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Development of sustained release in situ nasal gel of ondansetran HCl using mucoadhesive polymers

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Research Article

Development of sustained release in situ nasal gel of ondansetran HCl using mucoadhesive polymers

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Abstract

In situ gel dosage forms are solutions after administration undergoes gelation to form a gel. The objective of the current study is to develop, characterize and evaluate nasal *in situ* gel containing anti-emetic drug of OND-HCl® by a temperature induced method. In this method, Lutrol F-127®, is used as a thermos-reversible polymer, PVP K30®, HPMC K4M® and PEG 6000® as mucoadhesive polymers. The tests for gel formation, pH, viscosity, *in vitro* drug diffusion, drug content, gelation temperature, gelation time and mucoadhesive force were conducted for the developed formulations. The percentage drug content and pH of all the formulations were found to be in the range of 95% - 99% and 4.9-5.2, respectively. Considering the *in vitro* drug diffusion studies formulation, F7 was optimized. It is an effective formulation exhibiting a sustained drug diffusion of 93.98% for eight hours with viscosity 30 and 20 cps. From the results it is concluded that OND-HCl® nasal *in situ* gel produces a prolonged drug delivery for the treatment of chemotherapy induced nausea and vomiting.

Key words: *In Vitro* Drug Diffusion, FTIR, Nasal *In Situ* **Gel**, Ondansetron HCl

Introduction

OND-HCl® is a serotonin sub type-3 (5-hydroxytryptamine-3) receptor antagonist. It is an extensively exploited drug for the treatment of several therapeutic purposes like antiemetic, it is especially used in the prevention of post-operative nausea and vomiting (PONV), chemotherapy induced nausea and vomiting, (CINV) or radiation induced nausea and vomiting.[1] Bioavailability of drug is 50-60%, a half-life of 4-6 hours, and undergoes metabolism in the liver via CYP3A4, CYP1A2, CYP2D6. Intranasal delivery seems to be an alternative route of administration during such conditions. However, the drug resides in the nasal cavity for a short duration, which affects the absorption and bioavailability of the drug. Hence, while designing the nasal dosage forms, anatomic and physiologic characteristics of nasal mucosa and rapid mucocilliary clearance (MCC) that limits the time offered for the absorption of the drug from the applied dosage form has to be considered.[2,3] So, to lengthen/increase the residence time available at the nasal absorption site and thereby assist the drug uptake, a promising approach is to decrease MCC rapidly, by using/with the help of mucoadhesive formulations. Ordinary gels are inconvenient to administer and an accurate measurement of the drug dose is also not possible.[4] A nasal mucoadhesive *in situ* gel is found to be very attractive because of its fluid-like state prior to the nasal administration, and can thus be easily administered as a drop permitting accurate drug dosing. Thermosensitive smart polymers were used to achieve *in situ* gelation, which, upon sensing the nasal temperature, transforms into gel after instillation.[5] Thermo-reversible polymer used in the formulation of thermosensitive *in situ* nasal gel must have gelation temperature around nasal physiological temperature range (29°C to 34°C). Lutrol F127 (LF127®) has a tremendous thermosensitive gelling property, excellent water solubility, low toxicity, good drug diffusion characteristics and good chemical compatibility.

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Lutrol F127® is an ABA triblock copolymer comprising the hydrophobic polypropylene oxide and hydrophilic polyethylene oxide (PEO). LF127® exists as a viscous mobile liquid at a lower temperature but upon increasing the temperature a rigid semisolid gel network is formed, showing a temperature induced gelation.[6] Developing the OND-HCl® mucoadhesive thermo-reversible *in situ* nasal gel with enhanced nasal residence time and absorption through the nasal mucosal membrane, thereby enhancing the bioavailability of the drug, is the objective of the current study.

Materials and methods

Materials: OND-HCl® obtained from Swapnroop drugs and Pharmaceuticals, Mumbai, India. Lutrol F-127®, HPMC K4M®, PVP K30® obtained from HI Media Laboratories Pvt Ltd, Mumbai, India, and PEG 6000®, Benzalkonium chloride® were obtained from SD Fine Chem Laboratories Pvt Ltd, Maharastra, India.

