**Available Online at www.ipsgwalior.org**
**ISSN No. 2229-4309(Online), Vol - 2, Issue - 3, July 2016**
*Pharmacia: An International Journal of Pharmaceutical Sciences*

**RESEARCH ARTICLE**

# FORMULATION DEVELOPMENT AND EVALUATION OF IN SITU NASAL DRUG DELIVERY SYSTEM OF POORLY WATER SOLUBLE DRUGS UTILIZING MIXED SOLVENCY CONCEPT

Shivank Hazari*[1], M. K. Gupta[2], Ankit Agrawal[3], Neetesh Kumar Jain[4], Ankita Dubey[5]

*[1,2,3,4,5]Oriental College of Pharmacy & Research (Department of Pharmacy), Oriental University, Indore –India.

## ABSTRACT

*The goal of all sophisticated drug delivery systems is to deploy medications to specifically targeted parts of the body through a medium that can control the therapy's administration by means of either a physiological or chemical trigger.*
*The bioavailability of a drug and hence its therapeutic effectiveness are often influenced by the route selected for administration. For a medication to achieve its maximal efficacy a drug should be able to get administered easily so that better patient compliance can be achieved; and it should be capable of being absorbed efficiently so that better bioavailability can be accomplished. Release studies were performed in saturated solutions of various solubilizers and permeability coefficients were calculated. Higher permeability coefficients were obtained from mixed solubilizers as compared to individual solubilizers. From all the mixed solubilizers studied, highest permeability was exhibited by PEG $600_{7.5}$ + PEG $400_{7.5}$ + Propylene $Glycol_{7.5}$ + PVP $K30_{7.5}$ i.e. $1.522 \times 10^{-02}$ cm/hr.*

**Keywords:** *Nasal Drug Delivery, Mixed Solvency*

**Corresponding Author:**

Mr. Shivank Hazari
PG Research Scholar
Department of Pharmacy
Oriental University,Indore
Email: shivankhazari@gmail.com

## 1. INTRODUCTION

Drugs have been administered nasally for therapeutic and recreational purposes since ancient times. Psychotropic drugs and hallucinogens were snuffed for these purposes by the Indians of South America, and this practice is currently widespread among abusers of cocaine and heroin.

The interest in and importance of the systemic effects of drugs administered via the nasal route have expanded over recent decades. Nasal administration offers an interesting alternative for achieving systemic drug effects to the parenteral route, which can be inconvenient on oral administration, which can result in unacceptably low bioavailabilities[1]. The nasal epithelium is a highly permeable monolayer, the submucosa is richly vascularised, and hepatic first-pass metabolism is avoided after nasal administration. Other attractive features include the rather large surface area of the nasal cavity and the relatively high blood flow, which promotes rapid absorption. Furthermore, self-medication is easy and convenient. In the last decade, much interest has been given to the exploitation of the nasal route for delivery of drugs to the brain via a specific site, the olfactory region.[1-2]

### 1.1 Advantages of Nasal Drug Delivery Systems [4-5]

**1.** Rapid drug absorption and quick onset of action can be achieved.

**2.** Hepatic first – pass metabolism is absent.

**3.** Drug degradation that is observed in the gastrointestinal tract is absent.

**4.** The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

**5.** The nasal bioavailability for smaller drug molecules is good.

**6.** Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.

**7.** Studies so far carried out indicate that the nasal route is an alternate to Parenterals route, especially, for protein and peptide drugs.

**8.** Convenient for the patients, especially for those on long term therapy, when compared with Parenterals medication. e.g. Diabetics.

### 1.2 Limitations [4-5]

**1.** Nasal congestion due to cold or allergies may interfere with this method of delivery.

**2.** Frequent use of this route results in mucosal damage (e.g. infection).

**3.** Nasal cavity provides smaller absorption surface area when compared to GIT.

**4.** Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa.

### 1.3 Factors Affecting Nasal Drug Absorption [4-5]

Many factors affect the systemic bioavailability of nasally administered drugs. The factors can be attributed to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal passage and the type and characteristics of selected nasal drugs delivery system. These play significant role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are as follows:

**A.** Physicochemical properties of drug

- Molecular Weight

- Lipophilic-hydrophilic balance
- Enzymatic degradation in nasal cavity

**B.** Nasal Effect

- Membrane permeability
- Environmental pH
- Mucociliary clearance
- Cold, rhinitis

**C.** Delivery Effect

- Formulation (Concentration, pH, osmolarity)
- Delivery effects
- Drug distribution and deposition
- Formulation effect on mucociliary clearance
- Toxic effect on ciliary function and epithelial membranes

