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Ondansetron Hydrochloride Nasal Drop: A Novel Drug Delivery

Pooja Basrur[1], Yogesh Pawar[2], Priyanka Devarshi[3], Subhash Kumbhar[3]*

[1]SCES's, Indira College of Pharmacy, Tathawade, Pune, Maharashtra. 431033

[2]SECM Shri Gulbarao Deokar College of Pharmacy, Jalgaon, Maharashtra, India, 425001

[3]School of Pharmaceutical Sciences Sanjay Ghodawat University, Kolhapur, Maharashtra, India. 416118

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KEYWORDS

Ondansetron hydrochloride; Poloxamer; Polyethylene glycol; Sheep nasal mucosa.

ABSTRACT:

Introduction: The present work was intended to design alternative dosage form to the conventional tablets of the Ondansetron hydrochloride (OND); as its bioavaibility is approximately 56% when administered via oral route.

Objectives: To prepare novel solution of a drug with Polyethylene glycol (PEG-400), Poloxamer (F68) and Benzalkonium Chloride (BC) and evaluate its *ex-vivo* permeation.

Methods: A solution was prepared and it was evaluated with respect to pH, stability, drug release. Permeation studies were performed using Franz- diffusion cell through dialysis membrane and sheep nasal mucosa in buffer (7.4 pH).

Result: The formulation followed zero order release when a loading dose of 40 mg OND was used, created a flux of 42µg/cm^{2}h^{-1} and penetrated about 1mg/cm^2 of drug in a day.

Conclusion: Hence, the intranasal solution of OND may present a superior option to conventional tablets and may create reasonable change in the drug therapy for prevention of nauseaand vomiting associated with initial and repeat courses of emetogenic chemotherapy or in postoperative emesis.

1. Introduction

Currently, nasal drug delivery is very useful methods for drug. Nasal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively [jain NK 2001]. The nasal route can be considered for drugs with small doses or those which require rapid entry to the gjeneral circulation. The rate of absorption is very fast making the exposure time of the drug to the enzyme very short. Thus level of the enzymes in the nasal tissue (mg/g) is very low and can be easily saturated with the drug. Unpleasant sensation associated with awareness of the urge to vomit, is usually felt in the back of the throat and epigastrium, and is accompanied by loss of gastric tone, duodenal contractions and reflex of intestinal contents into the stomach [1,2]. Emesis is the forceful expulsion of gastric contents from the mouth and is brought about by the powerful sustained contraction of abdominal muscles; descend the diaphragm, and opening of gastric cardia. OND is a serotonin (5-hydroxytryptamine) subtype 3 (5-HT3) receptor antagonist used in the management of nausea and vomiting. 5-HT3 receptors, located centrally in the chemoreceptor trigger zone of the area postrema as well as peripherally on vagal nerve terminals, are key receptors in the nausea and vomiting response. OND has been used to prevent and control nausea and vomiting after cancer chemotherapy, radiotherapy and surgery [3]. OND should be administered 30 min before chemotherapy. The orally administered antiemetic drug tends to be discharged by vomiting. On the contrary, intravenous administration renders rapid effects to a patient, but the onset of effects is too rapid to cause undesirable effects [4]. In addition, it gives a local pain, and may cause an unexpected accident when it is not perfectly prepared. This fact strongly suggests that there is need of alternative dosage form administrable by other route to avoid oral first pass presystemic metabolism.Intranasal therapy can be chosen for serving this purpose. In addition to this if, alternative dosage form provides steady flux of drug in systemic circulation, avoiding fluctuations those observed with oral therapy, will greatly improve the quality of therapy and compliance.[5]

E. Cho et al. have reported that the addition of 10% SBCD to aqueous solution containing 10% PEG 300 and 0.01% BC could be a good candidate for ondansetron nasal delivery systems because of its safety profile, stable storage in refrigerator and solubilizing effect [5].

The present work is an attempt to create an alternative cost effective and simple dosage form.

