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Research Article

DEVELOPMENT OF METOCLOPRAMIDE HYDROCHLORIDE *IN SITU* GEL: NASAL DELIVERY AND PHARMACOKINETICS IN NEW ZEALAND RABBITS

UPENDRA C GALGATTE[1,2]*, PRAVIN D CHAUDHARI[3]

[1]Department of Pharmaceutics, Modern College of Pharmacy, Nigdi, Pune, Maharashtra, India. [2]Jawaharlal Nehru Technological University, Hyderabad, Telangana, India.[3]Department of Pharmaceutics, Modern College of Pharmacy, , Nigdi, Pune, Maharashtra, India.
Email: ucgpharm@rediffmail.com

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ABSTRACT

Objective: Systemic bioavailability of metoclopramide hydrochloride (MCH) is 32–80% by oral route. The study was targeted to develop *in situ* gel of MCH for nasal delivery and to study its pharmacokinetics in healthy rabbits. Pre-systemic metabolism can be overcome.

Methods: Poloxamer 407 (P407) aqueous solutions were prepared by cold method. In 3^2 factorial design, independent variables were Carbopol 934P (C934P) and polyethylene glycol 6000 (PEG 6000), and dependent responses were gelation temperature, mucoadhesive strength, and drug release. A Pharmacokinetic study was carried out in New Zealand rabbits. The optimized *in situ* gel (1 mg/ml) was compared with marketed Reglan® (2 mg/2 ml) injection.

Results: F2 was an optimized formulation. The study showed that P407 solutions formed a gel at nasal temperature 34°C having mucoadhesive strength 807.12±3.45 dyne/cm^2. MCH release was found to be 93.74±1.31% within 6 h. Histopathological examination of formulation F2 exhibited safety to the nasal mucosa. The pH of formulations was 5.1±0.1 to 5.6±0.1 in the range of pH of nasal cavity. Plasma samples were analyzed by liquid chromatography/mass spectroscopy (LC/MS). The area under curve AUC_{0-4} for *in situ* gel by nasal route was 2716±4.62 ng.h/ml and for marketed solution by intravenous route was 2874±1.08 ng.h/ml. These were comparable. Nasal bioavailability was found 94.50% from *in situ* gel. Duration of action was longer, and steady-state concentration was found for *in situ* gel.

Conclusion: *In situ* gel was capable to release MCH in systemic circulation. *In vivo* study in rabbits has proved the improved bioavailability of MCH administered nasally. The optimized gel preparation was found to be promising for improved bioavailability.

Keywords: Antiemetic, Mucoadhesive, Nasal, Poloxamer 407, Thermoreversible.

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INTRODUCTION

Metoclopramide hydrochloride (MCH) is a potent antiemetic. It is effective in the treatment of nausea and vomiting usually occurred with migraine, cancer therapy, and pregnancy. Although it is used in this treatment, it has oral bioavailability 32–80% due to large pre-systemic metabolism [1]. Although parenteral administration is recommended over oral, it has low patient compliance. On the other hand, oral doses are likely to get vomit before its systemic absorption. In such a situation, intranasal delivery would be the best alternative. However, low residence time of drug is a limitation of the nasal route. This may affect bioavailability of a drug. Hence, the dosage form or delivery system should be designed in such a way that it should overwhelmed the limitations by considering anatomical as well as physiological features of nasal cavity. This should ultimately result in a little or no any mucocilliary clearance of administered preparation [2]. Hence, mucoadhesive formulations can help the formulator to extend the residence time due to their adhesive property. This improves the possibility of getting more bioavailability of drug for local and systemic effects [3]. Normally pharmaceutical gels are viscous preparations being more semisolid in nature creates difficulty in administration into a nasal cavity. On the other hand, mucoadhesive powders, although can be sprinkled on nasal mucosa, are not favored by one or the other reason. They may give a gritty feel with or without irritation. To way out the situation, a mucoadhesive *in situ* gel appears promising approach in the hands of formulator. This is due to its liquid nature during administration in the form of a drop and viscous nature immediate after reaching to the site of nasal mucosa.

Poloxamer 407 (P407) is well-known polymer having thermosensitive gelling properties with low toxicity and irritation, water solubility at low temperature, and compatibility with other chemicals. In addition, it has also good drug release characteristics. It is an ABA triblock copolymer of the hydrophilic polyethyleneoxide unit and the hydrophobic polypropyleneoxide unit [4]. The polymer exists as a mobile viscous liquid at low temperatures, however, forms a semisolid gel with an increase in a temperature.

The rationale of the present work is to avoid first pass metabolism by non-invasive route thereby improving the bioavailability of MCH. Therefore, the objective of the present study was to develop a thermosensitive mucoadhesive *in-situ* gel which would enhance nasal residence time of MCH and absorption of MCH across the nasal mucosa. Therefore, a pharmacokinetic study was investigated by using such a gel in New Zealand rabbits.

