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ORIGINAL ARTICLE

Ondansetron-loaded chitosan microspheres for nasal antiemetic drug delivery: an alternative approach to oral and parenteral routes

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Abstract

Background: The aim of this study was to develop chitosan microspheres for nasal delivery of ondansetron hydrochloride (OND). *Method*: Microspheres were prepared with spray-drying method using glutaraldehyde as the crosslinking agent. Microspheres were characterized in terms of morphology, particle size, zeta potential, production yield, drug content, encapsulation efficiency, and in vitro drug release. *Results*: All microspheres were spherical in shape with smooth surface and positively charged. Microspheres had also high encapsulation efficiency and the suitable particle size for nasal administration. In vitro studies indicated that all crosslinked microspheres had a significant burst effect, and sustained drug release pattern was observed until 24 hours following burst drug release. Nasal absorption of OND from crosslinked chitosan microspheres was evaluated in rats, and pharmacokinetic parameters of OND calculated from nasal microsphere administration were compared with those of both nasal and parenteral administration of aqueous solutions of OND. In vivo data also supported that OND-loaded microspheres were also able to attain a sustained plasma profile and significantly larger area under the curve values with respect to nasal aqueous solution of OND. *Conclusion*: Based on in vitro and in vivo data, it could be concluded that crosslinked chitosan microspheres are considered as a nasal delivery system of OND.

Key words: *Chitosan; microsphere; nasal delivery; ondansetron hydrochloride; spray-drying*

Introduction

Anticancer chemotherapy is associated with many side effects including acute and delayed nausea and vomiting. In particular, vomiting is an extremely unpleasant side effect for the patients and some of the agents cause severe vomiting, for example, platinum complexes[1]. To prevent strong nausea and vomiting and increase patients' quality of life, serotonin (5-hydroxytriptamine) subtype-3 (5-HT_3) antagonists have been used in treatment[2]. Ondansetron is one of the selective 5-HT_3 receptor antagonist used for preventing nausea and vomiting caused by chemotherapy, radiotherapy, and postoperation[3,4]. Its oral bioavailability is only about 60%, mainly because of hepatic first-pass[5]. It also undergoes intestinal metabolism, for example, CYP3A4 and intestinal secretion via P-glycoprotein (P-gp)[6].

Ondansetron hydrochloride (OND) is currently available in intravenous (i.v.) solutions and oral dosage forms (film-coated tablets, orally disintegrating tablets, and oral solutions). However, oral and parenteral administration of antiemetics could be inconvenient for patients taking emetogenic cancer therapy. For instance, following oral administration, antiemetic drugs could be discharged by vomiting; consequently, oral delivery of these compounds could be limited because of nausea and vomiting. When those compounds are administered intravenously, the onset of effects is very rapid and parenteral administration is also not a patient-friendly route because of the possibility of

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adverse reactions and fear of needle. Taking into account these limitations of delivering OND orally or intravenously, nasal administration of OND could be considered as an alternative route to prevent nausea and vomiting associated with such therapy. In addition, nasal delivery of OND could also overcome the hepatic first-pass effect and improve the drug bioavailability. Hussain et al.[7] demonstrated that OND was readily and rapidly absorbed with intranasal application and it was found as effective as the i.v. route for OND delivery. Recently, Cho et al.[8] also evaluated the effects of vehicles and penetration enhancers on permeation of OND through nasal mucosa and indicated that nasal delivery systems of OND formulated was feasible for nasal administration. In our previous work, OND-loaded biodegradable microspheres were prepared with emulsification/spray-drying technique using various polyester polymers (poly(D,L-lactide) and poly(D,L-lactide-co-glycolide)) to obtain a prolonged drug release. All microspheres were negatively charged because of the polymers (PLA or PLGA) used[9].

In nasal drug delivery, the most important limitation factor is rapid mucociliary clearance, which is the cause of a limited contact period allowed for drug absorption through the nasal mucosa[10,11]. Thus, mucoadhesive nano- and micro-particles have been formulated to overcome the rapid mucociliary clearance, thereby increasing drug absorption through nasal cavity[12–14].