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2. Objectives

To study preformulation parameters of drug and polymer.To prepare solution of OND suitable for nasal administration.To evaluate the solution by studying its viscosity, pH, drug release by *in vitro* and *ex vivo* methods.

3. Methods

Chemicals: Gift samples OND USP were provided by Indoco Remedies Ltd. from Rabale, New Mumbai; Polyethylene Glycol 400 and Poloxamer F68 from Analab fine chemicals. Mumbai; andother chemicals of analytical grade were used.

Instruments: Double Beam UV-Visible Spectrophotometer (SHIMADZU UV-1700), Franz Diffusioncell.

Drug Excipients Interaction Study

Analysis of FTIR and DSC data was evaluated for interactions between excipients and the drug.

Fourier Transform Infrared Spectroscopy

FTIR spectrophotometer (SHIMADZU AFFINITY 1-8400 S) of OND was recorded by potassium bromide dispersion technique. Dry sample of drug and potassium bromide was mixed 1:1 and filled into the die cavity of sample holder and an IR spectrum was recorded using [6]. The resultant spectrumof the drug was compared with reference spectrum of OND. Infrared spectrum obtained for pure Ondansetron hydrochloride and poloxamer 188 with the ratio of 1:1 this formulation was used to verify the chemical compatibility which was used in the formulation development. The FTIR spectrometer (Jasco model, Tokyo, Japan) and the sample was scanned from 4000- 400cm-1 [7].

Differential Scanning Calorimeter

In order to obtain Thermograms of Ondansetron and polymers, aluminium pans were used in a Differential Scanning Calorimeter (DSC). For each sample, a fresh temperature parameters was set from 30 °C to 300 °C. 10 mg of sample and alumina were placed in aluminum pan; in sample and control compartment of furnace respectively. Nitrogen gas flow rate was adjusted to 50 mL/min. Measurement was started.[8,9]

Standard Calibration Curve

A stock solution of 100 µg/mL concentration was obtained. pipette out 0.25mL, 0.5mL, 0.75mL,1mL, 1.25mL, 1.5mL, 1.75mL, 2mL, 2.25mL to 2.5mL samples were taken and diluted with phosphate buffer to make the final volume of 10 mL. The absorbances of solutions were measured at 249 nm using the SHIMADZU-1700 UV/Visible Spectrophotometer.[10]

Preparation of intranasal solutions:

A 3^2 factorial design was used for the purpose of optimization **(**Table 1). The concentration of penetration enhancer and solubaliser were selected as the two factors. Three levels were fixed highest, intermediate and lowest (Table 2). All the formulations were prepared by dissolving all the ingredientsin distilled water. All the nine batches, of the prepared formulations contained 4 mg of drug per ml. Poloxamer 188 dissolved completely in water along with OND. Poloxamer 188 were used as permeation enhancer polymer in the concentration range of 45- 55mg and PEG-400 was used as solubiliser, benzalkonium chloride was used as preservative The different compositions of all the formulations were given in (Table 3). All the operations were carried out in a sterile aseptic condition in the laminar flow chamber.[11]

Table 1: Formulation of nasal solutions by factorial design

Formulation code	Levels In Coded Form	
	X1	X2
F1	1	1
F2	1	0
F3	1	-1
F4	0	1
F5	0	0
F6	0	-1
F7	-1	1
F8	-1	0
F9	-1	-1

* 0.01% Benzalkonium chloride

Evaluation methods:

The prepared batches were evaluated for their pH, viscosity, DSC, stability, in vitro permeation studiesand Ex vivo drug permeation studies.

1. pH :

The pH of the nasal formulation is very important mainly to avoid irritation of the nasal mucosa, to prevent the growth of pathogenic microorganism, to sustain normal physiological ciliary movement [12,13]. To avoid nasal irritation, the pH of the nasal formulation adjusted between 4.5 - 6.5 and pH of the all prepared formulations was measured for pH using by digital pH meter meter (Equip-tronics EQ-610) [14].

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Table 2: Translation of coded values to actual values.

