



Preparation of an oil suspension containing ondansetron hydrochloride as a sustained release parenteral formulation

Thi-Thao-Linh Nguyen¹ · Van-An Duong¹ · Han-Joo Maeng¹ · Sang-Cheol Chi¹

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Abstract

Ondansetron hydrochloride (ODS) is a selective 5-hydroxytryptamine type 3 antagonist for nausea and emesis prevention in neoplastic patients. To reduce dosing frequency and side effects and improve patient compliance, a sustained release parenteral formulation of ODS was developed. Microparticles of methylcellulose (MC) and ODS were prepared using the spray-drying method and suspended in oils to form oil suspensions. The formulations were evaluated for residual moisture, drug content, size distribution, DSC, XRD, FTIR, SEM, drug release, and pharmacokinetic studies. The effects of polymers and oils on the drug release were evaluated. MC showed the most prominent sustained release effect among various polymers examined with the optimum MC/ODS ratio of 2:1 (*w/w*). The particle size of the produced microparticles was in the mean diameter of approximately 3 μm . Physicochemical characterization suggested that ODS existed in an amorphous matrix within the microparticles and interacted with MC via hydrogen bonds. Corn oil was selected as the appropriate oil for suspension due to the sustained release of ODS and the appropriate viscosity. The optimized sustained release formulation of ODS was the corn oil suspension of spray-dried microparticles containing MC and ODS (2:1, *w/w*). It showed an *in vitro* drug sustained release up to 120 h, while the oil suspension of ODS without any polymer released the drug within 2 h. Following subcutaneous administration in rats, the optimized formulation could prolong the drug release until 72 h with the enhanced bioavailability in comparison with the ODS solution. The oil suspension of spray-dried microparticles might be an efficient approach for prolongation of the drug effect in the management of nausea and emesis.

Keywords Ondansetron hydrochloride · Sustained release · Parenteral formulation · Oil suspension · Spray drying · Microparticles

Introduction

Ondansetron hydrochloride (ODS), a selective inhibitor of 5-hydroxytryptamine type 3 (5-HT₃) receptors, has been widely

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used for the prevention of nausea and emesis in patients undergoing chemotherapy, radiotherapy [1], and postoperative treatment [2]. These side effects may occur until 24 h after the therapy (delayed nausea and vomiting) [3]. Therefore, the treatment of ODS in the patients extends from the beginning to 1–2 days after the completion of the therapy [4]. Oral administration of the drug is associated with a short elimination half-life (3–6 h) and low bioavailability (60%) [5]. In addition, the drug tends to be discharged by vomiting after oral administration [1]. Oral or parenteral administration of ODS is usually accompanied by undesirable side effects, including headache, constipation, and diarrhea [6]. These side effects are prominent in parenteral administration due to the rapid release of the entire amount of the drug in a short time. In addition, the drug concentration quickly decreases after administration of conventional parenteral formulations resulting in the requirement of repeated injections [6–8]. For the prevention of chemotherapy-induced nausea and vomiting, the drug administration needs to be repeated several times a day until the end

of the chemotherapy, which may reduce the treatment efficacy and patient compliance. Therefore, it is needed to develop sustained release parenteral formulations of ODS, which is advantageous for cancer patients who are treated with emetogenic chemotherapy [7, 8].

The goal of sustained release formulations is to control the therapeutic drug levels in blood or tissue for an extended period. Compared with conventional parenteral formulations, sustained release parenteral formulations offer better patient compliance, reduce dosing frequency, improve systemic availability by avoiding the first-pass metabolism, and decrease the incidence of side effects [9]. Generally, the development of sustained release parenteral formulations containing a water-soluble drug-like ODS is particularly challenging due to the rapid diffusion and absorption of the drugs into the bloodstream [10]. Recently, some sustained release formulations of ODS and other hydrophilic drugs were developed to overcome the above-mentioned drawbacks. They include transdermal patch [11, 12], microspheres [13, 14], and nanostructured lipid carriers [15]. Among several approaches to prepare sustained release parenteral dosage forms, oil suspension was a potential candidate for water-soluble drugs. It usually comprises a powder containing a drug and a polymer suspended in vegetable oils [16]. The incorporation of drugs into a polymeric matrix could effectively control the drug release [9]. In addition, oils could delay the dissolution of the drug and protect it from water, enzymes, and ions, resulting in the drug sustained release [17]. The drug-polymer powder could be produced by certain methods. Among them, spray drying is one of the most effective techniques to entrap hydrophilic drugs in polymeric matrixes. Furthermore, it can produce organic solvent-free microparticles for elimination of explosion and toxicity by spray drying with aqueous solutions [18, 19].

In oil suspension, the use of polymers was essential to achieve the sustained release of hydrophilic drugs [16]. Various polymer-based drug delivery systems have been developed and evaluated for systemic applications [20–24]. Certain polymers were previously used to produce sustained release microparticles of hydrophilic drugs such as hyaluronic acid [9], ethylcellulose [25], and ethyl acrylate-methyl methacrylate copolymer [26]. In this study, methylcellulose (MC) was used to incorporate ODS into microparticles. MC is a cellulose derivative with hydrophilic property attributed to the residual hydroxyl and the oxygen groups at the ether and acetal linkages. It is a biodegradable and thermo-responsive polymer, which has shown the safety in human for drug delivery and regenerative applications [27, 28]. The introduction of methyl groups with hydrophobic zones allows MC to behave as a surfactant [29]. Its absorbance at fluid interfaces reduced interfacial tension and enhanced the droplet stability [30, 31]. Furthermore, MC was approved as a parenteral ingredient by the FDA and currently used in several injectable

formulations [32, 33]. It was a potential polymer for drug microencapsulation by spray drying since it could work as an emulsifier and as the microparticles' matrix [34].

The present study described the development, optimization, and characterization of an oil suspension containing ODS as a sustained release parenteral formulation. The oil suspensions consisted of spray-dried microparticles of the drug and MC suspended in pharmaceutically acceptable oils. The optimized formulation was subjected to pharmacokinetic studies in rats following subcutaneous (SC) administration to evaluate the sustained release characteristic.

Materials and methods

Materials

Ondansetron hydrochloride (ODS) dihydrate was purchased from Gedeon Richter (Hungary). Polyvinylpyrrolidone K30 (PVP) and methylcellulose (MC, MW 88,000) were obtained from Sigma-Aldrich (MO, USA). Hydroxypropylcellulose (HPC, MW 370,000, Klucel™ GF Pharm) was purchased from Ashland (KY, USA). Hydroxypropylmethylcellulose (HPMC, MW 90,000, Metolose® 90SH-15000SR) was supplied by Shin-Etsu (Japan). Corn oil and castor oil were purchased from Daejung (South Korea). MCT (Miglyol®810) was kindly supplied by Cremer Oleo (Germany). HPLC grade acetonitrile and water were purchased from Avantor (PA, USA). Water was de-ionized and purified using a Milli-Q purification system (Millipore, MA, USA). Other reagents (analytical grade) were used without further purifications.