Chitosan is a natural polymer that has mucoadhesive properties[15] because of its positive charges at neutral pH, which enable an ionic interaction with the negative charges of sialic acid residues on the mucus[16]. This highly mucoadhesive characteristics of chitosan provide a longer contact period for drug transport through nasal mucosa and prevents the clearance of the formulation via mucociliarly clearance mechanism[17,18]. Therefore, chitosan microspheres have been extensively evaluated as a drug delivery system[19–21].

In this study, we aimed to formulate OND-loaded bioadhesive microspheres with chitosan and to investigate feasibility of OND nasal delivery with chitosan microspheres. OND-loaded chitosan microspheres were prepared with spray-drying method using glutaraldehyde (GLA) as the crosslinking agent. Microspheres were characterized in terms of the particle size, zeta potential, morphological properties, production yield, drug content, encapsulation efficiency, and in vitro drug release. Nasal absorption of OND from chitosan microspheres was also evaluated in vivo in rats, and pharmacokinetic parameters of nasal OND-loaded microsphere administration were compared with those of aqueous solution of OND applied intravenously and nasally.

Materials and methods

Reagents and chemicals

OND was kindly supplied by Nobel Drug Company (Istanbul, Turkey). Chitosan [high-molecular weight, its deacetylation degree >75%, and viscosity of aqueous solution (0.5%) in 1% acetic acid was 220 cP at 20°C] was from Aldrich (Munich, Germany). GLA solution (25%, v/v) was from Merck (Darmstadt, Germany). All solvents and chemicals were of analytical or high-pressure liquid chromatography (HPLC) grade.

Preparation of microspheres

The compositions of microspheres were summarized in Table 1. Microspheres were prepared by 1:1 of drug to polymer ratio. Chitosan (750 mg; 0.5%, w/v) was dissolved in acetic acid solution (1%, v/v) and OND (750 mg) was dissolved in this solution. GLA as crosslinking agent was added at different concentrations (0.3%, 0.6%, and 0.9%, v/v) into the former solution. Microspheres were obtained by spraying the solution with spray-dryer (190 Mini Spray Dryer, Büchi, Flawil, Switzerland) using a standard 0.7-mm nozzle. The total volume of solution used for each formulation was 150 mL. The process conditions were as follows: inlet temperature 155–165°C, outlet temperature 90–100°C, aspirator setting 100% capacity, pump setting 4 mL/min, and spray flow rate 600 NL/h. Microspheres (F1) were also prepared with the same procedure but without GLA. After drying procedure, microspheres were harvested from the apparatus collector and weighed. The yields of production were calculated for each batch.

Table 1. Composition, drug content, encapsulation efficiency, particle size, and zeta potential of OND-loaded chitosan microspheres.

Microspheres	GLA (%)	Theoretical drug content (%)	Actual drug content (%)	Encapsulation efficiency (%)	VMD (μm)	Zeta potential (mV)
F1	0.0	50	47.51 ± 0.18	95.02 ± 0.40	9.48 ± 1.45	+16.37 ± 2.22
F2	0.3	50	44.82 ± 0.51	89.65 ± 1.14	5.35 ± 0.54	+14.10 ± 1.87
F3	0.6	50	40.53 ± 0.64	81.06 ± 1.41	5.12 ± 0.52	+12.40 ± 1.25
F4	0.9	50	37.63 ± 0.66	75.27 ± 1.46	3.85 ± 0.41	+11.33 ± 0.80

GLA, glutaraldehyde; VMD, volume mean diameter. Data are presented as mean ± SD ($n = 3$).

Scanning electron microscopy

The morphology of the OND-loaded chitosan microspheres was analyzed by scanning electron microscopy (SEM). The samples of microspheres were coated with gold-palladium under argon atmosphere and then observed with Joel JSM-5600 Model (Joel, Tokyo, Japan).