Variable levels	High	Medium	Low
	(+1)	(0)	(-1)
X1= Quantity of PEG-400 in mL	0.6	0.5	0.4
X2= Quantity of Poloxamer 188 in mg	55	50	45

Table 3: Formulations with various ratios of PEG-400: Poloxamer-188

Form Code	PEG400 (mg)	Poloxamer F68 (gm)	Benz. Chloride (mL)	OND (mg)	Water to make (mL)
F1	0.6	0.055	0.001	40	10
F2	0.6	0.050	0.001	40	10
F3	0.6	0.045	0.001	40	10
F4	0.5	0.055	0.001	40	10
F5	0.5	0.050	0.001	40	10
F6	0.5	0.045	0.001	40	10
F7	0.4	0.055	0.001	40	10
F8	0.4	0.050	0.001	40	10
F9	0.4	0.045	0.001	40	10

2. Viscosity:

Viscosity measurement of different formulations in phosphate buffer, pH 6.3 which was measured at different rpm (5, 10, 20, and 50,100) of rotating spindle and average viscosity was recorded in each case in order to find out the effect of viscosity of vehicles on drug release using Brokefield Viscometer DV-II [15].

3. Clarity test

The test was performed to find out whether the formulation is free from the particulate matter or not. The sample was taken in the test tube, was observed against black and white background under light using clarity testing apparatus [16].

4. Sterility Study:

The test for sterility was designed to check the presence of microorganisms in the formulation. Soya bean casein digested media was used in this study to find out both bacteria and fungi. One portion of media was used for detection of bacteria at 37 º C for 24h, and another portion used for the detection of fungi at 23º C for 7 days.

5. Stability Study:

Shortlisted nasal solutions were tested for accelerated stability. Solutions were stored in clean, dry, airtight, moisture proof bottles, keep away from light. They were subjected to Elevated temperature and humidity conditions of 40 ± 2^0C/ 75 ± 5 % RH. The samples were withdrawn at 30, 60, 90 days and evaluated for pH, viscosity at 100 rpm and drug content[17].

6. In-vitro Permeation Study Using Franz Diffusion Cell

In vitro permeation study was carried out by the Franz diffusion cells (FDC) and dialysis membrane 110 (Himedia) was used as filtration medium. Dialysis membrane was mounted betweenthe compartments of the diffusion cell and kept in intimate contact with intranasal formulation. The receptor liquid was 10 mL of PB stirred at 100 rpm on a magnetic stirrer; the whole assembly was keptat 37±0.5°C by circulating constant temperature (38±0.5^{0}C. The permeability coefficient is calculated with equation-1.

$$Kp = Flux/C_V$$

CV is the total donor concentration of the formulation per cm^{-1}. All formulations were subjected to *ex vivo* studies

The steady state flux (Jss) was calculated from slope of the straight portion of line in the plot of drug amount permeated Vs time for different formulations and compared with theoretical target flux. Permeability coefficient (Kp) was calculated by dividing the flux with the amount of drug in the nasal spray. The lag time was calculated from intercept on time axis in the plot of cumulativeamount permeated Vs time. The theoretical target flux was calculated using Equation Target,

$$Flux = CSS \times ClT \times B.Wt. / A$$

Where, CSS is target steady state therapeutic concentration of Ondensetron Hydrochloride (i.e. 4 µg/L), ClT is total clearance of OND from human body, B.Wt. is average body weight of adult human being (i.e. 60 Kg) and A is the area of nasal mucosa that allowed penetration of the drug into receptor compartment of Franz Diffusion Cell. Therefore the target flux for OND for given FDC was 166µg /cm2.h-1. [18,19]

Preparation of sheep nasal mucosa:

Sheep nasal mucosa was procured within 1 hour after death of the animal from local slaughterhouse, Pune. Mucosa was carefully dermatomed, washed with demineralised water, transferred immediately to Saline (pH 7.4) solution and carried to the laboratory of the present work. The membrane was cleaned to remove adhering mucous and other cartilage pieces. The cleaned membrane was mounted on KC cell for permeation study.