Preparation and optimization of thermo-reversible LF127® gels:

The plain and drug-loaded LF127® gels were prepared by a cold method described by Schmolka. *et al.*[6] For drug-loaded LF127® gels, the drug was stirred with a sufficient quantity of 0.01N citric acid and kept overnight at 4°C in a refrigerator. LF127® was then added slowly with continuous stirring, and finally the volume was adjusted. The dispersions were then stored in a refrigerator until a clear solution was obtained. Optimization of plain and drug-loaded LF127® gel was done by varying the concentration of LF127® and evaluating them for the gelation temperature. Batches containing optimized concentration of LF127® are used for further investigation. Three different concentrations of mucoadhesive polymers were screened. HPMC K4M® (0.5% to 1.5%), PVP K30® (0.1% to 0.5%), and PEG 6000® (0.1% to 0.5%) were tried as a mucoadhesive polymer.[6] Plain LF127® was prepared following the same method omitting the drug.

Preparation of mucoadhesive thermo-reversible nasal gels:

OND-HCl®, mucoadhesive polymer, and Benzalkonium chloride® were dissolved in 4 mL of 0.01N citric acid by agitation at room temperature. The optimized concentration of LF127® in the final formulation is 18% w/v. After cooling the solution to 4°C, a specified amount of LF127® i.e., 1.8 g, is dissolved in 3 mL of 0.01N citric acid solution, and this was added completely and slowly with agitation to the drug and the polymer solution. Finally, the volume was adjusted by using cold distilled water.

Table 1: Effect of Concentration of LF127® (Poloxamer407) on gelation temperature.

Ingredients	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10
OND-HCl® (g)	-	-	-	-	-	0.1	0.1	0.1	0.1	0.1
Lutrol F-127®, (g)	1.6	1.7	1.8	1.9	2.0	1.6	1.7	1.8	1.9	2.0
Distilled water (mL) q.s. to	10	10	10	10	10	10	10	10	10	10
Gelation temperature observed (°C)	**45**	**37**	**26**	**24**	**20**	**50**	**42**	**35**	**30**	**26**

Table 2: Formulation of OND-HCl® nasal in situ **gel (F1) to (F9)**

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ondansetron HCl (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Lutrol F-127®, (g)	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
PVP K 30 (g)	0.01	0.03	0.05	-	-	-	-	-	-
HPMC K4M® (g)	-	-	-	0.01	0.03	0.05	-	-	-
PEG 6000® (g)	-	-	-	-	-	-	0.05	0.1	0.15
Propylene glycol (mL)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Benzalkonium chloride® (mL)	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Distilled water (mL) q.s to	10	10	10	10	10	10	10	10	10

The resulting dispersion was then kept at 4°C overnight until a clear transparent solution was formed.[7,8] (Table 1 followed by Table 2)

Compatibility studies (FT-IR spectroscopic studies):

Compatibility between the drug and polymer were studied by using FTIR spectrophotometer (JASCO 460+). Infrared spectra of all the ingredients used in the formulation are scanned individually. Also, the infrared spectrum of physical mixture drug and polymers are scanned between 4000 cm^{-1} to 400 cm^{-1}.

Characteristic peaks of OND-HCl® are mentioned in the Table 3. These characteristic peaks are retained in the spectra of drug and physical mixture. Thus, after a perusal of Figure 3 to 7 and Table 3, it is clear that there is no interaction between the drug and polymers used.

Figure	FTIR Spectrum	Peak at wave number (cm^{-1})	Functional groups
3	OND-HCl®	3407.6 3175.22 1637.27 1631.2 1458.89 1281.47	-OH stretching -CH Ar stretching >C=O stretching >C=C<Ar stretching $-CH_2$ bending $-CH_3$ bending
4	OND-HCl® + Lutrol F-127®,	3402.6 3040.23 1637.27 1536.99 1466.6 1280.5	-OH stretching -CH Ar stretching >C=O stretching >C=C<Ar stretching $-CH_2$ bending $-CH_3$ bending
5	OND-HCl® + PVP K 30®	3412.42 3175.22 2948.63 1637.27 1581.2 1482.03 1281.47	-OH stretching -CH Ar stretching -CH Ali stretching >C=O stretching >C=C<Ar stretching $-CH_2$ bending $-CH_3$ bending
6	OND-HCl® + HPMC K4M®	3417.24 3175.22 1638.23 1531.2 1479.13 1280.5	-OH stretching -CH Ar stretching >C=O stretching >C=C<Ar stretching $-CH_2$ bending $-CH_3$ bending
7	OND-HCl® + PEG 6000®	3492.33 2697.93 1637.27 1536.99 1466.6 1280.5	-OH stretching -CH Ar stretching >C=O stretching >C=C<Ar stretching $-CH_2$ bending $-CH_3$ bending

