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Research Article

Fast-Dissolving Sublingual Nanofibers of Ondansetron Hydrochloride: Formulation, Physicochemical Characterization, and Clinical Evaluation on Post-cataract Surgery Patients

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Abstract

Background: Ondansetron hydrochloride (OND) is an antiemetic agent belongs to the 5-HT3 receptor antagonist class administrated widely in relieving nausea and vomiting which is the most common complication occurred after surgery. This study aimed to design and evaluate the physicochemical along with clinical effects of fast-dissolving nanofiber (FDN) of OND administrated sublingually to enhance the bioavailability, effectiveness, and patient compliance compared to orally disintegrating tablets (ODT).

Methods: Nanofibers were prepared by the electrospinning method, using polyvinyl alcohol and alpha-cyclodextrin as polymers and sodium saccharin as the sweetener. Physicochemical and mechanical characteristics of nanofibers were examined then the clinical evaluation was performed. Eighty patients volunteering for cataract surgery were randomly divided into two groups, one received FDN, and the other treated with ODT of OND after recovery and in case of relieving nausea. The severity of nausea was assessed using a visual analogue scale in the 6 and 24 h intervals after drug administration. The SPSS 25 statistical software and statistical tests were used to analyze the obtained data.

Results: Nanofibers possessed a mean diameter of 159 ± 30 nm beside suitable physicochemical and mechanical characteristics. Statistical evaluations showed that both FDN and ODT formulations had an equal anti-emetic effect ($P>0.05$) on reducing the severity of nausea but the FDN formulation caused significantly higher levels of patients' satisfaction ($P<0.05$) compared to the ODT.

Conclusion: Although both formulations had an almost equal anti-emetic effect, due to the benefits of this novel formulation including rapid disintegration, the ODT can be replaced by FDN.

Introduction

Nausea and vomiting (NV) are common complications experienced by 20-40% of adult patients after general anesthesia if preoperative anti-nausea prophylaxis has not been used.[1] These are usually stressful conditions for both patient and the surgeon causing sleep disturbances and a feeling of discomfort in the patient.[2] Among the anti-nausea medications, recently, the 5-hydroxytryptamine subtype 3 (5-HT3) receptor antagonist class has received much attention due to suitable efficacy and lower side effects.[3] Ondansetron hydrochloride (OND), is a 5-HT3 receptor antagonist, used to prevent and treat NV especially which caused by chemotherapy and anesthesia.[4] The anti-emetic effects of OND, caused by the antagonistic activity on serotonin receptors, at the end of the vague nerve and its central receptors at the vomiting center, led to prevented NV by inhibiting the vomiting reflex. OND is an almost water soluble drug (water solubility= 29.5±1.0 mg/ml)[5] which is belonged to Biopharmaceutics Classification System (BCS) class I due to the high solubility and permeability. The administration of conventional oral OND dosage forms related to a few limitations including low bioavailability which occurred due to extensive hepatic metabolism lowering its bioavailability to 60% of the

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infusion form and the possibility of causing anaphylactic shock after intravenous injection.[6]

From the past to present day, more than 50% of pharmaceutical products are given orally as solid dosage forms because of a variety of reasons including ease of use, the possibility of self-administration, noninvasiveness, accurate dosage, and especially patient acceptance.[7,8] One of the major challenges of solid dosage forms is the problem in swallow occurred not only in the elderly and children but also in young people due to dysphagia.[8,9] To overcome this challenge, formulations that can dissolve or disintegrate rapidly in the oral cavity have been developed. Sublingual administration defines as placing the drug in the sublingual, to absorb into the bloodstream directly through the surface of the tongue or the floor of the mouth, 3 to 10 times greater than the oral route.[10,11] The rapid onset of action along with eliminating the effect of hepatic metabolism led to a reduction of required administration frequency to a single dose.[12]

The fast-dissolving formulation is one of the high-potential delivery systems developed as a result of advances in the pharmaceutical industry which can be used for oral administration of different medications. This formulation has increased acceptance in elderly patients, children, and young people with dysphagia.[8] Zydis® was the very first fast-dissolving technology introduced in 1986 and several technologies are still improving.[8,13] Even the fast-dissolving drug delivery systems have limitations including suffocation risk, high-price production and packaging process, and difficulty in storing and using due to fragility.[14] Due to these limitations, films were developed using a water-soluble polymer that allows the drug to dissolve very quickly creating a rapid onset of action.[15] The film formulation is a stable preparation that creates comparable efficacy to liquid formulations and can be considered as a good alternative to other forms of medication for patients experiencing difficulty in swallowing or having NV.[16,17]

The electrospun nanofibers are polymeric high porosity structures which can release the drug in a modified manner and are used as novel fast-dissolving delivery systems. The polymeric nanofibers and films are promising systems for delivery of drug with different routes of administration, especially as ocular inserts and fast-dissolving sublingual dosage form.[18-22] The drug in the nanofibrous structure poses the amorphous or nanocrystalline state, which increases the solubility and dissolution rate.[23] The high surface-to-volume ratio of nanofibers, the flexibility in surface properties, the porous structure, and the good mechanical strength make nanofibers applicable to a variety of applications in biomedicine including fast-dissolving drug delivery systems.[19] This study was designed to prepare fast dissolving nanofiber (FDN) of OND using the electrospinning technique. The Physicochemical and mechanical characteristics of nanofiber were examined then the clinical evaluation was performed. Finally, the clinical data were analyzed to compare the FDN with orally disintegrating tablets (ODT).