Particle size analysis

Particle size distribution of OND-loaded chitosan microspheres were carried out by laser light scattering using a Malvern MasterSizer (Malvern Instruments, Worcestershire, UK). The average particle size was expressed as the volume mean diameter (VMD, μm). All measurements were performed in triplicate.

Zeta potential of microspheres

Zeta potential of the microspheres prepared was determined using laser doppler electrophoresis (ZetaSizer, Malvern Instruments). The particles were suspended in 10 mM NaCl solution and sonicated for 5 minutes before charge determination.

Determination of drug content

OND-loaded chitosan microspheres were dissolved in acetonitrile. After dilution with mobile phase, the drug incorporated into the microspheres was determined using HPLC method described below. All measurements were performed in triplicate.

In vitro drug release study

In vitro drug release behavior from chitosan microspheres was determined by incubating the microspheres (5 mg) in 1.5 mL of water at 37°C. The samples were placed in an orbital-shaker (Thermo Electron Corp., Waltham, MA, USA) rotating at 175 rpm. At appropriate time intervals, 100 μL of samples were withdrawn and replaced with the same amount of fresh medium. Samples were diluted with mobile phase and then analyzed using HPLC. Each experiment was performed in triplicate.

Analytical procedure

Samples were analyzed by modified and validated HPLC method[7]. The analyses were performed on Shimadzu LC-10A (Kyoto, Japan) with Rheodyne injection valve and 20 μL loop. UV–Visible detector was set at 305 nm. Separations were carried out at 30°C on a Luna C18 column (4.6 × 250 mm, 5 μm, Phenomenex, Torrance, CA, USA), with a guard column (4.0 × 3.0 mm) packed with the same material. The mobile phase used in in vitro and in vivo studies consists of acetonitrile–10 mM *O*-phosphoric acid (70:30 and 25:75, v/v, respectively) at a flow rate of 1.0 mL/min. Retention times of OND are 3.2 and 5.8 minutes for the in vitro and in vivo studies, respectively. Calibration standards were in the range of 1.0–10.0 and 25–200 ng/mL for the in vitro and in vivo studies, respectively. The limit of quantification was determined as 0.020 and 0.025 μg/mL for the in vitro and in vivo studies, respectively. Precision of both methods was found to be less than 2.5% of relative standard deviation.

Sample treatment

One hundred microliters of plasma sample was deproteinized by adding 400 μL of acetonitrile and then vortex-mixed for 1 minute and centrifuged at 4500 × *g* for 5 minutes. The supernatant was evaporated until dryness under nitrogen in a block heater at 50°C. The residue was dissolved in 100 μL of mobile phase, and 20 μL of this solution was injected into the HPLC system.

In vivo studies

Animals

It has been established that the rat is an excellent animal model to study nasal absorption of drugs[22]. Male and female white Wistar rats were used (250–280 g). The in vivo experimental protocol was approved by the scientific Ethical Committee of the Istanbul University (Cerrahpasa Faculty of Medicine Approval Number 18529/2007). Rats were fasted 12 hours before the experiments with limited access to water.

Formulations and applications

For i.v. administration, isotonic aqueous solution of OND was prepared and then the solution was filtered through membrane filter (0.2 μm, Millipore®, Billerica, MA, USA) to obtain sterile solution. I.v. application was performed as single dose (2 mg/kg) on tail vein of rats.

Preparation of aqueous solutions of OND for nasal applications: 10 mg of OND (pure drug powder) was dissolved in 1 mL of purified water. Preparation of suspension of OND-loaded microspheres for nasal applications: crosslinked OND-loaded microspheres (F2, F3, and F4) of 5 mg were suspended in 0.5 mL water by using vortex. Noncrosslinked microspheres (F1) could not be suspended well in the aqueous medium because of aggregate formation; therefore, F1 formulation was not evaluated in vivo.