MATERIALS AND METHODS

Materials

MCH was kindly gifted by Leben Lab. Pvt., Ltd. Akola, India. P407 was kindly provided by BASF, Mumbai, India, and Carbopol 934P (C934P) from Ranq Remedies, Thane, India.

Method

Preparation of mucoadhesive in situ gel

P407 (19% w/v) and MCH equivalent to 10 mg were solubilized in distilled water containing PEG 6000. This was left at 4–6°C

until a clear solution was obtained. In that, C934P was added with continuous stirring and again kept for overnight, and then, sorbitol and benzalkonium chloride were added and prepared formulation which was stored in cool place and evaluated for different parameters [5].

Formulation optimization

A 3^2 factorial design [6] was applied to the formulation that showed the satisfactory gelation temperature (GT), mucoadhesive strength, and *in vitro* drug release to see the effect of varying concentration of C934P (X_1) and PEG 6000 (X_2) on various responses, i.e., GT(Y_1), mucoadhesive strength (Y_2), and percent drug release (Y_3). In this design, there were two variables and three levels of each variable.

Evaluation of formulations

A compatibility study was carried out to establish whether any chemical interaction exists between drug and excipients used in formulation [7]. These studies were carried out using Fourier transform infrared spectrometer (FTIR) (4100, JASCO, Japan).

The GT of the aqueous solution of P407 was measured using procedures reported by Miller and Doravan [8]. A test tube containing about 2 ml of a gel was immersed in a water bath, and temperature was increased with increments of 2°C and left to equilibrate for about 5 min at each new temperature. The samples were examined for gelation (T_1). This is the characteristic point of gel where the meniscus of the gel inside the test tube does not move even after slanting through 90°.

The pH of formulation was determined by taking 1 ml P407 solution and diluted by distilled water to make 25 ml. pH of the resulting solution was determined using digital pH meter (Equip-Tronics EQ-610, India).

To determine drug content, a formulation of 1 ml was taken in 10 ml volumetric flask, diluted with distilled water to 10 ml. One ml from this solution was again diluted with 10 ml of distilled water. Finally, the absorbance of prepared solution was measured at 272 nm using UV visible spectrophotometer (Shimadzu UV-1800, Japan) [9].

The P407 solution sample was retained in small sample adapter of Brookfield programmable RVDV-II+Pro viscometer (Brookfield Eng. Lab., Inc. USA) for viscosity estimation. The water circulation jacket was managed to buildup the temperature of the sample gradually up to 40°C [10]. Viscosity at various temperatures was documented.

The mucoadhesive strength was measured in terms of detachment stress of the formulation. This was determined using a modification of the mucoadhesive strength measuring device used by Choi *et al*. [11] A fresh nasal mucosa of sheep was cut into a section. This was mounted on a glass vial fortified with the mucosal side out into glass vial. The vials were stored at 36°C for 5 min. The vials were adjusted in such a way that the gel was placed between the mucosal sides of both vials. The height of vials was adjusted as one vial is connected to balance and the other fixed with the P407 gel (0.5 ml). Instead of putting physical weights, water from a burette was allowed to trip in a beaker drop by drop till the complete detachment of vials. The two vials detach as the weight of water increased gradually. This assembly was prepared in laboratory. Mucoadhesive strength (dyne/cm^2) was the bare minimum weight of water that detached the two vials. Mucoadhesive strength = mg/A where, m is weight required for detachment in gram, g is acceleration due to gravity (980 cm/s^2), and A is area of mucosa exposed.

***Ex vivo* permeation studies**

A fresh nasal mucosa was carefully removed from the nasal cavity of a sheep obtained from a local slaughterhouse. By taking utmost care while handling, the mucosa was fit in a diffusion cell exposing a permeation area of 2.98 cm^2. Phosphate buffer pH 6.4 at 34±1°C was added to the acceptor chamber. The temperature within the chambers was maintained at 34°±1°C throughout the experiment. A time of 20 min of pre-incubation was left; pure drug solution and formulation equivalent to 10 mg of MCH was placed in the donor chambers of two different diffusion cells [12]. At pre-determined time points, 1 ml samples were withdrawn from the acceptor compartment, and the same volume was replaced with phosphate buffer pH 6.4 after each sampling. This was continued till the last sampling that is for a period of 6 h. The samples withdrawn were filtered through Whatman filter paper and kept ready for analysis. The amount of drug permeated was determined using UV-visible spectrophotometer at 272 nm using calibration curve where linearity range was 2 µg/ml to 10 µg/ml and $R^2 = 0.9998$.

Histopathological evaluation of mucosa

A fresh sheep nasal mucosa was stored in 10% v/v of formalin solution to avoid bacterial growth. After removal of unwanted portion from the mucosal membrane, it became ready for use. Histological study was carried out on fresh sheep nasal mucosa treated with 1 ml optimized gel formulation for 6 h. After treatment, tissue was cut and stained with eosin. Mucosa treated with phosphate buffer pH 6.4 was a negative control. At the same time the mucosa treated with isopropyl alcohol was positive control [5]. These tissue sections were examined under a light microscope (Motic, DMW-B1-223 ASC) to detect any harm to the tissues during *in vitro* permeation.