Clarity

The clarity of various formulations was determined by visual inspection under black and white background with letters on a contrast colour, and it was graded as follows: turbid, +; clear, ++; and very clear (glassy), +++. The solution is graded as clear when the view of the letters in the background is prominent, and the solution is graded as very clear when the view of the letters in the background is most prominent.

pH of formulation

pH meter (Equiptronics, Model EQ-610), which was calibrated using solutions of pH 4.5 and 7, is used to measure the pH of all the formulations.[9]

Gelation temperature

Visual observation method:

2 mL of the formulation was taken in a test tube and immersed in a water bath in which the temperature was increased from the room temperature at a constant rate of 1°C every two minutes until the gel is formed. Then the test tube was tilted at an angle of 90° to observe the movement of the meniscus; if there is no movement of the meniscus, the gelation of the sample is confirmed.[10]

Gelation time:

For assessing the gelation time, a glass slide was used. Provision was made to keep the slide in hot water for about 15-20 minutes for equilibrating temperature (37°C). One drop of the formulation was placed on the glass slide which was maintained at an angle of 120°, and the time taken for converting it into gel was recorded.[7] (Figure 1)

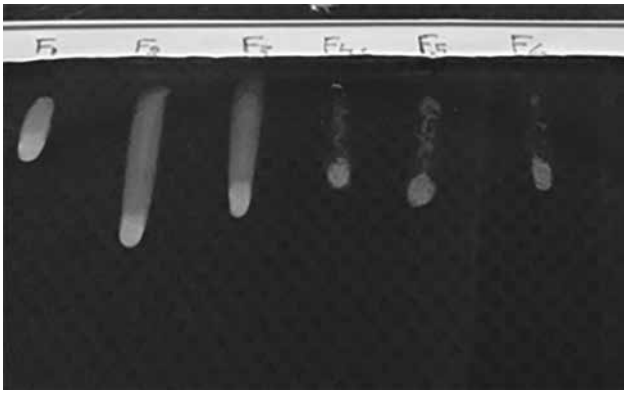

Figure 1: Photography taken during the measurement of gelation time

Viscosity measurement of the nasal *in situ* gel:
Viscosity of the prepared formulations was measured by using Brookfield LVDV-E Viscometer using spindle RV/HA/HB/-1 at 25°C. The spindle was lowered perpendicularly into 50mL volume of gel, which was to be measured. The spindle is rotated at 50 rpm speed, and the viscosity of the preparation is measured.[11]

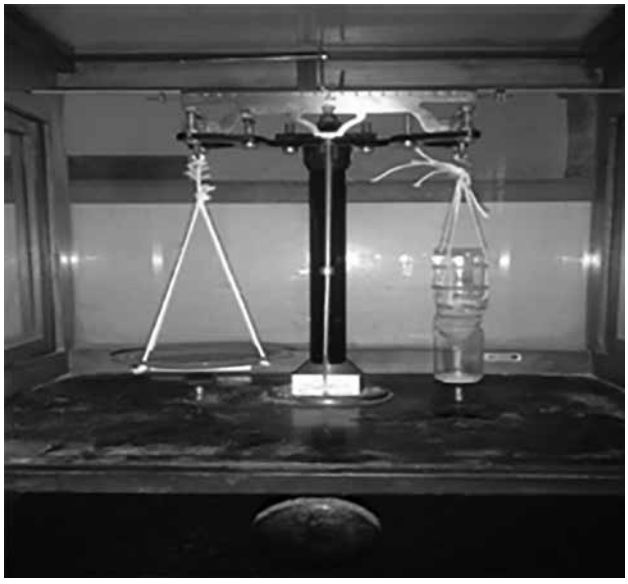

Figure 2: Modified chemical balance used for determination of mucoadhesive strength of formulation.

Determination of drug content:
The drug content is determined by taking 1 mL of the formulation and 2 mL of methanol in a 100 mL volumetric flask, which contained a few mL of nasal simulated fluid in. It was stirred vigorously. Then, it was made up with nasal simulated fluid up to 100 mL. From the above solution, 10 mL was withdrawn and further diluted to 100 mL with nasal simulated fluid. The absorbance of the above solution was measured at 248 m by using UV-Vis spectrophotometer (Shimadzu UV- 1800).[12,13]

