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DESIGN AND EVALUATION OF pH- TRIGGERED METOCLOPRAMIDE HYDROCHLORIDE MUCOADHESIVE IN SITU NASAL GELLING SYSTEM

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ABSTRACT

Purpose: *Patients having nausea and vomiting associated with cancer and radiation therapy, surgery, as well as pregnancy with difficulty to swallow are a population of choice for this kind of treatment, especially in the case of nausea. There is a need for nasal drug delivery of Metoclopramide hydrochloride in Specific patient populations where the use of commercially available intravenous and oral dosage forms may be inconvenient and/or unfeasible.*

The poor bioavailability and therapeutic response exhibited by the conventional nasal sprays and drops due to rapid nasal elimination of the drug may be overcome by the use of in situ gelling systems that are instilled as drops into the nasal cavity and undergo a sol-to-gel transition in the nasal cavity. Hence, the purpose of the present work was to formulate and evaluate a nasal drug delivery system for an Anti migraine- antiemetic drug, Metoclopramide Hydrochloride, based on the concept of pH-triggered in situ gelation. ***Methods:*** *Polyacrylic acid (Carbopol® 934) was used as the gelling agent in combination with hydroxyl propyl methylcellulose (Methocel K4M) which acted as a viscosity enhancing agent. Compatibility studies of the drug excipients were carried out using differential scanning calorimetry (DSC) and FTIR. The prepared formulations were characterized for clarity, pH, drug content, sol-to-gel transition (gelation study) , viscosity study, in vitro drug release and stability.* ***Results:*** *The clarity, pH and drug content of the developed formulation were found to be satisfactory. The developed formulation was therapeutically efficacious, stable and provided sustained drug release over*

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an 8-h period. ***Conclusions:*** *The developed formulation is a viable alternative to conventional nasal drops by virtue of its ability to enhance bioavailability through its longer nasal residence time and ability to produce sustained drug release. Also important factor is the ease of instillation and the reduced frequency of instillation resulting in better patient acceptance.*

KEYWORDS : *pH-triggered, in-situ, antimigraine, mucoadhesive, metoclopramide hydrochloride*

INTRODUCTION

For systemic therapy, drugs are traditionally administered by oral and parenteral routes. However in many instances, oral administration is unsuitable when the drug undergoes significant degradation in the gastrointestinal tract or is metabolized to a high degree via the first pass effect in the liver [1]. Nonparenteral routes for drug delivery include nasal, buccal, pulmonary and transdermal routes. All these application routes are suitable for self-administration in an ambulatory setting. The nasal application is the only route of administration, which offers rapid onset of action; high absorption of small molecular weight hydrophobic drugs, relatively high bioavailability, and avoidance of first pass effect and ease of administration by patients favors this route of application [2]. Traditionally, the nasal route has been used for delivery of drugs for local treatment such as nasal congestion, allergy, migraine and infections.

Metoclopramide hydrochloride, a substituted benzamide, is a dopamine receptor antagonist active on gastrointestinal motility. Its antiemetic efficacy has been demonstrated for prevention of nausea and vomiting associated with cancer and radiation therapy, surgery, as well as pregnancy. Patients with difficulty to swallow are a population of choice for this kind of treatment, especially in the case of nausea. In this perspective nasal administration of Metoclopramide hydrochloride represents an interesting alternative administration route to others [3]. Several strategies were tested to improve nasal absorption of drugs; one of them was the use of bioadhesive polymers. Bioadhesive can increase nasal absorption of drugs with several ways such as increasing the residence time of drugs in the nasal cavity, opening tight junctions between the epithelial cells. Carbomers are bioadhesive polymers used in attempts to formulate mucoadhesive drug delivery systems for application to various mucosal sites such as nasal application [4, 5]. Another approach is the use of absorption enhancers, such as surfactants, bile salts, fusidate derivatives, fatty acids, phospholipids and Cyclodextrins [6, 7].

The present studies were designed to see whether intranasal administration of Metoclopramide Hydrochloride could be an efficient route for systemic delivery. So, the mucoadhesive dosage forms of Metoclopramide Hydrochloride were prepared such as in situ gel using combination of CRB 934P and HPMC K4M. In vitro and ex vivo release characteristics of all the formulations were investigated. Histological examinations with light microscopy were used to assess the effect of formulations on the nasal mucosa after ex vivo experiments. In vitro experiments were carried on sheep nasal mucosa.

There are several ways of prolonging the presence of drugs in the nasal area, such as increasing the viscosity of the dosage form by adding water-soluble polymers [8, 9]. An alternative approach aimed at decreasing mucociliary clearance time of drugs and, consequently, their bioavailability is the use of polymeric solutions which change to a gel as a result of exposure to the physiological temperature, pH or ionic composition of the nasal fluid [10]. Depending on the method employed to cause sol-to-gel phase transition in the nasal cavity, the following three types of systems are recognized: pH-triggered systems e.g.

cellulose acetate hydrogen phthalate latex [11], temperature-dependent systems e.g. Pluronics [12] and Tetronics [13] and ion-activated systems e.g. GelriteTM [14], and gellan [15].