Nasal applications of both aqueous solution of OND and suspension of OND-loaded microspheres were administered to rats after brief ether inhalation at dose of 2 mg/kg. Nasal applications were made by using an

adjustable micropipette at maximum of 50 μL. For all nasal applications, total dose was applied to both nostrils to maximize the nasal mucosal surface area exposed to the drug.

Blood collection

Blood samples (0.5 mL) were collected in Li-Heparine tubes (Venoject, Roma, Italy) before drug administration (0 hour) and after drug administration at predetermined intervals (10, 20, 30, 40, 60, 90, and 120 minutes) following application of both i.v. and nasal aqueous solutions of OND. After nasal application of microsphere formulations, blood samples were obtained at the end of 0.5, 1, 1.5, 2, 4, 8, 10, and 24 hours. Blood samples were collected from orbital sinus vein of eyes of rats. Samples were centrifuged immediately at 3000 × *g* and the plasma stored at −20°C until analysis. Plasma concentrations of OND were determined using HPLC method described as above.

Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis was carried out employing the TopFit program (Heinzel G., Wolosczak R., Thomann P., Gustav Fischer Verlag, Stuttgart, Jena, New York, 1993). The maximum plasma concentration of OND (C_{max}) and the time to reach this concentration (t_{max}) were determined from the plasma concentration–time curves after nasal applications. Elimination constant (k_{el}) and area under the curve (AUC) for 0–2h and 0–24h (AUC_{0-2h}, AUC_{0-24h} values) were calculated by using plasma concentration–time curves of OND. The AUC calculations are based on the linear trapezoidal rule. Extrapolation to infinity was included ($AUC_{2h-\infty}$, $AUC_{24h-\infty}$ values) and calculated by using formula below. Total AUC was described as $AUC_{(0-\infty)}$ and calculated[23].

$$AUC_{(2h-\infty)} = \frac{C_{(2h)}}{k_{el}}$$

$$AUC_{(0-\infty)} = AUC_{(0-2h)} + AUC_{(2h-\infty)} \text{ or}$$
$$AUC_{(0-\infty)} = AUC_{(0-24h)} + AUC_{(24h-\infty)}$$

Statistical methods

In vitro and in vivo data obtained from experiments are reported as mean ± SD (n = 5). Statistical analysis of significance was performed using GraphPad-Prism 4.0 software (San Diego, CA, USA); the differences were evaluated by t-test. $P < 0.05$ was considered to be indicative of significance.

Results and discussion

Characterization of microspheres

OND-loaded noncrosslinked and crosslinked chitosan microspheres were prepared with spray-drying method. The characteristics of the microspheres are presented in Table 1.

Spray-drying method used in this study appears to be a suitable and simple method to prepare OND-loaded chitosan microspheres. This method is also reproducible, rapid, and easy to scale up, when compared with the other encapsulation techniques such as emulsification solvent evaporation. However, the yield of production is calculated about 40% for all formulations (Table 1). This relatively low production yield values can be due to the small batch size (each batch was prepared with 150 mL of solution). Besides, the loss of the material during the spray-drying process was explained with the polymer film adhesion on the cyclon walls[24]. The low yield values for spray-drying process were also because of the loss of lightest particles through the exhaust of the spray-dryer apparatus as it is not equipped with a trap to recover the lighter and smaller particles as reported by other researchers[24,25].

Noncrosslinked chitosan microspheres cannot be dispersed in water because of swelling and dissolution. Hence, crosslinking agents were generally used to solidify the microspheres[26–29]. Thus, OND-loaded chitosan microspheres were produced using different concentrations (0.3%, 0.6%, and 0.9%) of GLA solution as crosslinking agent. To investigate crosslinking agent used on microsphere characterization, noncrosslinked microspheres were also prepared using the same procedure (Table 1). Crosslinked chitosan microspheres had a yellow-brown color, especially that color was more intense with increasing GLA concentration. Similar observation was reported previously[30].

The morphology of OND-loaded chitosan microspheres was examined by SEM. SEM image of OND-loaded chitosan microspheres (chosen as an example) is presented in Figure 1. SEM analyses revealed that all OND-loaded chitosan microspheres were spherical in shape and microspheres have a smooth surface characteristic.

