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**Original Article**

# Formation and Development of Ondansetron Hydrochloride Nasal *in situ* gel

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**ABSTRACT:**
**Objective:** In view of the present study, the object of the study was to formulate and evaluate nasal *in situ* gel contains Ondansetron hydrochloride.
**Methodology:** Ondansetron hydrochloride loaded colloidal dispersion were prepared for nasal drug delivery using various polymers like carbopol (0.4%) and HPMC (1%) concentrations. The optimized formulation contains benzalkonium chloride as a preservative, sodium chloride as a tonicity adjuster, 0.5 M NaOH to maintain pH. The finished formulation was characterized for its clarity, pH, viscosity, drug content, net content, weight loss on storage, *in vitro* diffusion and *in vitro* bioadhesive strength.
**Result:** Ondansetron hydrochloride was successfully formulated as a pH induced *in situ* gel for nasal administration and have potential to avoid first pass effect than oral route.
**Conclusion:** The results of the study conclusively proved the suitability a nasal *in situ* gel of Ondansetron hydrochloride which was developed and formulated in this study is ideal for nasal administration for the treatment of antiemetic.

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## INTRODUCTION

Ondansetron hydrochloride is a 1,2,3,9-terahydro-9-methyl-(2-methyl-1-H-imidazol-1-yl)methyl-4H-carbazol-4-one, mono hydrochloride . Ondansetron hydrochloride is a short acting drug for the treatment of nausea and vomiting. Chemotherapeutic agents and radiotherapy cause release of 5-HT in the small intestine initiating the vomiting reflux by activating vagal afferents via 5HT3 receptor. It blocks the initiation of these reflexes. It has a short biological half-life of 3.1h.

The most commonly reported adverse events with Ondansetron hydrochloride are headache, constipation and diarrhea, which are mild to moderate in severity and rarely necessitate treatment withdrawal [1,2]. Various polymers are used to improve bioavailability of the drug administered by nasal route. Improving nasal residential time, the enhancement of nasal absorption by penetration enhancer and without altering its pharmacological activity [3].

Studies concerning the safety of cyclodextrin in nasal drug formulations demonstrate the non-toxicity of the cyclodextrin and also clinical data shows no adverse effects. Some cyclodextrin reports state that it is effective and safe excipients in nasal *in situ* gel.

The advantages of administering drugs nasally are rapid absorption, higher bioavailability, lower doses, fast onset of action; bypass that of the GIT, reduced risk of overdose, self-medication, ease of convenience, improved patient compliance feasibility of beneficial adjunct product to an existing product and reduced risk of infectious disease transmission [4].

The pH of the formulation as well as that of nasal surface, can affect a drug's permeation. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5. Drug absorption can be affected by tonicity of the formulation. Generally, an isotonic formulation is preferred [5].

Solubility is also important parameter Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), glycerides and Labrasol (saturated polyglycolyzed $C_8$-$C_{10}$ glycerides) can be used to enhance the solubility of drugs [6]. Aqueous solubility of a drug is always a limitation for nasal drug delivery in solution. Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations [7,8].

Antioxidants to prevent drug degradation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxytoluene and tocopherol.Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. Their permeation can improve by administered in combination with absorption enhancers which induce reversible modification on structure of epithelial barrier [9]. The number of enhancer are use such as Carboxyl esterase, Cyclodextrin, Sodium caprylate, Sodium deoxycholate,Sodium glycholate and Sodium salicylate. *In situ* gel forming formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems [10].

*In situ* forming polymeric formulations are drug delivery system that are in solution form before administration in the body, but once administered, undergo gelation *in situ*, to form a gel. Gellan gum and xanthan gum were used as *in situ* gel forming polymers [11].

## MATERIALS AND METHODS

Ondansetron Hcl was provided as a gift sample from Vapi care pharma Pvt. Ltd., Vapi. Gujarat India, HPMC K15 M gift from Micro lab Ltd, Mumbai and Carbopol 934P, Benzalkonium chloride, Sodium chloride and Sodium metabisulphite purchase from Molychem Ltd, Mumbai. Other materials and excipients used in the preparation of colloidal dispersions were I.P Grade. Acetonitrile, water and methanol used were of HPLC grade. All other ingredients used throughout the study were of analytical grade.

## RESULTS AND DISCUSSION

### Preformulation studies

Preformulation study means to investigate the physical and chemical properties of particular drug to develop it into a suitable, safe, effective and stable formulation. Preformulation studies were carried out in order to find out of the drug excipient interactions and solubility. UV absorption spectrum used to find out the interaction between the drug and excipients. Viscosity measurements of 0.05% polymeric dispersion were measured in order to find out the effect of viscosity of vehicles on drug release using Fungilab Digital Viscometer DV. pKa was determined by half neutralization of pH.

