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Facile fabrication of bowl-shaped microparticles for oral curcumin delivery to ulcerative colitis tissue

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ABSTRACT

Oral microparticles (MPs) have been considered as promising drug carriers in the treatment of ulcerative colitis (UC). Here, a facile strategy based on a conventional emulsion-solvent evaporation technique was used to fabricate bowl-shaped MPs (BMPs), and these MPs loaded with anti-inflammatory drug (curcumin, CUR) during the fabrication process. The physicochemical properties of the resultant BMPs were characterized by dynamic light scattering, scanning electron microscope, confocal laser scanning microscope and X-ray diffraction as well as contact angle goniometer. Results indicated that BMPs had a desirable hydrodynamic diameter (1.84 ± 0.20 μm), a negative zeta potential (-26.5 ± 1.13 mV), smooth surface morphology, high CUR encapsulation efficiency and controlled drug release profile. It was found that CUR molecules were dispersed in an amorphous state within the polymeric matrixes. In addition, BMPs showed excellent hydrophilicity due to the presence of Pluronic F127 and poly(vinyl alcohol) on their surface. More importantly, orally administered BMPs could efficiently alleviate UC based on a dextran sulfate sodium-induced mouse model. These results collectively suggest that BMP can be exploited as a readily scalable oral drug delivery system for UC therapy.

1. Introduction

Ulcerative colitis (UC) is a chronic, relapsing and debilitating inflammatory disease, which mainly distributes erratically in distal bowel [1,2]. It affects millions of individuals worldwide and persists in their lifetime because there is no permanent cure [3]. Therefore, patients with UC have to take the medication throughout their whole life. Currently, the medical treatment of UC mainly relies on the application of aminosalicylates, corticosteroids, immunosuppressive drugs and antibiotics with the goals of controlling inflammation and achieving mucosal healing [4,5]. However, long-term utilizations of these medications are associated with serious adverse effects, such as osteoporosis, acute pancreatitis and infection as well as diarrhea [6]. Thus, it is of critical importance to develop alternative agents with high therapeutic efficacy and low side effects.

Curcumin (CUR), a natural dietary substance obtained from turmeric, has attracted increasing attention in UC treatment because it can scavenge free radicals, reduce inflammatory cytokine production and inhibit tumor growth [7,8]. Recent studies have demonstrated that CUR is able to protect mice from UC and maintains remission of UC in patients on a standard therapy [7,9–12]. It is worth noting that no systemic toxicity has been detected with the treatment of CUR. In spite of numerous advantages of CUR, its further application in clinics has been seriously restricted due to its strong hydrophobicity, instability after light exposure, high intestinal metabolic rate and rapid excretion from the body [13–15]. To overcome these problems, a lot of carriers (e.g., pellets, nanoparticles and micelles) have been exploited to deliver CUR to colitis tissue, which could improve the solubility of CUR, protect it from degradation and facilitate it delivery to targeted sites [5,16,17].

Orally administered microparticulate carrier has been recognized as a promising drug delivery system for UC therapy, which benefits from its high drug loading amount, sustained drug release capacity, and colitis tissue-targeted ability based on the epithelial enhanced permeation and retention (eEPR) effect [18]. This effect is mainly attributed to the reduction of mucus thickness, alter-

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ation in mucus compositions, and disruption or even complete loss of colonic epithelial layer [19]. The dysfunction of epithelial barrier would facilitate the movement of microparticle (MP) from colonic lumen toward mucosal surface, gradually penetrating into colitis tissue [2]. Therefore, MPs have a good potential to maximize the therapeutic efficacy and minimize the adverse effects. It is known that the shape of carriers is a critical parameter that determines their potential medical applications [20]. Accordingly, modulation of particle shape has become an important strategy in the development of novel therapeutic agents [21–23]. Particularly, bowl-shaped particle is an appealing drug carrier due to their special encapsulation capability and controlled drug release behavior [24]. In previous researches, bowl-shaped particles were prepared with a big opening on their surface [24,25]. In a typical fabrication process, amorphous or semicrystalline polymeric beads were suspended in aqueous solution and swollen after the addition of organic solvents, followed by freezing with liquid nitrogen and evaporation of organic solvents below 0 °C. However, this method required extreme conditions (e.g., liquid nitrogen) and non-FDA-approved polymers, and also affected by multiple critical factors. More recently, mesoporous organosilica particles with bowl-shaped structures were produced, which was also based on very complicated preparation processes [26].

Herein, we described the first attempt to facilely fabricate bowl-shaped CUR-loaded MPs (BMPs) via a well-established double-emulsion solvent evaporation method under mild circumstances. Furthermore, we characterized their physicochemical properties and therapeutic efficacy against an experimental mice model of UC.