Determination of mucoadhesive force:
The mucoadhesive strength of each formulation was determined by measuring the force required to detach the formulation from a goat nasal mucosal tissue by using a modified chemical balance. A section of the nasal mucosa was cut from the goat's nasal cavity and the mucosal side was instantly fixed into each glass vial using a rubber band. The vials with nasal mucosa were stored at 37°C for 5 minutes. Then, the next vial with a section of mucosa was connected to the balance in an inverted position while the first vial was placed on a height-adjustable pan. A fixed amount of sample of each formulation was placed onto the nasal mucosa of the first vial. Then, the height of the second vial was adjusted so that mucosal surfaces of both vials come into an intimate contact. Two minutes contact time was given to ensure an intimate contact between the sample and tissues. Then, the weight was increased in the pan until the vials got detached. The bio adhesive force, expressed as the detachment stress in dyne/cm^2, was determined from the minimal weights that detached the tissues from the surface of each formulation using the following equation. The nasal mucosa was changed for each measurement. (Figure 2)

Where, m =Weight required for detachment of two vials in gm

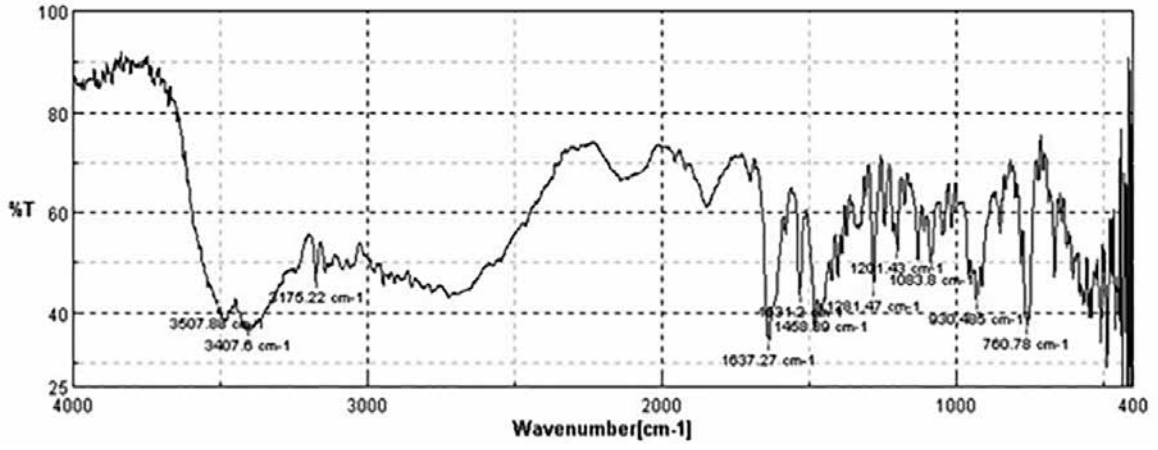

Figure 3: FT-IR spectrum of pure drug OND-HCl®

g = Acceleration due to gravity [980 cm/s^2]

A = Area of tissue exposed

The nasal mucosa was changed for each measurement. (Figure 2)

***In vitro* drug diffusion studies:**

2 mL of the formulation was taken in a glass tube of diameter 2 cm and tightly covered with dialysis membrane (Hi-Media, pore size 2.4 nm). Then, the boiling tube was inverted and tied to the paddle of the USP type II dissolution apparatus. Nasal simulated fluid was taken as a dissolution medium. The paddle's height was adjusted as the dissolution medium taken was 250mL and maintained at a temperature of 37 ± 0.5°C, with the speed of 50 rpm.

2 mL of the sample was withdrawn at 1 hour intervals for up to 8 hours. A fresh medium is replaced to maintain the sink condition. The samples are suitably diluted and analyzed by a UV spectrophotometer at 248 nm using nasal simulated fluid as a blank. The drug concentration is calculated by a calibration curve,

Results and discussion

FT-IR spectra

FT-IR spectrum of the pure drug OND-HCl® is shown in Figure 3. FT-IR spectra of the physical mixture of the drug with different polymers like Lutrol F-127®, PVP K 30®, HPMC K4M®, PEG 6000® are shown in Figures 4 to 7. The characteristic peaks of the drug are observed in the spectra of mixture of the drug and the polymer. However, the intensity of the peaks are reduced, and this might be due to a very low concentration of the drug in the mixture. This indicates that there is no interaction between the drug and the polymer. (Table 3 and, Figures 3, 4, 5, 6 and 7)