Preparation of spray-dried microparticles and oil suspension

The feeding solution was prepared by dissolving ODS and a polymer in water. The polymer concentration in feeding solutions was kept at 0.25% (w/v) to obtain an appropriate viscosity for spray drying. The solution was spray-dried using a spray dryer equipped with a high-performance cyclone and a 0.7-mm two-fluid nozzle (Buchi B-290, Buchi Labortechnik AG, Switzerland). The spray dryer was operated under the following conditions: the inlet temperature of 120 °C, the outlet temperature of 67–70 °C, a pump flow rate of 8 mL/min, a spray flow rate of 600 L/h, and an aspirator of approximately 35 m³/h. After the spray drying, the resultant powder was stored in airtight glass vials at 4 °C and protected from light. The feeding rate and the spray flow rate were varied to investigate their effect on the spray-dried microparticles. Various spray-dried microparticles were prepared with different polymers at various polymer/drug ratios (Table 1). ODS microparticles without polymer and MC microparticles without ODS were also produced. Spray-dried microparticles (equivalent to 40 mg of

Table 1 Composition, residual moisture, drug content, and particle size of various spray-dried microparticles

Code	Polymer	Polymer/drug ratio (w/w)	Residual moisture (%)	Drug content (%)	D_{50}^a (μm)
spODS	—	—	5.4 ± 0.1	—	3.27 ± 0.17
spMC	MC	—	5.1 ± 0.1	—	3.47 ± 0.04
spPVP-2	PVP	2:1	4.5 ± 0.1	32.4 ± 0.8	3.50 ± 0.09
spHPC-2	HPC	2:1	5.0 ± 0.2	31.8 ± 0.6	3.16 ± 0.14
spHPMC-2	HPMC	2:1	4.8 ± 0.1	32.1 ± 0.7	3.06 ± 0.09
spMC-0.25	MC	0.25:1	4.8 ± 0.1	76.6 ± 0.8	3.17 ± 0.27
spMC-0.5	MC	0.5:1	5.0 ± 0.2	64.3 ± 1.3	3.11 ± 0.21
spMC-1	MC	1:1	4.5 ± 0.2	47.2 ± 1.4	3.08 ± 0.05
spMC-2	MC	2:1	5.0 ± 0.5	31.8 ± 0.5	2.96 ± 0.02
spMC-4	MC	4:1	5.1 ± 0.3	19.1 ± 0.4	3.11 ± 0.05

^a D_{50} denotes the value of particle diameter at 50% in the cumulative distribution

ODS) were added to 1 mL of an oil and stirred gently with a magnetic stirrer until a homogenous suspension was formed. MCT, corn oil, and castor oil were used to prepare the oil suspensions and evaluate the effect of oil viscosity on the drug release. The optimized formulation for pharmacokinetic studies was prepared in a clean bench with the polymer-drug solution filter (0.22 μm) prior to spray drying.

Analysis of ODS using HPLC method

The HPLC system (Agilent Technologies, CA, USA) consisted of a quaternary pump, an auto-sampler, and a UV detector. The column was a Phenomenex® C18 column (5 μm particle size, 250 $\times$ 4.6 mm, Phenomenex, CA, USA). An aliquot of samples (10 μL) was injected into the HPLC system. The mobile phase for ODS analysis consisting of acetonitrile and 0.02 M acetate buffer pH 4.8 (40/60, v/v) was filtered and degassed before use. The flow rate was 1.0 mL/min and the detection wavelength was 310 nm.

Characterization of spray-dried microparticles and oil suspensions

The residual moisture and drug content of microparticles

The analysis of residual moisture content of the produced microparticles was carried out using a volumetric Karl Fischer titrator (V30, Mettler Toledo, OH, USA). ODS content in the spray-dried microparticles was determined using the HPLC method after dissolving an exact amount of the microparticles in water and appropriately diluting with the mobile phase.

Size distribution

The size of spray-dried microparticles was determined using a dry powder disperser (Aero S) of Mastersizer

3000 laser-diffraction system (Malvern Instruments, UK). Samples were fed into a sample feed hopper. The feeding rate was set at 50% for all samples. The values of the microparticle diameter at 50% undersize in the cumulative distribution (denoted as D_{50}) and size distribution were determined.

Differential scanning calorimetry (DSC)

Thermal analyses of MC, ODS, their physical mixture (MC/ODS ratio of 2:1, w/w), and spMC-2 microparticles were carried out using differential scanning calorimetry (DSC 8000, PerkinElmer, MA, USA). The DSC was equipped with an intracooler and a nitrogen purge at 20 mL/min. Samples (2–5 mg) were placed in aluminum pans with covers and heated at a rate of 20 $^{\circ}\text{C}/\text{min}$ over a temperature range of 30–250 $^{\circ}\text{C}$.

X-ray powder diffraction (XRD)

XRD patterns of MC, ODS, their physical mixture (MC/ODS ratio of 2:1, w/w), and spMC-2 microparticles were obtained using an X-ray diffractometer (MiniFlex600, Rigaku, Japan) at room temperature. The samples were irradiated with Ni-filtered $\text{CuK}\alpha$ radiation at 40 kV and 15 mA. The scanning rate was 2 $^{\circ}/\text{min}$ with a step width of 0.02 $^{\circ}$ over a diffraction angle of 2 θ and a range of 3–90 $^{\circ}$.

Fourier-transform infrared spectroscopy (FTIR)

MC, ODS, their physical mixtures (MC/ODS ratio of 0.25:1 and 2:1, w/w), and spMC-2 microparticles were subjected to FTIR analysis using an FTIR spectrophotometer (Tensor 27, Bruker, MA, USA), ranging between 500 and 4000 cm^{-1} with a resolution of 4 cm^{-1} . Each sample was subjected to an average of 16 scans.

Scanning electron microscopy (SEM)

Morphological analyses of MC, spMC, and spMC-2 microparticles were carried out using SEM (S-4800, Hitachi, Japan). The samples were mounted on aluminum sample mounts and sputter coated with gold-palladium followed by the observation of surface morphology with 15 kV of acceleration voltage and 13.9 mm of working distance. The magnification was 5000–10,000.

Viscosity determination

The viscosities of various oils (MCT, corn oil, and castor oil) and oil suspensions prepared with them were determined using a rheometer (Physica MCR 302, Anton Paar, Austria) with a shear rate of 10 s^{-1} . The system temperature was fixed at 25°C using a circulating water bath (Lab Companion, Korea). The instrument was set up with a parallel-plate geometry using a 25-mm diameter plate (PP25 type) and a gap of 0.5 mm.

Drug solubility in water and oils

ODS solubility in water, MCT, corn oil, and castor oil was determined using the method established by Higuchi and Connors [35]. Excessive amounts of ODS were added to vehicles in glass tubes and the suspensions were shaken at $37 \pm 0.5^\circ\text{C}$ (50 rpm) for 48 h using an isothermal water bath (HST 205 SW, Hanbaek ST, South Korea). The suspensions were centrifuged using a tabletop centrifuge (1730R, Labogene, CA, USA) at 14,000 rpm for 30 min, and the clear supernatant was adequately diluted with the mobile phase prior to HPLC analysis.

In vitro drug release studies

The release studies were carried out using the rotating dialysis cell model as previously described [36, 37] with some modifications. In brief, the produced microparticles were suspended in 1 mL of an oil and transferred into dialysis bags (MWCO 3.5k, Spectra/Por, Spectrum Laboratories, CA, USA). The dialysis bags were fixed to the paddles of a dissolution tester (DST-810, Labfine, South Korea). The media was 200 mL of phosphate buffer pH 7.4. The drug release studies were carried out at the temperature of $37 \pm 0.5^\circ\text{C}$ and the paddle rotating speed of 50 rpm. Samples were withdrawn at each pre-determined time interval and diluted appropriately with the mobile phase followed by HPLC analysis. The drug release was expressed as a percentage of cumulative ODS released based on the drug content analysis. T75, the time required for 75% dissolution of ODS, was determined from dissolution profiles.