***Ex-vivo* Permeation Using Franz Diffusion Cell:**

Franz diffusion cells (FDC) were used for *ex-vivo* permeation studies. The sheep nasal membrane was mounted between the compartments of the diffusion cell with the mucosal surface facing the donor compartment. The mucosal surface of the membrane was kept in intimate contact with intranasal formulation under test.

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The receptor liquid was 10 mL of saline (7.4pH) stirred at 200 rpm on a magnetic stirrer; at temp 37±0.5°C by circulating constant temperature (38±0.5^{0}C) water through jacket of FDC. [18,19]

Drug estimation during permeation studies:

OND release from formulations was tested with a FDC having a receiver compartment volume of 10 ml and the effective diffusion area was 3.799 cm^2. The receptor phase (Buffer pH 7.4) was continuously stirred and kept at a temperatureof 37 ± 0.5°C. A sample of 0.5 mL was taken from the receiver solution at predetermined time intervals. The amount of drug permeated was estimated using spectrophotometric method and concentration was corrected for sampling effects according to (Haytonand Chen 1982) equation-2.

$$C^1n = Cn\,(V_T/V_T - V_S)\,(C^1_{n-1}/C_{n-1})$$

Where, C^1_n is the corrected concentration of the nth sample, C_n is the measured concentration of OND in the nth sample, C_{n-1} is the measured concentration of the OND in the (n -1)th sample, C^1_{n-1} is thecorrected concentration of OND in the (n-1)th sample, V_T is the total volume of the receiver fluid and V_S is the volume of the sample drawn. All permeation studies were repeated thrice to confirm the results.[20]

Result Discussion:

Drug Interaction Study with Excipients

Table 4: Identification of drug by FTIR Spectroscopy

Functional group	Peak positions (Wave number cm^{-1})
O-H stretching	3544
C=O stretching	1638
CH_3 stretching	1469
C-N stretching	1279

Fourier Transform Infrared Spectroscopy

The graphs of FTIR will be of use in determining the functional groups as well as the potential physical and chemical interactions that take place during the process of combining the dug with the excipients. Figure 1 The FTIR spectrum of OND dispersed in KBr showed the same characteristic peaks as in reference spectrum of OND. It showed dominant characteristic peaks of OND; especially C=N, O-H, CH_3, C-N stretching vibrations at 3544,1638,1469,1279 which confirmed that drug sample was authentic one.