Design of bioavailability study

New Zealand white strain six male rabbits weighing 1.75–2.5 Kg were procured from National Toxicology Centre, Pune. The rabbits were housed properly 7 days in animal house with good ventilation and plenty of water before the commencement of animal study. For bioavailability and pharmacokinetic determination, the study includes administering the optimized gel formulation by nasal route and intravenous (i.v.) route. The protocol was approved having approval no MCP/IAEC/33/2011 by the Institutional Animal Ethical Committee of Modern College of Pharmacy, Nigdi, Pune. The rabbits fasted for 18 h before and during the pharmacokinetic study. The animals were conscious throughout the duration of the experiments and were held in rabbit restrainers during blood sampling. A 0.1 ml gel (in sol form equivalent to 1 mg metoclopramide) was deposited into the right nostril of the rabbits of Group 1 using a micropipette inserted 1 cm into the right nostril. Reglan® (2 mg/2 ml), the marketed formulation, 1 ml was injected into the marginal ear vein of Group 2 [13]. After experimentation, rabbits were kindly preserved taking utmost care of them in the animal house.

Sample collection and analysis

Respective formulations were administered to each group as mentioned above. The blood samples were withdrawn from ear marginal vein at time intervals of 10, 60, 120, 180, and 240 min and collected in EDTA tubes to prevent clotting of blood. Further, plasma was separated from blood samples by centrifuging at 5000 rpm for 10 min. Plasma samples were collected and stored at −20°C untill analysis. Drug concentrations in plasma samples were determined using liquid chromatography–mass spectrometry (LC/MS) method.

Frovatriptan succinate 20 µl was used as an internal standard. This was extracted from plasma samples. Extracting solvent was mixture of diethyl ether and dichloromethane, 1:1 v/v. A 2 ml was added and mixed then centrifuged at 10,000 rpm. After flash precipitation, the supernatant was decanted with chilled methanol. All the contents were evaporated with the help of nitrogen evaporator at 35°C. Samples were reconstituted with 200 µl of mobile phase and used for LC/MS analysis. LC (Shimadzu Prominence) with MS detector (API 400 QTR) was used. Analytical column C-18, 150 mm × 4.6 mm with 5 µm (Chromatopack), and analyst software (Applied Biosciences; AB SCIEX) was used. For plasma, the mobile phase was made up of 0.1% formic acid in methanol (organic):ammonium acetate buffer 10 Mm (aqueous) in the proportion of 85:15 v/v. The flow rate was maintained at 1.0 ml/min at ambient temperature. Study samples of plasma were run after extraction. These samples were run along with the calibration curve for quantitative analysis.

Pharmacokinetic studies

GraphPad Prism software of version 5.01 was used to estimate pharmacokinetic parameters. The area under the curve (AUC), peak

plasma concentration (C_{max}), and time to attain peak concentration (T_{max}) were obtained from these plots. These were estimated from the study samples (plasma) versus time plot.

RESULTS

Evaluation of formulations

FTIR spectrum of pure drug and optimized batch were obtained. They are shown in Fig. 1. All the characteristic peak of MCH were present in formulation indicating compatibilities between drug and polymers and confirmed that there is no significant change in chemical integrity of drug.

Independent variables and dependent variables with their levels are shown in Table 1.

Table 2 shows that formulation having a low level (0.25% w/v) of C934P showed lower GT, whereas formulation having a high level of C934P (0.75% w/v) showed higher GT. It indicates that the mucoadhesive polymer used, i.e., C934P had significant effect on GT, and addition of water-soluble PEG 6000 produces an increase in GT. The response surface plot studied for GT(Y_1) is depicted in Fig. 2a.

Results of mucoadhesion test are shown in Table 2. These results indicate that C934P (X_1) and PEG 6000 (X_2) both have effect on mucoadhesive strength. As the level of C934 P increases, the mucoadhesive strength increases, and as the level of PEG 6000 increases, the mucoadhesive strength decreases. The response surface plot studied for the response (Y_2), i.e., mucoadhesive strength Fig. 2b shows significant effect of variables on the response (Y_2). The pH of all formulation was found in the range of 5.1±0.1 to 5.6±0.1 which lies in the nasal pH range 4.5–6.4.

Table 2 shows the results of percent drug content for all formulations. The drug content varies in the acceptable range. This was carried out in triplicate.

Table 2 shows the viscosity values obtained for all formulations. The viscosity directly depends on the polymeric content of formulation.

Table 1: Factors and levels in the optimization of *in situ* gel formulation

Independent variables	Levels		
	(−1) Lower	(0) Middle	(+1) Upper
C934P (X_1) %w/v	0.25	0.5	0.75
PEG 6000 (X_2) %w/v	0.5	1	1.5

C934P: Carbopol 934P; PEG 6000: Polyethylene glycol 6000. Levels in columns indicate quantities.

