabricated as emulsifier to modify SLNs. Some influence factors of lipolysis medium were investigated to establish in vitro lipolysis model for SLNs. The results showed that the lipolysis curves were fluctuant and variable when the amounts of SLNs were low. The lipolysis of SLNs increased with pancreatic enzyme activity ascending from 150 to 450 USPU/mL and achieved a threshold between 450 and 600 USPU/mL. The lipolysis of STMC-SLNs increased with the initial calcium concentration rising from 0 to 1.4 mM, but had no obvious change from 1.4 to 5 and 10 mM. Besides, SLNs lipolysis increased with bile acid salt and phospholipid concentration increasing. Finally, SLNs stability in GIT was tested with the optimized in vitro lipolysis model. The results revealed that as compared to P188-SLNs and Tween-SLNs, STMC-SLNs lipolysis decreased by 27.33% and 48.55%, and LTMC-SLNs decreased by 22.64% and 43.86%, respectively. Besides, the drug precipitations for STMC-SLNs and LTMC-SLNs were significantly decreased. These results demonstrated that both STMC-SLNs and LTMC-SLNs had excellent gastrointestinal stability.

1. Introduction

Since the first description by Müller et al. was published in the early 1990s, solid lipid nanoparticles (SLNs) as alternative drug delivery systems to other colloidal drug delivery systems like lipid emulsions, liposomes, and polymeric nanoparticles has gained increasing interest [1,2]. SLNs are composed of physiologically tolerated lipid components which remain in the solid state at room temperature and body temperature, and they are in submicron size range (10–1000 nm) [3,4]. SLNs are widely used in oral drug delivery. Because of poor stability performance of SLNs in the gastrointestinal tract (GIT) after oral administration, it is necessary to improve the gastrointestinal stability of SLNs. As the glycerides are usually used as the lipid matrix materials of SLNs, SLNs tend to be degraded by lipase and colipase in GIT after oral administration [5]. Then, the encapsulated drug of SLNs might be exposed in stomach or intestine, which may lead to drug precipitation and thereby result in reduced absorption of the poorly water-soluble drugs [6]. As for macromolecule drug such as protein and peptide, the exposure of the incorporated drug from SLNs in GIT would lead to the digestion, degradation, and inactivation of the drug due to the acidic and enzyme-rich harsh environment [7].

To improve the gastrointestinal stability of SLNs, N-stearyl-N-trimethyl chitosan (STMC) and N-linoleoyl-N-trimethyl chitosan (LTMC), two comb-shaped amphiphilic macromolecular materials (CAM) with hydrophilic backbone and hydrophobic branches, were used as the emulsifier and stabilizer to prepare and modify SLNs for the first time in this study. We hypothesized that the hydrophilic backbone of CAM might form the sunflower-petals like loops on the surface of nanoparticles and exhibit the steric hindrance effect against lipase enzyme (Fig. 1). And thereby the lipid matrix of SLNs might be shielded from the degradation by lipase enzyme in GIT due to the steric hindrance effect of the sunflower-petals like loops of CAM on the surface of nanoparticles.

It has been reported that the effective stabilization have been achieved using CAM as emulsifier in emulsion formulations. Conventional straight chain surfactants such as poloxamer 188 (P188)

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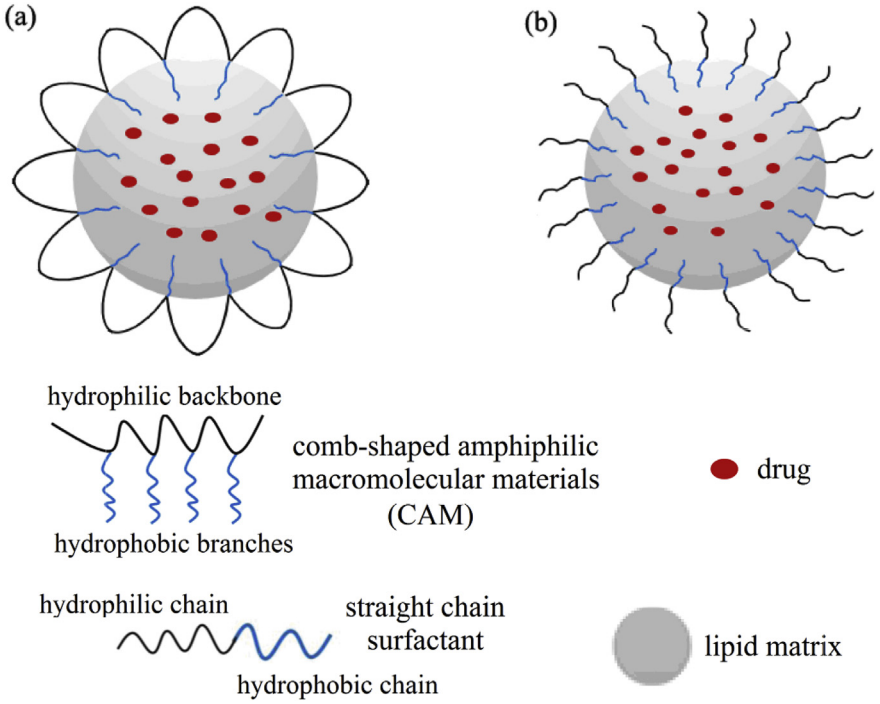