**1.4 Nasal Drug Delivery System**

Nasal drug delivery system can be classified in to:

- Nasal drops
- Nasal sprays / Nebulizers
- Aerosols
- Suspension spray / Nebulizers
- Nasal powders
- Gels

**2.0 Formulation and Evaluation of In Situ Nasal Gel of Domperidone** [8-9]

**2.1 Procedure:** In situ nasal gel of Domperidone was prepared by using cold technique. Appropriate amount of poloxamer 407 was weighed in a 250 ml beaker, containing weighed amount of cold distilled water (double distilled water containing 0.002% w/v benzalkonium chloride, as preservative) was kept at 4°C until a clear solution was obtained. Then an aqueous blend of mixed solubilizer (PEG $400_{7.5}$ + PEG $600_{7.5}$ + Propylene $Glycol_{7.5}$ + PVP $K30_{7.5}$) containing 2 mg/g of Domperidone, was accurately weighed and added to the above solution. The above preparation was mixed thoroughly on magnetic stirrer with a magnetic bar in the beaker to make the homogeneous gel. [9-10]

**Table 1: Composition of Domperidone in situ nasal gel formulation**

| S. No. | Ingredient | Quantity (g) |
|---|---|---|
| 1. | Poloxamer 407 | 19.00 |
| 2. | Carbopol 934P | 0.100 |
| 3. | AR/BLEND/DPD (DPD in 2 mg/g concentration) | 40.00 |
| 4. | Distilled water | 41.00 |
| 5. | Benzalkonium Chloride | 0.002 |

**2.2 Physico-Chemical Properties of Optimized Formulation of Domperidone In Situ Nasal Gel**

Physico-chemical properties of Domperidone in situ nasal gel formulation are presented in table 2. The formulation was found to be clear by visual examination against white and black backgrounds. The pH of the formulation was determined by using pH meter (Cyberscan® 510). The drug content was determined by dissolving 200 microliter of formulation in 50 ml methanol and volume was made up to 100 ml with de-mineralized water in a 100 ml volumetric flask. Then was estimated spectrophotometrically using double beam UV-visible spectrophotometer (Shimadzu® 1700) at 284 nm against reagent blank.

**Table 2: Physico-chemical properties of optimized formulation of Domperidone in situ nasal gel Formulation**

| S.No. | Parameter | Observation |
|---|---|---|
| 1. | Clarity | Clear |
| 2. | pH | 6.32 |
| 3. | Drug content (%) | 99.8% |
| 4. | Transition temperature | 37ºC |
| 5. | Spreadability | Good |

### 2.3 In-Vitro Drug Release Study of Optimized Formulation of Domperidone In Situ Nasal Gel [8-10]

#### 2.3.1 Medium for Drug Release Study

To maintain the proper sink conditions, 50 % v/v methanolic buffer (acetate buffer of pH 5.5 + methanol) was used as the medium for drug release study from optimized formulation.

#### 2.3.2 Experimental Conditions

Apparatus - Franz diffusion cell
Release Medium - 50 % v/v methanolic buffer (acetate buffer of pH 5.5 + methanol)
Volume - 13 ml
Temperature - 37˚C
Speed - 50 rpm

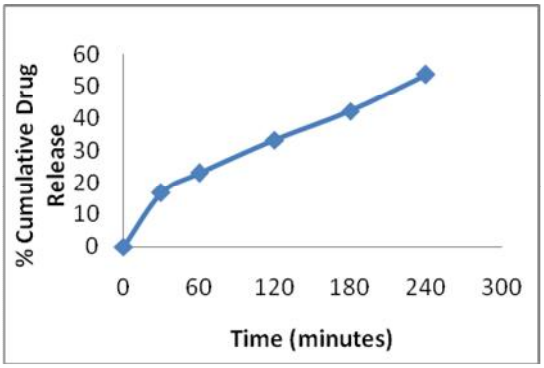
#### 2.3.3 Procedure [10-11]

The drug release of the domperidone in situ gel formulation batch was studied using Franz diffusion cell. Assembly was set and the temperature was maintained at 37˚C, then 1 ml of nasal in situ gel of domperidone was applied in the donor compartment, which was separated by the receptor compartment with the dialysis membrane (Hi Media dialysis membrane). A 2-2 ml aliquots of samples were withdrawn at regular time intervals and replaced with an equal volume of 50% v/v methanolic buffer. The samples were appropriately diluted with de-mineralized water and analyzed spectrophotometrically for domperidone content using double beam UV-visible spectrophotometer (Shimadzu® 1700) at 284 nm. Cumulative percent drug released is shown in table 3 and graphically represented in fig 1. [8-9]

