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FORMULATION AND EVALUATION OF MUCOADHESIVE *IN-SITU* NASAL GEL OF CYCLOBENZAPRINE HYDROCHLORIDE

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Keywords:

Cyclobenzaprine hydrochloride, Thermo-sensitive, Nasal *in-situ* gel, Poloxamer 407, HPMCK4M, PEG, Sustain release

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ABSTRACT: Cyclobenzaprine hydrochloride (CBZ) is a muscle relaxant. It has 33% bioavailability due to its first pass effect and hence posses problems in the development of oral sustained release formulations. Mucoadhesive thermo reversible *in-situ* nasal gel of Cyclobenzaprine HCl was designed and developed to sustain its release due to the increased nasal residence time of the formulation. Poloxamer 407 (PF 127) was selected as it has excellent thermo sensitive gelling properties. HPMCK4M was added to impart mucoadhesive to the formulation, and PEG 400 was used to enhance the drug release. 3^2 Factorial designs were employed to assess the effect of concentration of HPMCK4M and PEG 400 on the performance of *in-situ* nasal gel systematically and to optimize the formulation. An optimized *in-situ* nasal gel was evaluated for appearance, pH, drug content, gelation temperature, mucoadhesive force, viscosity and *ex-vivo* permeability of drug through nasal mucosa of a goat. Additionally, this formulation was proved to be safe as histopathological studies revealed no deleterious effect on nasal mucosa of a goat after prolonged exposure of 21 days to the optimized formulation. Thus the release of Cyclobenzaprine HCl can be sustained if formulated in an *in-situ* nasal gel containing poloxamer 407 to achieve its prolonged action.

INTRODUCTION: Nasal drug delivery system is a potential route for direct delivery of drug to the central nervous system through the olfactory region by bypassing hepatic first-pass metabolism [1]. Cyclobenzaprine hydrochloride (CBZ) is a centrally acting, skeletal muscle relaxant which acts primarily within the central nervous system at brain stem level. It's bound to the serotonin receptor that reduces muscle tone by decreasing the activity of serotonergic neurons. It undergoes rapid and extensively first-pass metabolism in the gastrointestinal and liver. This leads to lower bioavailability of Cyclobenzaprine hydrochloride. Therapy with commercially available CBZ tablets is effective in the relief of spasticity and painful musculoskeletal conditions, but the drawbacks of a commercially available oral formulation of CBZ have low oral bioavailability (33% to 55%) due to the first-pass metabolism. Hydrophilic natures of commercially available conventional formulations have main hindrances due to low permeation through biological barrier [2].

The nose forms a part of the body's defense mechanism against foreign assault, and therefore, a major disadvantage of nasal administration is the rapid mucociliary clearance of substances from the nasal cavity causes poor absorption of the drug. Therefore the mucoadhesive polymer is used to decrease the mucoadhesive clearance to longer the residence time [3].

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A nasal mucoadhesive *in-situ* gel is liquid like before nasal administration and undergoes gelation upon contact with nasal mucosa is conferred *via* the use of Thermoreversible polymers. They are a novel state of matter having both solid and liquid-like properties which can be delivered as a fluid and solidifies within the body's environment where the temperature is higher than the sol-gel transition temperature [4]. The formulation has the advantage to prevent the anterior leakage of the dosage form and enhance the nasal bioavailability due to longer residence time in the nasal cavity. For better patient compliance, it is desirable to deliver the drug quickly through the nasal mucosa because it is difficult to hold the gel in the nasal cavity for more than 7-8 h. So, we have used the permeation enhancer [4, 5, 6].

MATERIALS AND METHODS:

Materials: Cyclobenzaprine hydrochloride was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad. All other chemicals were purchased from commercial sources as poloxamer 407, HPMCK4M, PEG400; benzalkonium chloride was received as a gift sample from Chem dyes Corporation, Ahmedabad.

Methods:

Characterization of Drug:

Fourier Transform Infrared Spectroscopic Studies (FT-IR): The IR studies were carried out by the pressed pellet technique using a KBr press. Potassium bromide was taken and kept in a hot air oven for two hours for the removal of any moisture if present. The drug powder sample was mixed with dried KBr crystals, and the mixture was pressed to form pellets using KBr press. The prepared pellet was placed in the sample holder and kept in the instrument to record the IR peaks. Drug-excipient compatibility was studied by Infrared spectroscopy. The spectra were compared for compatibility study.