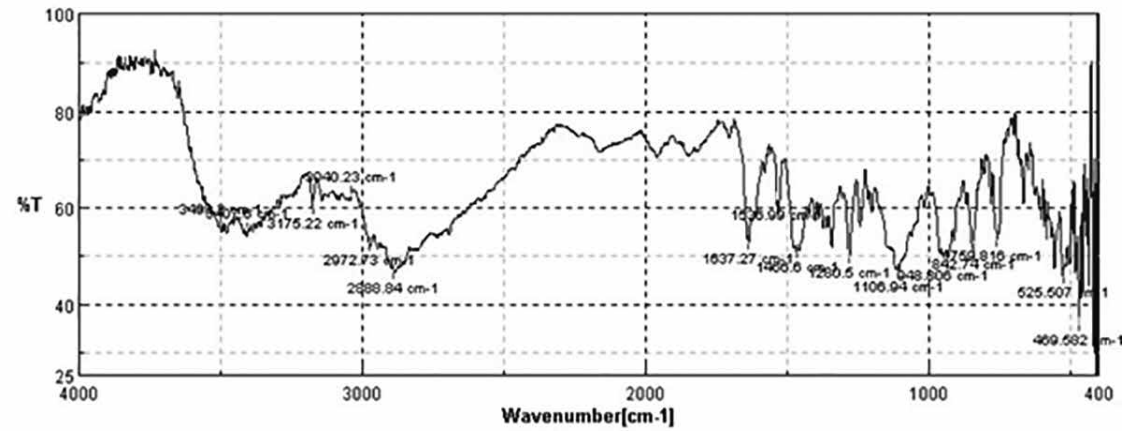

Figure 4: FT-IR spectrum of pure drug OND-HCl®+ Lutrol F127®

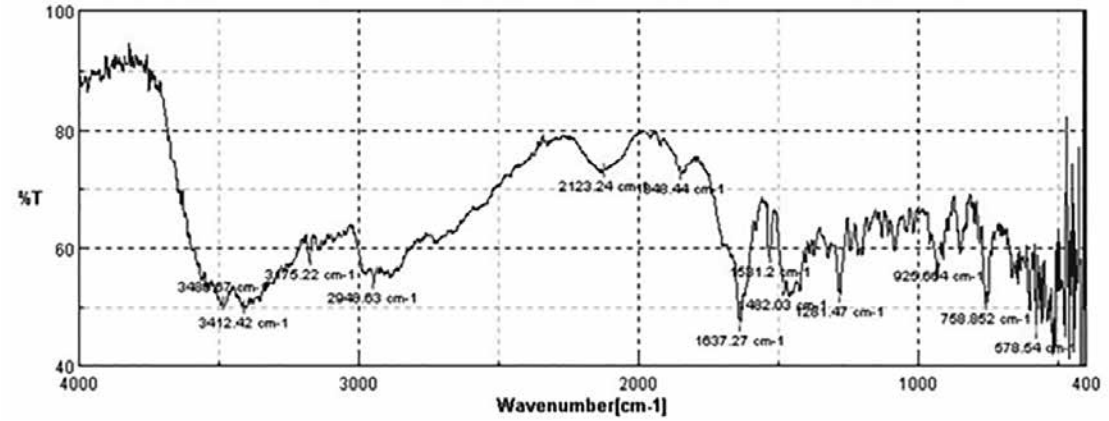

Figure 5: FT-IR spectrum of pure drug OND-HCl® + PVP K 30®

Table 4: Characterization of OND-HCl® in situ nasal gel formulations.

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clarity	+++	+++	+++	+++	+++	+++	+++	+++	+++
pH	5.1	5.0	5.2	5.1	4.9	5.0	5.0	4.9	5.0
Gelling temperature (°C)	34	33	33	32	32	31	35	37	40
Gelling time (Sec)	6	11	14	6	6	7	13	14	15
Drug content (%)	98	99	99	95	96	98	97	95	98
Muco-adhesive force (dyne/cm²)	936.3	1248.4	1560.5	1248.4	1248.4	1560.5	2808.91	3121.01	3433.12
Viscosity (cps)	26.7	29.5	33.3	30.0	66.2	100.0	20.0	22.1	23.7

Table 5: Percentage drug diffusion of OND-HCl® formulations prepared with three different polymers.