The specific identification tests were carried out in order to find out the drug excipients interactions. Infrared spectrum obtained for pure Ondansetron hydrochloride and spray dried (lyophilized) formulation was used to verify the chemical compatibility of Ondansetron with the excipients used in the formulation development. IR Spectrum which was taken for identification which, prepared by pellet technique with 2-3 mg of sample and potassium bromide using a FTIR spectrometer (Jasco model, Tokyo, Japan) and the sample was scanned from 4000-400$cm^{-1}$.

An excess amount of Ondansetron hydrochloride was added to various vehicles and shaken in a water bath set at 370C±0.50C for more than 48h.The solutions were centrifuged at 3000 rpm for 5 min, and the supernatant was assayed by HPLC after appropriate dilution.

**Table 1: Composition of nasal in-situ gel of OND HCl**

| Ingredients (mg) | Formulations | | | | | |
|---|---|---|---|---|---|---|
| | B1 | B2 | B3 | B4 | B5 | B6 |
| OND | 500 | 500 | 500 | 500 | 500 | 500 |
| Carbopol 934 | 50 | 100 | 150 | 200 | 250 | 300 |
| HPMC K4M | - | - | - | 250 | 500 | 750 |
| NaCl | 180 | 180 | 180 | 180 | 180 | 180 |
| Benzalkonium chloride | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 |
| Distilled water | q.s. up to 50ml | q.s. up to 50ml | q.s. up to 50ml | q.s. up to 50ml | q.s. up to 50ml | q.s. up to 50ml |

### Evaluation of situ gel formulation

#### I. Appearance

The developed formulations were inspected visually for clarity in sol and gel form.

#### II. pH of the Formulation

pH of the formulation was determined by using pH meter. The pH meter was first calibrated using solutions of pH 4 and pH 7.0

#### III. Gelling Capacity of Formulation

Aqueous solutions of different concentrations of Carbopol were prepared and evaluated for gelling. The optimized concentration of Carbopol was then used and mixed with various concentration of HPMC K4M evaluated for their gelling capacity in order to identify the compositions most suitable for use as *in situ* gelling systems. The gelling capacity was determined by placing 2ml of the system in a vial containing 1 ml of freshly prepared Phosphate Buffer pH 5.5 and equilibrated at 37˚C and visually assessing the gel formation.

**Table 2: pH and Gelling capacity of prepared formulations**

| Formulation code | pH | Gelling Capacity |
|---|---|---|
| **B1** | 4.10 | - |
| **B2** | 4.64 | - |
| **B3** | 4.68 | ++ |
| **B4** | 4.45 | ++ |
| **B5** | 4.61 | +++ |
| **B6** | 4.91 | ++++ |

### IV. Measurement of gel strength

50 g of gel was placed in a 100 ml graduated cylinder and gelled at 37°C using thermostat. A weight of 35g was placed onto the gelled solution and allowed to penetrate 5 cm in the gel. Time taken by weight to sink 5cm was measured.

**Table 3: Gel strength of prepared formulations**

| Formulations code | Gel strength (in sec) |
|---|---|
| **B3** | 33 ± 1.50 |
| **B4** | 39 ± 2.50 |
| **B5** | 45 ± 3.00 |
| **B6** | 53 ± 2.00 |

### V. Drug Content

One ml of each formulation was taken in 50 ml volumetric flask and diluted with Phosphate buffer pH 5.5 and shaken thoroughly to dissolve the drug in Phosphate buffer. The solution was filtered through Whatman filter paper, 1 ml of above solution was pipetted and diluted to 10 ml twice. The drug content of the drug was estimated spectrophotometrically by using standard calibration curve plotted at 310 nm

**Table 4: Drug contents in formulations**

| Formulation code | % Drug content |
|---|---|
| **B1** | 96.82 ± 0.45 |
| **B2** | 94.70 ± 0.60 |
| **B3** | 93.96 ± 0.53 |
| **B4** | 95.88 ± 0.61 |
| **B5** | 97.36 ± 0.22 |
| **B6** | 94.33 ± 0.48 |

### VI. Viscosity Determination

Determination of viscosity was done through Fungilab Digital Viscometer at 100 rpm using L4 spindle at $37^0$C.

**Table 5: Viscosities of prepared formulation**

| Formulation Code | Viscosity cps (n=3) | |
|---|---|---|
| | Sol | Gel |
| **B1** | - | - |
| **B2** | 598 | - |
| **B3** | 2074 | 2412 |
| **B4** | 3098 | 3721 |
| **B5** | 3518 | 4013 |
| **B6** | 5011 | 7089 |

### VII. Mucoadhesive strength:

The mucoadhesive force of all formulation were determined by mucoadhesive measuring device which is modified balance that was developed in our lab as per Young *et al* method using goat nasal mucosa and phosphate buffer pH 5.5 as moistening fluid. The mucoadhesive potential of each formulation was determined by measuring the force required to detach the formulation from goat nasal mucosal tissue by using modified balance.