UV Spectroscopy: Accurately weighed 10 mg of Cyclobenzaprine hydrochloride was dissolved in 100 ml of buffer media to get the stock solution of 100 µg/mL. From this stock solution aliquots of 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 ml were withdrawn and further diluted to 10 ml with buffer media to obtain a concentrations range of 5 to 30 µl/mL. The absorbance of the solutions was measured at 290 nm by using UV-Vis spectrophotometer. A graph of concentration *vs.* absorbance plotted and a standard calibration curve was obtained.

Preparation of Mucoadhesive Thermoreversible Nasal *in-situ* Gel: There are two methods of preparation of gels, cold method, and hot method. Cold method is most preferred. In this study, the cold method was adopted for the preparation of the gel. The Cyclobenzaprine hydrochloride, PEG 400 and mucoadhesive polymers were stirred in the calculated amount of distilled water at room temperature. The dispersions were cooled down to 4 °C; the poloxamer 407 was added slowly with continuous stirring. The dispersions were then stored in a refrigerator until clear solutions were obtained.

TABLE 1: INDEPENDENT VARIABLE

Independent variable	Level	Concentration of HPMCK4M (% w/w)	Concentration of PEG400 (% v/v)
	-1	0.2	0.5
	0	0.4	1.0
	+1	0.6	1.5

TABLE 2: FORMULATION OPTIMIZATION OF CYCLOBENZAPRINE HYDROCHLORIDE USING 3^2 FACTORIAL DESIGNS

Batch no.	Drug (mg)	Poloxamer 407 (% w/v)	Concentration of HPMCK4M (% w/v)	Concentration of polyethylene glycol (% v/v)	Benalkonium chloride (% v/v)
B1	25	18	0.20	0.5	0.01
B2	25	18	0.40	0.5	0.01
B3	25	18	0.60	0.5	0.01
B4	25	18	0.20	1.0	0.01
B5	25	18	0.40	1.0	0.01
B6	25	18	0.60	1.0	0.01
B7	25	18	0.20	1.5	0.01
B8	25	18	0.40	1.5	0.01
B9	25	18	0.60	1.5	0.01

Evaluation Parameters of Cyclobenzaprine Hydrochloride Nasal *in-situ* Gel:

Clarity: The visual inspection of each formulation was done to test the clarity of the formulation.

Viscosity: The viscosity of the formulation was measured by Brookfield RV-E viscometer with the use of spindle number 6 at 20 RPM. The viscosity of the batches was measured by Brookfield viscometer at different temperature ranging from 4 ºC and 32 ºC. The temperature was increased by putting the solution into the water bath. The spindle number 6 was used and it kept constant for each batch. The graph of viscosity against temperature was plotted.

pH of Formulation: pH of each formulation was determined by using pH meter (LI 610, Elico). The pH meter was first calibrated using solutions of pH 4 and pH 7.

Drug Content: 1 ml of solution was taken in a 25 ml volumetric flask, then serial dilution was made using buffer pH 6.4 make the concentration of the solution ten mcg/mL. Then the absorbance of the final solution was examined using UV-spectrophotometer at λ_{max} 295 nm.

Gelation Temperature: To evaluate gelation temperature, the gel was first cooled to 4 ºC. Then from it, 10 ml of the gel was taken in a 20 ml beaker. After that, the gel was placed on a hot plate magnetic stirrer, and a magnetic bid was inserted into it. The gel was constantly stirred at 100 rpm with an increase in temperature at 1 ºC/min. The temperature at which the magnetic bid stopped its rotation was noted as the gelation temperature.

Mucoadhesive Force: The mucoadhesive potential of each formulation was determined by measuring the force required to detach the formulation from nasal mucosal tissue by using a modified analytical balance. A section of nasal mucosa was cut from the goat's nasal cavity and instantly fixed with a mucosal side out onto each glass vial using a rubber band. The vials with nasal mucosa would be stored at 37 °C for 5 min. Another vial with a section of the mucosa was connected to the balance in an inverted position while the first vial was placed on an adjustable height pan. A fixed amount of sample of each formulation was placed onto the nasal mucosa of the first vial. Then the height of the second vial was adjusted so that mucosal surfaces of both vials come in intimate contact. Two minutes contact time was given to ensure intimate contact between tissues and the sample. Then weight would be kept rising in the pan until vials get detached. The bioadhesive force, expressed as the detachment stress in dyne/cm^2, was determined from the minimal weights that detached the tissues from the surface of each formulation using the equation,

$$\text{Detachment stress (dyne/cm}^2) = m \times g/a$$

Where, m = Weight required for detachment of two vials in g, g = Acceleration due to gravity [980 cm/s^2], a = area of tissue exposed.