Stability studies

The spMC-2 microparticles were stored in stability chambers (FLT-700D, Labfine, South Korea) under two conditions ($25 \pm 2^\circ\text{C}/60 \pm 5\%\text{RH}$ and $40 \pm 2^\circ\text{C}/75 \pm 5\%\text{RH}$) and in a refrigerator (4°C). After 6 months, samples were collected for evaluation of particle size and drug content. Samples were also analyzed by DSC and XRD.

Pharmacokinetic studies

All animal experiments were carried out following guidelines of Gachon University and the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978). The animal study was approved by Animal Care and Use Committee of Gachon University (No. GIACUC-R2019015). Male Sprague-Dawley rats (8–9 weeks, 250–300 g) were supplied by Nara Biotech (South Korea). The animals were acclimatized for 1 week before the experiment at ambient conditions with a 12-h light/dark cycle. They had unrestricted access to food and water. Control group ($n = 6$) received ODS solution in saline at a dose of 2 mg/kg. Test group ($n = 6$) received the optimized formulation (spMC-2/Corn) at a dose of 4 mg/kg. The samples were administered subcutaneously into the loose skin over the neck using 23-gauge needles. At predetermined time points (0-predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h), 0.25 mL of blood was collected from tail vein and centrifuged (14,000 rpm, 4°C , 15 min) to collect the plasma.

For sample preparation, granisetron (20 ng/mL in acetonitrile solution) was used as an internal standard (IS). An amount of IS solution (100 μL) was added to 50 μL of plasma samples, followed by vortex-mixing in 1 min for deproteinization. After centrifugation, 100 μL of the supernatant was collected for the analysis.

ODS concentration was determined by a previously described LC-MS/MS method with some modifications [38]. The LC-MS/MS system (Agilent Technologies, CA, USA) consisted of an electrospray tandem triple quadrupole mass spectrometer (Agilent 6490 QQQ) coupled with an HPLC system (Agilent 1290). The drug, IS, and endogenous plasma substances were separated on a column (Synergi 4 μm polar-RP 80A, $150 \times 2.0 \text{ mm}$, Phenomenex, CA, USA) which was maintained at 30°C . The column was equipped with a guard-column (SecurityGuard 4.0 $\times$ 3.0 mm, Phenomenex, CA, USA). The mobile phase was a mixture of 0.1% formic acid and acetonitrile (40:60, v/v) with a flow rate of 0.2 mL/min. The temperature of the autosampler was 4°C and the injection volume was 2 μL . The electrospray ionization source was operated in positive mode. Quantification was performed using multiple reaction monitoring with the transitions m/z 294.1 $\rightarrow$ 170.0 for ODS and m/z 313.1 $\rightarrow$ 138.1 for IS. The optimized collision energies were 22 eV and 28 eV for ODS

and IS, respectively. Data acquisition and integration were performed using the Mass Hunter version A.06.00 software (Agilent Technologies, CA, USA).

Non-compartmental analysis using WinNonlin 5.0.1 (Pharsight, NC, USA) was applied to calculate pharmacokinetic parameters including the half-life ($t_{1/2}$), the mean residence time (MRT), the area under the curve from 0 to the last time point (AUC_{last}), and infinity (AUC_{inf}). The peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were defined from individual profiles.

Statistics

Each experiment was carried out in triplicate (except the pharmacokinetic studies). Data were presented as mean values with standard deviations (SDs). Statistical analysis was performed using GraphPad Prism 8.2.1. The Student's *t* test and ANOVA were carried out to evaluate significant differences at the 95% level.

Results

Preparation of spray-dried microparticles

All the spray-dried microparticles containing polymer-ODS were successfully produced in the form of fine white powder with mean diameters of approximately 3 μm (Table 1). The residual moisture content of the spray-dried microparticles was approximately 5%. Considering the residual moisture, the drug content of the produced microparticles (shown in Table 1) was consistent with theoretical values, indicating the success of microencapsulation and the stability of ODS during the spray drying [39].

The effects of the spray flow rate and the feeding rate on the particle size of the spray-dried product were evaluated. Various batches of spMC-2 microparticles were prepared with different flow rates, and feeding rates and the particle size of the products are shown in Table 2. An increase in particle size was observed as the feeding rate increased, which was consistent with a previous report [18]. The particle size was increased in the order of batch D < batch C < batch B corresponding to a decrease in the spray flow rate of the spray dryer. The results indicated that smaller microparticles were formed by higher spray flow rate, which complied with previous results [40]. Size distributions of four batches of spray-dried microparticles are presented in Fig. 1. Batch D microparticles corresponding to the highest spray flow rate exhibited the narrowest size distribution and most of the microparticles were less than 10 μm .

Four batches of spMC-2 microparticles with different sizes were used to evaluate the effect of particle size on drug release from corn oil suspensions. As shown in Fig. 2a, the drug

release from the oil suspensions of microparticles with different sizes was not significantly different ($p > 0.05$), indicating that particle size may not considerably affect the release of ODS. However, batch D microparticles were preferred, since oil suspensions containing the microparticles with small particle size were easily injected, which may contribute to patient compliance. Further investigations were carried out with the feeding rate of 8 mL/min and the spray flow rate of 600 L/h.

Effect of polymer on drug release

Certain water-soluble polymers (PVP, HPC, HPMC, and MC) were used in this study to produce microparticles loaded with ODS at the polymer/ODS ratio of 2:1 (w/w). The oil suspension of spODS microparticles showed more than 80% and 92.5% of the drug released at 2 h and 4 h, respectively (Fig. 2b), indicating that the poor solubility of ODS in oils could only lead to a sustained release profile of ODS up to 4 h. There were no differences among drug release from oil suspensions of spODS, spPVP-2, and spHPC-2 microparticles ($p > 0.05$), suggesting that ODS release from oil suspensions was not affected by PVP and HPC. In contrast, the oil suspension of spHPMC-2 microparticles exhibited a sustained release profile of ODS with approximately 95% of the drug released at 12 h. The oil suspension of spMC-2 microparticles showed a prominent sustained release of the drug compared with others with about 75% of ODS released at 72 h. MC was selected as the polymer of choice for further studies.

Effect of ratio of MC/ODS on drug release

To investigate the effect of MC/ODS ratio on drug release, five different spray-dried microparticles of MC and ODS were prepared with the ratio of MC/ODS from 0.5:1 to 4:1 (w/w) as shown in Table 1. The microparticles were then suspended in corn oil for drug release studies. As shown in Fig. 3a, the drug release was not significantly altered when increasing MC/ODS ratio from 0.25:1 to 0.5:1 ($p > 0.05$). However, increasing the MC/ODS ratio from 0.5:1 to 2:1 resulted in a significant decrease in drug release ($p < 0.05$). In addition, as shown in Fig. 3b, increasing the MC level in this range could improve T75 significantly, indicating that MC played a crucial role in modulating the release of ODS [9]. Further increase of MC/ODS ratio from 2:1 to 4:1 resulted in a negligible change in drug release, indicating that drug sustained release reached a plateau and that increasing MC/ODS ratio higher than 2:1 did not significantly improve drug sustained release. Based on the results, the MC/ODS ratio of 2:1 was selected as the optimal composition for further investigations.

The drug release data were fitted to various release models (first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas) using DDSolver [41]. As shown in Table S1, the drug release data followed the Korsmeyer-Peppas model with

Table 2 Particle size of spMC-2 microparticles produced with different spray flow rates and feeding rates

Microparticle	Spray flow rate (L/h)	Feeding rate (mL/min)	D_{50}^a (μm)
A	360	16	$15.7 \pm 2.3^*$
B	360	8	9.84 ± 0.44
C	480	8	$4.65 \pm 0.43^*$
D	600	8	$2.96 \pm 0.02^*$

^a D_{50} denotes the value of particle diameter at 50% in the cumulative distribution (mean $\pm$ SD, $n = 3$)

* Significantly different from batch B data ($p < 0.05$)

correlation coefficient value > 0.95 . The diffusional exponent (n) values were from 0.2101 to 0.3618, confirming the drug release by Fickian diffusion under the concentration gradient [42].