The viscosity increases with increase in concentration of C934 P and decreases with PEG 6000.

In vitro study

The *in vitro* release kinetics were carried out for all formulations using pH 6.4 as diffusion medium. It was found that a concentration of PEG 6000 increases drug release increase as it act as release enhancer and mucoadhesive polymer decreases drug release. The response surface plot studied for the response (Y_3), i.e., percent drug release, shown in Fig. 2c, showed the significant effect of variables on the response (Y_3).

In vitro permeation studies

Formulation F2 demonstrated good drug release profile with favorable gelation and viscosities. Hence, the formulation F2 was chosen as an optimized formulation to observe the permeation of drug through nasal mucosa. *In vitro* permeation was observed for aqueous drug solution and formulation F2. The drug release was estimated using UV spectrophotometer at 272 nm. It was observed that drug release from the optimized formulation F2 was 93.74% at the end of 6 h and from aqueous solution was 86.81% within 3 h as shown in Fig. 3.

The release of MCH from the gel formulation was found to be up to 6 h and that may be due to the inverse relationship between viscosity and drug release.

Histopathological evaluation of mucosa

The microscopic observation specifies that the optimized formulation has no any significant effect on the microscopic structure of mucosa as shown in Fig. 4a-c. No any cell destruction or removal of the epithelium from the nasal mucosa was observed after application of formulation and buffer pH 6.4.

Multiple regression analysis for 3^2 factorial design

The responses obtained from factorial design were subjected to multiple regression analysis. Responses studied were GT (°C), mucoadhesive strength (dyne/cm^2), and drug release (%).

The polynomial form for the response (Y_1) GT (°C),

$$Y_1 = 23.34+36.89X_1-5.14X_2+2.68X_1X_2+4.00X_1^2-32.00X_2^2 \quad (1)$$

The polynomial form for the response (Y_2) mucoadhesive strength (dyne/cm^2),

$$Y_2 = 89.44+264.11X_1+23.71X_2+360.15X_1X_2+89.23X_1^2+34.62X_2^2 \quad (2)$$

The polynomial form for the response (Y_3) drug release (%),

$$Y_3 = 89.44+6.29X_1+9.33\ X_2-3.88\ X_1X_2-2.99X_1^2+0.085X_2^2 \quad (3)$$

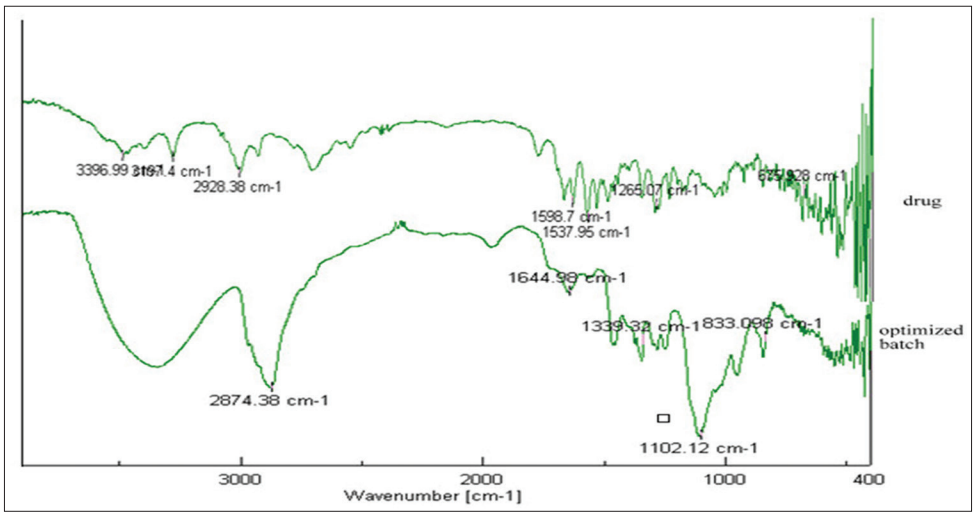

Fig. 1: Fourier transform infrared spectrum of metoclopramide hydrochloride and optimized batch F2

