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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF OPTIMIZED BATCH IN SITU GEL OF ONDANSETRON HYDROCHLORIDE

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ABSTRACT

Nasal route for drug delivery is the route which has been utilized from ancient times for recreational purpose. The main advantage of this route is the presence of highly permeable monolayer epithelium and rich vascularised submucosa, By this route hepatic first pass metabolism is avoided and also drug can be easily administered to brain by crossing blood brain barrier, but the main drawback of these routes is that a very low volume can be instilled (0.25 to 0.5 ml) in droplet form therefore drug loading becomes a major problem in exploring and utilizing this route. Present study aims to overcome this problem of drug loading by utilization of novel concept of mixed solvency and minimizing the drug clearance by formulating in situ muco-adhesive gel. By this concept the solubility of this drug can be easily increased at nasal cavity pH and a higher drug loading is also expected. As the drug loading of these antiemetic drugs is increased at nasal pH, the amount of drug crossing the olfactory region and blood brain barrier (BBB = highly lipophilic) will be increased. More amount of drug will reach brain's CTZ centre and will help in prevention and treatment of emesis.

Keywords: submucosa, metabolism, emesis.

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1. INTRODUCTION

Nasal route for drug delivery is the route which has been utilized from ancient times for recreational purpose. The main advantage of this route is the presence of highly permeable monolayer epithelium and rich vascularised submucosa, which is responsible for fast and complete absorption of drugs, mainly lipophilic in nature. By this route hepatic first pass metabolism is avoided and also drug can be easily administered to brain by crossing blood brain barrier, but the main drawback of these routes is that a very low volume can be instilled (0.25 to 0.5 ml) in droplet form therefore drug loading becomes a major problem in exploring and utilizing this route. Another major problem faced by this route is the rapid mucocilliary clearance of xenobiotic. Particles are transported within the visco elastic mucus blanket at a uniform rate irrespective of their viscosity, size density or composition. Even larger particles, with diameter up to 500 µg are expelled from the nasal cavity within 10 to 20 min[1-2].

Ondansetron hydrochloride dihydrate are antiemetic drug & practically insoluble in water and also exhibit a pH dependent solubility. The pH of the nasal cavity is around 5.5 - 6.5 and at this pH both of these drugs are slightly soluble. In pharmaceutical field, it is often required to prepare aqueous solutions of a variety of insoluble drugs. The ability to increase the aqueous solubility can be a valuable aid for increasing the efficacy and/or reducing adverse effects for certain drugs. Following approaches can be employed to enhance the aqueous solubility of poorly soluble drugs like Alteration of pH , Effect of dielectric constant, Use of surfactants, Complexation, Hydrotropic solubilization, Chemical modification of the drug[3].

Cosolvency is suggested to be superior to other solubilization methods, such as micellar solubilization, miscibility, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification. It only requires mixing the drug with the cosolvent in water. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system[3-4].

2. MATERIAL AND METHOD

Preformulation Studies

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of Preformulation studies is to develop a portfolio of information about the drug substance, so that this information useful to develop different dosage forms. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Melting point of Ondansetron Hydrochloride

The melting point of Ondansetron hydrochloride was determined using the open capillary method. The drug sample was filled into a capillary and it was attached with thermometer and placed in a Thiel's tube filled with liquid paraffin. The tube was heated and the temperature at which the drug melted was noted[3-4].

Solubility Study of Ondansetron Hydrochloride

The solubility of Ondansetron Hydrochloride was tasted in various common solvents. A definite quantity of drug was dissolved in respected ml of each solvent at room temperature. The solubility was observed only by visual inspection.

Partition Coefficient (log P) Determination

The partition coefficient (P) is the quotient of two concentrations and is usually given in the form of its logarithm to base 10 (log P). It is an important parameter in nasal drug delivery system. Partition coefficient of Ondansetron Hydrochloride drug sample was determined by saturating 10 ml of octanol with 10 ml of phosphate buffer pH 7.4 in a separating funnel. Intermediate shaking was done manually for 3 hrs. 10mg of drug was added to a separating funnel and intermediate shaking was done for 6 hrs. The two solvent layers were separated through separating funnel and separately filtered through a Whatman® filter paper No 41 and the amount of Ondansetron Hydrochloride dissolved in each phase, was determined spectrophotometrically at 284 nm against reagent blank prepared in the same manner on a UV-visible spectrophotometer (Shimadzu® 1700). The Partition coefficient was calculated as the ratio of concentration of drug in octanol to the concentration of drug in phosphate buffer and then its logarithm was taken.