TIME in hrs	Polymers used for preparation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	13.33	6.16	6.9	9	6.62	6.5	11.12	9.5	8.5
1	30.44	30.14	27.02	25.07	15.38	12.80	22.08	21.95	16.31
2	79.21	65.14	57.68	42.72	31.29	21.27	62.76	51.50	35.19
3	98.80	86.42	82.39	58.11	51.35	32.82	69.41	68.26	47.97
4	-	99.95	96.98	67.32	52.70	43.08	76.84	73.80	60.85
5	-	-	99.03	76.60	69.06	52.17	89.38	78.69	65.08
6	-	-		83.45	71.70	61.33	89.54	79.96	70.59
7	-	-		86.60	73.09	66.81	91.33	80.55	73.64
8	-	-		92.27	88.23	74.83	93.98	91.17	81.71

Preparation of nasal *in situ* gel

Initially, we tried to prepare nasal *in situ* gel of ODN-HCL® by three methods i.e., by a pH induced method, an ion induced method, and by a temperature induced method. In the pH induced method, carbopol was selected as the gelling agent. While adding the drug solution into the carbopol solution, the drug started to solid out immediately, showing incompatibility.

With the ion induced method, gellan gum was used as a gelling agent during the mixing of the drug solution and gellan gum solution. Because of the ionic nature of the OND-HCl®, the precipitation occurred, showing incompatibility. So the ion induced method was also not suitable for the preparation of the OND-HCl® nasal *in situ* gel.

Whereas, in the case of the temperature induced method, using Lutrol F-127® as a thermo-reversible polymer turned out to be a suitable method for the preparation of OND-HCl® nasal *in situ* gel.

All the formulations were prepared using the ingredients given in Table 2 for the temperature induced method. The final volume of the formulation was adjusted with cold distilled water because the poloxamer 407 showed greater solubility at a lower temperature (5°C) when compared to room temperature. This is because poloxamer 407 forms an excessive hydrogen bonding between the water and its ethereal oxygen.[8]

Characterization of OND-HCl® *in situ* nasal gel formulations.

All nine formulations of OND-HCl® *in situ* gel were found to be clear. The pH of the *in situ* gelling solution was found to be 4.9 to 5.2. The viscosity of *in situ* nasal gel formulation was in the following order: formulations with HPMC K4M®; > formulations with PVP K30®; > and formulation with PEG 6000®. Gelation temperature range suitable for nasal gel was 32–35 °C. As the concentration of the Lutrol F127 was increased, gelation temperature was decreased, as shown in Table 1. Gelation