The present work aimed to formulate an pH induced in situ gel for Metoclopramide Hydrochloride with Carbopol 934P and to investigate its viscosity, in vitro release, the nasal mucoadhesion force and gel strength.

1. MATERIALS AND METHODS

2.1 MATERIALS

Metoclopramide Hydrochloride and Carbopol 934P were gift samples from Sun pharmaceutical Ltd. (Baroda, India), HPMC K4M was a gift sample from Gujarat Pharmalab Pvt Ltd. (Ahmadabad, India) Calcium chloride, Sodium hydroxide (S. D. Fine Chemicals, Mumbai, India) were obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

2.2. Preformulation Studies:

2.2.1 Determination of λmax of Metoclopramide Hydrochloride

A stock solution of 100µg/ml of Metoclopramide hydrochloride was prepared by dissolving 10 mg in 100 ml of deionized distilled water. The resulting solution was scanned between 200 nm to 400 nm using double beam UV-visible spectrophotometer 2201-systronics, India.

2.2.2 Differential scanning calorimetry and FTIR study were used to evaluate the thermal behavior of pure drug and physical mixture of the drug and excipients.

Drug- excipients compatibility study:

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to evaluate the thermal behavior of pure drug and physical mixture of the drug and excipients using a DSC-60, shimadzu corporation, Japan. Samples, 5–10 mg, were weighed and sealed in standard aluminum pans and then scanned over a temperature range from 50 to 300^{0}C at a heating rate of 10.00 ^{0}C/min.

2.3 Preparation of in situ gelling system: [16]

The formulations as given in Table 1 were prepared by dispersing Carbopol 934P in double distilled deionized water with continuous stirring (Thermostatic hot plate with magnetic stirrer, Remi, Mumbai) until completely dissolved and allowed to hydrate overnight. For the preparation of solution, first HPMC K4M was added in deionized water and allowed to hydrate. Then Carbopol was sprinkled over this solution and allowed to hydrate overnight. After complete hydration of polymers a separate solution of Metoclopramide hydrochloride and Sodium Chloride was added to the polymeric solution. The resultant solution was thoroughly mixed, Benzalkonium Chloride was then added and mixing was confirmed until a uniform and clear solutions were formed. Final volume was made by adding required volume of deionized water. All the formulations were adjusted to pH 4.5 to 5.5 by using freshly prepared 0.5 M Sodium Hydroxide solution.

Table 1: Formulas for developed pH dependent nasal *in-situ* gel for Metoclopramide hydrochloride

Formulation code	P-1	P-2	P-3	P-4	P-5	P-6	P-7	P-8	P-9	P-10	P-11	P-12
*Metoclopramide hydrochloride (%w/v)	10	10	10	10	10	10	10	10	10	10	10	10
Carbopol934P (%w/v)	0.2	0.4	0.6	0.2	0.4	0.6	0.2	0.4	0.6	0.2	0.4	0.6
HPMC K4M (%w/v)	--	--	--	0.2	0.2	0.2	0.4	0.4	0.4	0.6	0.6	0.6

Benzalkonium chloride(%w/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
De-ionized water (ml)	25	25	25	25	25	25	25	25	25	25	25	25

*Each formulation contain 10mg/ml of Metoclopramide hydrochloride

2.4 Evaluation of in Situ Gels

2.4.1 Appearance [18]

The developed formulations were inspected visually for clarity in solution form by observing in white and black background.

1.4. 2. pH of the Gel [15]

pH of the each formulation was determined by using pH meter (Systronics MK-VI. Naroda, Ahmadabad.) The pH meter was first calibrated using solutions of pH 4 and pH 7.

1.4. 3. Gelation Studies [18]

Gelation studies were carried out in glass culture tube.The studies were carried out using 0.5 M Sodium hydroxide, which resembles nasal fluid. The formulation (250µl) was carefully placed into the cavity of the cup using a micropipette and 2 ml of gelation solution was added slowly. Gelation was assessed by visual examination.

2.4. 4 Content uniformity [19]

Formulations were tested for content uniformity. Vials (n =3) containing the formulation were properly shaken for 2–3 min. One mL of the formulation was transferred into a 100-mL volumetric flask. Fifty mL of simulated nasal fluid was added. The formed gel was completely crushed with the help of a glass rod, followed by vigorous shaking until the formed gel got completely dispersed to give a clear solution. The volume was adjusted to 100 mL with simulated nasal fluid. The solution was filtered through a 0.45-mm filter membrane and the drug concentration was determined with a UV-Visible spectrophotometer at 272.4 nm.