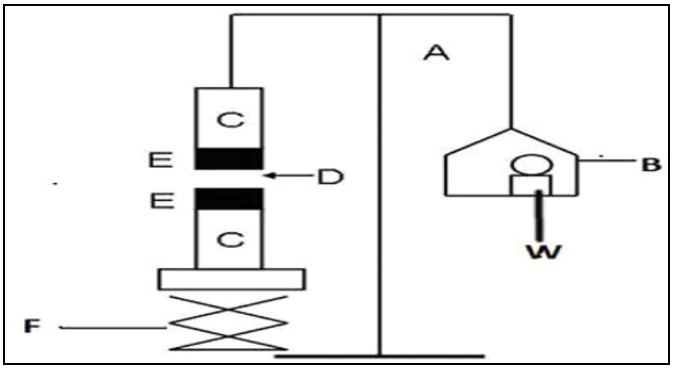

FIG. 1: MODIFIED BALANCE FOR MUCOADHESION STUDY. A) Modified balance, B) Weighing pan, W) Weight, C) Glass vial, D) Poloxamer gel, E) Nasal mucosa, F) Height adjustable pan [49]

***In-vitro* Permeation Studies:** The goat nasal mucosal tissue was inserted in the Franz diffusion cell. The phosphate buffer of pH 6.4 was added to the acceptor chamber. 1 ml of gel was placed in the donor compartment. At a predetermined time point, 2.5 ml sample was withdrawn from the acceptor compartment, replacing the sampled volume with phosphate buffer pH 6.4 after each sampling for a period of 5 h. The absorbance was measured spectrophotometrically at λ_{max} 295 nm.

Histological Study: Histological study had been carried out for the optimized formulation. Histological study of the control mucosa (treated with phosphate buffer pH 6.4), negative mucosa (treated with dichloromethane) and test mucosa (treated with formulation) of the goat were put in an incubator. The cross-section of the mucosa was stained with hematoxylin-eosin. The mucosal structure is seen when treated with the formulation as compared to the control and negative.

Stability Study: Stability studies were conducted according to the ICH guidelines for an optimized batch of *in-situ* gel. A sufficient quantity of prepared *in-situ* gel, in screw-capped vials, were stored in desiccators containing the solution of NaCl which gave relative humidity of 75 ± 5%. The desiccator is placed in a hot air oven at a temperature of 40 ± 2 °C for 21 days for thermoreversible gel. Samples were withdrawn at 7, 14, 21 days. The appearance, pH, drug content and drug release were studied.

RESULTS AND DISCUSSION:

Fourier Transforms Infrared Spectroscopy (FTIR): FTIR spectrum of Cyclobenzaprine hydrochloride was recorded, and spectral interpretation was done. The characteristics IR absorption peaks of Cyclobenzaprine hydrochloride at 3009.80 cm^{-1} (C-H Aromatic stretching), 2956.97 cm^{-1} (C-H Aliphatic stretching), 2439.75 cm^{-1} (HCl salt stretching), 1484.41 cm^{-1} (N -CH_3 Deformation), 778.41 cm^{-1} (C-H Aromatic out of plane deformation) were there in drug sample spectrum; which confirmed the purity of Cyclobenzaprine hydrochloride. Compatibility study was carried to check for any possible interaction between the drug and the excipients used. FTIR spectroscopic study results discovered no new peak appearance or disappearance of existing peaks, discarding any chemical interaction probability among drug and polymer used. Thus, IR spectroscopy results depicted that Cyclobenzaprine hydrochloride was compatible with selected polymer and excipients.