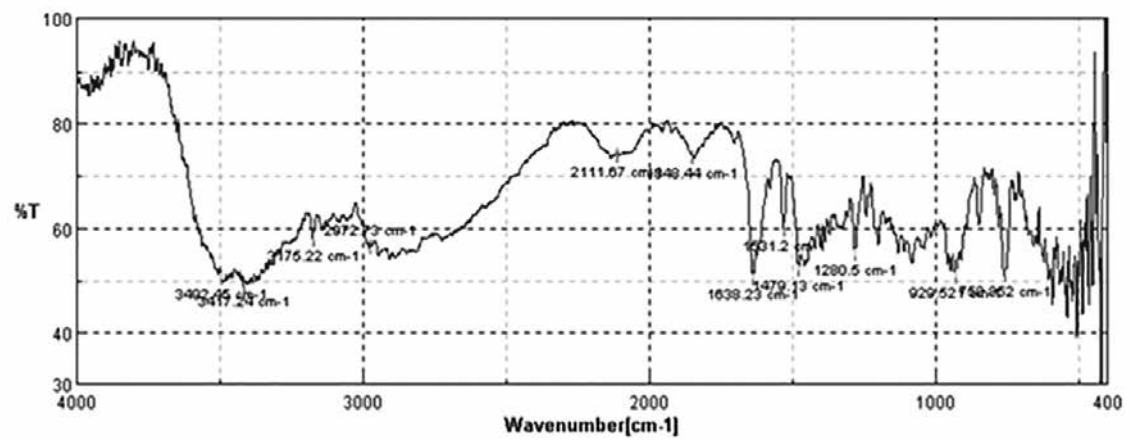

Figure 6: FT-IR spectrum of pure drug OND-HCl® + HPMC K4M®

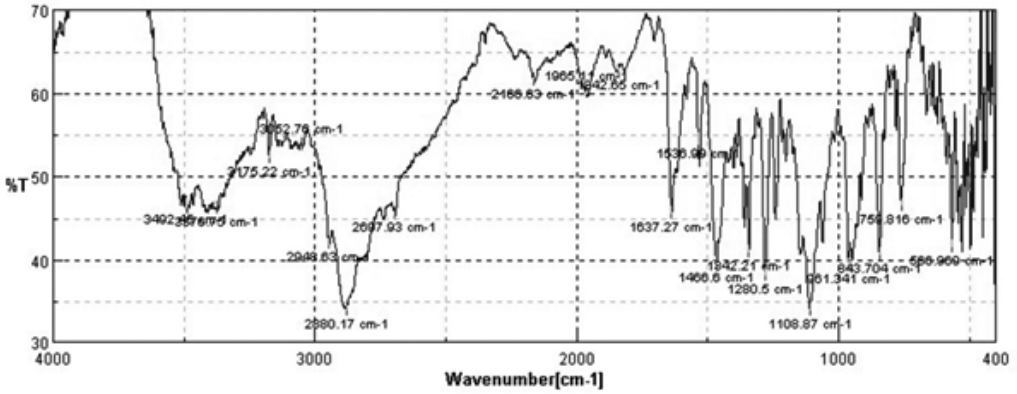

Figure 7: FT-IR spectrum of pure drug OND-HCl® + PEG 6000®

temperature of the prepared formulation (F1 to F9) was in the range of 31° to 40 °C. Gelation time of the prepared formulation was in the range of 6 to 15 seconds. The drug content was estimated for all the batches and it was found to be in the range of 95 – 99.98%, as shown in Table 4.

It shows that as the concentration of PVP K30®, HPMC K4 M and PEG 6000® increased, the mucoadhesive strength increased as well, as shown in Table 4. The mechanism of mucoadhesion can be attributed to the hydrogen bonding between the gel formulation and oligosaccharide chains of mucosal membrane (via carboxyl groups of PVP K30®, Hydroxyl group of PEG 6000®). The mucoadhesive force of the prepared formulation is in the range of 936.3 dyne/cm^2 to 3433.12 dyne/cm^2. (Table 4)

In vitro drug diffusion study:

Nine formulations of OND-HCl® nasal *in situ* gels were prepared using three mucoadhesive polymers such as PVP K30®, HPMC K4M® and PEG 6000®. Each polymer was used at three different concentrations (0.1, 0.3 and 0.5% w/v). The percentage of the drug diffusion for all nine formulations is shown in Table 5, and the dissolution profiles are shown in Figures 8 to 10. Upon increasing the percentage of polymer, the drug diffusion was decreased. After 8 hours of diffusion studies, it was found that the formulation F7 diffusion has the maximum percentage of drug i.e,, 93.98%. Hence, the formulation was optimized (Table 5, and Figures 8, 9 and 10).

Conclusions

In this study, sustained diffusion nasal *in situ* gels of OND-HCl® was prepared by thermo-reversible mechanism, using Lutrol F-127®, (polaxamer 407) as a gelling agent, and PVP K30®, HPMC K4 M and PEG 6000® as mucoadhesive polymers. It was found that an increase in the concentration in the polymeric ratio decreases the drug diffusion and

was able to sustain for 8 hours. The formulation F7, containing 18% Lutrol F-127®, & 0.5% PEG 6000®, showed a good drug diffusion over a period of 8 hours. These entire formulations showed acceptable results for Viscosity, pH, drug content, gelling temperature, gelling time, mucoadhesive force, etc. Thus, formulation F-7 was found to be the most promising formulation on the basis of acceptable *in situ* gelling properties and drug diffusion studies.

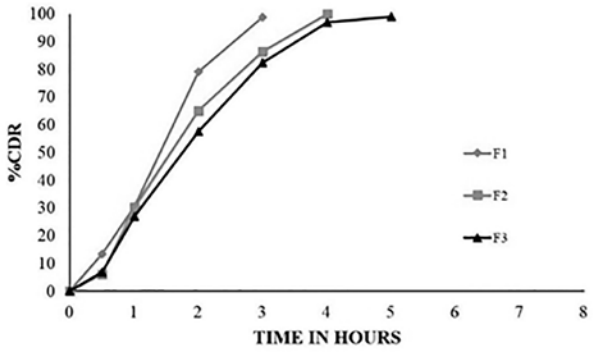

Figure 8: In vitro drug diffusion profiles of F1- F3 formulation prepared with polymer PVP K30®.