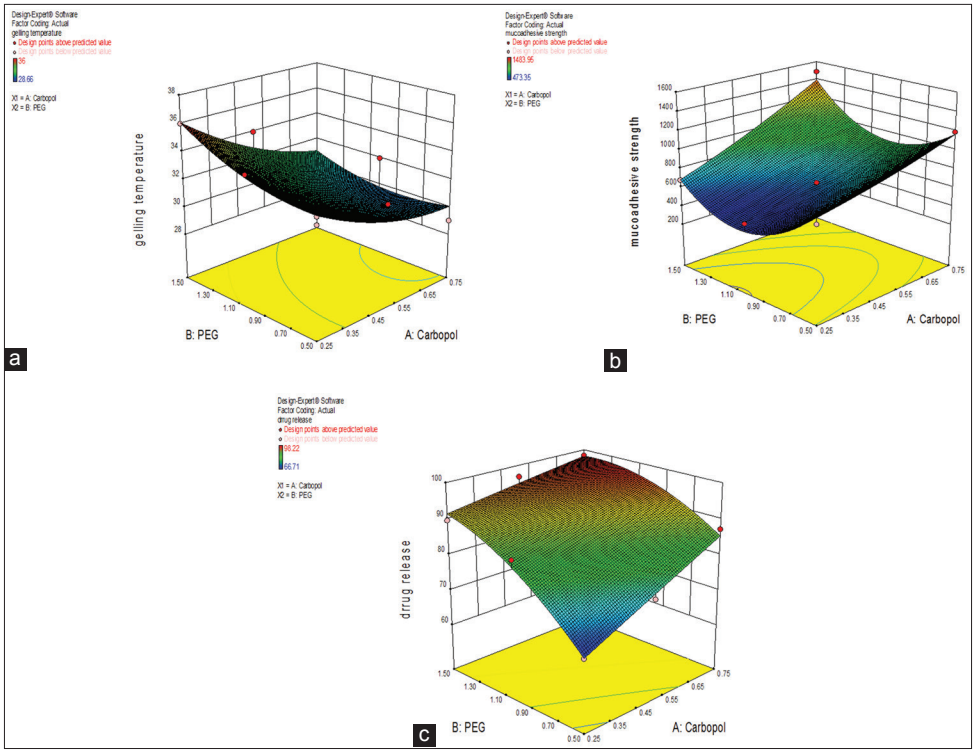

Fig. 2: Response surface plot (a) gelation temperature, (b) mucoadhesive strength, and (c) % drug release

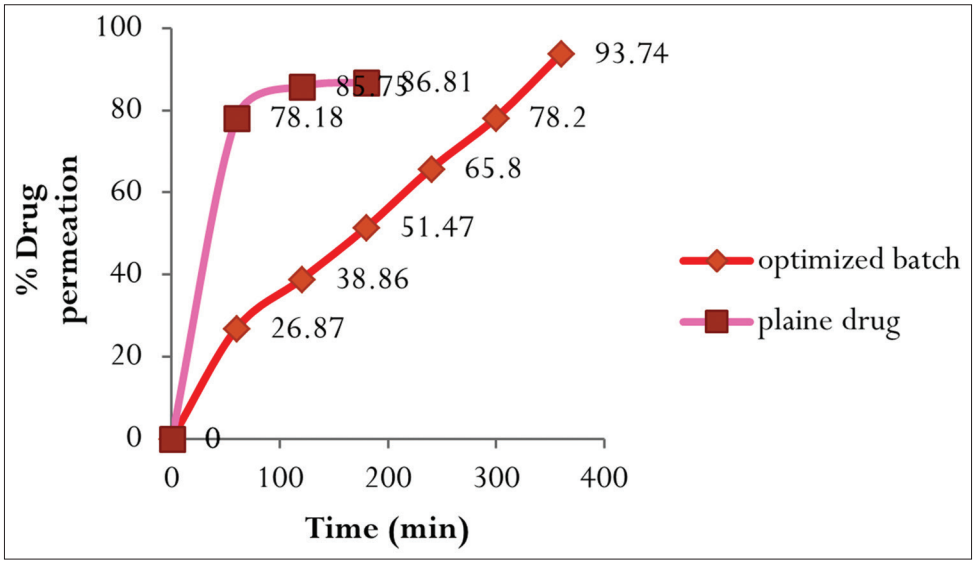

Fig. 3: Percent cumulative release of optimized batch and plain drug through nasal mucosa

Table 2: Evaluation parameters of formulation

Batch	Gelation Temperature (GT) (oC)	Gel melting Temperature (GMT) (oC)	pH	Drug Content (%)	Mucoadhesive strength (dyne/cm^2)	Viscosity(cps)
F1	32.70±1.10	41.21±1.25	5.2±0.1	99.89±1.27	653.81±2.30	1505±2.89
F2	34.71±1.11	40.44±1.19	5.3±0.1	100.6±1.21	807.12±3.45	1218±1.42
F3	28.62±1.20	45.22±1.11	5.2±0.1	96.12±1.29	474.35±1.10	921±1.15
F4	33.31±1.22	41.34±1.13	5.1±0.1	94.90±1.20	1010.89±2.75	1120±2.50
F5	32.10±2.11	38.77±1.11	5.1±0.1	96.70±1.24	1189.43±2.70	1365±3.25
F6	29.32±1.14	42.46±2.00	5.5±0.1	96.76±1.26	743.87±1.78	930±1.20
F7	35.31±1.21	38.55±1.13	5.3±0.1	94.25±1.27	680.56±1.62	1284±3.06
F8	35.30±1.10	39.23±1.12	5.6±0.1	91.22±1.21	1485.82±3.16	1210±1.78
F9	31.73±1.19	38.24±1.19	5.6±0.1	103.55±1.20	921.63±2.88	1125±2.60

Mean ± S.D.; n=3

Analytical procedure

MS tune of MCH is shown in Fig. 5. Figure indicates m/z ratio for metoclopramide parent ion at 227.2 and m/z ratio for metoclopramide daughter ion at 300.2.