FORMULATION OF GEL

Selection of Gelling Agents

Gelling capacity of various polymers, i.e., Poloxamer 407, sodium alginate and gellan gum; in presence of simulated nasal fluid, hydrotropic and solubilizing agents was estimated, for the selection of appropriate polymer, having good phase transition property for in-situ gel formation. Poloxamer 407 is a temperature responsive polymer which shows phase transition behaviour when temperature is raised from 25°C to 37°C. Therefore solutions of poloxamer 407 at different concentrations were studied for this property. It was observed that they exhibit desired phase transition behavior at concentration range of 15% w/v to 25% w/v. Poloxamer 407 (Pluronic® F127, BASF Mumbai, India) gels were prepared by using cold technique. Appropriate amount of poloxamer 407 was weighed in screw cap vials, 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 a blend of mixed solubilizers (PEG 400_{10} + Propylene $Glycol_{10}$ + PVP $K30_{10}$) was added in order to make it in concentration range of 15% w/w-25% w/w. Here the concentration of blend was kept constant, i.e. 2 g, and the concentration of poloxamer 407 and distilled water was varied according to the concentration required[5-6].

Table no 1: Composition of different concentration of poloxamer 407 solutions.

S. No	Amount of blend (400 + PG + K30) (g)	Amount of poloxamer 407 (g)	Distilled water with 0.002 % w/v benzalkonium chloride (g)	Concentration of Poloxamer 407 in the final solution (% w/w)	Formulation Code
1	2.0056	0.7503		15	AR/PTS/
2	2.0061	0.8005	2.2931	16	AR/PTS/
3	2.009	0.8501	2.1601	17	AR/PTS/
4	2.0072	0.8998	2.1062	18	AR/PTS/
5	2.0081	0.9499	2.0504	19	AR/PTS/
6	2.0089		2.0139	20	AR/PTS/
7	2.0092	1.0509	1.9542	21	AR/PTS/
8	2.007	1.0997	1.9047	22	AR/PTS/
9	2.0063	1.1497	1.856	23	AR/PTS/
10	2.0074	1.1999	1.8078	24	AR/PTS/
11	2.0039	1.2499	1.7504	25	AR/PTS/

Table 2: Composition of ondansetron hydrochloride *in situ* gel formulations with different concentrations of carbopol 934P.

S.No	Ingredients	Quantity (g) Formulation code					
		Blank	AR/ODS/ MS/0.1	AR/ODS/ MS/0.2	AR/ODS/ MS/0.3	AR/ODS/ MS/0.4	AR/ODS/ MS/0.5
1	407	0.95	0.95	0.95	0.95	0.95	0.95
2	934P	-	0.005	0.01	0.015	0.02	0.025
3	ODS (ODS	2	2	2	2	2	2
4	carmine	0.0125	0.0125	0.0125	0.0125	0.0125	0.0125
5	water	2.05	2.05	2.05	2.05	2.05	2.05
6	m chloride	0.002	0.002	0.002	0.002	0.002	0.002

ODS= Ondansetron hydrochloride

Preparation Method

Nasal gel of Ondansetron Hydrochloride was prepared by using cold technique.[24-25] 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 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[5-6].

Table no.3: Ingredients.

S.No.	Ingredient	Quantity (g)
1	Poloxamer 407	19
2	Carbopol 934P	0.1
3	AR/BLEND/DPD (DPD in 2 mg/g concentration)	40
4	Distilled water	41
5	Benzalkonium Chloride	0.002

3. RESULT AND DISSCUSSION

Preformulation Studies

Table no.4: Physico-chemical properties of optimized formulation.

S.No.	Parameter	Observation
1	Clarity	Clear
2	pH	6.31
3	Drug content (%)	99.90%
4	Transition temperature	37°C
5	Spreadability	Good

Melting point of Ondansetron Hydrochloride

Melting point was determined by Thiele's tube method. Melting point of Ondansetron Hydrochloride was found to be in the range of 176-181°C which was in compliance with the official value.

Solubility Study of Ondansetron Hydrochloride

Table no.5: Solubility of Ondansetron Hydrochloride in different solvents

S.No.	Solvent	Amount of drug dissolved (mcg/ml)	Inference
1	Distilled water	0.0959	Practically Insoluble
2	Ethanol	78.98	Soluble
3	50% v/v methanolic buffer**	24.23	Sparingly Soluble
4	Hydrochloric acid buffer pH (1.2)	15.31	Sparingly Soluble
5	Hydrochloric acid buffer pH (2.0)	26.29	Sparingly Soluble
6	Hydrochloric acid buffer pH (2.8)	64.49	Slightly Soluble
7	Acetate buffer pH (4.0)	32.39	Soluble
8	Acetate buffer pH (5.0)	30.79	Sparingly Soluble
9	Phosphate buffer pH (6.0)	1.51	Slightly Soluble
10	Phosphate buffer pH (7.0)	0.09	Practically Insoluble
11	Phosphate buffer pH (8.0)	0.03	Practically Insoluble
12	Alkanine Borate pH (9.0)	0.02	Practically Insoluble
13	Alkanine Borate pH (10.0)	0.02	Practically Insoluble

Table no.6: Results of solubility studies of Ondansetron Hydrochloride in 30% w/w mixed blends of various solubilizers.