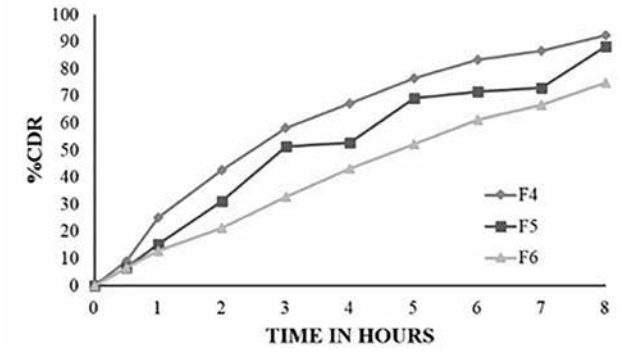

Figure 9: In vitro drug diffusion profiles of F4- F6 formulations prepared with polymer HPMC K4M®.

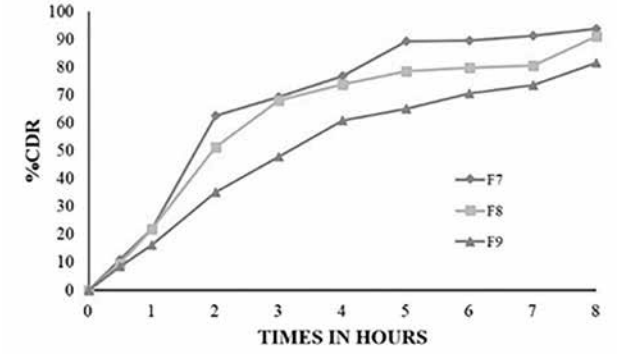

Figure 10: In vitro drug diffusion profiles of F7- F9 formulations prepared with polymer PEG 6000®.

Among all the three methods, pH induced method and ion induced method were not suitable, especially for OND-HCl® due to incompatibility problems. The temperature induced method was able to produce *in situ* nasal gel of OND-HCl with the help of LF127® as a thermos-reversible polymer.

References

1. Anilkumar A, Gopala Krishna Murthy TE, Prameela RA. Formulation of ondansetron hydrochloride matrix Tablets with microenvironmental pH modifier for improved dissolution and bioavailability under hypochlorhydria. Asi J Pharm 2016;10(3):188-96.
2. Hussein A. Intranasal drug delivery. Adv Drug Deliv Rev 1998;29:39–49.
3. Ugwoke MI, Verbeke N, Kinget R, Agu RU, Vanbilloen H, Baetens J. Scintigraphic evaluation in rabbits of nasal drug delivery system based on carbopol 971 P and carboxymethylcellulose. J Control Diffusion 2000;68:207–14.
4. Behl CR, Pimplaskar HK, Sileno AP, DeMeireles J, Romeo VD. Effects of physicochemical properties and other factors on systemic nasal drug delivery. Adv Drug Deliv Rev 1998;29: 89–116.
5. Shinde, JS. i*n situ* mucoadhesive nasal gels of metoclopramide hydrochloride: preformulation and formulation studies. J Pharm Res 2018;1(1):88–96.
6. Mandar J, Bhandwalkarl and Amelia MA. Thermo-reversible nasal *in situ* gel of venlafaxine hydrochloride: formulation, characterization, and pharmacodynamic evaluation. AAPS Pharm SciTech 2013;14(1):101-10.
7. Ashok K, Rajpoot, Hitesh K, Neelam J, Harish CV. Formulation and evaluation of mucoadhesive nasal *in situ* gel of diclofenac sodium. MIT Inter J Pharma Sci 2015;1(2):21-5.
8. Upendra CG, Praveen DC. Preformulation study of poloxomer 407 gels: effects of additives. International Journal of Pharmacy and Pharmaceutical Sciences 2014; 1(6): 130-3.
9. Vyshnavi V, Indira S, Prathima Srinivas. Formulation and evaluation of nasal niosomal *in situ* gels of loratadine. International Journal

of Pharmaceutical Sciences and Drug Research 2015;7(1):13-21.

10. Jyotivardhan J, Anantvar SP, Narkhede SVG, Karvin Mehta. Formulation and evaluation of thermo-reversible *in situ* nasal gel of metoprolol succinate. IJPPS 2012;4(3):96-102.
11. Inayat BP, Vijay C, Irfan F, Prakash S. Formulation design and evaluation of nasal *in situ* gel as a novel vehicle for azelastine hydrochloride. Int J Drug Del 2013;5:284-90.
12. Parmar V, Lumbhani AN. Development and evaluation of ion-dependent *in situ* nasal gelling systems of metoclopramide hydrochloride as an antimigraine model drug. Int J Latest Res Sci Tech 2012;1(2):80-9.
13. Kallakuri M., Seetha Devi A. Formulation and evaluation of nasal *in situ* gel of levofloxacin hemihydrates. Indo Ame J Pharm Res 2014;4(12):5817-27.