Spray-dried microparticle characterization

Pure ODS, MC, their physical mixture of MC/ODS, and spMC-2 microparticles were characterized using DSC, XRD, and FTIR. As shown in Fig. 4, the DSC thermogram of ODS exhibited a sharp endothermic peak at 184.5°C , corresponding to the melting point of the drug, which indicated a crystalline substance [43]. The DSC thermogram of MC showed no peak over the examined temperature range. In the DSC thermogram of spMC-2 microparticles, the disappearance of ODS endothermic melting peak suggested molecular encapsulation of the drug into MC and the formation of amorphous ODS in spray-dried microparticles. The existence of the drug and the polymer in a spray-dried amorphous

matrix complied with previous studies [44, 45]. On the other hand, the ODS melting peak was observed in the physical mixture of MC and ODS.

The diffraction pattern of pure ODS powder (Fig. 5) revealed several high-intensity peaks at diffraction angles (2θ) of 12.3 , 16.9 , 23.1 , 24.1 , and 27.9° , suggesting that ODS existed as the crystalline drug [46]. Pure MC showed a crystalline diffractogram with two intense peaks at 8.9 and 20.1° [47]. The diffraction pattern of the physical mixture corresponded to the superposition of ODS and MC with overlapping diffraction peaks. On the other hand, the diffractogram of spMC-2 microparticles showed only one broaden peak at 20.1° corresponding to crystalline MC. The complete disappearance of crystalline peaks of ODS indicated the entirely amorphous nature of ODS in the spray-dried microparticles.

The results of FTIR characterization are shown in Fig. 6. The FTIR spectrum of MC showed a characteristic absorption band at 1060 cm^{-1} (C–O–C stretching) and an intense absorption band at 3452 cm^{-1} (O–H stretching) [47]. The FTIR spectrum of the pure ODS showed intense absorption bands at 3481 and 3409 cm^{-1} (N–H stretching in primary amide group). The peaks at 1636 cm^{-1} and 1612 cm^{-1} were associated with C=O stretching in the amide group and C=C stretching in the aromatic ring of ODS [46]. In the physical mixtures, the absence of additional peaks and shifts in the current peaks suggested that there was no significant interaction between MC and ODS. The physical mixture containing a higher proportion of MC exhibited an intense absorption band of C–O–C stretching, which overlapped ODS bands. In the FTIR spectrum of spMC-2 microparticles, the N–H stretching peak was broadened compared with the physical mixture and shifted to 3476 cm^{-1} . It may be attributed to hydrogen bond formation between the –OH groups of MC and the –NH function of ODS during spray drying, which confirmed the previous explanation of DSC and XRD analysis. Similar results reported previously indicated that ODS might interact with other carriers via the amine group [48]. The results suggested that ODS and MC might finely disperse within the microparticles without chemical interaction and the drug structure was maintained during spray drying [39].

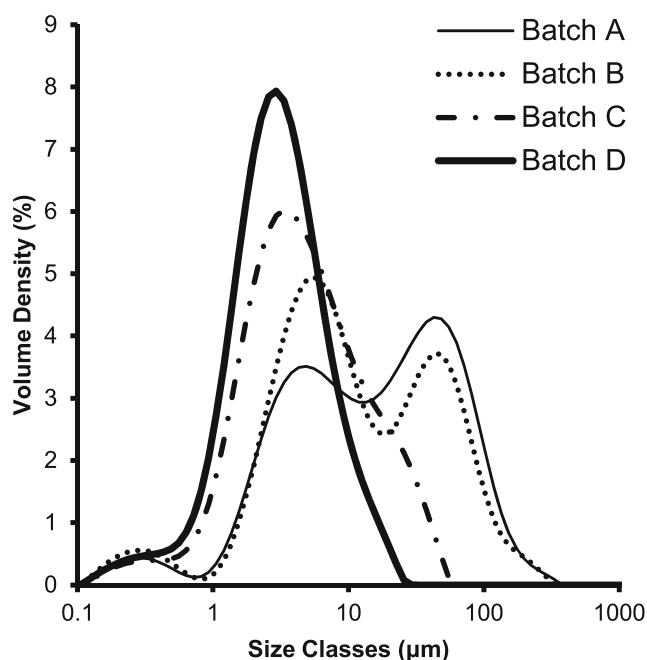


Fig. 1 Size distribution of different batches of spMC-2 microparticles produced with different feeding rates and spray flow rates

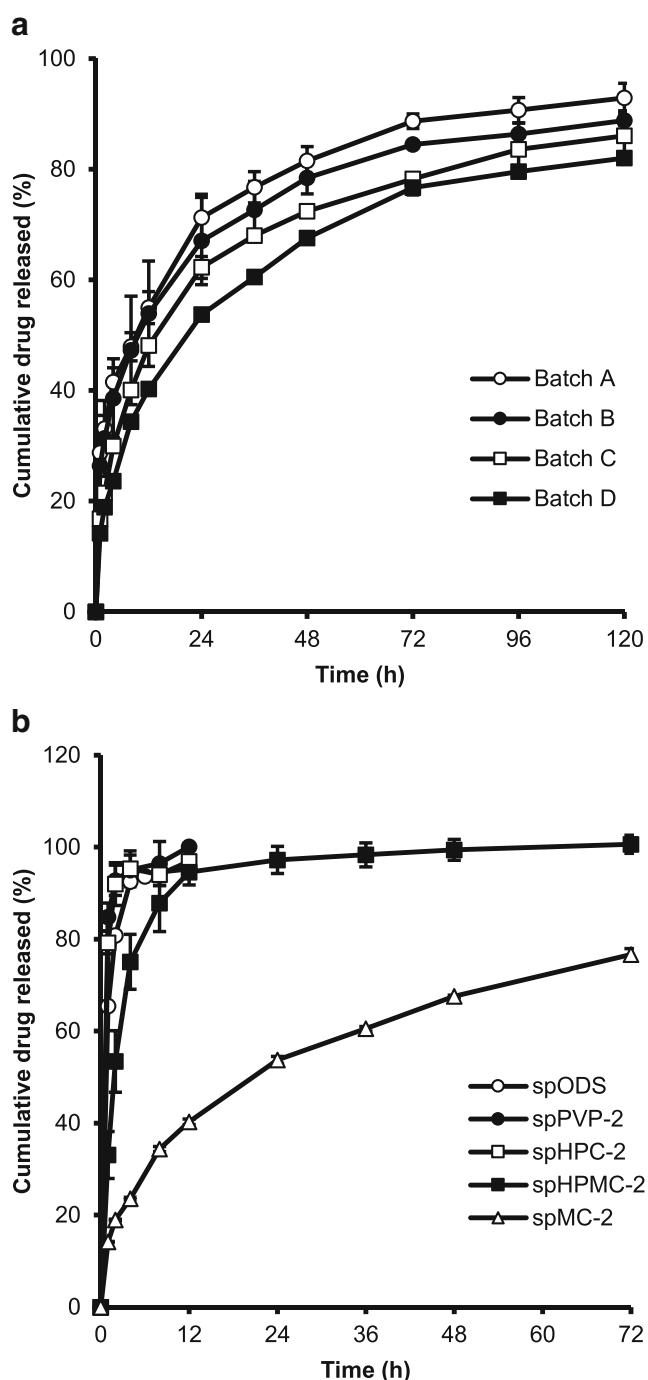


Fig. 2 Effect of particle size on drug release from oil suspensions containing different batches of spMC-2 microparticles (a) and effect of polymers on ODS release from oil suspensions in corn oil (b) (mean $\pm$ SD, $n = 3$)

SEM images of pure MC, spMC, and spMC-2 microparticles are illustrated in Fig. 7. While the original MC comprised large particles with various shapes (Fig. 7a), the spray-dried MC and spMC-2 microparticles were wrinkled and included particles less than 5 μm (Fig. 7b, c), which were consistent with the results of particle size analysis. After spray drying, MC was changed to microparticles with the increased surfaced

area, which enhanced its surfactant activity. The incorporation of ODS with MC did not considerably affect the morphology of the spray-dried MC.