Figure 1: IR spectrum of OND

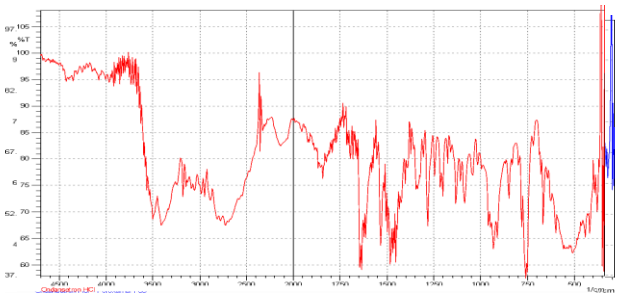

Figure 2: IR spectrum of OND and Poloxamer 188

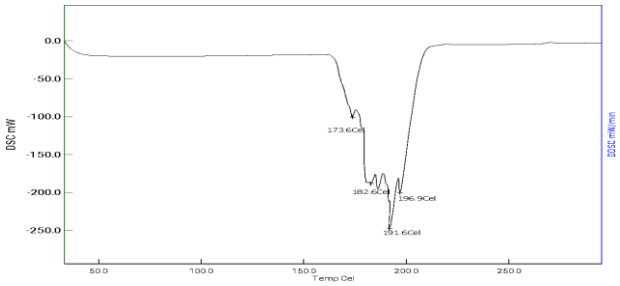

Figure 3: DSC thermogram of pure drug OND

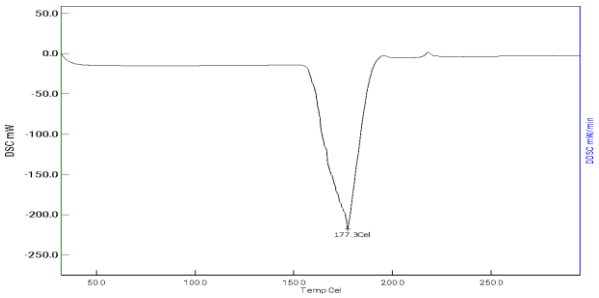

Figure 4: DSC thermogram of Formulation containing OND

Differential Scanning Calorimeter

The DSC scan of OND pure and OND in formulation were observed. The thermogram of OND showed a sharp melting event at 177.3 ºC with enthalpy of fusion -210.0 Mw. There was shift in the melting point of OND in the formulation. Its melting point was observed at 173.6 with enthalpy of fusion -110.0 Mw. This indicates minor drug-polymer interaction between OND and Poloxamer 188

Standard Calibration Curve

The concentration of drug between 2.5and 25 µg/mL shows good linearity in calibration curve by using the spectrophotometric method (beers lamberts law). R2 for

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the relationship between concentration and absorbance which can be seen in the Figure 6 was 0.9993, and the resulting equation was y = 0.0426x-0.0029

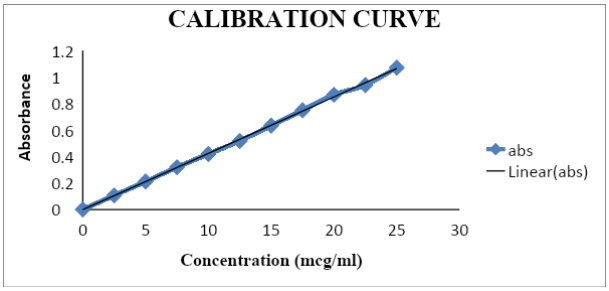

Figure 5: Calibration curve of OND

pH:
The nasal mucosa pH is somewhere in the range of 3 to 10. All prepared gel formulations were having their pH between 5.8 to 6.8; which is in the same range as that of the nasal mucosa (Table 5).

Viscosity:
Viscosities of all formulations were studied using spindle 21 of Brookfield DV-II model. Prolonging residence time in the nasal cavity is possible by increasing the viscosity of the vehicle. The viscosity of formulation increase with the increase in PEG400 concentration.[77] (Table 5)

Clarity:
The appearance of the content of the container and closure system was analyzed for the nine formulations. There is no change in color, texture and clarity of the formulation which was presentedin Table 3.

Sterility:
All the formulations were found to be sterile in both detection of bacteria and fungi.

Stability studies:
Stability studies were conducted as per ICH guidelines at 75% RH and 400C temperature. There was no significant difference observed in all evaluation parameters after a period of six month.

Invitro Permeation Study:
The results of the in vitro drug release study for the formulations F1 to F9 are shown in Figure 7. Drug release from the medium was found to be decreased with an increase in the drug polymer ratio. F1 formulation was found to be fast release 10-15 min, which was satisfactory. Poloxamer 188 used as permeation enhancer polymer, which enhances the absorption of the drug in nasal mucosa. Formulation F1 was most satisfactory in all respects as compared to all other formulations. The effect of levels of PEG-400 and Poloxamer 188 were predicted using 3D graph where flux was found to be distributed with continuous and normal Gaussian distribution Figure 8. The effect of PEG-400 and Poloxamer 188 on viscosity is depicted in Figure 9. On the basis of data obtained from the formulations subjected to optimization, a general statistical model can be depicted with respect to the above data. The model developed can be characterized by using polynomial equation representing the respective response data