Materials and Methods

Materials

Ondansetron hydrochloride was obtained from Sigma-Aldrich (Milan, Italy). Alpha-cyclodextrin (α-CD), Polyvinyl alcohol (PVA) (99% hydrolyzed, average Mw = 72,000 Da), and Sodium saccharin were purchased from Merck (Darmstadt, Germany). All the chemicals used were of pharmaceutical grade.

Preparation of OND-loaded FDN

Initially, 20% w/v solution of PVA and 10% w/v solution of α-CD was prepared by addition of polymers to the deionized distilled water under magnetic stirring overnight at room temperature. The nanofiber which was developed with a sandwich structure consisted of three different layers prepared by consecutive electrospinning of three polymeric solutions. The outer layers (first and last electrospun layers) were sweetened polymeric layers enhancing the tolerability of formulation by covering the bitter flavor of the drug. To prepare the proper solutions for outer layers, 100 mg of sodium saccharin was dissolved in 10 mL of the α-CD solution, then 10 mL of the PVA solution was added to the mixture under stirring for 1 h to obtain a clear solution. The inner layer electrospinning solution was prepared by dissolving OND at a 10% w/w (of the total polymers) concentration in a mixture of PVA (10 mL) and α-CD (10 mL) solutions. The electrospinning process was carried out by a 1 mL/h injection rate (Fanavaran Nano-Meghyas syringe pump, SP1000, Iran) under 17 kV voltage applied by a high-voltage DC supplier (Fanavaran Nano-Meghyas, HV35P OV, Iran). A rotating collector covered by aluminum foil was collecting the nanofibers. The injector to collector distance was adjusted at 15 cm and the whole procedure took place at 25 °C. The deposited nanofiber was separated from the foil after full evaporation of solvents then was cut into pieces (1×1 cm^2), each containing 4 mg of OND. PVA was used due to the potential to improve flexibility and simplify the handling process in preparation of nanofibers. Cyclodextrins are polymers with solubility enhancing potential. Based on the previous results addition of cyclodextrins to polyvinyl alcohol led to preparation of more uniform nanofibers which is beneficial in preparing suitable dosage forms for clinical applications and obtaining reproducible data. Moreover, cyclodextrins are suitable for masking the bitter flavor of oral administrated drugs.[24-26]

Physicochemical Characterization of OND-Loaded FDN

Thickness and Weight Variations

To ensure the reproducibility of obtained results the separated pieces of nanofiber should be uniform in thickness and weight. The thickness and weight of nanofiber were measured for 5 different pieces with similar dimensions. A mean ± SD was reported for each parameter.

Surface pH

Nanofiber requires to possess a surface pH in the

appropriate range which is not harmful to the oral mucosa. Three samples were placed in a Petri dish, soaked with 1 mL of distilled water and the pH was measured by a pH meter (827 pH lab, Metrohm, Swiss) then an average was taken.

Folding endurance

The folding endurance is defined as the resistance of flexible formulations like nanofibers and films against tearing and breaking after consecutive folding. Nanofiber was folded at the same point repeatedly until tearing and the mean number of tolerated folding was reported as folding endurance.

Disintegration time

The wet sponge method was used to assess the time required for the disintegration of the nanofiber. A sponge was initially soaked with 250 mL of phosphate buffer, then the samples were placed on the surface of it. The average time which was taken for the complete disappearance of samples was reported as the disintegration time.[27]

Drug content uniformity

A High-Performance Liquid Chromatography (HPLC) device was used to measure the drug content of samples. Pieces weighing 5 mg were dissolved in distilled water under stirring for 12 h at room temperature. The mixture of 80% v/v methanol and 20% v/v trimethylamine buffer with pH adjusted at 3 by the addition of phosphoric acid, was chosen as the mobile phase. A concentrated stock (1mg/mL) was injected into the device for the determination of drug-related chromatographic peak. The retention time of OND was detected to be 2.28 min. A calibration curve was constructed for the measured area under the curve versus concentration measured for standard solutions (S_1=100, S_2=50, S_3=25, …, S_7=1.5625). The regression equation of y=13430x+51994 with R^2 equals to 0.9998 was obtained and used for estimation of drug content.

Scanning electron microscopy (SEM)

To create magnification on the surface morphology of nanofibers a scanning electron Microscope (KYKYEM-6200, China) was used. The accelerating voltage was set to 20 kV, and the samples were examined under vacuum conditions after gold-coating. The mean diameter of fibers was measured using ImageJ software.

Fourier-transform infrared spectroscopy (FTIR)

To detect any interaction between drug and polymers, the FTIR spectrum of nanofiber was recorded and analyzed from 4000 to 400 cm^{-1} using a Prestige-21 (Shimadzu, Japan) spectrophotometer. The KBr pressed tablets were developed to detect the spectra of drug, polymers, and nanofiber.