**Table 3: Results of release studies from domperidone in situ nasal gel formulation**

| S.No. | Time (minutes) | Cumulative Drug Release per $cm^2$ (mcg) | Percent Cumulative Drug Release |
|---|---|---|---|
| 1. | 60 | 40.36 | 15.87 |
| 2. | 120 | 63.87 | 25.12 |
| 3. | 180 | 95.36 | 37.50 |
| 4. | 240 | 123.24 | 48.46 |
| 5. | 300 | 150.84 | 59.32 |
| 6. | 360 | 185.75 | 73.05 |

**Figure.1: Graphical representation of Ex-vivo release studies from Domperidone in situ nasal gel formulation**




**Result:** Developed Domperidone in situ nasal gel formulation showed a profile with 53.79% permeation of drug in 4 hr through the nasal epithelium membrane. The flux calculated was 10.818 mcg/$cm^2$hr and the permeability coefficient was $1.35 \times 10^{-02}$ cm/hr.

**2.4 Rheological Studies** [9-10]

Viscosity determination of the developed Domperidone in situ gel formulation was done using Brookfield viscometer (LVT model). Viscosity of the sample solution was measured over a range of 0.3 to 30 rpm speed. The hierarchy of speed was reversed from 30 to 0.3 rpm. The average of the two dial readings was used to calculate the viscosity. To evaluate viscosity change at cool condition and at body temperature, rheological measurements were taken after increasing the temperature of nasal in situ gel to 37°C.

**Result:** Viscosity of sol and gel was found to be 65 cps and 850 cps respectively at 12 rpm.

**2.5 Stability Studies**

The physical stability, including appearance, color, and pH of the formulation was studied under various storage conditions. None of the samples showed any change in color or appearance under all storage conditions for one month period. The drug content of the formulation was estimated initially and then after one month using double beam UV-visible spectrophotometer (Shimadzu® 1700). The observations so recorded are presented in table 4.[4-5]

**Table 4: Stability data for optimized in situ nasal gel of Domperidone**

| S. No. | Time | Storage Condition | Color | Clarity | pH | Drug Content |
|---|---|---|---|---|---|---|
| 1. | Initial | NA | Creamish | Clear | 6.32 | 99.80% |
| 2. | One month | 2-8°C | Creamish | Clear | 6.32 | 99.53% |
| | | RT | Creamish | Clear | 6.31 | 98.46% |
| | | 40°C | Creamish | Clear | 6.28 | 98.15% |

**Table 5: Composition of Ondansetron Hydrochloride in situ nasal gel formulation**

| S. No. | Ingredient | Quantity (g) |
|---|---|---|
| 1. | Poloxamer 407 | 19.00 |
| 2. | Carbopol 934P | 0.100 |
| 3. | AR/BLEND/ODS (ODS in 45 mg/g concentration) | 40.00 |
| 4. | Distilled water | 41.00 |
| 5. | Benzalkonium chloride | 0.002 |

**3.0 Formulation and Evaluation of In Situ Nasal Gel of Ondansetron Hydrochloride** [9-10]

**3.1 Procedure:** In situ nasal gel of ondansetron hydrochloride was prepared by using cold technique. Appropriate amount of poloxamer 407 was weighed in a 250 ml beaker, containing weighed amount of cold distilled water (double distilled water containing 0.002% w/v benzylkonium chloride, as preservative) was kept at 4°C until a clear solution was obtained. Then an aqueous blend of mixed solubilizer (PEG $400_{10}$ + Propylene $Glycol_{10}$ + PVP $K30_{10}$) containing 45 mg/g of ondansetron hydrochloride, was accurately weighed and added to the above solution. The above preparation was mixed thoroughly on magnetic stirrer with a magnetic bar in the beaker to make the homogeneous gel. [9-10]

**3.2 Physico-Chemical Properties of Optimized Formulation of Ondansetron Hydrochloride In Situ Nasal Gel**

Physico-chemical properties of Ondansetron hydrochloride in situ nasal gel formulation are presented in table 9.7. The formulation was found to be clear by visual examination

against white and black backgrounds. The pH of the formulation was determined by using pH meter (Cyberscan® 510). The drug content was determined by dissolving 200 microliter of in situ gel in 50 ml methanol and volume was made up with de-mineralized water up to 100 ml in a volumetric flask. Then it was estimated spectrophotometrically using double beam UV-visible spectrophotometer (Shimadzu® 1700) at 310 nm against reagent blank.