2.4.5 Rheological Studies [18]

Viscosity of the administered formulation is an important factor in determining residence time of drug in the nasal cavity. The prepared solutions were allowed to gel in the simulated nasal fluid and then the viscosity determination were carried out by using Brookefield viscometer LVDVE model in spindle no S-63 for gel and S-61 and S-62 for solution, angular velocity ran from 10-100 rpm. Viscosity of the formulations increased with increase in polymer concentration. The hierarchy of shear rate was reversed and average of two reading was used to calculate viscosity (Figure 1 and 2)

2.4.6 Gel strength determination [8]

A sample of 50g of the nasal gel was put in a 100 ml graduated cylinder and gelled in a thermostatically controlled water bath at 37°C. A weight of 35 g was placed onto the gelled solution. The gel strength, which is an indication for the viscosity of the nasal gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5 cm into the gel.

2.4.7 Determination of Mucoadhesive Strength [9]

The mucoadhesive strength was determined by using the modified method reported by Choi et al[10].The mucoadhesive potential of each formulation was determined by measuring a force required to detach the formulation from nasal mucosal tissue. A section of sheep nasal mucosa was fixed on each of two glass slides using thread. 50mg of gel was placed on first slide and this slide placed below the height adjustable pan. While another slide with mucosal section was fixed in inverted position to the underside of the same pan. Both the slides with gel formulation between them held in contact with each other, for 2min to ensure intimate contact between them. Then weight was kept rising in second pan until slides get detached from each other. The mucoadhesive force expressed as the detachment stress in dynes/cm^2 was determined from the minimal weight that detached the mucosal tissue from surface of each formulation.

Mucoadhesive Strength (dynes/cm^2) = mg/A, (1)
Where, m = weight required for detachment in gram,
g= Acceleration due to gravity (980cm/s^2),
A = Area of mucosa exposed.
The nasal mucosa was changed for each measurement.

2.4.7 In-vitro Release Studies

Drug release from gel was tested with nasal diffusion cell, using dialysis membrane (mol.wt.12, 000-14,000) with permeation area of 2 cm2. 20ml of simulated nasal fluid pH 6.4 was added to the acceptor chamber. Gel containing drug equivalent to 10mg was placed in donor compartment. At predetermined time points (1 hr), 1ml sample were withdrawn from the acceptor compartment, replacing the sampled volume with SNF after each sampling for a period of 8 hrs. The samples were suitably diluted and measured spectrophotometrically at 272.4nm. The concentration of drug was determined from a previously constructed calibration curve. (y = 0.039x + 0.003, R^2 = 0.9988)

2.4.8 In –vitro Permeation Study [9]

Fresh nasal tissue was removed from nasal cavity of sheep obtained from local slaughter house. Tissue was inserted in the nasal diffusion cell (Franz diffusion cell) with permeation area of 0.785 cm^2. Similar way as in drug release study gel containing drug equivalent to 10mg was kept in donor compartment. At predetermined time point sampling was done. Blank samples (without drug) were run simultaneously throughout the experiment. Amount of drug permeated was determined by UV-spectrophotometry. Cumulative percentage drug release after1h (t_1) and 8 h (t_8) were calculated using the Beer-Lambert calibration curve in the linearity range of 0–20 μgmL^{-1}.

2.4.9 Histopathological Evaluation of Mucosa [11]

The histopathological evaluation of tissue incubated in phosphate buffer (pH 6.8) for 8 h after collection was compared with tissue incubated in diffusion chamber with formulation. Tissue was fixed in 10% buffered formalin, routinely processed and embedded in paraffin. Sections were cut on glass slides and stained with hematoxylin and eosin. Sections were examined under a light microscope to detect and damage to the tissue.

2.4.10 Statistical analysis

The data were analyzed by using two-way analysis of variance (ANOVA). P values lower than 0.05 were considered statistically significant.

2.4.11 Stability study

pH triggered in situ nasal gel formulation (P-11) containing Carbopol934P 0.4 and HPMCK4M 0.6% mucoadhesive polymers were tested for stability under the actual condition of storage (refrigeration condition). Gels were stored in clean, dry, airtight moisture proof bottles, kept away from light. The gel samples were withdrawn after 30 days and evaluated for gelation temperature, gel strength, mucoadhesive strength, pH and drug content. To assess long term stability of the prepared gelling systems at 40 °C/75% relative humidity (RH) in the stability chamber for 3 months. The samples were withdrawn at different time intervals (0, 1, 2 and 3 months) and observed for physical characteristics, drug content and in vitro drug release characteristics. The results were supported by statistical analysis using student't' test and ANOVA (significance level $p < 0.05$).