Fig. 1. The schematic diagram of STMC-SLNs or LTMC-SLNs (a) and SLNs modified with common straight chain surfactants (b).

were adsorbed on the emulsion droplet surface with a way of single-point attachment, while CAM showed the multi-point attachment with its hydrophilic chains [8]. By comparison, CAM showed the strong adsorption force on the emulsion droplet surface in low concentration of CAM, as well as in the environment of high electrolyte or temperature [8,9]. The specific adsorption force has the ability of enhancing the stability of the colloidal system [8,9]. Accordingly, CAM might be a more appropriate and innovative option for increasing SLN stability.

Chitosan (CS) is the cationic polysaccharide derived from natural chitin through deacetylation, which have gained attractive interest in different industrial applications [10,11]. However, the poor aqueous solubility of CS above pH 5 limits its application [10,12]. Additionally, the surface activity of CS is low due to no large hydrophobic groups in its chemical structure [13]. Therefore, its alkylated and quaternary aminated derivations, STMC and LTMC, were synthesized to improve the aqueous solubility of CS by N-trimethylation and afford excellent surface activity by the introduction of alkyl chain. And STMC or LTMC was used as emulsifier to prepare and modify SLNs in this work. It was supposed that SLNs modified with STMC or LTMC (STMC-SLNs or LTMC-SLNs) might form the sunflower-petals like loops on particle surface (Fig. 1) and show steric hindrance effect against the lipase enzyme, resulting in reduced lipid digestion and improved stability of SLN in GIT. It is worth noting that CS and one of its derivations, hydroxypropyl trimethyl ammonium chloride chitosan (HACC) had been used to modify SLNs to improve gastrointestinal stability of SLNs by Shi et al. [14]. In their work, CS or HACC-modified SLNs were obtained by dispersing SLNs in CS or HACC solution after SLNs had been prepared. CS or HACC was absorbed on the surface of CS or HACC-modified SLNs via noncovalent interactions and could not form the sunflower-petals like loops on SLN surface. CS or HACC is neither an emulsifier nor CAM, but a water-soluble derivation of CS without conjugated hydrophobic chain. Therefore, STMC or LTMC-modified SLNs were quite different from CS or HACC-modified SLNs.

In vitro lipolysis test is usually performed to predict lipid digestion behavior and gastrointestinal stability of lipid-based formulations (LBFs) after oral administration [15,16]. Various in vitro lipolysis models had been developed to simulate lipolysis of LBFs in GIT [17]. In vitro lipolysis tests were generally conducted in the lipolysis medium containing the physiological relevant substrates such as pancreatic enzyme, calcium, bile acid salt (BS) and phospholipids [15,17]. But the species and concentrations of the substrates contained in these lipolysis medium are different. There were no uniform standard among various in vitro lipolysis models, and the lipolysis medium may have potential influence on the lipolysis of LBFs [15,18]. Therefore, it is necessary to study the various factors of lipolysis medium involved in the enzymatic lipolysis process and establish a feasible in vitro lipolysis model for SLNs.

In this study, STMC and LTMC, were synthesized and used as the emulsifier to prepare and modify SLNs. Various factors of lipolysis medium, including pancreatic enzyme activity, the concentrations of calcium, bile acid salt (BS) and phospholipid, were systematically investigated to establish in vitro lipolysis model for SLNs. Finally, the superiority of STMC or LTMC to conventional straight chain surfactants as emulsifier to improve the gastrointestinal stability of SLNs was tested in the optimal in vitro lipolysis model.

2. Materials and methods

2.1. Materials

Chitosan (CS, molecular weight 100 kDa, 90% deacetyiation) was obtained from Nantong Xingcheng Biological Industrial Limited Co. Ltd (Jiangsu, China). Sodium iodide (NaI), methyl iodine (CH_3I) and linoleic acid were supplied by Xi'a Reagent Co. Ltd (Sichuan, China). 1-Methyl-2-pyrrolidinone (NMP), N-Hydroxysuccinimide (NHS), N-(3-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC.HCl) and Tween-80 were purchased from Aladdin Reagent Co. Ltd (Shanghai, China). Stearic acid was bought from Tianjin Damao Chemical Reagent Co. Ltd (Tianjin, China). Compritol® 888 ATO was kindly donated by Gattefossé (St. Priest, France). Kolliphor® P188 (poloxamer 188, P188) was purchased from BASF (Ludwigshafen, Germany). Porcine pancreatin from porcine pancreas (8 × USP specifications activity) and Trizma®maleate were obtained from Sigma-Aldrich (Saint-Louis, USA). Bile salt (BS, 95%) and phospholipid (≥90%, from egg yolk) were obtained from Solarbio (Beijing, China). 4-bromobenzylboronic acid (4-BBBA) was bought from the company of