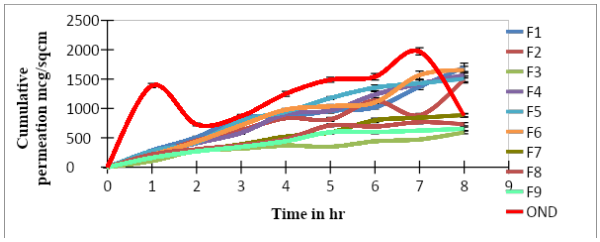

Figure 6: Permeation flux of OND created by various formulations (in vitro)

***Ex-vivo* Permeation Study:**

Permeation studies were repeated three times to confirm the results in each case (n=3). Different permeation patterns were observed with change in ratio of Poloxamer 188 and PEG-400. Comparison of *ex vivo* drug permeation profiles is shown in Figure5. Values of flux and Kp are given in Table 2 Considering performance in ex-vivo permeation, formulation F1 was found to be the best; producing reproducible flux with 0.9719 R^2 value. Formulation F1 containing 3.15 mg/cm^2 of OND created a fluxof approximately 220.94µg/cm^{2}h^{-1} against expected theoretical target flux 166 µg/cm^{2}h^{-1} and penetrated about 1.7mg/cm^2 of drug in an eight hours with less deviation in flux as well as total amount permeated in eight hours (Figure 10).

Table 5: Characterizations of the intranasal solutions

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
pH	6.4	5.8	6.1	6.3	6.5	6.2	6.3	6.5	6.3
Viscosity	525	620	120	45	595	115	150	134.5	585

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Clarity	T	T	T	T	T	T	T	T	T
Sterility	S	S	S	S	S	S	S	S	S
Permeation	0.0561	0.0561	0.0561	0.0561	0.0561	0.0561	0.0561	0.0561	0.0561
Regresson (R^2)	0.9388	0.9388	0.9388	0.9388	0.9388	0.9388	0.9388	0.9388	0.9388
Flux in µg/cm^2.h^{-1}	220.94	149.15	56.14	196.16	185.7	203.08	107.07	84.92	73.05

T=Transparent, S=Sterile, n=3

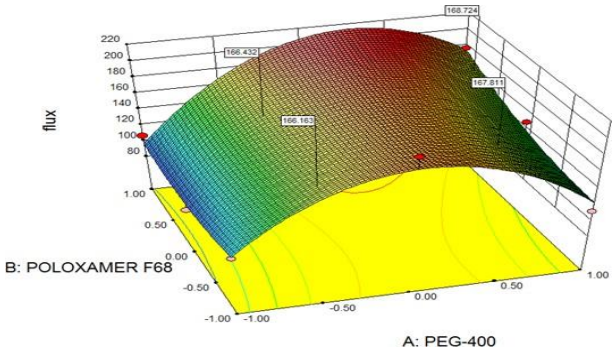


Figure 7: Response surface plot showing the influence of amount of PEG-400 and Poloxamer on flux

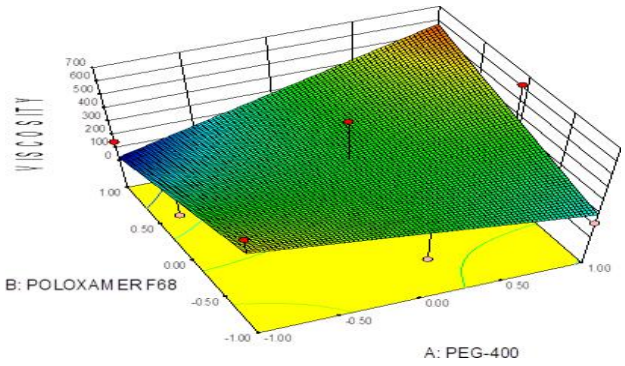
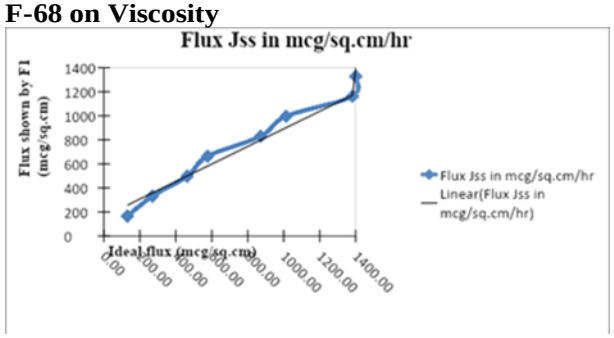