Bioavailability study

Pharmacokinetic parameters were calculated from the observed plasma concentration time profiles. The values of C_{max}, maximum time taken to attend plasma concentration (T_{max}), and AUC_{0-4} (ng.h/ml) are shown in Fig. 6. MCH attained a high concentration of 23.50±5.02 ng/ml and decreases after 120 min for nasal *in situ* gel. For i.v. marketed preparation, after 60 min, C_{max} was 45.70±6.12 ng/ml. It was observed that concentration of drug in plasma (C_{max}) was achieved twice higher by i.v. as compared to nasal *in situ* gel. The T_{max} was 120 min and 60 min for nasal *in situ* gel and i.v., respectively. The AUC_{0-4} was 2716±4.62 and 2874±1.08 ng.h/ml for nasal *in situ* gel and i.v. solution, respectively, but the bioavailability for nasal *in situ* gel was found to be 94.50%.

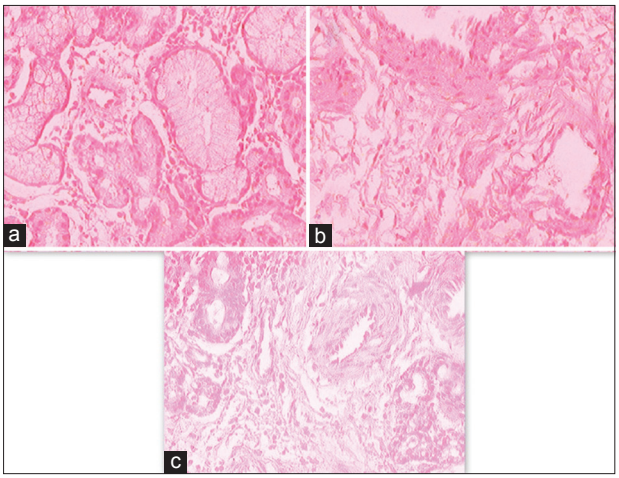

Fig. 4: Histopathology of nasal mucosa (a) nasal mucosa treated with optimized *in situ* gel formulation, (b) nasal mucosa treated with phosphate buffer pH 6.4 (negative control), (c) nasal mucosa treated with isopropyl alcohol (positive control)

DISCUSSION

The prepared formulations were colourless, viscous with no any aggregations and grittiness[14]. The physiological range of the nasal mucosa temperature lies between 32 and 35°C [15]. Our target was to develop a nasal mucoadhesive thermoreversible gel with a phase transition temperature in the range 25–34°C, which would remain liquid at room temperature and gel after nasal administration. P407 decreases GT as its concentration increases because as temperature increases, the number of micelles formed increasesas a consequence of the negative coefficient of solubility of block copolymer micelles. Sooner or later, the micelles become immmobile and a gel is formed [16]. The pH of the formulation was kept in the range of 5.1±0.1 to 5.6±0.1 to avoid irritation to the nasal mucosa, and other-related changes by formulation could produce. A Viscosity of formulation increases in the presence of mucoadhesive polymer and decreases with PEG 6000. Response surface plot, regression equation, and p-values showed that C934P had significant effect on GT and mucoadhesive strength. It lowers GT due to its ability to bind with polyethylene oxide chain present in poloxamer molecules. This in turn promotes dehydration and causing an increase in entanglement of nearby molecules [10]. But the addition of PEG 6000 increases GT due to an interference of PEG with a process of micellar association of poloxamer chain [17]. Since PEG 6000 act as release enhancer but its addition was discontinued when the GT of in-situ gel approaches 34°C. The mucoadhesive strength increases with increasing concentration of C934P. This acts as a good mucoadhesive polymer due to the presence of a high percentage of (58–68%) carboxylic group [18]. Hydrogen bonding is favored in the presence of these groups with sugar residue from oligosaccharide chains in the mucus membrane. This further results in the creation of strong linkage between polymer and mucus membrane. Hence, higher mucoadhesive strength leads to prolonged withholding that could overcome mucocilliary clearance and thereby increased absorption across mucosal tissue. This in line improves bioavailability. PEG 6000 and C934P had a significant effect on metoclopramide release. There was a decrease in drug release with C934P increase as a viscosity of formulation increases since C934P leads to acid-base interaction and formed a reservior of ion pair of the carbopol metoclopramide hydrogel which could contribute slow drug release [19]. However, PEG 6000 shows release enhancing effect due to its higher water solubility and lowering viscosity effect [20].