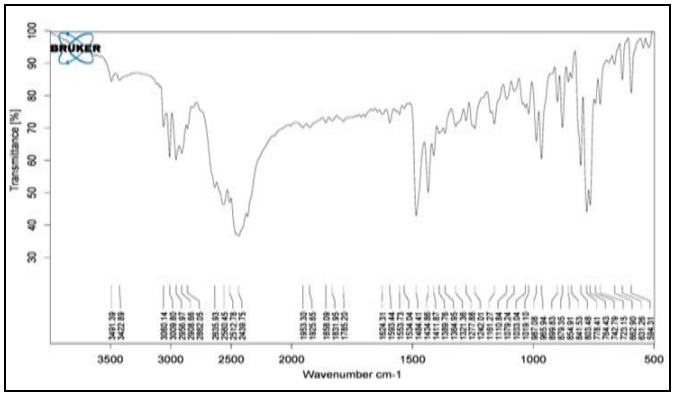

FIG. 2: FTIR SPECTRA OF CYCLOBENZAPRINE HCl

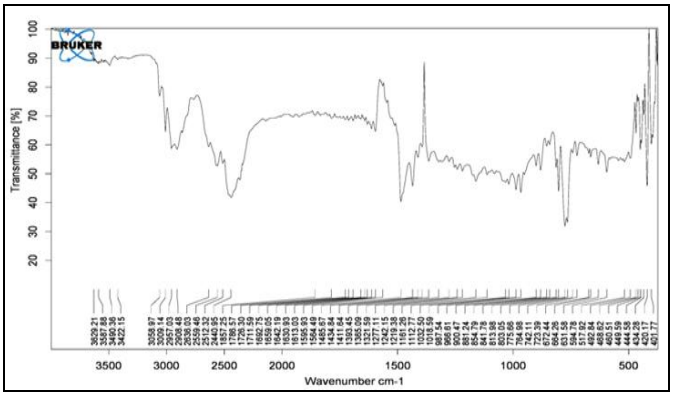

FIG. 3: FTIR SPECTRA OF DRUG AND EXCIPIENTS

TABLE 3: PRINCIPLE PEAKS OBTAINED FROM IR SPECTRA OF THERMOREVERSIBLE *IN-SITU* GEL

Group	Cyclobenzaprine HCl (cm^{-1})	Formulation	Observation
C-H Aromatic stretching	3009.80	2957.03	No interaction
C-H Aliphatic stretching	2956.97	2908.48	No interaction
HCl salt stretching	2439.75	2440.95	No interaction
N –CH_3 Deformation	1484.41	1485.67	No interaction
C-H Aromatic out of plane deformation	778.41	772.61	No Interaction

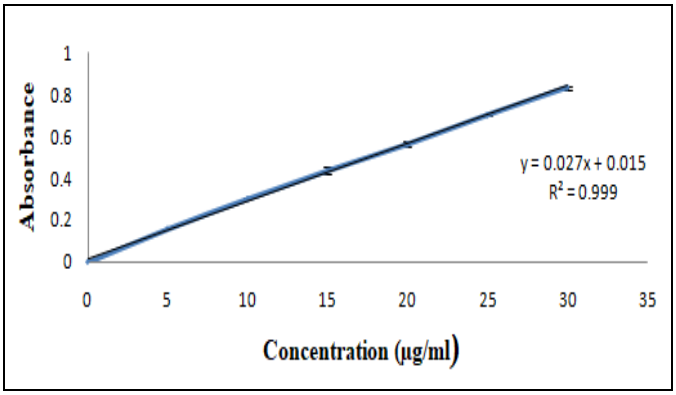

FIG. 4: CALIBRATION CURVE OF CYCLOBENZAPRINE HYDROCHLORIDE IN BUFFER pH 6.4 AT λ_{max} 295 nm

TABLE 4: RESULTS OF CALIBRATION CURVE OF CYCLOBENZAPRINE HCl IN BUFFER pH 6.4

S. no.	Concentration (µg/mL)	Absorbance ± S.D.
1	0	0
2	5	0.159 ± 0.0020
3	10	0.302 ± 0.0041
4	15	0.437 ± 0.0148
5	20	0.564 ± 0.0155
6	25	0.703 ± 0.0066
7	30	0.834 ± 0.0102

(Where n =3, Mean = ±SD)

Regression coefficient was found to be 0.999 which showed a linear relationship between absorbance and concentration.

Results of Evaluation Parameters of *in-situ* Gel Formulation: Clarity: The formulation was found to remain clear.