In Vitro Dissolution Study

The *in vitro* release of drug from the ODT and FDN formulations were investigated using USP type II paddle apparatus filled with 500 ml of HCL 0.1 N as stimulant of gastrointestinal fluid. The formulations were evaluated for 10 min at 50 rpm and 37 °C. The test was performed in triplicate. The samples were withdrawn in 30 seconds interval and the released drugs were evaluated by HPLC.

Clinical evaluation

Sample size

The sample size was calculated based on the results obtained in a previous study investigating the effect of OND disintegrating tablets on postoperative NV which claimed that 50% of patients experience a 30% reduction in the severity of NV after taking the OND disintegrating tablets.[28] It was observed that 40 subjects were required (significance level=0.05, test power=90%) for each of the intervention and control groups.

Study population, criteria, and randomization

Permission was obtained from the Kermanshah University of Medical Sciences Ethical Committee with the ethical identification of IR.KUMS.REC.1398.109. The study was approved in the Iranian Registry of Clinical Trials on August 17, 2019, with the registration number of IRCT20180120038450N2. Eighty patients over the age of 18 years who were candidates for cataract surgery and general anesthesia, classified in American Society of Anesthesiologists (ASA) scale as ASA-1 and ASA-2, were randomly assigned to one of the intervention or control groups of the study (Random allocation took place based on the lottery). Patients were explained about the type of medication and criteria of the study and were asked to sign a written consent for participation in the study. All information was kept confidential in sealed envelopes and both patients and investigators were blinded to the allocated groups. Based on the exclusion criteria patients with the following conditions were ruled out of the study: the history of motion sickness and NV during 24 h before the surgery, history of chronic diseases, taking anti-nausea medications and corticosteroids 24 h before the operation, pregnancy and breast-feeding.

Study protocol

The baseline characteristics of patients were recorded in questionnaires. Initially, all subjects were asked about the severity of their conditions in a 0-10 Visual Analogue Scale (VAS) by the investigators; the patients in the control group were received one dose ODT (Oditron 4 mg, Pars Daru, Tehran, Iran) while the patients belonged to the intervention group were treated with one dose of FDN (1×1 cm^2 pieces containing 4 mg OND). The participants of FDN and ODT groups were respectively instructed to use the preparations sublingually and on top of the tongue, until it vanishes. The severity of NV was assessed through the first 6 to 24 h after treatment. The general satisfaction with the administrated dosage form like the taste tolerability and the experience of any side effect after

taking the drug was also examined. The satisfaction level of the patient by the received treatment was rated in a 4-level scoring system (1=very dissatisfied, 2=dissatisfied, 3=satisfied, 4=very satisfied). In the case of vomiting, 0.1 mg/Kg intramuscular injection of Metoclopramide was administrated.

Statistical analysis

The SPSS software version 25 was used to analyze the extracted data. Statistical analysis was performed by the Chi-Square, Fisher, Mann-Whitney, Kolmogorov-Smirnov, and Friedman detailed tests, along with variance analysis of duplicate sizes, and independent T-test.

Results and Discussion

Physicochemical characterization of OND-loaded FDN

Thickness and weight variations

The different separated pieces of nanofiber were observed to have an almost uniform thickness and weight which confirm the uniformity of formulation (Table 1). This is essential for a nanofiber formulation to be uniform to ensure the accuracy and reproducibility of the results. The mean thickness of nanofiber was measured to be 302.5 ± 5.3 µm which is suitable for administration as a sublingual fast-dissolving formulation according to previous studies.[29]

Surface pH

The pH of the formulation was very close to neutral (6.7 ± 0.08) and therefore the risk of damage to the oral mucosa was greatly reduced (Table 1). In 2015, Alipour *et al.*[29] developed and evaluate the fast-dissolving films of OND. It was observed that the surface pH of the optimized formulation was about 6.65 ± 0.06 which is similar to the one measured for the developed formulation in this study.

Folding endurance

Generally, the flexibility of nanofibers is evaluated by measuring the folding endurance. The importance of appropriate flexibility for a fast-dissolving sublingual formulation is to be soft enough, not to harm the oral mucosa, and strong enough not to be separated into pieces before disintegration. The folding endurance was measured to be more than 300 times showing the suitable strength and flexibility of formulation (Table 1). In 2010, Koland *et al.*[30] detected a folding endurance over 300 times for a similar formulation prepared by PVA, polyvinyl pyrrolidone, and Carbopol 934P.

Disintegration time

Based on the former findings of previous studies, nanofibers prepared by water-soluble polymers, mostly disintegrate rapidly in less than 30 seconds after exposure to the aqueous medium.[31] The same result was obtained in this study (Table 1).

Drug content uniformity

The drug content of different samples separated from nanofibers was estimated using the regression equation obtained by HPLC analysis. The nanofiber was found to have a uniform drug content. Figure 1 is representing the calibration curve and the chromatographic peak of OND.

Scanning electron microscopy (SEM)

As it is obvious in Figure 2, the diameter, shape, and overall appearance of the nanofibers were uniform without any defects and beads showing the fact that drug and polymers were appropriately distributed in the formulation. The mean fiber diameter was equal to 159 ± 30 nm.