**Table 6: Physico-chemical properties of optimized formulation of ondansetron hydrochloride in situ nasal gel formulation Code (AR/ODS/FB/2706)**

| S.No. | Parameter | Observation |
|---|---|---|
| 1. | Clarity | Clear |
| 2. | pH | 6.31 |
| 3. | Drug content (%) | 98.90% |
| 4. | Transition temperature | 37ºC |
| 5. | Spreadability | Good |

### 3.3. In-Vitro Drug Release Study of Optimized Formulation of Ondansetron Hydrochloride In Situ Nasal Gel [8-10]

#### 3.3.1 Medium for Drug Release Study

To maintain the proper sink conditions, 50% v/v methanolic buffer (acetate buffer of pH 5.5 + methanol) was used as the medium for drug release study from optimized formulation.

#### 3.3.2 Experimental Conditions

Apparatus - Franz diffusion cell
Release Medium - 50% v/v methanolic buffer (acetate buffer of pH 5.5 + methanol)
Volume - 13 ml
Temperature - 37°C
Speed - 50 rpm

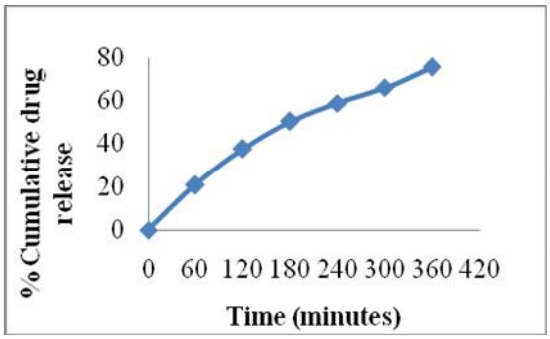
#### 3.3.3 Procedure

The drug release of the ondansetron hydrochloride in situ nasal gel was studied using Franz diffusion cell. Assembly was set and the temperature was maintained at 37°C, then 0.5 ml of in situ nasal gel of ondansetron hydrochloride was applied in the donor compartment, which was separated by the receptor compartment with the dialysis membrane (Hi Media Dialysis membrane). 2-2 ml aliquots of samples were withdrawn at regular time intervals and replaced with an equal volume of 50% v/v methanolic buffer. The samples were appropriately diluted with de-mineralized water and analyzed spectrophotometrically for Ondansetron hydrochloride content using double beam UV-visible spectrophotometer (Shimadzu® 1700) at 310 nm. Cumulative percent drug released is shown in table 2.8 and graphically represented in fig.2. [8-9]

**Table 7: Results of release studies from Ondansetron hydrochloride in situ nasal gel formulation (AR/ODS/FB/2706)**

| S. No. | Time (minutes) | Cumulative Drug Release / $cm^2$ (mg) | Percent Cumulative Drug Release |
|---|---|---|---|
| 1. | 60 | 588.56 | 20.78 |
| 2. | 120 | 1073.24 | 37.39 |
| 3. | 180 | 1420.02 | 50.15 |
| 4. | 240 | 1661.52 | 58.68 |
| 5. | 300 | 1864.64 | 65.85 |
| 6. | 360 | 2144.60 | 75.74 |

**Fig.2: Graphical representation of release study of Ondansetron hydrochloride from in situ nasal gel formulation (AR/ODS/FB/2706)**




**Result:** Developed ondansetron hydrochloride in situ nasal gel formulation showed a profile with 75.74 % permeation of drug in 6 hrs through the dialysis membrane. The flux calculated was 12.62 mcg/cm$^2$hr and the permeability coefficient was 1.419 × 10$^{-03}$cm/hr.

### 3.4 Rheological Studies

Viscosity determination of the developed domperidone in situ gel formulation was done using Brookfield viscometer (LVT model). Viscosity of the sample solution was measured over a range of 0.3 to 30 rpm speed. The hierarchy of speed was reversed from 30 to 0.3 rpm. The average of the two dial readings was used to calculate the viscosity. To evaluate viscosity change at cool condition and at body temperature, rheological measurements were taken after increasing the temperature of nasal in situ gel to 37°C. [9-10]

**Result:** Viscosity of sol and gel was found to be 60 cps and 840 cps respectively at 12 rpm.

### 3.5 Stability Studies

The physical stability, including appearance, color, and pH of the formulation was studied under various storage conditions. None of the samples showed any change in color or appearance under all storage conditions for one month period. The drug content of the formulation was estimated initially and then after one month using double beam UV-visible spectrophotometer (Shimadzu® 1700). The observations so recorded are presented in table 8.