Effect of oil viscosity on drug release

MCT, corn oil, and castor oil were selected as the low-, medium-, and high-viscosity vehicles, respectively, to investigate the oil viscosity effect on the drug release. These oils are currently used in parenteral products [49]. The solubility of ODS in these oils is almost similar, about 0.7 mg/g at 37 $^{\circ}\text{C}$. As presented in Fig. 8a, corn oil and castor oil suspensions showed a slower drug release compared with MCT suspension ($p < 0.05$). Viscosities at 25 $^{\circ}\text{C}$ of MCT, corn oil, castor oil as well as their corresponding suspensions are shown in Fig. 8b. The viscosity of the oil was increased as the microparticles were added to form the oil suspension. The microparticles acted as obstacles to hinder the oil flow and thereby increased the viscosity [50]. The viscosities of the oil suspensions increased in the following order: MCT < corn oil < castor oil. The higher viscosities of corn oil and castor oil suspensions may reduce the diffusion of the drug into the outer aqueous fluid, resulting in the better sustained release of the drug. However, the viscosities of the oils were inversely related to the injectability of oil-based parenteral formulations. The low viscosity of MCT suspension resulted in the smooth injection through a 26-gauge needle. In the case of castor oil, extra pressure was needed to inject its suspension. Due to the high viscosity, castor oil was injected through a 23-gauge needle at a low speed. When a bigger needle was used (18-gauge needle), the castor oil suspension was easier to be injected; however, it may cause pain to patients. Moreover, the in vitro drug release was quite similar between corn oil and castor oil suspensions. Therefore, corn oil as a medium-viscosity vehicle was preferred for both good injectability and sustained release of the drug [49]. The optimized formulation was the suspension of spMC-2 microparticles in corn oil (spMC-2/corn). It could be smoothly injected into subcutaneous spaces in rats via a 23-gauge needle.

Stability studies

As shown in Table S2, there was no significant difference in drug content of spMC-2 microparticles before and after storage under various conditions ($p > 0.05$), indicating the stability of ODS during storage. Particle size was slightly increased (Table S2), suggesting that the agglomeration of particles might occur; however, the increases were negligible. During storage, amorphous materials tend to recrystallize [51]. However, the DSC and XRD studies (Figs. S1 and S2) indicated that there was no change in the amorphicity of spMC-2 microparticles following storage under various conditions for 6 months [52].

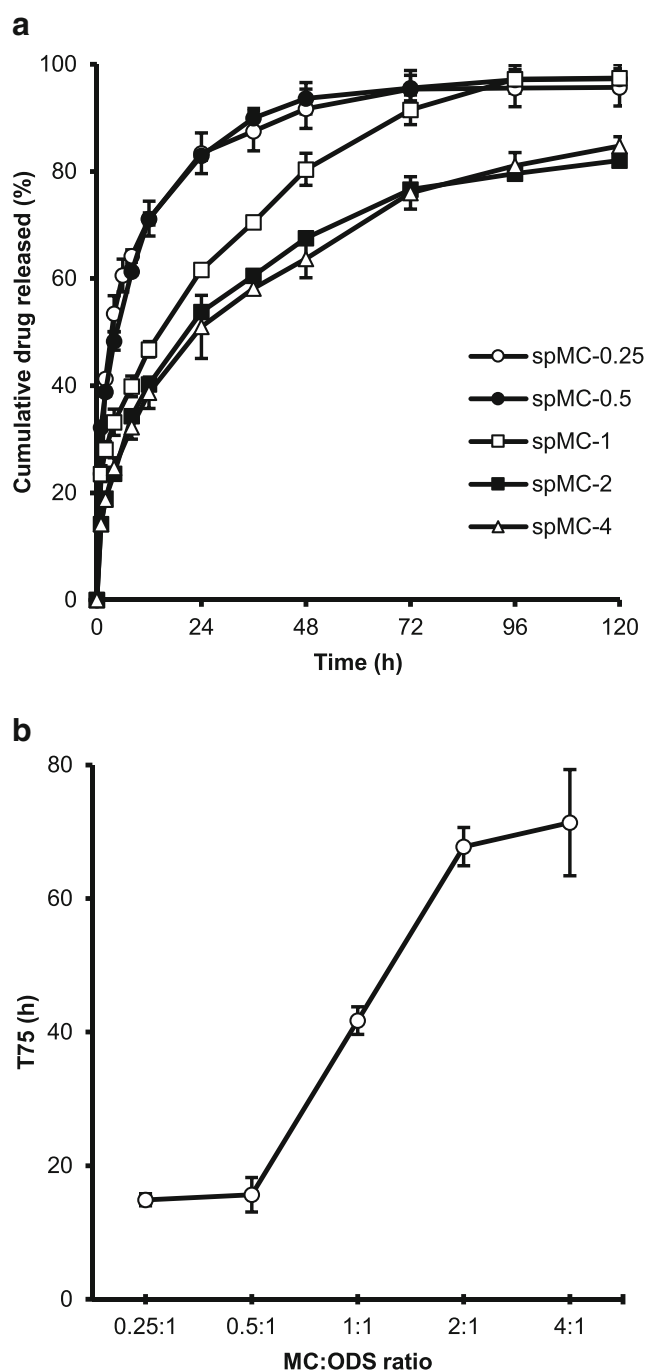


Fig. 3 Effect of MC/ODS ratio on drug release from oil suspensions (a) and T75 (the time for 75% of ODS release) (b) (mean $\pm$ SD, $n = 3$)

Pharmacokinetic studies

The plasma concentration-time profiles of ODS in rats are presented in Fig. 9 and the pharmacokinetic parameters are summarized in Table 3. The plasma concentration of ODS following the SC injection of ODS solution (control) was elevated and rapidly dropped to the baseline level within 12 h with a T_{max} of 0.50 h, as expected for a water-soluble drug. The MRT was relatively short (3.18 h). In contrast, the

optimized formulation exhibited a significant sustained release characteristic with the presence of the drug in blood until 72 h. The T_{max} was extended to 3.33 h and the MRT was increased by approximately 24.7-fold compared to that of the control group. Despite the administration of a 2-time higher dose, the C_{max} significantly decreased compared to that of the control group. Furthermore, the bioavailability expressed as $AUC_{inf}/dose$ was enhanced approximately 2.9-fold in comparison with that of the control group.

Discussion

To prepare an oil suspension containing ODS as a sustained release parenteral formulation, the spray-dried microparticles of a polymer and the drug were prepared beforehand followed by the dispersion of these microparticles in pharmaceutically acceptable oils. The polymers were used to entrap the hydrophilic drug in a polymeric matrix to reduce the drug release [9], while the oil suspensions could prolong drug release due to the poor solubility of the drug in oils and the immiscibility of oils with water [49]. The spray-drying technique could provide size-controllable microparticles with modifiable drug release [53–55]. The utilization of aqueous systems in spray drying for the drug microencapsulation is becoming popular due to the absence of organic solvents, which usually incur risks of toxicity, explosion hazards, fire, and product contamination [25, 26]. Since ODS is a water-soluble drug with a solubility of 46.2 ± 5.4 mg/mL (37 °C), the spray-drying process could be performed with an aqueous solution without using any organic solvent, in which the drug and a polymer were simultaneously dissolved.