Figure 8: Response surface plot showing the influence of amount of PEG400 and Poloxamer F-68 on Viscosity



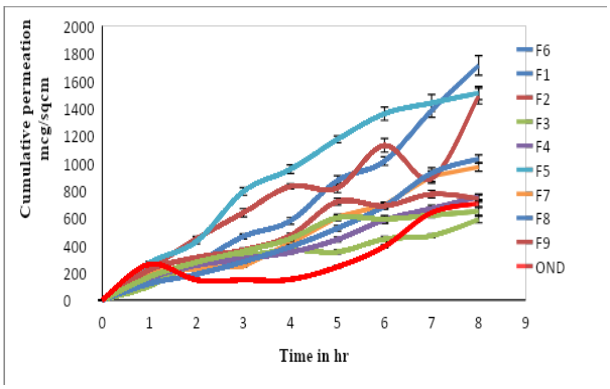


Figure 9: Permeation flux of OND created by various formulations (ex vivo)

***Ex-vivo* Permeation Study:**

Permeation studies were repeated three times to confirm the results in each case (n=3). Different permeation patterns were observed with change in ratio of Poloxamer 188 and PEG-400. Comparison of *ex vivo* drug permeation profiles is shown in Figure5. Values of flux and Kp are given in Table 2 Considering performance in ex-vivo permeation, formulation F1 was found to be the best; producing reproducible flux with 0.9719 R^2 value. Formulation F1 containing 3.15 mg/cm^2 of OND created a fluxof approximately 220.94µg/cm^{2}h^{-1} against expected theoretical target flux 166 µg/cm^{2}h^{-1} and penetrated about 1.7mg/cm^2 of drug in an eight hours with less deviation in flux as well as total amount permeated in eight hours (Figure 10).

CONCLUSION:

Transnasal drug delivery system is a novel approach to administer drug by controlling it's both, therate and the extent of drug into systemic circulation. Ondansetron hydrochloride was selected as a drug for the present study. Different formulations were prepared using various combinations of Poloxamer188 and PEG400 to get desirable release profile. On the basis of observed results it is revealed that the polymer Poloxamer188 was permeation enhancer and PEG400 was good solubiliser.

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Further it was concluded that the colloidal dispersion presents a better option to deliver drug through nasal mucosa. Transnasal drug delivery reduces the dose size by minimizing first pass metabolism observed with oral administration of this drug. It was experimentally determined that the optimized formulation of Ondansetron (40mg), Poloxamer188 (4.5mg), and PEG400 (0.4mg) was efficient to provide adequate physical strength and the desired pH (4.0-6.5). It was calculated and expected theoretically that the flux of drug 166µg/cm^{2}h^{-1} is required to fulfill the therapeutic need of the patient on the basis of available drug information. The permeation study indicates that, a flux of 220.94µg/cm^{2}h^{-1} (R=0.9719) is achieved on lab scale in *ex-vivo* permeation to met therapeutic need. Therefore, this novel nasal drop can replace conventional tablet dosage form in patients where oral route administration is not possible due to circumstantial reasons. The success of this dosage form shall depend on patient compliance, nasal retention time of the formulation, and cost of the product as compared to conventional tablets.