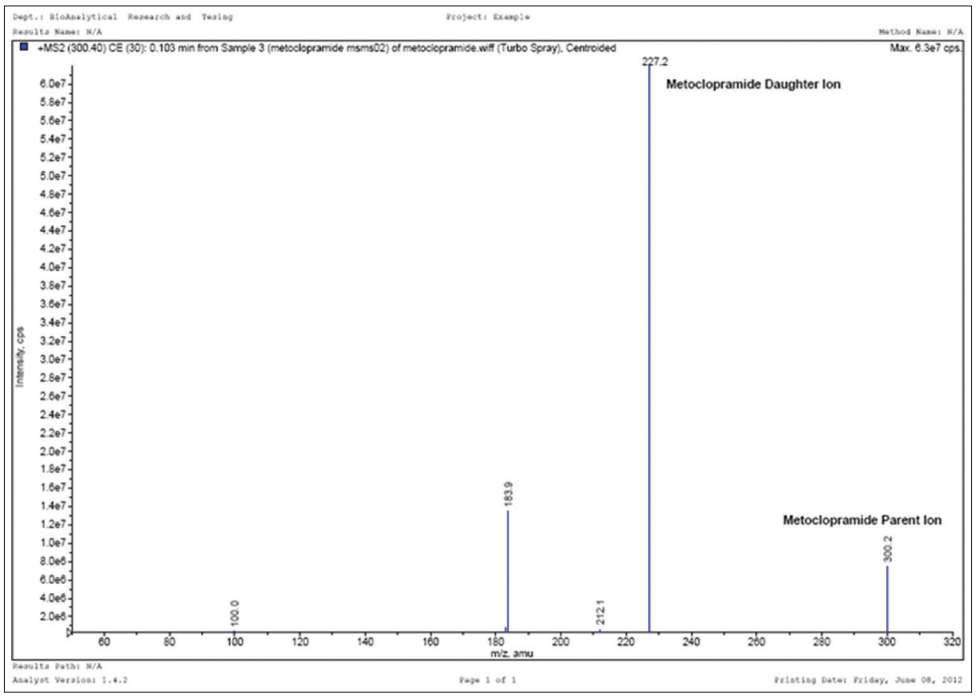

Fig. 5: Mass spectrometry tune of metoclopramide hydrochloride

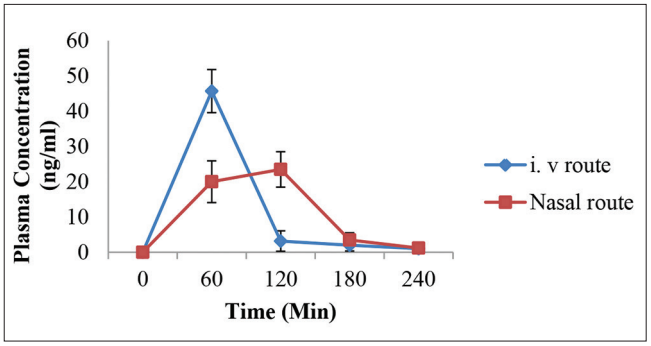

Fig. 6: Drug concentration in plasma after nasal and i.v. administration

Similar results were obtained by Thanvi DA [8]. Some formulations showed Fickian and some showed non-Fickian (anamolous) release kinetic revealed by (n) values between 0.26 and 0.94, which indicate that release of MCH followed diffusion and coupled erosion diffusion mechanism [21].

The use of mucoadhesive formulation was not only limited to their bioadhesive efficacy but safety is also concerned. Hence, it was necessary to investigate the safety of optimized formulation. The histopathological study revealed the safety of tested formula. An *ex vivo* study was performed to observe permeation of drug through the nasal mucosa. The release of MCH from gel formulation was found lower as compared with aqueous drug solution. This can be explained with the inverse relation between viscosity and drug release. A Viscosity of the formulation influences the release of MCH from gel formulation [5].

The pharmacokinetics of the optimized formulation, F2, were studied in rabbits. The marketed preparation through i.v. administration was decided to select for comparison because marketed preparations are already clinically proven, and maximum AUC is obatined by i.v. route. Thereby, we can decide really where the prepared *in situ* gel stands for systemic bioavailability by nasal route. From pharmacokinetic studies, it can be concluded that *in situ* gel formulation was capable to release the drug in systemic circulation since bioavailability by nasal route was found to be 94.50%, which is closer to i.v. route [13]. The point to be noted here is that the values of AUC are comparable for both nasal and i.v. route though there is a difference in the T_{max} and C_{max} of both the formulations. Although the physical nature of the formulation is different (*in situ* gel and solution) and route of administration is also different (nasal and i.v., respectively), the bioavailability is likely to be produced the same. Fig. 6 clear cut states that the duration of the action is greater for *in situ* gel by nasal route than solution by i.v. route. This is because the significant steady-state concentration is found available in the blood for a considerable time. This is supported by the slow elimination rate of drug observed in the curve through *in situ gel.* The steady-state concentration or a plateau observed in the curve indicates that the *in situ* gel was in contact with a nasal mucosa of rabbit for a longer time incapacitating a mucociliary clearance successfully. Noha *et al.* reported earlier that bioavailability of MCH was 40-80 % if gel of MCH administered orally. And also it has been proved that bioavailability can be improved if MCH is formulated into an in-situ gel and administer nasally. Therefore, the order of bioavailability is i.v. > nasal> oral. These findings are in full support with the findings mentioned by Duchateau *et al.* [22]. According to them, the order of bioavailability for alprenolol was the same.