A Section of nasal mucosa was cut from goat nasal cavity, moistened with Phosphate buffer pH 5.5 and instantly fixed with mucosal side out onto pan. *In situ* gel was applied on the circular rubber cap. The rubber cap was allowed to adhere on nasal cavity and placed in undisturbed condition for 2 min. The weight was then increased gradually on second pan. The point (weight in gram) at which the formulation detached from the goat nasal cavity was noted.

**Table 6: Mucoadhesive strength of preparation:**

| Formulation code | Weight req. for detachment (gm) | Mucoadhesive force in dynes/cm$^2$ |
|---|---|---|
| **B3** | 5.4 | 1685.35 |
| **B4** | 6.5 | 2028.12 |
| **B5** | 7.8 | 2434.39 |
| **B6** | 8.5 | 2652.86 |

### VIII. *In-vitro* drug release:

The *in-vitro* drug release of in-situ gel was carried on the Franz diffusion cell. The freshly cut nasal cavity of goat from local slaughter house was placed on donor compartment. The receiver compartment was filled with 6 ml of Phosphate buffer pH 5.5. The 1 ml of gel was placed on the nasal cavity and drug release study was carried out. Before the study all parameters of Franz diffusion cell were settled (water bath temperature at 37°C, RPM 100).

The 1 ml sample was withdrawn from receiver compartment and replaced with same amount of drug free medium. The first withdrawn of sample was after 30 min and then hourly. Each sample was then diluted with Phosphate buffer pH 5.5 upto 10 ml and analyzed spectrophotometrically at 310 nm.

**Table 7: *In vitro* Release of drug from prepared formulation**

| Sr. no. | Time in Hrs | Cumulative % drug release | | | |
|---|---|---|---|---|---|
| | | B3 | B4 | B5 | B6 |
| **1.** | 00 | 00 | 00 | 00 | 00 |
| **2.** | 0.5 | 35.61 | 32.94 | 34.87 | 28.12 |
| **3.** | 1 | 41.12 | 45.48 | 49.5 | 41.35 |
| **4.** | 2 | 47.87 | 53.74 | 58.00 | 53.49 |
| **5.** | 3 | 53.8 | 61.55 | 70.30 | 64.75 |
| **6.** | 4 | 71.44 | 81.13 | 83.09 | 71.95 |
| **7.** | 5 | 80.20 | 91.09 | 95.22 | 85.77 |

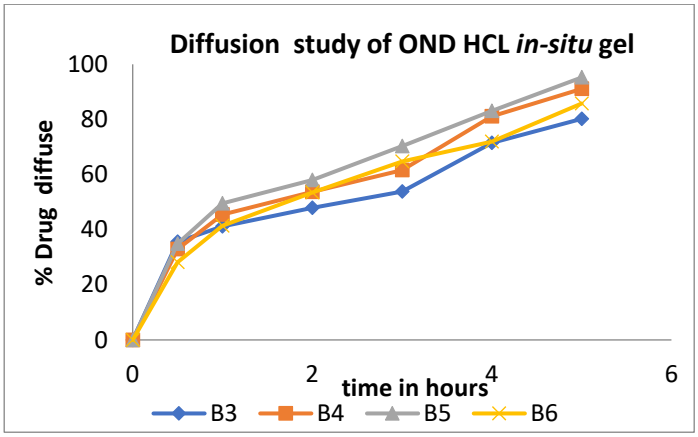


**Fig. 1: Drug release profile from formulation B3 to B6**

## CONCLUSION

From the results it can be conclude that Ondansetron hydrochloride was successfully formulated as a pH induced *in situ* gel for nasal administration and have potential to avoid first pass effect than oral route. The carbopol was the key ingredient of this formulation which is responsible for the sol to gel conversion, 0.4%w/v of Carbopol gives the clear solution at 4.5 pH and at the nasal pH it forms a clear gel.

The optimized batch i.e. B5 provided the controlled *in vitro* release of drug for 5 hrs from the formulation. The formulation was also able to adhere strongly to nasal membrane which may advantage to protect the drug from drain out. The OND gel with HPMC enhance the nasal residence time due to higher viscosity and mucoadhesive strength.

With increasing in the concentration of polymer the bioadhesive force, gel strength and drug retardation also increases. Thus, it can be concluded that 0.4% carbopol and 1% HPMC concentration is an ideal gel for controlled nasal delivery system. The optimized formulation can be competent alternative to conventional nasal drop.

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