Fourier-transform infrared spectroscopy (FTIR)

The FTIR spectrum of nanofiber is illustrated in Figure 3. The peak at 3246 cm^{-1} is assigned to the OH groups of both PVA and α-CD polymers. The peak that appears at 2916 cm^{-1} is related to the stretching vibration of asymmetric CH_2 in PVA. At 1629 cm^{-1}, there is a peak attributed to the carbonyl groups of PVA and OND. Peaks at 1247 and 1029 cm^{-1} are assigned to vibrational stretching of C-N in OND and acetyl groups of PVA, respectively. The vibrational peak related to the C=O groups of α-CD appears as a merged peak at 1029 cm^{-1}. The peak at 756 cm^{-1} is assigned to vibrational bending of C-H in the phenyl group of OND. As it was described, the characteristic peaks of the drug along with polymers are detectable in the spectrum of nanofiber indicating that there is no significant interaction took place between drug and polymers during the preparation process.

In vitro dissolution study

The result of *in vitro* release study is represented in Figure 4. The FDN released 50.70 ± 2.76% of OND in the first 30 sec while ODT release 10.38 ± 1.08% of the drugs in the same interval. The FDN released almost all of its content in the first 120 sec, faster than ODT with releasing the OND in 210 sec. The more rapid release of drug from the FDN formulation can be because of more hydrophilicity achieved by formulating the drug in the nanofibrous form and the porous structure formed more pocket for penetration of water into the formulation.

Clinical findings

Baseline characteristics

In this study, 80 patients participated divided into intervention (n=39) and control (n=41) groups. None of the patients had a history of NV before anesthesia

Table 1. The measured physicochemical characterization of the developed nanofiber formulation.

Formulation	Weight (mg)	Thickness (µm)	pH	Folding endurance (times)	Disintegration time (s)	Diameter (nm)
FDN	45.2 ± 0.8	302.5 ± 5.3	6.70 ± 0.08	>300	<30	159 ± 30

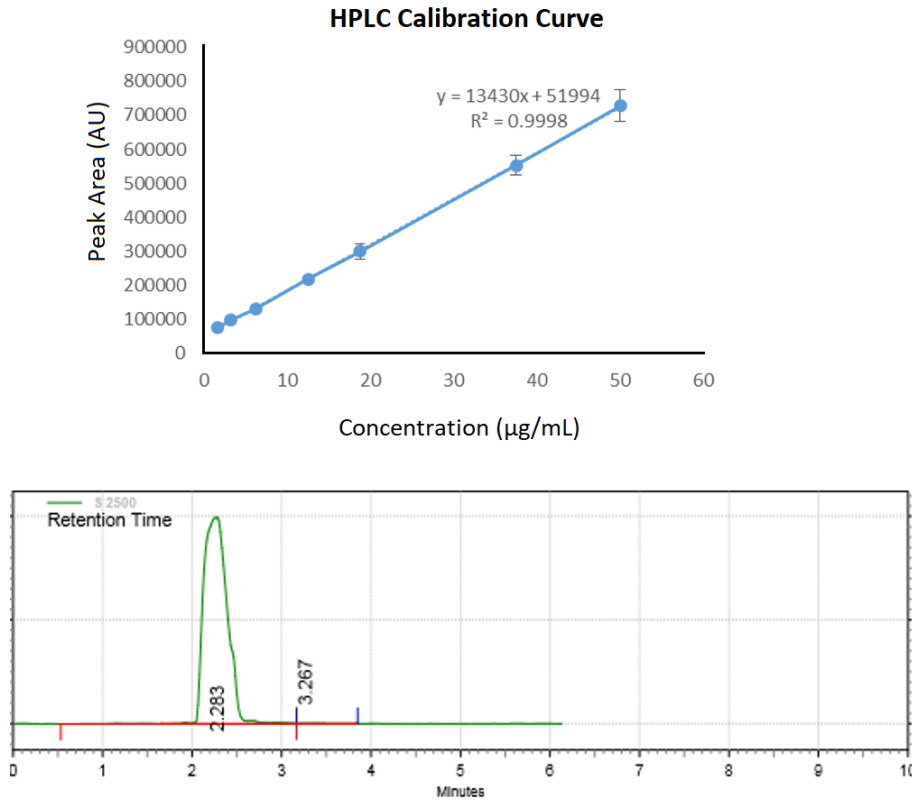

Figure 1. The calibration curve and the chromatographic peak of OND in HPLC analysis.