All microspheres showed a normal distribution of size. The particle size analysis of OND-loaded chitosan microspheres was characterized by the VMD ranged 3.85 ± 0.41–9.48 ± 1.45 μm (Table 1). Particle size analysis indicated that crosslinked microspheres had significantly smaller particle size than those of noncrosslinked chitosan microspheres ($P < 0.05$) (Table 1). Microspheres containing 0.9% of GLA (F4) had the smallest particle size, with 3.85 ± 0.41 μm. However, there were no remarkable differences in particle size between

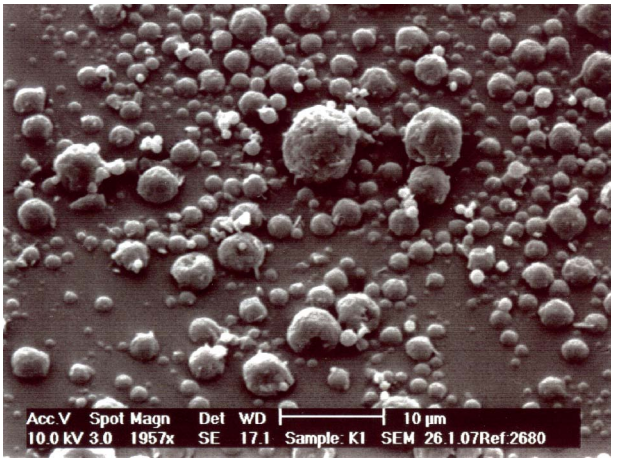

Figure 1. Representative SEM photograph of OND-loaded chitosan microsphere. Magnification ×1000.

microspheres having 0.3% and 0.6% of GLA ($P > 0.05$). The study of He et al.[29] was also relevant. They also showed that increasing the level of crosslinking (both GLA or formaldehyde) decreased the particle size of chitosan microspheres. In addition, as explained in the literature, if the particle size is <10 µm, then particles could be deposited in the upper respiratory tract of nose, whereas if particle size is <0.5 µm then it would be exhaled[31]. Regarding these considerations, OND-loaded chitosan microspheres seems to have suitable particle size for nasal applications (Table 1).

Zeta potential of the OND-loaded chitosan microspheres was measured in 10 mM NaCl solution at 25°C. The highest zeta potential (+16.37 mV) was measured for noncrosslinked microspheres, consisting of chitosan and OND. Zeta potential of crosslinked chitosan microspheres ranged between +11.33 and +14.10 mV (Table 1). The positive zeta potential of the chitosan microspheres decreased slightly with an increase in the amount of the crosslinking agent (Table 1). Similar observation was reported in the literature[28,29]. It should also be noted that drug loading also leads to decrease in the zeta potential of chitosan microspheres. We did not measure zeta potential of drug-free chitosan microspheres in this study. However, this effect has already been reported by the other researchers[25,28,29].

These results demonstrated that all OND-loaded microspheres had positive charge, indicating the presence of chitosan on the surface of microspheres, regardless of crosslinking agent concentration. This observation is important because positively charged microspheres will interact with negatively charged mucus, and consequently, bioadhesion of microspheres would increase contact period of drug on the surface of nasal mucosa[12,29].

Actual drug content and encapsulation efficiency of OND-loaded chitosan microspheres were given in Table 1. All microspheres had high actual drug content and encapsulation efficiency, ranged between 33.94–42.84% and 75.27–95.02%, respectively. Increase of crosslinking agent (GLA) concentration resulted in decrease of encapsulation efficiency; particularly, encapsulation efficiency of OND-loaded microspheres containing highest concentration of GLA (F4) was significantly decreased (Table 1). This could be attributed to the interaction of GLA with OND, forming a complex that could be spray dried separately from the microspheres[27,30].