TABLE 5: VISCOSITY CHANGE WITH INCREASING TEMPERATURE OF *IN-SITU* GELS

Formulation Code	Viscosity in cp	
	At 4ºC (at 100 rpm)	At 32ºC (at 100 rpm)
B1	210 ± 0.004	3240 ± 0.248
B2	225 ± 0.142	3750 ± 0.021
B3	235 ± 0.213	4450 ± 0.048
B4	220 ± 0.118	3270 ± 0.247
B5	220 ± 0.174.	3700 ± 0.231
B6	230 ± 0.167	3850 ± 0.114
B7	200 ± 0.128	3650 ± 0.007
B8	210 ± 0.041	3650 ± 0.024
B9	230 ± 0.188	3800 ± 0.140

(Where n =3, Mean = ±SD)

Viscosity: Viscosity measurement of the formulations at 4ºC and 32ºC temperatures showed that there was an increase in viscosity with an increase in temperature. The viscosity of the formulation remains low up to a certain temperature. This is because the formulation remains in a liquid state up to that temperature. Then with the increase with temperature the formulation change into a gel. As a result, the viscosity of the formulation gets increased.

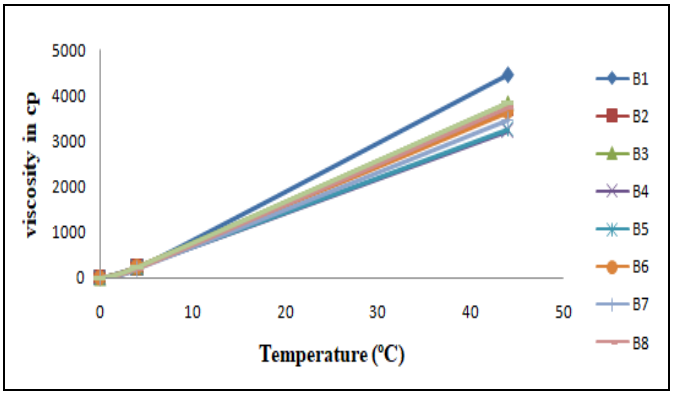

FIG. 5: EFFECT OF TEMPERATURE ON VISCOSITY

pH of Formulation: The pH of the solution was measured by pH meter. The pH of all batches found as shown in the table. The pH of the solution found in the range between 5.1 - 6.3. All formulations may tolerable to nose because they lied in nasal tolerable pH range (5-7).

Drug Content: The drug content of all batches was found in between 92% w/v to 97% w/v.

Gelation Temperature: For the formation of the gel micelles formation is important. Temperature plays a crucial role in the formation of micelles. The mucoadhesive polymer also affects in the gelation temperature. As the concentration of the HPMCK4M increased with 0.2 to 1.0% w/v the gelation temperature was also decreased. While increasing the concentration of the PEG from 0.5 to 1.5% v/v the gelation temperature increases.

Mucoadhesive Force: The mucoadhesive force was measured by a modified analytical balance. Mucoadhesive force is required to increase the nasal residence time of the gel. So mucoadhesive force is also an essential parameter for the nasal gel. The formulation should have an excellent mucoadhesive force to provide optimum resistance to the mucociliary clearance of the gel. The formulations have a distinct effect on the mucoadhesive force of the gel. The mucoadhesive polymer itself is not only the mucoadhesive force provider. There is a distinct effect of the poloxamer 407 on the mucoadhesive force. Not much but the permeation enhancers also affect the mucoadhesive force of the gel. If studying in respect to the poloxamer 407, it was found that the poloxamer 407 has a bioadhesive force due to binding of the hydrophilic oxide group to oligosaccharide chain. The results are shown in **Table 6**. From batch B1 to B3, the mucoadhesive force of the formulation was increased as the concentration of HPMCK4M increased.