3. RESULTS AND DISCUSSION

Metoclopramide Hydrochloride exhibited λmax at 272.4 nm. Linearity was observed in the range of 2 to 20µg/ml with the r^2 value of 0.998. FTIR and DSC studies were carried out on pure drug as well as its combination with selected polymers. At the outset, as a preformulation study, IR characteristics of Metoclopramide hydrochloride with the polymer resemble almost the IR structural characteristics of pure drug indicated the compatibility between the drug and polymers. The infrared spectra of Metoclopramide hydrochloride and physical mixture of formulation containing drug, carbopol and HPMCK4M shows in figure 1 and Figure 2 respectively. Drug spectrum shows prominent peaks at 3379.05 cm^{-1}, 3396.41 cm^{-1}, 1595.02 cm^{-1}, 703.97 cm^{-1} corresponding to the -NH stretching, -OH stretching, C=O and C-Cl stretching respectively (Figure 1). Drug: polymer mixture spectrum (Figure 2) shows absence of characteristic drug peaks at

3379.05 cm^{-1}. Subtraction spectrum did not show the characteristic peak of drug at 3379.05 cm^{-1} corresponding to –NH stretching. In both cases it was observed that the characteristic bands did not shift appreciably, suggesting the lack of any interaction between the drug and excipients.

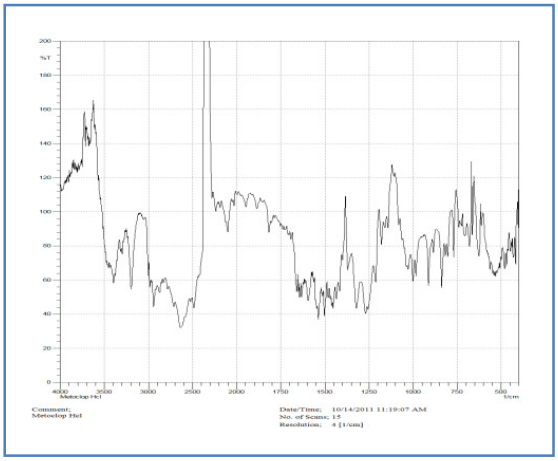

Figure 1: FTIR spectra of pure Metoclopramide hydrochloride

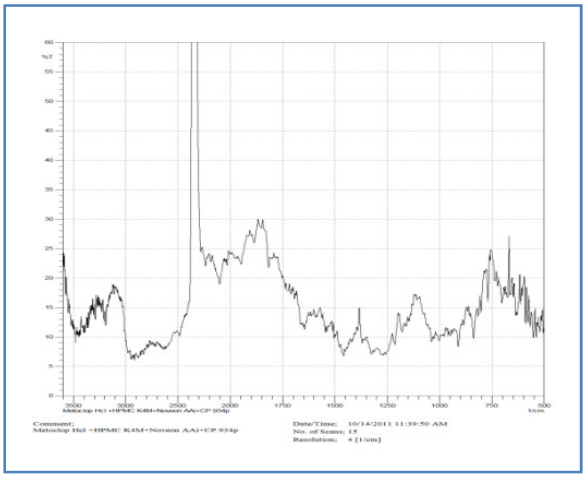

Figure 2: FTIR spectra of physical mixture of Metoclopramide HCl + HPMC K4M + Carbopol 934P

DSC thermograms were recorded for pure Metoclopramide hydrochloride and physical mixture of drug and polymers (Figure 3 and 4). In both cases it was observed that the characteristic endotherm (corresponding to melt of the drugs) did not shift appreciably, suggesting the lack of any interaction between the drug and excipients.

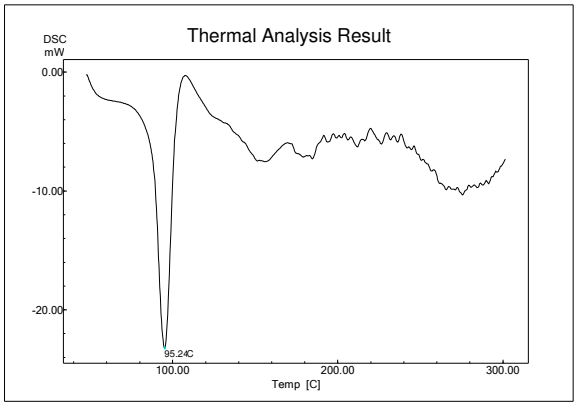

Figure 3: DSC spectra of pure Metoclopramide hydrochloride

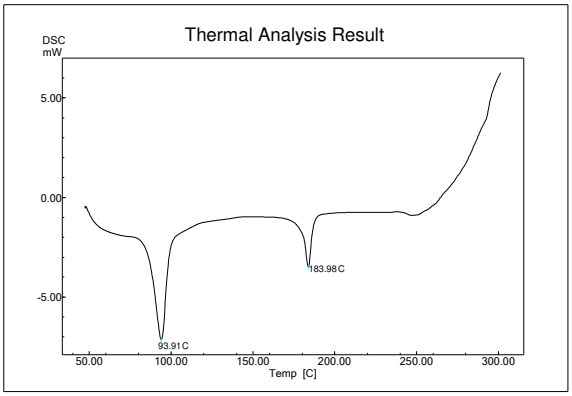

Figure 4: DSC spectra of physical mixture of Metoclopramide hydrochloride + HPMC K4M+ Carbopol 934P