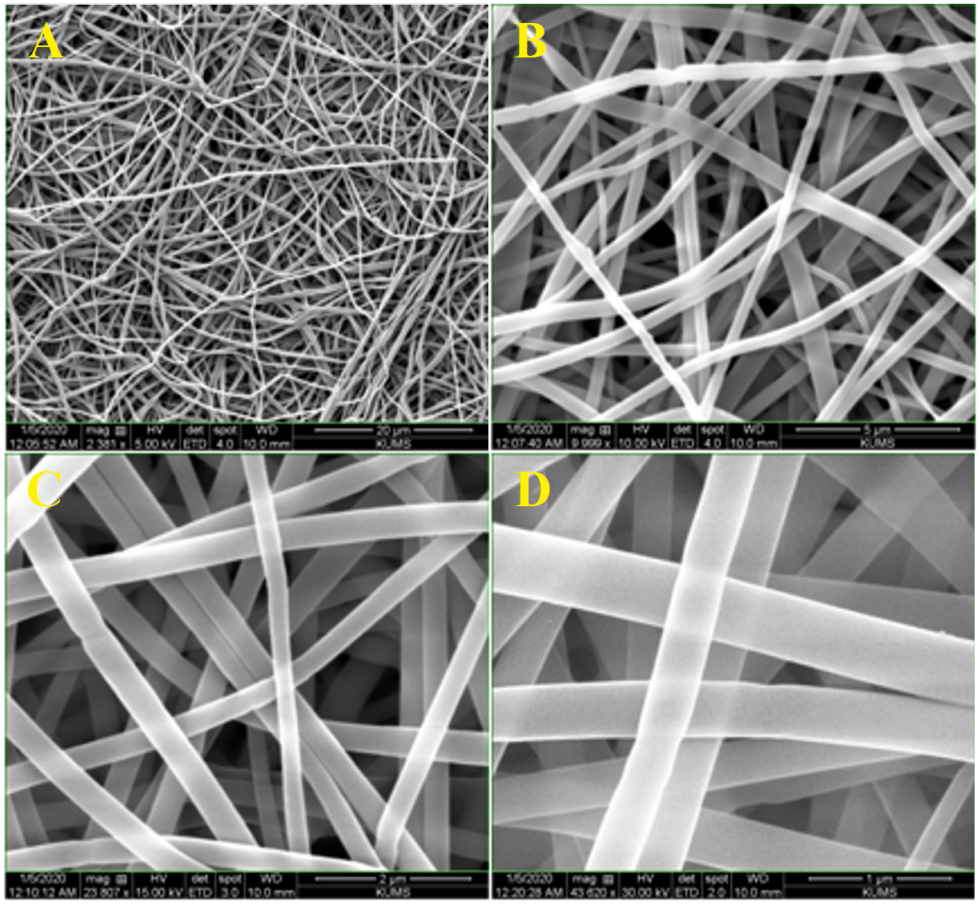

Figure 2. The SEM images of nanofiber with different magnifications. The indicated scales in each image represented A: 20 µm, B: 5 µm, C: 2 µm, D: 1 µm.