TABLE 6: pH, DRUG CONTENT, GELLING TEMPERATURE, GEL STRENGTH, MUCOADHESIVE FORCE OF THE THERMOREVERSIBLE *IN-SITU* GEL

Batch code	Appearance	Drug content	Gelling temperature	pH ± SD	Mucoadhesive force (Dyne/cm^2) ± SD
B1	Clear solution	94.83 ± 0.058	38 ± 0.5	5.1 ± 0.02	578 ± 8.14
B2	Clear solution	96.13 ± 0.072	37 ± 0.5	5.9 ± 0.0012	470 ± 14.1
B3	Clear solution	93.78 ± 0.026	36 ± 0.5	4.8 ± 0.0087	670 ± 12.7
B4	Clear solution	92.84 ± 0.010	41 ± 0.5	4.7 ± 0.0048	1050 ± 16.54
B5	Clear solution	98.87 ± 0.050	31 ± 0.5	5.8 ± 0.0008	736 ± 12.12
B6	Clear solution	94.35 ± 0.092	24 ± 0.5	5.0 ± 0.023	712 ± 10.15
B7	Clear solution	93.68 ± 0.046	45 ± 0.5	6.0 ± 0.0006	546 ± 16.74
B8	Clear solution	93.95 ± 0.022	29 ± 0.5	6.2 ± 0.008	672 ± 12.14
B9	Clear solution	96.38 ± 0.016	23 ± 0.5	4.8 ± 0.0026	1040 ± 14.98

(Where, n =3, Mean = ± SD)

***In-vitro* Drug Release of Thermoreversible *in-situ* Gels of B1 to B9:** As the concentration of the HPMCK4M increased the release of the drug was decreased. In the batch B1, B2 and B3, the immediate release of the drug were observed in the 1st hour. After that, it was released the drug slowly, and up to 5 h more than 90% drug was released. Batch B4, B5 and B6 also showed immediate release in the first hour but in comparison with B1 to B3 only about 40% drug was released. And after that, about 90% of drugs was released in 5 h. Batch B7 to B9 only about 90% drug was released in 5 h because of increased concentration of PEG. Optimized batch decided from the above evaluation parameters (pH, drug content, gelling capacity, gelation temperature, gel strength, and muco-adhesive force) B5, B7 and B8, only B5 batch showed drug release more than 90% w/v in 5 h. While in batch B7 and B8, only 92% to 93% w/v drug release was obtained in 8 h. So for the thermoreversible *in-situ* batch, B5 was the optimized batch.

TABLE 7: % CUMULATIVE DRUG RELEASE PROFILE OF THERMOREVERSIBLE GEL OF B1 TO B9

Time (Min.)	% CDR B1	% CDR B2	% CDR B3	% CDR B4	% CDR B5	% CDR B6	% CDR B7	% CDR B8	% CDR B9
0	0	0	0	0	0	0	0	0	0
30	16.42	20.54	14.12	30.08	21.38	16.28	24.38	22.56	14.08
60	34.92	42.36	25.82	36.98	29.92	18.04	36.47	35.58	20.52
90	60.45	54.28	30.68	40.57	34.20	23.48	42.56	38.00	34.22
120	65.23	58.94	36.48	48.28	40.92	30.98	50.48	42.84	38.46
150	72.82	66.58	38.84	60.72	54.00	38.89	58.76	50.48	48.92
180	78.92	68.12	43.78	68.08	57.84	42.44	62.35	61.32	56.48
210	83.96	73.15	48.40	76.43	68.32	47.68	68.84	68.57	60.22
240	86.86	78.81	54.92	84.56	76.08	58.38	77.64	76.38	68.68
270	89.92	80.78	58.84	87.24	84.24	62.34	84.54	80.58	79.84
300	91.86	84.72	64.98	92.84	94.05	66.48	93.28	92.36	81.22

TABLE 8: RESULT OF COMPARISONS OF FLUX OF PURE DRUG AND FLUX OF *IN-SITU* GEL FORMULATION

Flux of Pure Cyclobenzaprine hydrochloride				Flux of Optimized Batch		
Time (h)	% Drug release	Drug permeate	Flux (mg/cm^2/min)	% Drug release	Drug permeate	Fiux (% mg/cm^2/min)
0	0	0	0	0	0	0
30	6.24	0.156	0.008125	21.38	0.534	0.027813
60	10.92	0.273	0.007109	29.92	0.748	0.019479
90	16.62	0.415	0.007214	34.20	0.855	0.014844
120	24.50	0.612	0.007975	40.92	1.022	0.013307
150	29.68	0.742	0.007729	54.00	1.35	0.014063
180	33.64	0.841	0.0073	57.84	1.446	0.012552
210	36.78	0.919	0.006842	68.32	1.708	0.012708
240	39.442	0.986	0.006419	76.08	1.902	0.012383
270	41.42	1.035	0.005992	84.24	2.106	0.012188
300	43.67	1.091	0.005686	94.05	2.351	0.012245