In vitro drug release

The in vitro release profiles of OND-loaded chitosan microspheres as a function of time are depicted in Figure 2. As can be seen, all crosslinked OND-loaded chitosan microspheres showed an obviously burst effect. The highest burst effect was observed by the microspheres (F4) containing the highest concentration of GLA (0.9%) with an accumulate drug release of about 79% within 30 minutes. The burst drug release effect of crosslinking agent has also been observed by other researchers[27,30]. Initial burst release of drug can also be because of the small particle size. Because the decreased diffusion path length and the increased surface area in contact with release medium led to high drug release from microspheres. A high drug release from noncrosslinked microspheres was expected. However, the noncrosslinked microspheres (F1) had low burst effect. About 30% of the drug was released within 30 minutes from noncrosslinked microspheres and all the drug entrapped in the microspheres was released in 24

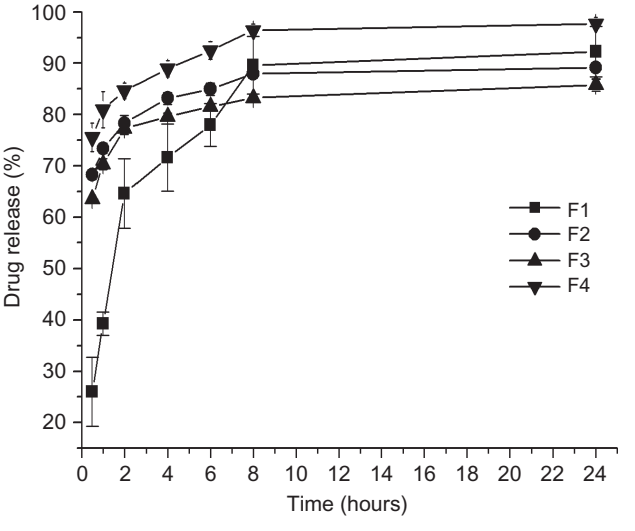

Figure 2. In vitro release profiles of OND from chitosan microspheres. Each point represents mean ± SD ($n = 3$).

hours. This could be explained by the fact that non-crosslinked microspheres could not be suspended in the release medium because of aggregate formation[28].

In vivo studies

The mean plasma level–time curves obtained after administration of OND intravenously and nasally (both aqueous solution of OND and suspension of OND-loaded microspheres) to rats are presented in Figure 3. Pharmacokinetic parameters of OND calculated from the data obtained with i.v. and nasal applications are shown in Table 2.

Considerably high OND concentration in the plasma was reached in 10 minutes (t_{max}) after nasal application of OND aqueous solution (Figure 3). This result indicated that OND was rapidly absorbed through nasal tract,

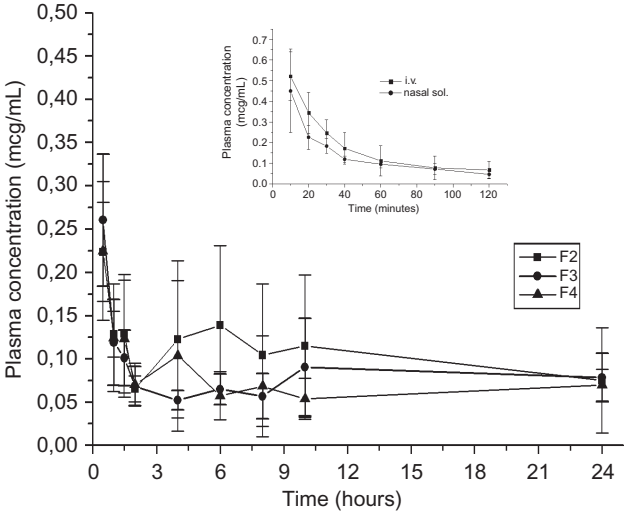

Figure 3. Plasma levels of OND in rats after application of nasal OND-loaded microspheres (insert graph: plasma levels of OND in rats after i.v. and nasal applications of OND solution). The dose of OND was 2 mg/kg for both i.v. and nasal route. Each point represents mean ± SD (n = 4–5).

which would be advantageous for the rapid onset of the therapeutic effect of the drug.