Appearance, pH and Drug content

All the formulations were translucent and were found to be clear. The pHs of the formulations P-1 to P-12 were 5.64 ± 0.21 to 6.43 ± 0.25. Drug content was in the range of 96.58 ± 2.10 to 100.69 ± 0.21. All these observations are listed in table 2.

Table 2: Physichochemical evaluation of various pH dependent in situ gelling formulations

Form. Code	Gelling capacity	pH	Appearance	Drug content (%) S.D	Gel strength (Sec)	Mucoadhesive force (dynes/cm$^{2)}$ ±S.D.
P-1	-	6.14 ±0.20	clear	99.76 ±0.12	12.60 ±0.57	2401.00 ±120.05
P-2	++	6.04 ±0.19	clear, Tranlucent solution	98.39 ±2.78	15.40 ±0.99	4381.83 ±120.05
P-3	++	5.80 ±0.10	clear	99.21 ±0.78	18.50 ±0.42	3301.38 ±180.07
P-4	+	6.43 ±0.25	clear	98.32 ±1.19	21.47 ±0.57	3921.63 ±151.06
P-5	+++	6.03 ±0.21	clear, Tranlucent solution	99.86 ±0.52	27.67 ±0.42	5202.17 ±242.59
P-6	+++	5.80 ±0.10	clear, Tranlucent solution	98.19 ±1.89	29.60 ±2.26	5022.09 ±91.69
P-7	+++	5.89 ±0.41	clear	99.83 ±1.24	26.87 ±1.27	5222.18 ±180.08
P-8	+++	6.27 ±0.12	clear	98.39 ±0.16	32.70 ±1.27	5822.43 ±681.75
P-9	++++	5.64 ±0.21	clear, milky white	96.58 ±2.10	37.50 ±1.06	7403.08 ±916.90
P-10	+++	6.13 ±0.59	clear	100.65 ±0.16	35.80 ±1.91	8203.42 ±1510.60
P-11	+++	5.98 ±0.25	clear	100.69 ±0.21	44.13 ±1.34	10404.33 ±346.55
P-12	++++	5.72 ±0.22	clear, milky white	100.82 ±0.18	49.90 ±1.77	11004.58 ±346.55

Values expressed as Mean±S.D, n =3

Gel strength and Bioadhesion force

Gel strength of carbopol based pH dependent in situ gelling formulations varied from 12.60± 0.57 to 49.90 ± 1.77sec.

Mucoadhesive strength was determined in term of detachment stress i.e. force required to detach the formulation from mucosal surface. Results of mucoadhesion strength of all formulations were found to be varied from 2401.00±120.05 to 11004.58 ± 346.55 as per the given data (Table 2). Determination of mucoadhesive strength in terms of detachment stress showed that adhesive property increases with addition of carbopol 934. It may be due to carbopol polymer which indicates that it is the availability of carboxyl group that determines bioadhesion. Carbopol has very high percentage of (58%-68%) of carboxyl group that under goes hydrogen bonding with sugar residues in oligosaccharide chain in mucus membrane, resulting in strengthened network between polymer and mucus membrane. [15].The stronger the mucoadhesive force, the more it can prevent the gelled solution getting detached from the nasal mucosa. But if the bioadhesive force is too excessive, the gel can damage the nasal mucosal membrane.

Rheological studies

The formulations (P-2 to P-12) showed Pseudo plastic behavior that is with increase in shear rate the viscosity of the formulation were reduced (Figure 5 and 6). At pH 4.4 the formulations exhibited low viscosity and were in solution form. An increase in pH to 6.5 (pH of nasal fluid) using 0.1 N NaOH transformed the solution into gel and showed increase in viscosity.