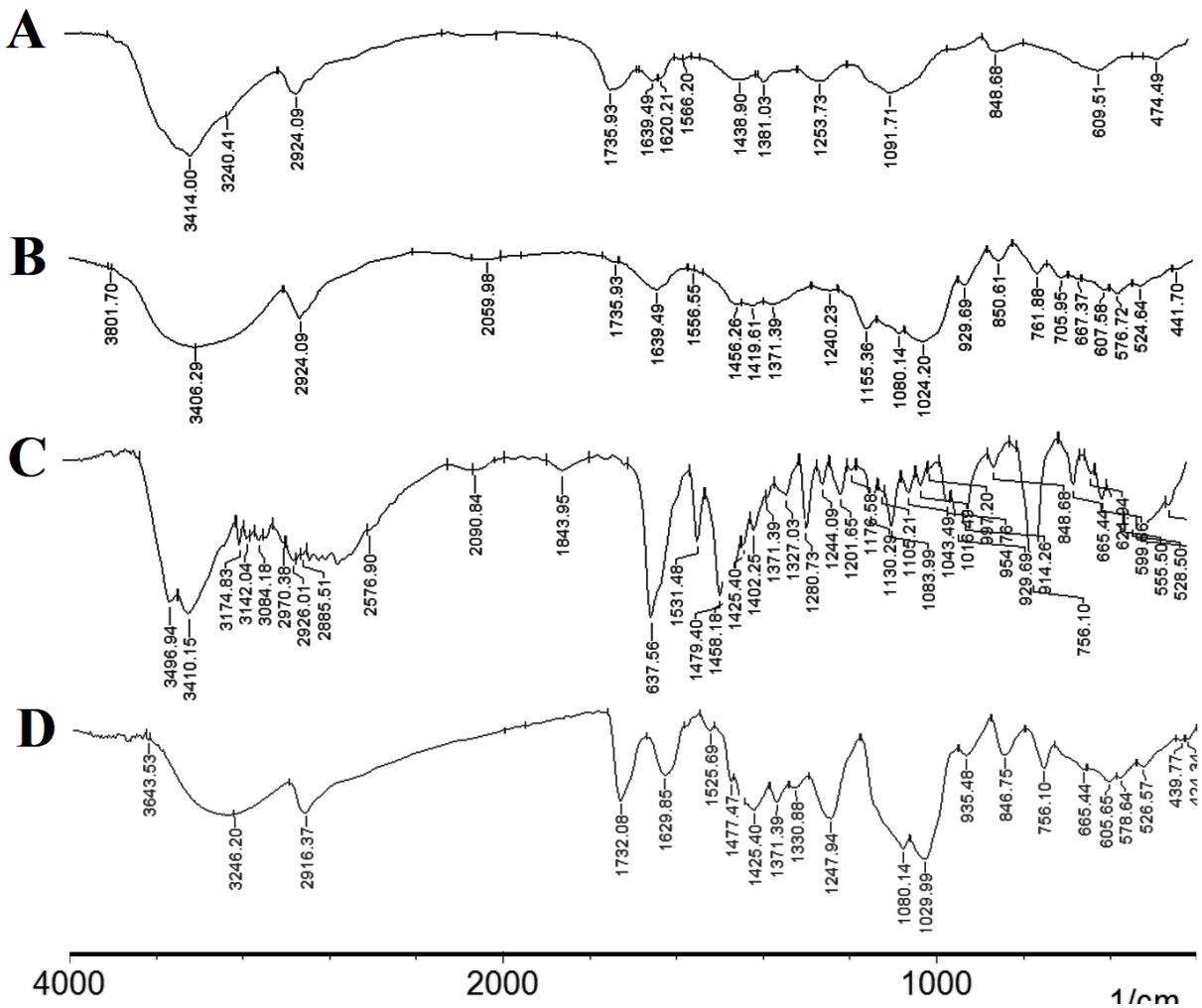

Figure 3. The FTIR spectra of A: PVA, B: α-CD, C: Ondansetron, and D: nanofiber.

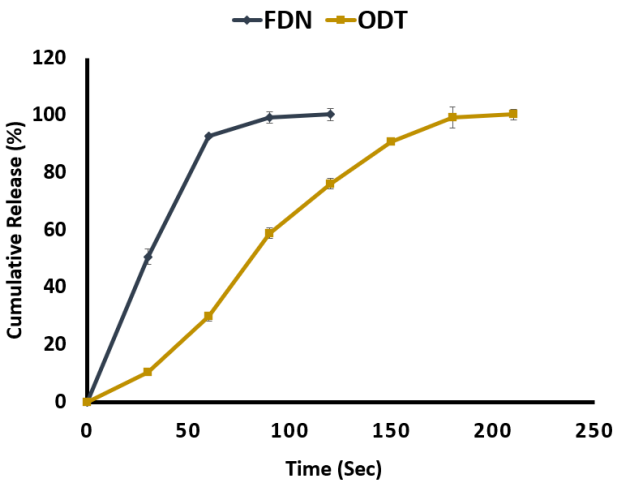

Figure 4. The *in vitro* release of ondansetron from the FDN and ODT formulation in HCL 0.1 N at 50 rpm and 36 °C.

along with other factors of exclusion criteria. To evaluate the similarity of the descriptive demographic baseline characteristics of the subjects participating in the study, including the gender, smoking history, and the duration of surgery and anesthesia, the Chi-Square test was used. The results of this test indicated that these variables are similar in the intervention and control group (P>0.05). Fisher's exact test confirmed the results of the Chi-Square test about the similar distribution of different variables in the control and intervention groups (P<0.05).

The distribution of numerical characteristics including age, weight, and body mass index (BMI) were evaluated using the Kolmogorov–Smirnov test. It was observed that the distribution of these variables was normal (P>0.05) for age and weight in the control group while it was non-normal (P<0.05) for the age and weight in the intervention group and BMI in both groups. Using the Mann-Whitney test, it was observed that these numerical variables were not significantly different in the control and intervention groups (P>0.05). Table 2 is classifying the detailed data.

Comparison of FDN and ODT

Analysis of the findings by the Friedman test showed that the administration of ODN-loaded FDN in the intervention group caused significant changes (P=0.001) in the mean score of NV severity during the time progress at a 95% confidence level. Similar results in the control group suggested that there was also a statistically significant

Table 2. Baseline characteristic of subjects participated in this study.

Variable	Control group (n=41)	Intervention group (n=39)	Test statistic (Z)	P-value
Gender				
Male	20 (48.8%)	25 (64.1%)	1.900	0.167
Female	21 (51.2%)	14 (35.9%)		
History of smoking				
No smoking	39 (95.1%)	38 (97.4%)	0.297	0.519
smoking	2 (4.9%)	1 (2.6%)		
Duration of surgery and anesthesia				
<30 min	38 (92.7%)	38 (97.4%)	0.951	0.327
30-60 min	3 (7.3%)	1 (2.6%)		
Age (years)				
Mean ± SD	62.7 ± 9.6	63.7 ± 12.9	-1.86	0.062
Min-Max	27-87			
Weight (Kg)				
Mean ± SD	70.2 ± 9.8	69.4 ± 11.6	-0.642	0.521
Min-Max	51-113			
BMI (Kg/m²)				
Mean ± SD	23.1 ± 2.4	23.3 ± 1.6	-0.023	0.982
Min-Max	17-26			

Table 3. The NV severity scored by VAS, before and during the administration of FDN and ODT in the intervention and control groups along with the statistical data obtained from comparison of these values between intervention and control groups by the Mann-Whitney test.