The feeding rate and spray follow rate were evaluated for their effect on the size of spray-dried microparticles. The high feeding rate is associated with large volumes of liquid to be dried, which consequently resulted in the increased droplet size and the formation of large particles (Table 2). Atomization by compressed air is an essential step of the spray drying affecting the particle size of the product. The higher spray flow rates could deliver the atomization energy to the bulk liquid more efficient and consequently reduce the size of the spray-dried microparticle (Table 2) [56]. Therefore, the feeding rate and the spray flow rate played an essential role in the formation of spray-dried microparticles and considerably affected their particle size and size distribution. During spray drying, the droplet temperature was lower than the outlet temperature since all the energy was used to evaporate water in a very short time [56]. Therefore, in the operating conditions, the temperature of the product was maintained below 70 °C. It attributed to the success of encapsulation and stability of ODS in the spray-dried microparticles as presented results.

Four batches of spMC-2 microparticles had different particle sizes (Table 2). However, when comparing the size

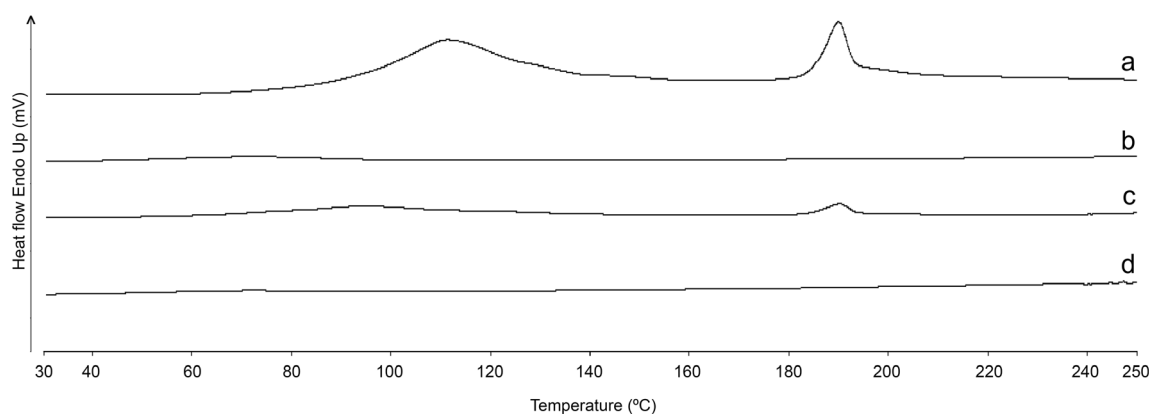


Fig. 4 DSC thermograms of ODS (a), MC (b), physical mixture (MC/ODS ratio of 2:1, w/w) (c), and spMC-2 microparticles (d)

Fig. 5 XRD patterns of MC (a), ODS (b), physical mixture (MC/ODS ratio of 2:1, w/w) (c), and spMC-2 microparticles (d)

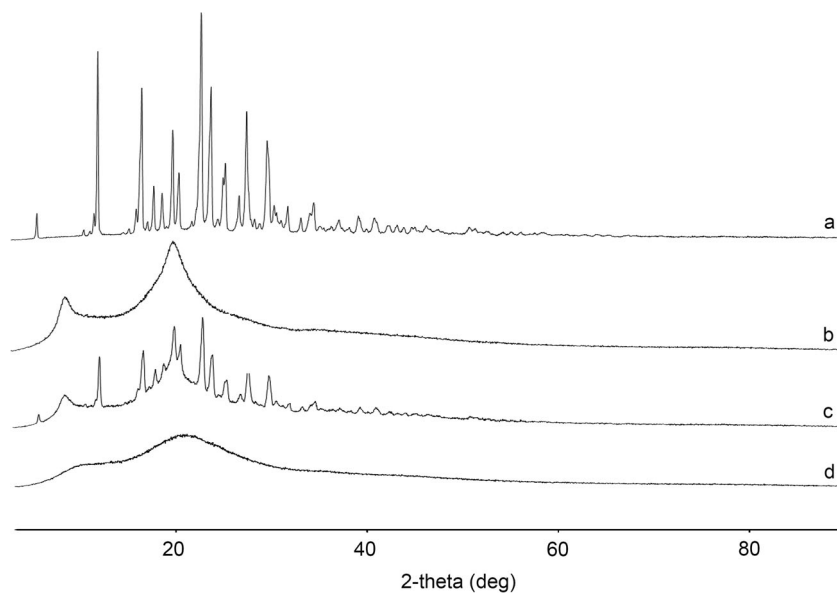
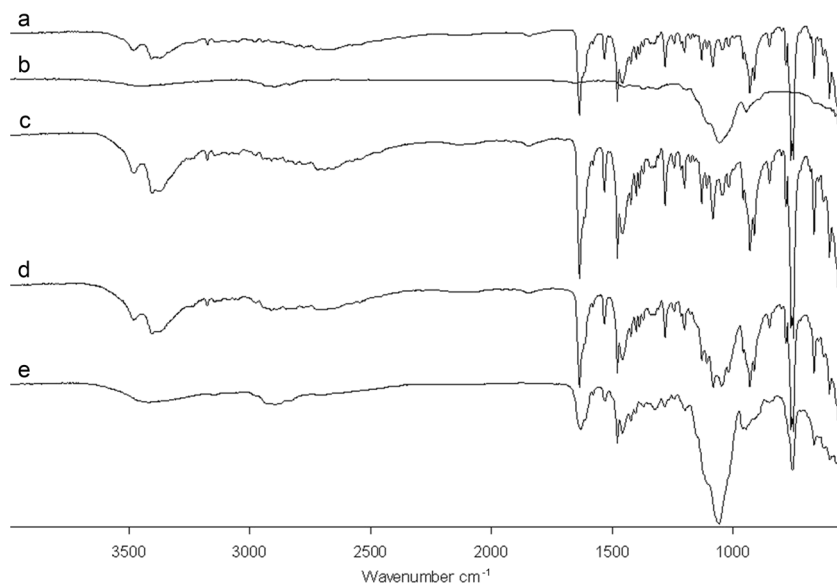


Fig. 6 FTIR spectra of ODS (a), MC (b), physical mixture (MC/ODS ratio of 0.25:1, w/w) (c), physical mixture (MC/ODS ratio of 2:1, w/w) (d), and spMC-2 microparticles (e)