The plasma concentrations of OND were found as 0.64 ± 0.12 and 0.45 ± 0.20 μg/mL, following administration of OND solution intravenously and nasally, respectively, at 10 minutes. The mean total AUC ($AUC_{0h-\infty}$) values calculated from data obtained from application of i.v. and nasal aqueous solution of OND were 0.49 ± 0.20 and 0.35 ± 0.09 μg.h/mL, respectively, showing no significant difference statistically ($P > 0.05$). These results supported that nasal administration seems a feasible route for the delivery of OND as reported by Hussain et al.[7]

As summarized in Table 2, following nasal administration, there was no significant difference between all OND-loaded microsphere formulation (F2, F3, and F4) with respect to both C_{max} and $AUC_{0h-\infty}$ values. In addition, although OND could not be detected in plasma following nasal application of aqueous solution after 2 hours, OND plasma level remained relatively constant beyond 24 hours with nasal administration of OND-loaded microsphere formulations (Figure 3). This could be explained by the encapsulation of OND in mucoadhesive chitosan microspheres. When the drug is administered with microspheres based on chitosan through nasal route, microspheres would adhere on the nasal mucosa surface because of the bioadhesive character of chitosan. It has already been demonstrated that bioadhesive chitosan microspheres have a significant effect on mucosal uptake of drugs[19].

In our previous study, following nasal application polyester microspheres, a sustained OND plasma profile was achieved up to 4 days in rats[9]. In this study, in vivo data indicated that higher plasma OND level was obtained with chitosan microspheres than those of polyester microspheres[9]. This might be explained by the fact that the extended retention time of microspheres in nasal cavity is because of bioadhesive properties of chitosan, resulting in high drug concentration in close contact with the absorption site[32]. It is also reported that chitosan has absorption-enhancing effect, which is

Table 2. Pharmacokinetic parameters obtained following intravenous and nasal administration of OND (2 mg/kg) to rats.

Pharmacokinetic parameters	Formulations of OND applied to rats				
	OND solution (intravenous)	OND solution (nasal)	F2 suspension (nasal)	F3 suspension (nasal)	F4 suspension (nasal)
t_{max} (min)	—	10	30	30	30
C_{max} (μg/mL)	—	0.45 ± 0.20	0.24 ± 0.05	0.27 ± 0.09	0.25 ± 0.06
$t_{1/2el}$ (hours)	0.96 ± 0.28	1.24 ± 0.79	24.14 ± 4.23	24.55 ± 9.50	25.43 ± 11.50
k_{el} (h^{-1})	0.78 ± 0.24	0.73 ± 0,37	0.03 ± 0.01	0.03 ± 0.02	0.05 ± 0.03
$AUC_{(0-\infty)}$ (μg.h/mL)	0.49 ± 0.20	0.35 ± 0.09	4.97 ± 3.15	4.44 ± 0.65	4.03 ± 2.24

t_{max}, the time to reach maximum concentration; C_{max}, the maximum plasma concentration; $t_{1/2el}$, elimination half-life; k_{el}, elimination rate constant; $AUC_{(0-\infty)}$, the mean total area under the curve.
Data are expressed as mean ± SD (n = 4–5).

characterized by opening tight junctions for paracellular transport as reported previously[13,14,33]. Therefore, the bioadhesion of OND-loaded chitosan microspheres and increased paracellular transport might enhance the absorption of OND following nasal application.

Conclusion

This work demonstrated that OND-loaded chitosan microspheres could be easily prepared by spray-drying method. The burst release of OND from chitosan microspheres would be advantageous for the rapid onset of the therapeutic effect of the drug. In vivo studies also supported that the plasma level of OND reached to the maximum level in 30 minutes after nasal administration of microspheres, and a sustained drug plasma profile was observed up to 24 hours. As a result of this study, OND-loaded chitosan microspheres could be considered as promising delivery system as an alternative to i.v. and oral application of OND.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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