Time interval	The severity of NV in VAS		Statistical parameter	
	Control group (Average ± SD)	Intervention group (Average ± SD)	Mann-Whitney	P-value
Before starting the intervention	3.34 ± 1.08	3.28 ± 1.23	-0.428	0.669
After 0-30 min	2.14 ± 1.03	1.94 ± 1.02	-0.918	0.359
After 30-60 min	1.00 ± 0.89	0.84 ± 0 .93	-0.914	0.360
After 1-2 h	0.20 ± 0.48	0.23 ± 0.53	-0.367	0.714
After 2-3 h	0.02 ± 0.15	0.02 ± 0.16	-0.036	0.972

difference in the mean score of NV severity during the study (P=0.001).

The Mann-Whitney test was carried out to compare the mean score of NV severity in intervention and control groups during different time intervals. The detailed data are tabulated in Table 3. There was no significant difference between the mean score of nausea at the baseline and before the OND administration in the intervention and control group (P = 0.669). This similarity in the NV severity was preserved during the whole study and it was observed that there was no significant difference in the NV severity at 30 min, 60 min, 2 h, and 3 h after administration of ODN-loaded FDN and ODT between the two groups (P>0.05). In none of the groups, patients had nausea for more than 3 to 24 hours. The results of the repeated measure test using the Greenhouse–Geisser correction showed that the severity of NV decreased significantly over time in both groups (P < 0.05) while there was no significant difference between the two groups (P > 0.05). In other words, both drugs had the same function in controlling NV. There were not any complaints of major and clinically significant adverse reactions reported by the participants of the studies after administration of both dosage forms.

Based on the results of Fisher's exact test, there was a significant difference between the two groups in terms of drug satisfaction (P<0.05). According to the findings, a higher level of satisfaction was found in the intervention group treated with OND-loaded FDN (Table 4). The reasons for patients' satisfaction were due to the ease of use, the good taste, and the rapid dissolution of the drug in the saliva without the risk of suffocation or intolerance. None of the dosage forms in the intervention and control groups caused dissatisfaction of the participants. Figure 5 is representing the summary of this study.

Due to a variety of benefits, fast-dissolving systems have been developed and examined in many previous studies. In 2016, Aboutaleb *et al.*[32] developed a fast-disintegrating tablet of domperidone. to increase the bioavailability of this poor water-soluble antiemetic agent. The developed tablets were evaluated in rabbits and higher bioavailability was observed for them in comparison with the conventional marketed formulation.[32] In another similar study, the bioavailability of OND gel formulation was examined in parallel with 9 rabbits and 6 human volunteers. The potential effect of OND gel on the prevention of NV caused by exposure to cisplatin was evaluated. OND gel significantly reduced the cisplatin-induced NV severity suggesting that OND Trans-Dermal Gel can be

Table 4. The comparison of frequency and distribution of subjects in the intervention and control groups based on the satisfaction levels.

Parameter	Control group (n=41)	Intervention group (n=39)	Test statistic (Z)	P-value
Very satisfied	1 (2.4%)	35 (89.7%)	61.55	0.001
Satisfied	40 (97.6%)	4 (10.3%)		
Dissatisfied	0	0	-	-
Very dissatisfied	0	0		

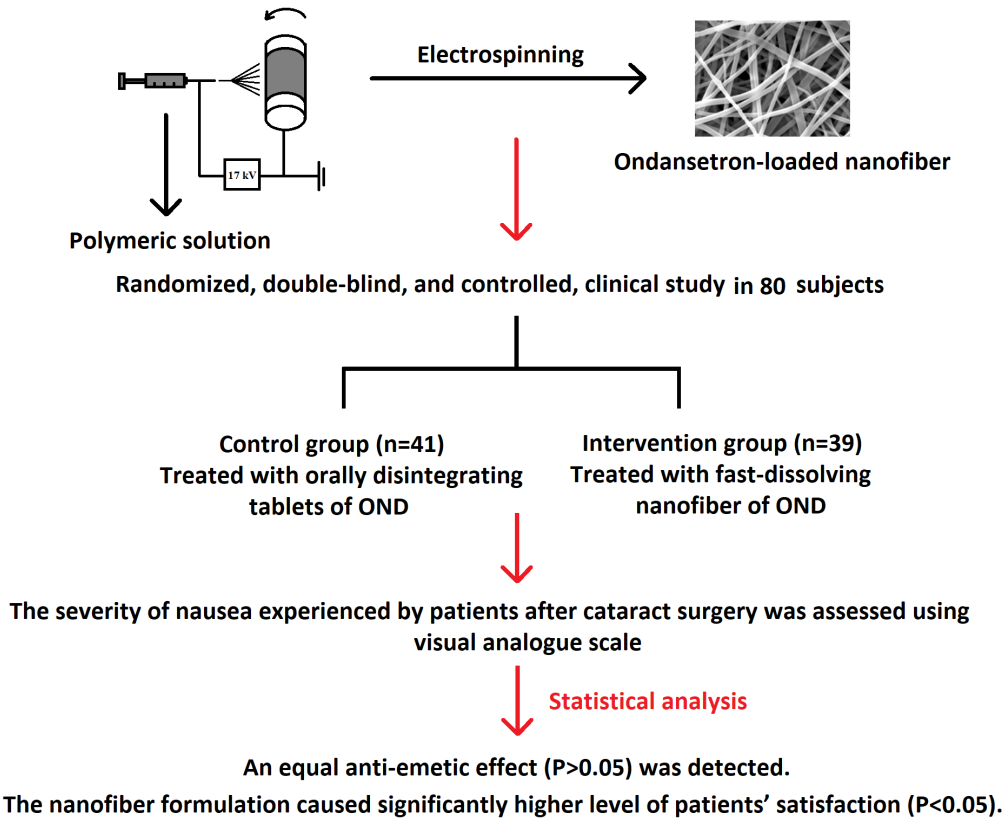

Figure 5. Graphical summary of the study.