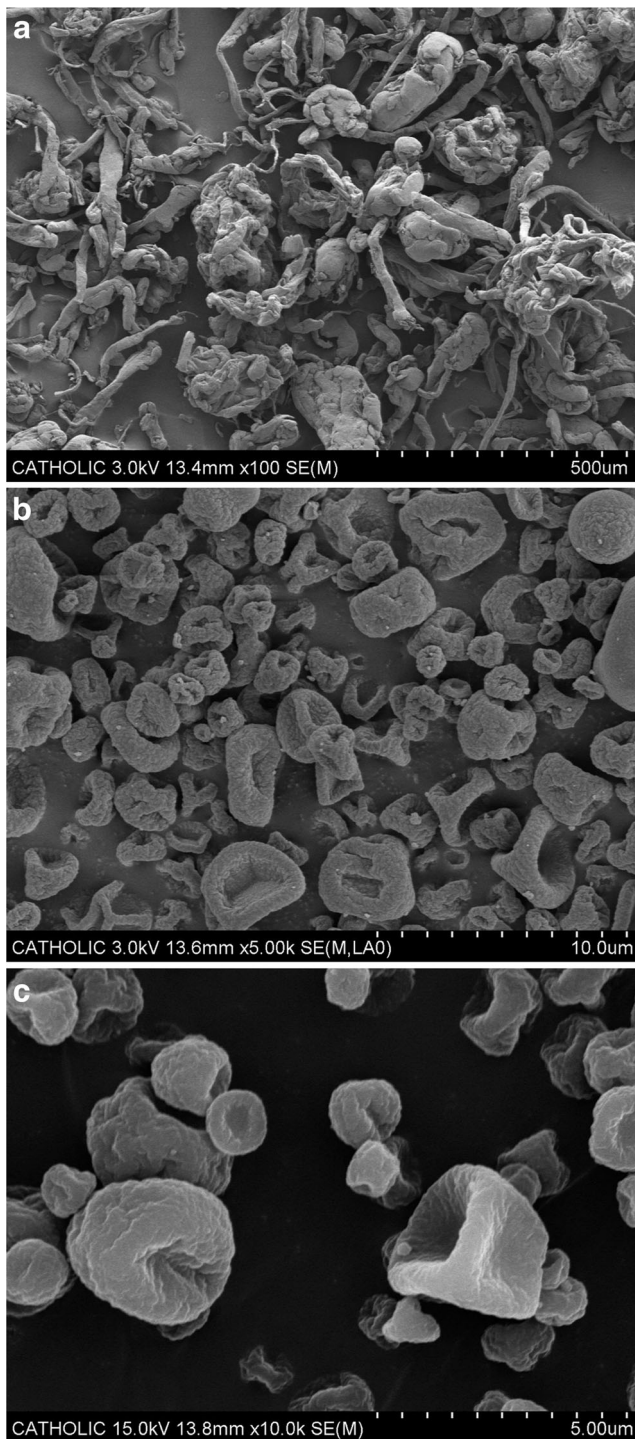


Fig. 7 Representative SEM images of MC (a), spray-dried MC (b), and spMC-2 microparticles (c)

distribution of those batches (Fig. 1), it could be observed that they had a relatively big overlapped portion. Therefore, the microparticles from these batches were not highly distinct, resulting in a slight difference in the drug release (Fig. 2a).

In this study, water-soluble polymers, including PVP, HPC, HPMC, and MC were used to incorporate ODS into microparticles. Among them, MC showed the most prominent effect

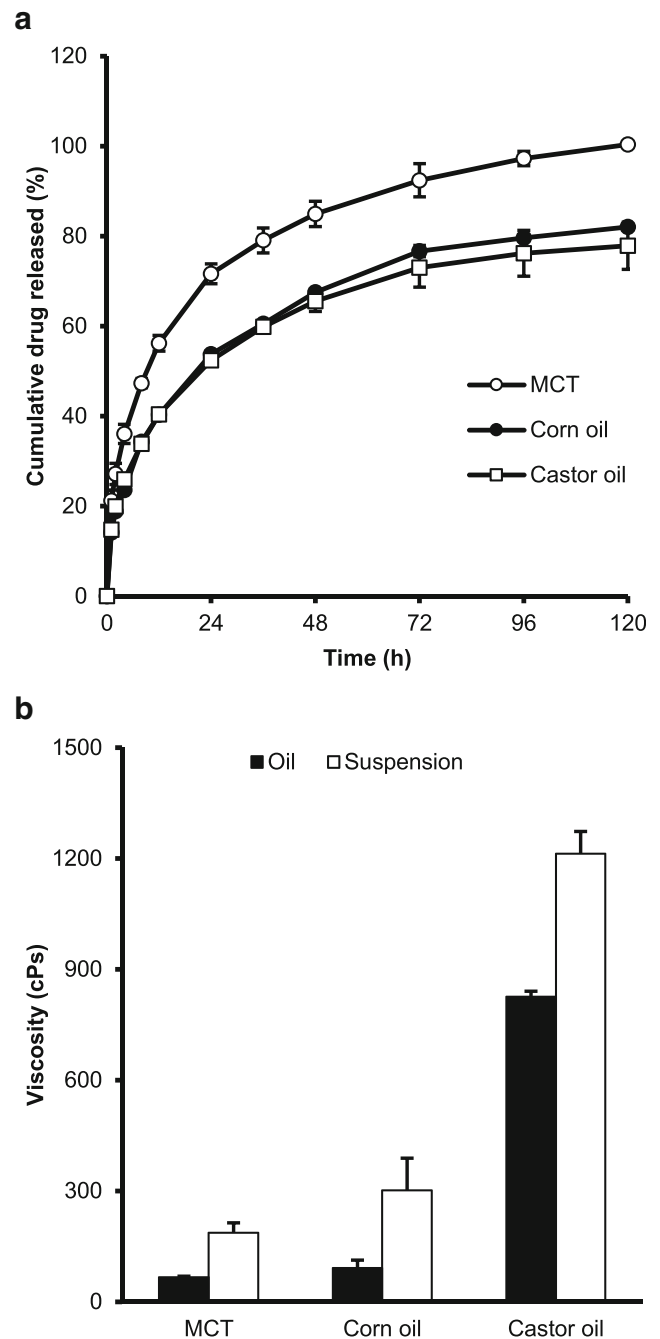
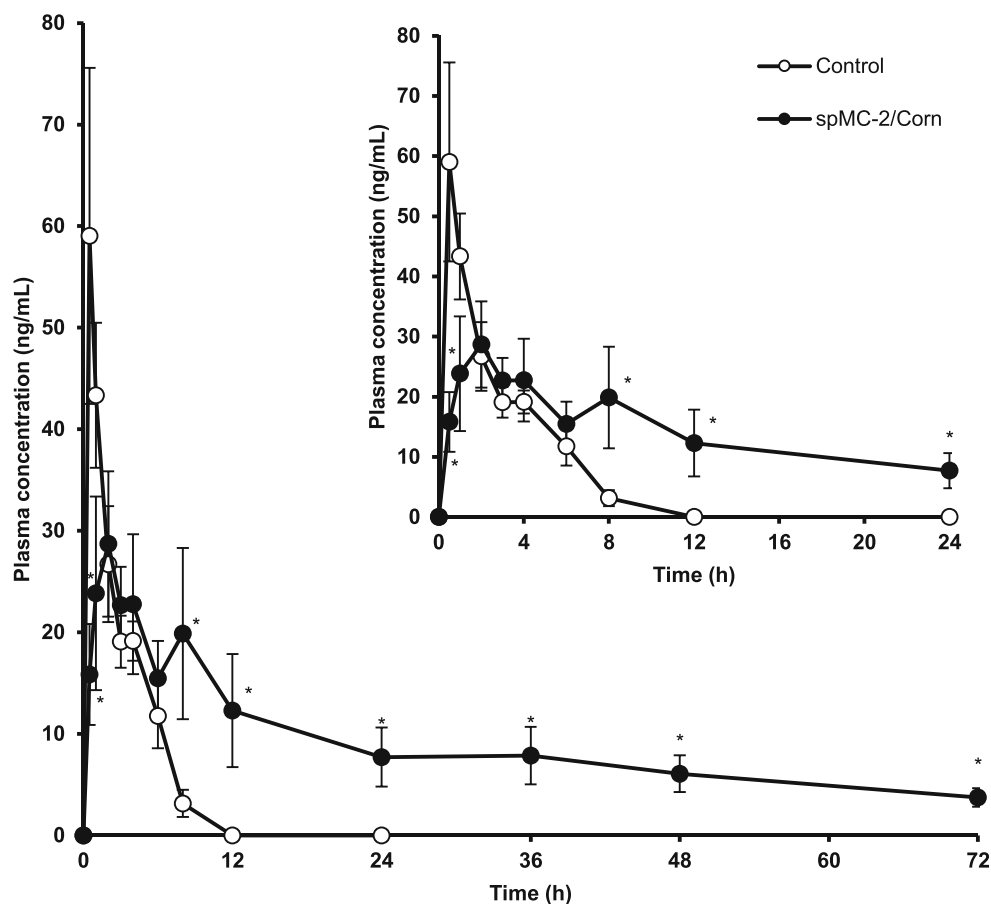