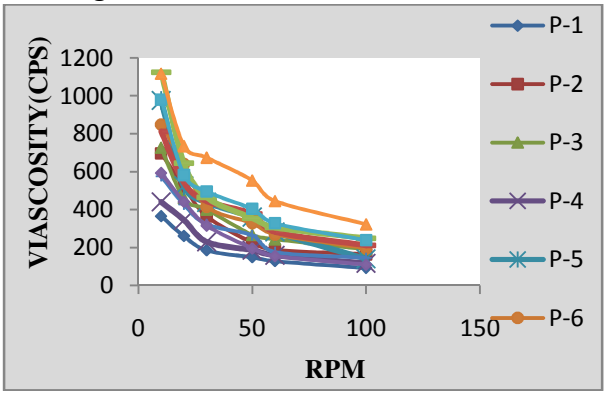

Figure 5: Rheological profile of pH - dependent in situ gelling formulations (Solution)

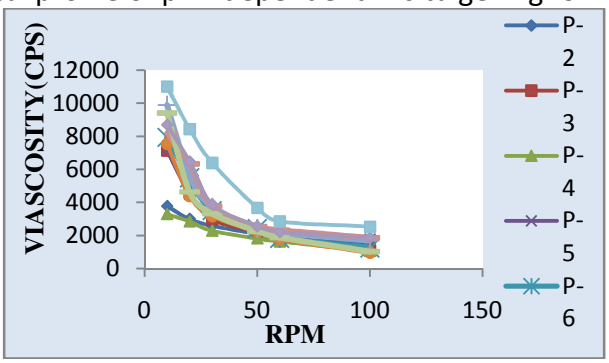

Figure 6: Rheological profile of pH - dependent in situ gelling formulations (Gels)

In vitro release study

In vitro drug release of the formulation P-1 to P-12 is showed in table 3 and 4, Figure 7 and 8. The formulations P-8 and P-11 showed good sustained release varied from 99.01 ± 1.55 and 96.25 ± 0.99 for the period of 8 h respectively.

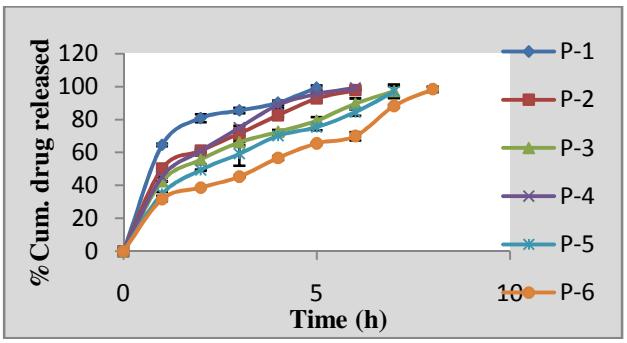

Figure 7: In vitro release profile of pH- dependent (Carbopol based) in situ gels (P1-P6)

Table 3: In vitro release profile of pH- dependent (Carbopol based) in situ gels (P1-P6)

Time(h)	%Cumulative drug released					
	P-1	P-2	P-3	P-4	P-5	P-6
	%CDR ±S.D.	%CDR ±S.D.	%CDR ±S.D.	%CDR ±S.D.	%CDR ±S.D.	%CDR ±S.D.
0	0.00	0.00	0.00	0.00	0.00	0.00
1	64.73 ±0.78	50.35 ±0.14	42.58± 0.21	45.24 ±0.16	34.93 ±1.19	31.65 ±1.07
2	80.95 ±2.42	61.22 ±1.03	55.71 ±2.58	61.02 ±1.07	49.40 ±0.37	38.67 ±0.14
3	85.62 ±1.66	71.61 ±1.29	66.24 ±1.81	75.17 ±1.29	59.25 ±7.19	45.32 ±0.27
4	90.32 ±1.38	82.73 ±1.07	72.55 ±1.37	89.05 ±1.85	70.23 ±0.27	56.75 ±1.07
5	99.49 ±1.35	92.88 ±1.81	79.41 ±2.30	95.64 ±0.53	75.53 ±1.83	65.58 ±0.59
6	--	97.96 ±0.59	89.71 ±3.34	99.33 ±0.81	84.62 ±2.17	70.01 ±2.57
7	--	--	97.33 ±4.19	--	97.18 ±3.37	88.30 ±0.78
8	--	--	--	--	--	98.48 ±1.65

Values expressed as Mean±S.D, n =3

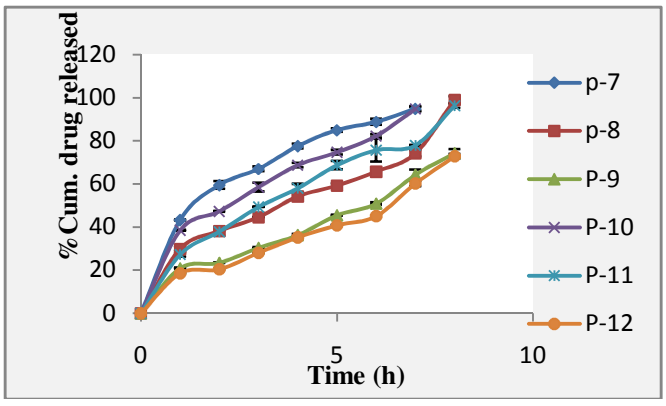

Figure 8: In vitro release profile of pH- dependent (Carbopol based) in situ gels (P7-P12)