a promising system for preventing NV triggered by anti-plastic drugs.[33] In a similar study, fast-disintegrating tablet of OND was prepared and compared with commercially available oral tablets. The results showed that there is no significant difference between the prepared formulation and conventional tablets in case of anti-emetic effects and they can be used interchangeably.[34] Grover *et al.*[28] performed a clinical study on the effect of a fast-dissolving tablet of OND in the prevention of NV experienced by patients after laparoscopic cholecystectomy. One hundred and ten patients were randomly divided into three groups. One group was treated with 4 mg of injectable OND, another with placebo tablets, and the last group with an 8 mg OND sublingual tablet. NV severity was evaluated and the data showed that there was no clear difference between the injectable and sublingual formulation of OND.[28] Similar results were observed in the present study. Another clinical study aiming to compare fast-dissolving film and the intravenous formulation of OND to prevent NV experienced after gynecological laparoscopy on 180 patients showed that the incidence of NV after surgery was approximately 46.5% in the group treated with injectable formulation, while it was 51.2% in the group given 4 mg film and 34.9% in the group received 8 mg film.[35]

Generally, it can be concluded that fast dissolving systems are promising systems for the delivery of drugs requiring rapid onset of action. Although these systems draw attention from years ago, according to the literature review, there were many studies evaluating and designing such systems for enhancing drug delivery, recently.[36-39] Despite the great advantages of these systems like lower disintegration time, higher patient compliance, and more effective delivery, to our knowledge, there are not any commercially manufactured products of fast-dissolving OND nanofibers. All of the commercially manufactured products include ODTs which usually are not sufficiently accepted by patients because of the longer disintegration time, more excipients, and bad taste or feeling caused to the patients. Besides, the bitter flavor of the ODT forms was almost improved in the FDN formulation. The importance of masking the bitter flavor in the oral disintegrating antiemetic forms is due to the possibility of exacerbation

of nausea and vomiting in the patients resulted from the bitter flavor of these forms which is practically in conflict with the aim of these forms.

FDN forms also can load the desired dose in a total weight of 40 mg while it is at least 2-times higher for the ODTs. Electrospinning, industrially used as a suitable technique to prepare nanofiber structures after optimization of items. This method has a high potential to optimize the dissolution rate, uniformity of the dosage forms, and reducing required excipient in formulations which are important factors in the preparation of oral forms. Further research with a higher sample size would be required to clearly clarify other aspects of this study in the future and overcome the limitations.

Conclusion

Fast-dissolving nanofibers containing Ondansetron hydrochloride were prepared by the electrospinning technique using polyvinyl alcohol and alpha-cyclodextrin polymers for sublingual drug delivery through the oral mucosa. The examination of physicochemical characteristics showed that the nanofibers were uniform, with a mean diameter of 159 ± 30 nm. The formulation also possessed sufficient flexibility and strength. The results of Infrared Spectroscopy indicated no drug-polymer interaction in nanofiber causing structural changes in the drug. Nanofibers disintegrate in less than 30 seconds in the aqueous medium, indicating that the formulation could disintegrate very rapidly when placed in the oral environment and that the drug release would occur very rapidly. In the clinical evaluation, nanofibers were compared with the orally disintegrating tablet, in terms of the anti-emetic effect on the nausea and vomiting severity after anesthesia. According to the results of statistical analysis, both groups reduced the severity of nausea and vomiting equally. According to the benefits of nanofibers such as improved water-solubility, enhanced potential for drug-loading, reduced number of required excipients, more acceptable flavor, not having the risk of suffocation, much faster disintegration, and ease of use for patients, this formulation led to more satisfaction in patients compared to orally disintegrating tablets and can be considered as a suitable replacement for this form to increase the patient compliance.

Ethical Issues

The whole procedures of present study were approved by the Institutional Animal Ethics Committee (approval number: IR.KUMS.REC.1398.109), Kermanshah University of Medical Sciences (Kermanshah, Iran). The study was approved in the Iranian Registry of Clinical Trials on August 17, 2019, with the registration number of IRCT20180120038450N2.

Author Contributions

Conceptualization: SM; Methodology: FD, SM and SK; Software: FN; Validation: SM. and FN; Formal analysis: SM, FN and SK; Investigation: SK and SM; Resources: SM; Data curation: SM, and SK; Writing–original Draft preparation: SK; Writing – Review and editing: SM and SK; Visualization: SM and FD; Supervision: SM; Project administration: SM; Funding acquisition: SM. All authors read and approved the manuscript.

Data Sharing

Applicants can obtain data by contacting the corresponding author.

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Conflict of Interest

The authors report no conflicts of interest.

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