CONCLUSION

The Mucoadhesive thermo reversible *in situ* gel prepared with P407 and C934P can be successfully used to deliver MCH effectively by nasal route. The AUC for nasal *in situ* gel was comparable with the marketed solution of MCH administered intravenously.

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AUTHORS' CONTRIBUTION

Upendra C Galgatte, Pravin D Chaudhari contributed to justify authorship criteria.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

REFERENCES

1 Mahajan HS, Gattani S. *In situ* gels of Metoclopramide hydrochloride for intranasal delivery: *In vitro* evaluation and *in vivo* pharmacokinetic study in rabbits. Drug Deliv 2010; 17:19-27.
2 Jadhav KR, Gambhire MN, Shaikh IM, Kadam VJ, Pisal SS. Nasal drug delivery system-factors affecting and applications. Curr Drug Ther 2007; 2:27-38.
3 Thorat YS, Sarvagod AM, Kulkarni SV, Hosmani AH. Treatment of mouth ulcer by curcumin loaded thermoreversible mucoadhesive gel: A technical note. Int J Pharm Pharm Sci 2015; 7: 399-402.
4 Ruel-Garie´py E, Leroux JC. *In situ*-forming hydrogels: Review of temperature sensitive systems. Eur J Pharm Biopharm 2004; 58: 409–26.
5 Majithiya RJ, Ghosh PK, Umrethia ML, Murthy RSR. Thermoreversible mucoadhesive gel for nasal delivery of Sumatriptan. AAPS PharmSciTech 2006; 7: E1-E7.
6 Pagar SA, Shinkar DM, Saudagar RB. Development and evaluation of in situ nasal mucoadhesive gel of metoprolol succinate by using 32 factorial design. Int J Pharm Pharm Sci 2014; 6: 218-23.
7 Kavita K, Rajas NJ. Sustained ophthalmic delivery of levofloxacin hemihydrate from an ion activated *in situ* gelling system. Int J PharmTech Res 2011; 3: 702-6.
8 Thanvi DA. Formulation and evaluation of in-situ gel of metoclopramide hydrochloride for nasal delivery [dissertation]. Pune University; 2012.
9 Miller SC, Donovan MD. Effectivity of poloxamer 407 gels on the miotic activity of pilocarapine nitrate in rabbits. Int J Pharm 1982; 12:142-52.
10 Shaikh H, Gattani S, Nerkar P. In-situ gelling system based on thiolated gellan gum as new carrier for nasal administration of dimenhydrinate. Int J Pharm Sci Nanotech 2009; 2:544-50.
11 Choi HG, Oh YK, Kim CK. *In situ* gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability. Int J Pharm 1998; 165: 23-32.
12 Sahu BP, Sharma HK. Nasal delivery of felodopine using hydrogel matrix. J Global Trends Pharm Sci 2011; 2: 296-309.
13 Noha MZ, Gehanne AA, Nahed DM, Seham S, Abd E. Enhance bioavailability of metoclopramide hydrochloride by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. Eur J Pharm Sci 2007; 32: 296-307.
14 Kassab HJ, Thomas LM, Jabir SA. Development and physical characterization of a periodontal bioadhesive gel of Gatifloxacin. Int J App Pharm 2017;9:31-6.
15 Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavity in health and disease. Adv Drug Del Rev 1998; 29: 3-13.
16 Kabonov AV, Batrakova EV, Alkahov VU. Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. J Control Release 2002; 82:189-212.
17 Edsman K, Carlfors J, Petersson R. Rheological evaluation of poloxamer as an in situ gel for ophthalmic use. Eur J Pharm Sci 1998; 6:105–12.
18 Efentakis M, Koutlis A, Vlachou M. Development and evaluation of oral multiple-unit and single-unit hydrophilic controlled-release systems. AAPS PharmSciTech 2000; 1: E34.
19 Jimenez-Kairuz AF, Allemandi DA, Manzo RH. Equilibrium properties and mechanism of kinetic release of metoclopramide from carbomer hydrogels. Int J Pharm 2003; 250:129-36.
20 Desai SD, Blanchard J. In vitro evaluation of pluronic F127-based controlled-release ocular delivery systems for pilocarpine. J Pharm Sci 1998; 87:226–30.
21 Peppas NA. Analysis of fickian and non-fickian drug release from polymers. Pharm Acta Helv 1985; 60:110–11.
22 Duchateau, Zuidema J, Albers W, Merkus M. Nasal absorption of alprenolol and metoprolol. Int J Pharm 1996; 34:131–6.