Fig. 8 Effect of MCT, corn oil, and castor oil on drug release from oil suspensions of spMC-2 (a) and viscosity of MCT, corn oil, castor oil, and their suspensions with spMC-2 at 25 °C (b) (mean $\pm$ SD, $n = 3$)

on sustained release of ODS from the oil suspension (Fig. 2b). MC could work as an excellent drug reservoir in spray-dried microparticles to control the drug release [9] whereas corn oil as a water-immiscible vehicle could reduce the drug diffusion to the aqueous fluid [17, 49]. As previously reported, the surface of microparticles required proper modification with a surfactant to improve the dispersibility of the microparticles in oils [16]. However, spMC-2 microparticles could be well suspended into oils without the help of a surfactant. This effect

Fig. 9 ODS plasma concentration-time profiles obtained following SC administration of ODS solution (control, 2 mg/kg) and the optimized formulation (spMC-2/corn, 4 mg/kg) to rats (mean $\pm$ SD, $n = 6$).
*Significantly different from control group ($p < 0.05$)



of MC could be attributed to its amphiphilic property [30, 34]. MC may exhibit hydrophilic interactions with ODS in the microparticles and hydrophobic affinity for oils. In the developed system, the sustained release of the drug was controlled by the polymer (as a reservoir to control the drug release [9, 17]) and the oil (to reduce the drug diffusion). The hydrophobicity of MC reduced the contact between the drug and the aqueous fluid. Other hydrophilic polymers did not have a

good interaction with the oil phase to maintain a stable suspension. They might not work as an excellent reservoir to protect and sustain the drug release since their high hydrophilicity led to a quick dissolution into the aqueous phase.

MC was a potential polymer for drug microencapsulation by spray drying since the water solubility of MC provided abilities for the preparation of organic solvent-free microparticles. In the spray-dried microparticles, ODS completely changed into an amorphous state as the results of DSC and XRD study. During the spray drying, ODS and MC are distributed homogeneously within the sprayed droplet, resulting in the formation of microparticles, in which the drug was eventually dispersed through the polymeric matrix [25]. In the early stages of spray drying with the solution of MC and ODS, water might quickly evaporate, resulting in particle shell formation, which covered the droplet and entrapped the bulk liquid inside [57]. The initial particle shell might be non-rigid, and further water evaporation induced shell folding, resulting in the wrinkled morphology of the microparticles [58].

The suspension of spMC-2 microparticles in corn oil (spMC-2/corn) was successfully developed as the optimized sustained release parenteral formulation. It showed an in vitro release profile of ODS up to 120 h. The sustained release of the drug is attributed to the water immiscibility of the oil, the poor solubility of the drugs in the oil, and the effect of the

Table 3 Pharmacokinetic parameters of ODS obtained following SC administration of ODS solution (control, 2 mg/kg) and the optimized formulation (spMC-2/corn, 4 mg/kg) to rats

Parameters	Control	spMC-2/corn
$t_{1/2}$ (h)	1.95 ± 0.49	$62.2 \pm 38.5^*$
T_{max} (h)	0.50 ± 0.00	$3.33 \pm 2.50^*$
C_{max} (ng/mL)	59.0 ± 16.5	$32.9 \pm 5.6^*$
AUC_{last} (ng h/mL)	163 ± 17	642 ± 113
AUC_{inf} (ng h/mL)	173 ± 16	995 ± 224
$AUC_{last}/dose$ (ng h/mL/[mg/kg])	81.6 ± 8.3	$160 \pm 28^*$
$AUC_{inf}/dose$ (ng h/mL/[mg/kg])	86.4 ± 7.8	$249 \pm 56^*$
MRT (h)	3.18 ± 0.51	$78.3 \pm 46.6^*$

Data are presented as means $\pm$ SDs ($n = 6$)

*Significantly different from control group ($p < 0.05$)

polymeric matrix. The formulation could be injected easily attributed to its small particle size (about 3 μm), surfactant effect of MC, and the appropriate viscosity of corn oil. These characteristics suggested that the optimized oil suspension was a potential sustained release parenteral formulation of ODS.

The sterilization of parenteral formulations is a critical issue. For oil suspension, the sterilization was possible to perform, including filtration of the drug-polymer solution, spray-drying in a clean room, and preparation of the final suspension in a clean bench [9, 16]. In the case that it is impossible to prepare a clean room for the spray-dryer, the spray-dried products are possible to be sterilized by heat or radiation. In our study, the filtration of the drug-polymer solution (0.22 μm) and the preparation in a clean bench were applied to the optimized formulation for the pharmacokinetic studies.

In the pharmacokinetic studies using rats, as the optimized formulation was expected to prolong the drug release for 2–4 days, the test group received a 2-time dose compared to the control group. Therefore, dose-normalized AUC was used to compare the bioavailability, which was calculated by AUC/dose. The pharmacokinetic results showed that the optimal formulation comprising spMC-2 microparticles in corn oil exhibited the prolonged release of ODS in rats. The initial burst release of ODS could result in the rapid release phase of the drug within 12 h. This rapid release phase could be advantageous for sustained release products. It suggested that the therapeutic drug concentration in blood could be rapidly achieved. The ODS plasma concentration was well maintained in the range of 12.3–28.7 ng/mL within the first 12 h without dramatic fluctuations. In this case, side effects, which usually occur with conventional parenteral formulations (e.g., IV and SC injection of the drug solution) due to the high elevation of drug level in the blood, could be reduced [6]. After injection, a small part of the microparticles might be in contact with the body fluid in the subcutaneous space. MC in the outer layer might transform into a viscous layer protecting the drug inside. The amount of drug released from those microparticles was possibly small at the beginning. However, after 6–8 h, those microparticles might be dissolved, and the drug inside could be released, resulting in a slight increase in the ODS plasma concentration at 8 h.

The increase in the bioavailability suggested the efficiency of the optimized formulation through prolongation of the drug release. In addition, the SC administration could extend the drug absorption and distribution, which therefore contribute to the drug sustained release [59]. In the case of ODS solution, these effects might result in a longer half-life and a lower C_{max} compared to previous data in IV administration [60]. In the optimized formulation, the sustained release phase could sufficiently ensure the prolonged action of the drug, which reduces dosing frequency and thereby enhances patient compliance. Our findings suggested that the oil suspension of spMC-

2 microparticles would be an attractive parenteral formulation for the management of chemotherapy-induced nausea and emesis. Encapsulation of water-soluble drugs with MC using spray-drying technique and utilization of oil suspensions provide a promising approach to develop a sustained release parenteral formulation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal studies All institutional and national guidelines for the care and use of laboratory animals were followed. The animal study was approved by Animal Care and Use Committee of Gachon University (No. GIACUC-R2019015).

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