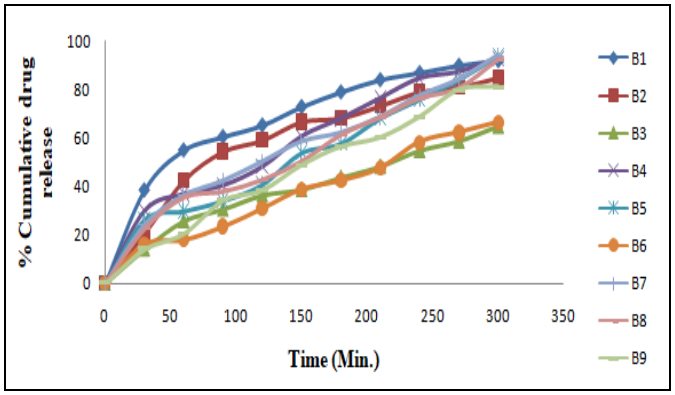

FIG. 6: % CUMULATIVE DRUG RELEASE PROFILE OF THERMOREVERSIBLE GEL OF BATCH B1 TO B9

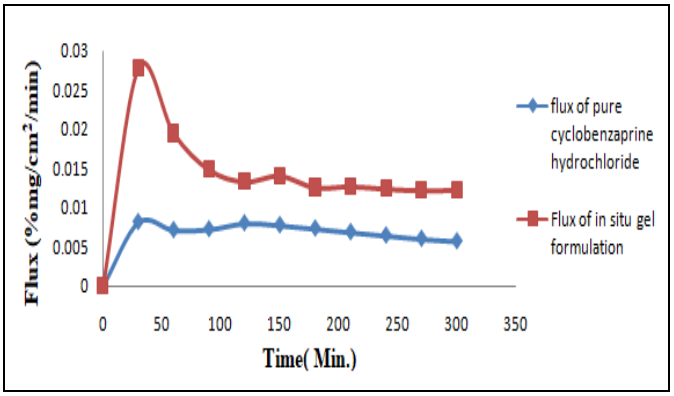

FIG. 7: COMPARISON OF FLUX OF PURE DRUG AND *IN-SITU* GEL FORMULATION

The result of Comparisons of Flux of Pure Drug and Flux of Formulation: From the results, it is concluded that the flux value of *in-situ* gel formulation is higher as compared to the pure drug which permeated through the goat nasal mucosa. The comparative fluxes of pure drug and formulation were shown in **Fig. 7**. It indicates that initially there was a high level of flux and further it decreases because of the burst effect followed by sustained release.

TABLE 9: STABILITY STUDY DATA FOR OPTIMIZED BATCH B-5

Characteristics	Time period		
	After 7 days	After 14 days	After 21 days
Appearance	clear	Clear	clear
pH	5.82 ± 0.023	5.94 ± 0.820	6.04 ± 0.064
Drug Content	97.88 ± 0.0056	97.42 ± 0.0048	96.26 ± 0.23
% Drug release	93.72 ± 1.4	93.28 ± 2.1	92.88 ± 1.6

Stability Study: From the stability studies of the optimized formulation for 21 days, it was found that there was not a significant change in appearance, pH, drug content and % drug release profile which indicated that the developed formulation of Cyclobenzaprine hydrochloride nasal *in-situ* gel was stable after 21 days.

CONCLUSION: Study aimed to achieve brain-targeted drug delivery of Cyclobenzaprine hydrochloride for the patients suffering from a skeletal muscle disorder. Nasal drug delivery system is a potential route for direct delivery of drug to the central nervous system through the olfactory region by bypassing hepatic first-pass metabolism which gives fast onset of action. Cyclobenzaprine hydrochloride if formulated as a nasal *in-situ* gel, it would remain in contact with the nasal mucosa for a longer period, deliver the drug from nose to brain *via* olfactory region. The *in-situ* gel was formulated by temperature-sensitive approach using simple mixing method or cold method.

In nutshell, the thermosensitive nasal *in-situ* gel of Cyclobenzaprine hydrochloride was successfully developed on a laboratory scale. Hence, developed thermo sensitive nasal *in-situ* gel of Cyclobenzaprine hydrochloride can be a new area of drug delivery in the future.

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Animal Ethical Committee approval letter no: 984/PO/E/S//06/CPCSEA.

CONFLICT OF INTEREST: The authors suggest that there is no conflict of interest.

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