2. Materials and methods

2.1. Materials

Poly(lactic acid/glycolic acid) (PLGA, Mw = 38–54 kg/mol), poly(vinyl alcohol) (PVA, 86–89% hydrolyzed, low molecular weight), Pluronic F127 (PF127), CUR, ammonium bicarbonate (ABC), dichloromethane (DCM) and dimethyl sulfoxide (DMSO) were supplied by Sigma-Aldrich (St. Louis, USA). Myeloperoxidase (MPO) Kit was supplied by Nanjing Jiancheng Bioengineering Institute (Nanjing, P. R. China). Dextran sulfate sodium (DSS, 36–50 kDa) was purchased from MP Biomedicals (Aurora, USA). Hematoxylin and eosin were supplied by Beyotime Institute of Biotechnology (Shanghai, P. R. China). All commercial products were used without further purification.

2.2. Fabrication of bowl-shaped microparticles (BMPs)

BMPs were fabricated via a water-in-oil-in-water (W/O/W) double-emulsion solvent evaporation method. Briefly, 100 mg of PLGA/PF127 mixture with a weight ratio of 3:1 was dissolved in DCM to form an oil phase. Subsequently, 150 μL of aqueous ABC solution (3%, w/v) was introduced dropwise into the oil phase while homogenizing using a Benchmark BV1000 Vortex Mixer. The mixture was then added into 4 mL of PVA solution (5%, w/v) to form a double emulsion, and this emulsion was poured into diluted 100 mL of PVA solution (0.5%, w/v). After evaporating the organic solvent (DCM) under low pressure for 3 h, BMPs were retrieved by centrifugation at 5000*g* for 20 min, followed by 3 washes using ultrapure water. Finally, the collected BMPs were freeze-dried in the presence of trehalose as a cryoprotectant. The dry BMPs were stored at −20 °C for further application.

2.3. Physicochemical characterization of BMPs

Particle sizes (μm) and zeta-potentials (mV) of BMPs were measured using a dynamic light scattering (DLS) technique using a Malvern Zetasizer Nano S90 (Malvern Instruments, London, UK). The average values and standard deviations for the particle sizes of BMPs as well as their zeta-potentials were calculated using 3 runs. The average values were based on the measurements on repeated BMPs.

Surface morphology of BMPs was observed using a scanning electron microscope (SEM, JSM−6510LV, JEOL, Japan). A drop of BMP suspension was placed onto a silicon chip and dried overnight in fume hood. The dried BMPs were pre-processed by coating platinum under vacuum before SEM examination.

Fluorescence microscopic images of BMPs were acquired using a confocal laser scanning microscope (Zeiss-800, Germany) while FITC and DIC channels were used. A drop of BMP suspension was deposited on a cover slide, and dried overnight in fume hood before test.

X-ray diffraction (XRD) spectra of pure CUR, pure PF127 and BMPs were recorded using a Cu Ka-ray at 40 kV and 30 mA ranging from 10° to 50° in an XRD-7000 instrument (Shimadzu, Japan).

2.4. Drug loading and encapsulation efficiency

Loading amount and encapsulation efficiency of CUR in BMPs were studied by measuring the intrinsic fluorescence intensity of CUR. BMPs were dissolved in DMSO, and CUR fluorescence

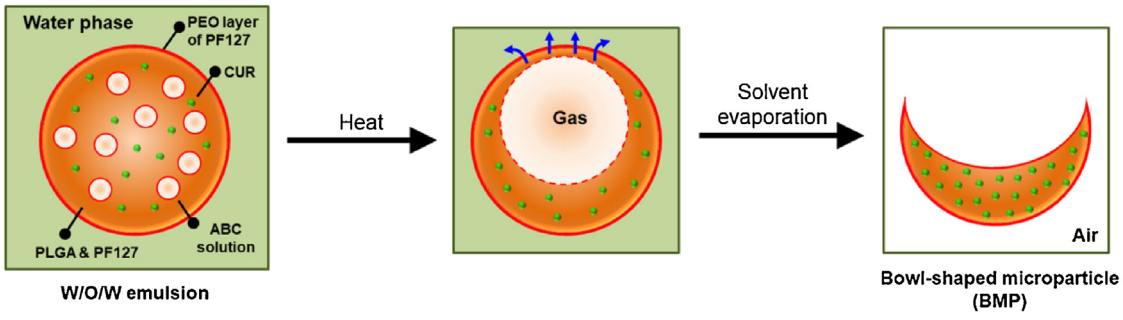

Fig. 1. Schematic illustration of the formation process of BMPs based on a double-emulsion solvent evaporation method.

Table 1
Parameters of BMPs (mean ± S.E.M.; n = 3).

	Particle size (μm)	Zeta potential (mV)	Drug loading (%)	Encapsulation efficiency (%)
BMPs	1.9 ± 0.2	−26.5 ± 1.1	4.5± 0.1	67.2 ± 2.7