**Table 8: Stability data for optimized in situ gel of Ondansetron hydrochloride**

| S. No. | Time | Storage Condition | Color | Clarity | pH | Drug Content |
|---|---|---|---|---|---|---|
| 1. | Initial | NA | Creamish | Clear | 6.31 | 98.90% |
| 2. | One month | 2-8°C | Creamish | Clear | 6.31 | 98.20% |
| | | RT | Creamish | Clear | 6.31 | 98.58% |
| | | 40°C | Creamish | Clear | 6.28 | 97.89% |

## 4. Summary and Conclusion

The aim of the present research study was to explore the possibility of employing the mixed solvent system to enhance drug loading and transnasal permeation of poorly water soluble drugs and formulation of its in situ nasal gel. The poorly water soluble drugs used were Domperidone and Ondansetron hydrochloride dihydrate.

The characterization of Domperidone drug sample was done using spectrophotometric analysis and melting point determination. All the observations and recorded data were identical to the values reported in literature. Calibration curves of Domperidone in distilled water, acetate buffer (pH 5.5) and 50% v/v methanolic buffer were prepared. The linearity of the calibration curves showed that Beer Lambert's law was obeyed in the concentration range of 10-50 mcg/ml at $\lambda_{max}$ 284 nm. Preformulation studies were

carried out to determine solubility, partition coefficient, and compatibility of drug with different excipients in various environmental conditions. The solubility of Domperidone drug sample was determined in distilled water, buffer solutions of pH 1.2, 2.0, 2.8, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, ethanol and 50% v/v methanolic buffer. Solubility data revealed that Domperidone is practically insoluble in water.50% v/v methanolic buffer (methanol + acetate buffer of pH 5.5) was chosen as receptor medium in release and permeation study, since the solubility in acetate buffer pH 5.5 was not sufficient to maintain sink condition. Log P value of Domperidone was determined in octanol/phosphate buffer (pH 7.4) was found to be 2.33 which indicates the lipophilicity of drug.

Solubility studies in aqueous solutions 30% w/w of various solubilizers were carried out. The order of observed solubility of drugs in solubilizers was found to be highest in PVP K30 > PVP K25 > PVP K40 > PVP K90 > PEG 600 > PEG 400. Solubility in aqueous solutions of mixed solubilizers was carried out in order to decrease the individual concentration of solubilizers used (to reduce the toxicity potential). Solubility studies were performed in aqueous solutions of three solubilizers taken in equal amount (10% w/w) keeping the total concentration constant (30% w/w). Solubility studies were also performed in aqueous solutions of four solubilizers taken in equal amount (7.5% w/w) keeping the total concentration constant (30% w/w). The solubility enhancement in aqueous solutions of mixed solubilizers was higher than that achieved using individual solubilizers (in almost all cases).

Release studies were performed in saturated solutions of various solubilizers and permeability coefficients were calculated. Higher permeability coefficients were obtained from mixed solubilizers as compared to individual solubilizers. Of all the mixed solubilizers studied, highest permeability was exhibited by PEG $600_{7.5}$ + PEG $400_{7.5}$ + Propylene $Glycol_{7.5}$ + PVP $K30_{7.5}$ i.e. $1.522 \times 10^{-02}$ cm/hr.

The characterization of Ondansetron hydrochloride dihydrate drug sample was done using spectrophotometric analysis and melting point determination. All the observations and recorded data were identical to the values reported in literature. Calibration curves of Ondansetron hydrochloride dihydrate in distilled water, acetate buffer (pH 5.5) and 50% v/v methanolic buffer were prepared. The linearity of the calibration curves showed that Beer Lambert's law was obeyed in the concentration range of 5-25 mcg/ml at $\lambda_{max}$ 310 nm. Preformulation studies were carried out to determine solubility, partition coefficient, and compatibility of drug with different excipients in various environmental conditions. The solubility of Ondansetron hydrochloride dihydrate drug sample was determined in distilled water, buffer solutions of pH 1.2, 2.0, 2.8, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, ethanol and 50% v/v methanolic buffer. Solubility data revealed that Ondansetron hydrochloride dihydrate is practically insoluble in water. 50% v/v methanolic buffer (methanol + acetate buffer of pH 5.5) was chosen as receptor medium in release and permeation study. Since the solubility in acetate buffer pH 5.5 was not sufficient to maintain sink condition. Log P value of Ondansetron hydrochloride

dihydrate was determined in octanol/phosphate buffer (pH 7.4) was found to be 1.381 which indicates the lipophilicity of drug.

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