S. No.	Mixed Solvent System (30% w/w)	Solubility (mg/ml)	Enhancement ratio
1	PVP $K30_{10}$ + PEG 400_{10} +Propylene $Glycol_{10}$	52.77	550.25
2	PVP $K30_{10}$ + PEG 600_{10} + Propylene $Glycol_{10}$	47.57	496.07
3	PVP $K30_{10}$ + PEG 400_{10} + PEG 600_{10}	40.14	418.59
4	PVP $K30_{10}$ + PEG 600_{10} + $Glycerine_{10}$	48.26	503.2
5	PVP $K30_{10}$ + Propylene $Glycol_{10}$ + $Glycerine_{10}$	29.66	309.26
6	PVP $K30_{7.5}$ + PEG $400_{7.5}$ + PEG $600_{7.5}$ + Propylene $Glycol_{7.5}$	43.2	450.47
7	PVP $K30_{7.5}$ + PEG $400_{7.5}$ + PEG $600_{7.5}$ + $Glycerine_{7.5}$	40.31	420.33

Values in subscript represent the individual concentration of solubilizer.

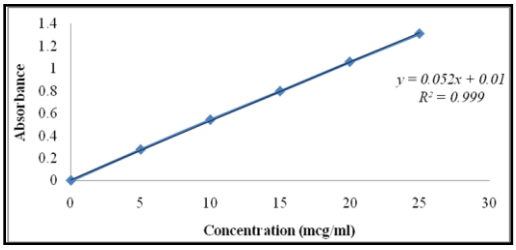
PREPARATION OF CALIBRATION CURVE

- In de-mineralized water

Table 7: Absorbance data for calibration curve of ondansetron hydrochloride in de-mineralized water at 310 nm (n=3).

S. No.	Concentration	Absorbance
1	0	0
2	5	0.276 ± 0.0081
3	10	0.542 ± 0.0130
4	15	0.797 ± 0.0112
5	20	1.059 ± 0.0026
6	25	1.311 ± 0.0077

Fig. 1: Calibration curve of ondansetron hydrochloride in de-mineralized water.



- **In acetate buffer of pH 5.5**

Table 8: Absorbance data for calibration curve of ondansetron hydrochloride in acetate buffer pH 5.5 of 310 nm (n=3).

S. No.	Concentration (mcg/ml)	Absorbance (mean ± S.D.)
1	0	0
2	5	0.250 ± 0.0020
3	10	0.495 ± 0.0118
4	15	0.757 ± 0.0083
5	20	0.994 ± 0.0086
6	25	1.248 ± 0.0081

Fig. 2: Calibration curve of ondansetron hydrochloride in acetate buffer of pH 5.5.

- In 50% v/v methanolic buffer of pH 5.5

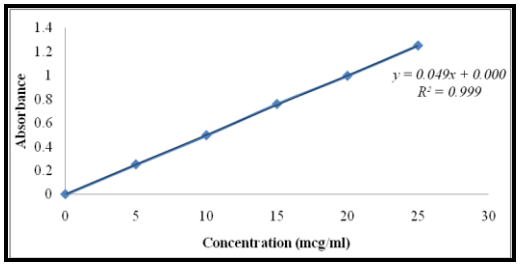
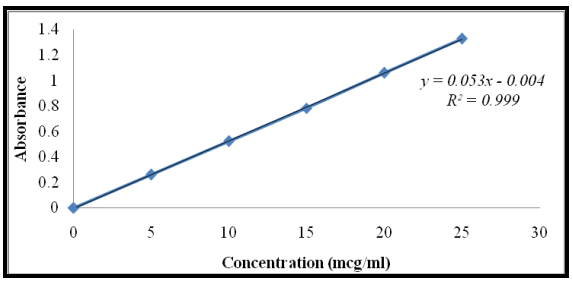


Table 9: Absorbance data for calibration curve of ondansetron hydrochloride in 50% v/v methanolic buffer at 310 nm (n=3).

S. No.	Concentration (mcg/ml)	Absorbance (mean ± S.D.)
1	0	0
2	5	0.262 ± 0.0025
3	10	0.524 ± 0.0124
4	15	0.784 ± 0.0092
5	20	1.060 ± 0.0105
6	25	1.329 ± 0.0091

Fig. 3: Calibration curve of ondansetron hydrochloride in 50% v/v methanolic buffer.



Partition Coefficient

The octanol-water partition coefficient (log P) of drug sample was found to be 13.81 which was similar to that reported in literature (2.4).[42]

IN-VITRO DRUG RELEASE STUDY

Table 10: Release studies from Ondansetron Hydrochloride *in situ* nasal gel formulation.

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	2144.6	75.74

4. CONCLUSION

Maximum increase in solubility is obtained in a 30% w/w mixed blend of (PVP $K30_{7.5}$ + PEG $400_{7.5}$ + PEG $600_{7.5}$ + Propylene $Glycol_{7.5}$), which is 550.250 times more as compared to solubility of Ondansetron Hydrochloride in water. Also, by utilizing the blend of four, the individual concentration is reduced minimizing the chances of toxicity and irritation.

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^2hr and the permeability coefficient was 1.419×10^{03}cm/hr.

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