Table 4: In vitro release profile of pH- dependent (Carbopol based) in situ gels (P7-P12)

Time(h)	%Cumulative drug released					
	P-7	**P-8**	**P-9**	**P-10**	**P-11**	**P-12**
	%CDR ±S.D	%CDR ±S.D.	%CDR ±S.D.	%CDR ±S.D.	%CDR ±S.D.	%CDR ±S.D.
0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.00	43.24 ±0.21	29.87 ±0.92	20.87 ±0.24	38.46 ±0.14	27.24 ±1.03	18.52 ±0.13
2.00	59.47 ±1.80	38.18 ±0.18	23.40 ±0.12	47.23 ±0.21	37.86 ±1.88	20.45 ±0.26
3.00	66.95 ±1.06	44.57 ±0.08	30.35 ±0.34	58.49 ±2.07	49.33 ±0.07	28.00 ±0.18
4.00	77.54 ±1.07	54.18 ±1.94	36.25 ±0.55	68.69 ±1.08	57.95 ±2.06	35.23 ±0.13
5.00	84.93 ±0.79	59.23 ±1.02	45.45 ±0.13	74.67 ±1.07	68.66 ±1.94	40.79 ±0.24
6.00	88.77 ±1.36	65.68 ±1.36	50.84 ±0.59	82.22 ±0.80	75.67 ±5.35	45.03 ±0.16
7.00	94.84 ±1.03	74.20 ±1.54	64.21 ±2.42	94.76 ±1.07	77.92 ±0.05	60.19 ±1.29
8.00	--	99.01 ±1.55	74.27 ±1.80	--	96.25 ±0.99	72.79 ±1.07

Values expressed as Mean±S.D, n =3

Drug release mechanism

The drug release data were subjected to various Pharmacokinetic parameters like Zero order, First order, Higuchi square root and Korsmeyer's Peppas model to know the Pattern of drug release showed in table 5. The r^2 values suggest that the drug release from the mucoadhesive system predominately followed Higuchi's square root of time kinetics, as the values for r^2 *Q* vs. *t*1/2 (0.936-0.999) were found. First order rate kinetic coefficient was varied from 0.840 to 0.993 and zero order kinetic coefficients were found to be 0.927 to 0.995. Whereas Release exponent, *n*, was >0.5 but <1, for P-1, 2, 3,4, 9,10,11 and P-12, indicating that release mechanism was followed an anomalous or non-Fickian release and suggesting a coupled erosion– diffusion mechanism for the tested Metoclopramide hydrochloride mucoadhesive system. Selected optimized formulation P-8 was followed Fickian release and P-11 was followed non- Fickian type release followed to zero order kinetics (Table 5).

Table 5: Regression co-efficient (r^2) values of different kinetic models.

Form Code	Zero order plots $R^{2(a)}$	First order plots $R^{2(a)}$	Higuchi's plots $R^{2(a)}$	Korsmeyer's peppas equation $n^{(b)}$	Types of release
P-1	0.968	0.840	0.936	0.250	Fickian
P-2	0.986	0.931	0.989	0.384	Fickian
P-3	0.995	0.966	0.991	0.403	Fickian
P-4	0.941	0.969	0.998	0.477	Fickian
P-5	0.991	0.988	0.999	0.489	Fickian
P-6	0.980	0.978	0.991	0.462	Fickian

P-7	0.979	0.984	0.993	0.413	Fickian
P-8	0.927	0.971	0.996	0.443	Fickian
P-9	0.983	0.972	0.972	0.516	Non- Fickian
P-10	0.990	0.978	0.995	0.425	Fickian
P-11	0.974	0.993	0.992	0.579	Non - Fickian
P-12	0.961	0.974	0.979	0.533	Non- Fickian

(a) Correlation coefficient

(b) The diffusional exponent is based on Korsmeyer-Peppas equation, $M_t/M_\infty=kt^n$

Ex- vivo diffusion studies

All the optimized formulation P-11 was carried drug permeation study on nasal mucosa. Results of cumulative % drug permeated were found to be 77.63 ± 0.89, 75.27 ± 1.01 and 90.60 ± 3.31 for 240 min respectively (Figure 9).