Refernces:

1. Kumar M, Misra A, Babbar A, Mishra A, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int. J. Pharm. 2008; 35 : 285–291.
2. Anwar H. Intranasal drug delivery. Adv. Drug Deliv. Rev. 1998;29: 39–49.
3. Machu T. Therapeutics of 5-HT3 Receptor Antagonists: Current Uses and Future Directions. Pharmacol Ther. 2011;130(3):338-47.
4. Cho E, Gwak H, Chun I. Formulation and evaluation of Ondansetron nasal delivery systems. Int. J. Pharm. 2008; 349:101–7.
5. Henry R, Lisbeth I, Gordon B, Paul H, Steven CQ. Intranasal delivery: Physicochemical and therapeutic aspects. Int. J. Pharm. 2007; 337:1–24
6. Pani NR, Nath LK, Acharya S, Bhuniya B. Application of DSC, IST, and FTIR study in the compatibility testing of nateglinide with different pharmaceutical excipients. J Therm Anal Calorim. 2012;108(1):219-26. doi: 10.1007/s10973-011-1299-x.
7. Kaushal AM, Chakraborti AK, Bansal AK. FTIR studies on differential intermolecular association in crystalline and amorphous states of structurally related non-steroidal anti-inflammatory drugs. Mol Pharm. 2008 Dec 1;5(6):937-45. doi: 10.1021/mp8000 98d,PMID 19434918.
8. Jagdale SC, Phule PS, Chavan GJ. Formulation and evaluation of modified pulsincap drug delivery system of rizatriptan benzoate. Int J Pharm Pharm Sci. 2014;6(5):48-52.
9. Lin SY, Wang SL. Advances in simultaneous DSC–FTIR microspectroscopy for rapid solid-state chemical stability studies: some dipeptide drugs as examples. Adv Drug Deliv Rev. 2012;64(5):461-78. doi: 10.1016/j.addr.2012.01.009, PMID 22300653.
10. Ghulam M, Izhar H, Shujaat AK, Arham S, Arshad M, Muhammad HH, et al. Development of a UV-spectrophotometric method for the simultaneous determination of aspirin and paracetamol in tablets. Sci Res Essays. 2011;6(2):417-21.
11. Piao H, Balakrishnana P, Cho H, Kim H, Kim Y, Chung S, et al. Preparation and evaluation of fexofenadine microemulsions for intranasal delivery. Int. J. Pharm. 2010; 395: 309–16.
12. Ghoi HG, Oh YK, Kim CK, In situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability. Int J Pharm 1998; 165: 23-32.
13. Naisbett B, Woodley J. The potential use of tomato lectin for oral drug delivery: Lectin bindingto rat intestine in vitro. Int J Pharm 1994; 107: 223-230.
14. Shier WT, Gregoriadis G. Lectins as drug carriers, in: Drug Carriers in Biology and Medicine, Academic Press, London; 1979. p. 43-70.
15. Banwell JG, Boldt DH, Meyers J, Weber FL, Miller B, Howard R. Phytohemaglutinin derived from red kidney bean (Phaseolus vulgaris): a cause for intestinal malabsorption associated withbacterial overgrowth in the rat. Gastroenterol 1983; 84:506-515.
16. David Rohler R and Barry R.Gold Spiel. Ondansetron: A serotonin receptor antagonist for anti neoplastic chemotherapy induced nausea and vomiting. Ann Pharmacother 1991; 25:3.
17. Feng F, Li Q, Chen H. Phase behavior of the microemulsions and the stability of the chloramphenicol in the microemulsion-based ocular drug delivery system. Int. J. Pharm. 2005;301: 237–246.
18. Karasulu H, Şanal Z, Sozer S, Guneri T, Ertan G. Permeation studies of indomethacin from different emulsions for nasal delivery and their possible anti-inflammatory effects. AAPS PharmSciTech. 2008; 9(2):342-48.
19. Tas C, Ozkan C, Savaser A, Ozkan A, Tasdemir U, Altunay H. Nasal absorption of metoclopramide from different Carbopol® 981 based formulations: in vitro, ex vivo and in vivoevaluation. Eur. J. Pharm. Biopharm. 2006; 64:246–54.
20. Kumbhar S, Pawar Y, Shaikh A, Kasture P. Design and ex- vivo evaluation of adhesive matrix type transdermal patch of buspirone hydrochloride. Int. J. Res. Pharm. Sci. 2012; 3:251-58.