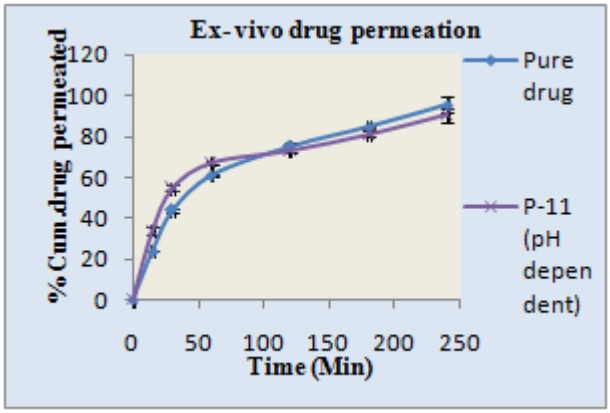

Figure 9: Ex- vivo drug diffusion profile of optimized formulations (P-11)

Histopathological studies

After ex-vivo diffusion studies of optimized formulation in phosphate buffer (pH 6.4) 240 min, Histopathological studies were carried out of mucosa. The light micrograph was taken of nasal mucosa following diffusion study of 8 h. Examination of tissue showed None of the severe signs such as appearance of epithelial necrosis, sloughing of epithelial cells was detected (Figure.10).

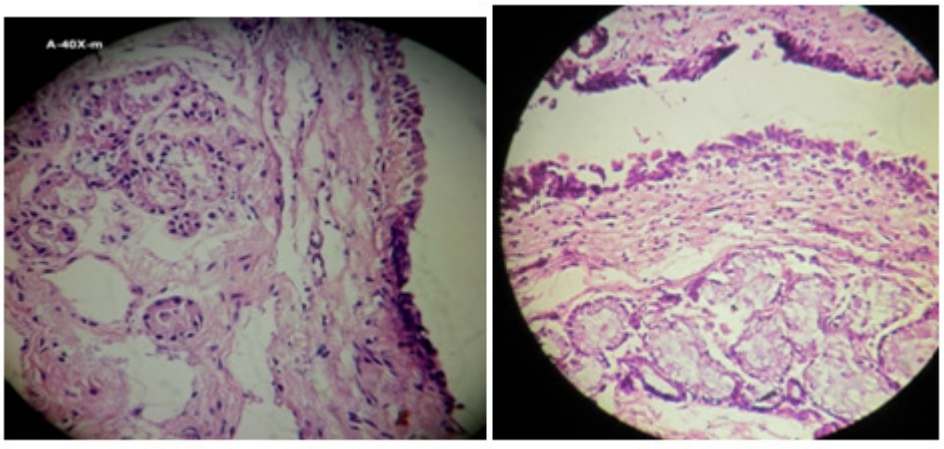

Figure 10: Light Photomicrograph of the Nasal Mucosa Normal Mucosa (A) and Metoclopramide hydrochloride pH-dependent in situ nasal gel treated Mucosa (B).

Stability studies

Stability studies was carried out of the most satisfactory formulations P-11 (containing0.4%Carbopol 934P with 0.6% HPMC K4M) at 30 ± 2 °C / 65 ± 5 % RH and 40 ± 2 °C / 75 ± 5 % RH for two months to assess their long term stability as per ICH guidelines.

At various time intervals of 30 days and 60 days end, samples were evaluated. There was no major change in the various physicochemical parameters evaluated like drug content, pH and clarity. There was no statistically significant difference between the initial values and the results obtained during stability studies (Table 6).

Table 6: In vitro parameters of most satisfactory formulations (P-11) during stability studies

Form. Code	Time (Days)	Evaluation Parameters			
		Storage conditions	Clarity	pH	Drug content(%)
P-11	0		clear	5.92±0.16	98.99±0.65
	30	At 30±2°C 65±5%RH	clear	5.70±0.10	98.25±1.39
		At 40±2°C 75±5%RH	clear	5.80±0.26	97.50±1.05
	60	At 30±2°C 65±5%RH	clear	5.930.15	97.41±0.59
		At 40±2°C 75±5%RH	clear	5.82±0.26	98.29±0.43

Values expressed as Mean±S.D, n =3

CONCLUSION:

Metoclopramide hydrochloride was successfully formulated in pH-triggered in situ gelling system using Carbopol® 934P (0.4%, w/v) as a pH-triggered In-situ gelling agent in combination with HPMC K4M (0.6%, w/v) as a viscosity enhancing agent. It was found that the gelling systems can flow easily under non-physiological condition (25 ◦C, pH 5.8) and undergo rapid gelation under physiological condition (35 ◦C, 6.8). The in situ gelling system can support sustained drug release over an 8-h period, and the release mechanism in vitro was dependent on two simultaneous processes: water migration in to the in situ gelling system and drug diffusion. Stability data recorded over a 3-month period under (4±1) ˚C, room temperature (25±1) ˚C, and accelerated temperature (45±1) ˚C condition indicated that the formulation was stable. In vitro results indicated that the in situ pH-triggered gelling system is a viable alternative to conventional nasal drops or nasal sprays by virtue of its ability to enhance bioavailability through its longer nasal residence time and the ability to sustain drug release. More importantly, it was a suitable medium for Metoclopramide hydrochloride, the pH-sensitive drug, to be used as novel intra nasal drug delivery system.

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