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Development and *In Vitro* Evaluation of Mucoadhesive *In Situ* Nasal Gel of Oxymetazoline Hydrochloride: A Novel Approach for Nasal Drug Delivery

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Abstract: Nasal mucosa has a high blood perfusion rate in the nasal cavity, which increases the drug's absorption and bioavailability in the systemic circulation compared to other routes. We need to apply a bio-compatible mucoadhesive polymer to increase the retention period of *in situ* gel with nasal mucosa. The objective of the present study was to formulate and evaluate *in situ* nasal gel of oxymetazoline hydrochloride. This drug delivery technology has the potential to bypass the initial metabolism of the medication and thereby enhance its bioavailability. A total 10 *in situ* nasal gels were created by combining hydroxypropyl methylcellulose (HPMC K-100) and xanthan gum in various polymeric ratios. All gel formulations that were produced (F1–F10) had pH values between 5.5 ± 0.008 to 6.0 ± 0.002. The gels' spreadability ranged from 10.1 ± 0.24 to 6.7 ± 0.67 g/cm/sec. All prepared gel compositions were found to have gelling temperature ranged from 33.2 ± 0.41 °C to 34.8 ± 0.36 °C, gelling time ranged from 4.0 ± 0.41 sec to 10.1 ± 0.16 sec and gel strengths ranging from 51.16 ± 0.66 to 62.14 ± 0.58. The range of 130.34 ± 0.57 to 211.75 ± 1.35 centipoises was found for the viscosity of the different prepared gels. All manufactured gel formulations were found to have a drug concentration ranging from 97.54 ± 0.43 to 99.68 ± 0.83 per cent. Oxymetazoline hydrochloride nasal gels F9 have a 99.98 % drug release rate in their *in vitro* diffusion drug release. According to the release order kinetics, all of the formulations—from F1 to F10—followed the Korsmeyer-Peppas model, as evidenced by the correlation coefficients R2=0.986 and 0.937, respectively. The drug release investigations conducted in a controlled laboratory environment showed that the formulated substances were capable of releasing the drug for a duration of 10 h. Furthermore, all of the formulations exhibited a consistent adherence to the Higuchi kinetics model. The accelerated stability investigations demonstrated that the gels remained stable throughout the six-month testing period. The DSC and XRD tests indicated the absence of any interaction between the medication and polymer. Based on these findings, it can be inferred that *in situ* nasal gels have the potential to be used as drug delivery systems for oxymetazoline HCl. This can help overcome first-pass metabolism and boost the bioavailability of the drug.

Keywords: *In situ*, Gels, Oxymetazoline Hydrochloride, *In vitro* diffusion, HPMC K-100, Xanthan gum

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Introduction

An imidazoline derivative and sympathomimetic amine is oxymetazoline hydrochloride (6-tert-Butyl-3-(4,5- dihydro-1H-imidazol-2-ylmethyl)-2,4-dimethylphenol hydrochloride). For nearly 40 years, oxymetazoline has been sold as an over-the-counter intranasal medication in the United States. It is a vasoconstrictor that operates directly on nasal membranes (Glazener *et al.*, 1983). There are several justifications for exploring alternative means of administering nasal medications instead of relying on conventional approaches. The nasal route offers convenience due to its ease of use, fast onset of action, and lack of gastrointestinal degradation or first-pass metabolization. Due to the small size of the medications designed for it, this route has excellent bioavailability. In cases when the bioavailability is not naturally great, it can still be enhanced, making the nasal route highly desirable (Sharma *et al.*, 2022; Çelik *et al.*, 2023). It is authorized for the treatment of allergic rhinitis and common cold-related nasal congestion. The creation and assessment of oxymetazoline nasal gels is the primary goal of this investigation to pass hepatic first pass metabolism and ensuing degradation in order to attain more consistent blood levels with smaller doses of medication (Thrush, 1995) to lengthen the residence period and decrease the frequency of dose dumping. Drugs administered intranasal have long been used to treat nasal congestion and rhinitis. The hepatic first-pass impact and gastrointestinal side effects can be mitigated by intranasal delivery (Yerikala *et al.*, 2017). Moreover, the abundance of blood and lymphatic capillaries beneath the nasal mucosa improves drug absorption. Because of these characteristics, administering medications intranasally can significantly increase their bioavailability. It has been reported that intravenous and intranasal administration achieves similar blood concentrations (Gizurason, 1993). Because the olfactory receptor cells are in direct contact with the central nervous system, nasal medication delivery also offers a means of accessing the brain that avoids the blood-brain barrier. The initial stage of medication absorption in the nasal cavity is mucus membrane crossing. because the mucus readily allows for the passage of tiny, uncharged particles. However, charged big molecules find it difficult to cross the mucous membrane. The protein called mucin is found in the mucus layer and it binds to solutes to slow down diffusion and structural changes in the mucus layer that are also brought on by changes in the environment (Saudagar, 2016; Sabale *et al.*, 2020; Choudhary *et al.*, 2021). Nowadays, sprays make up the majority of nasal medicines sold in stores. The short drug residence period (15–30 min) on the human nasal mucosal surface caused by the scavenging action of nasal cilia has some bearing on clinical efficacy (Ning, 2007). A physical state having characteristics halfway between those of solids and liquids is referred to as "gel." But it's frequently applied incorrectly to any fluid system that displays some degree of stiffness (Baghwan *et al.*, 2021).

Materials and Methods

Materials:

Received a free sample of oxymetazoline hydrochloride from CDH (Delhi, India). We bought xanthan gum, mannitol, polyethylene glycol (PEG), benzalkonium chloride, methanol, and hydroxypropyl methylcellulose (HPMC K 100) from SD Fine Chemicals (Bangalore, India). Analytical grade reagents and chemicals were used in this study.

Formulation of oxymetazoline hydrochloride in situ nasal gels:

The process parameters were optimized using a factorial design. Table 1 displays the ingredients of several oxymetazoline hydrochloride *in situ* nasal gel formulations. Following the drug's dissolution in methanol, 10 ml of distilled water were added. Stirring continuously was used to mix the solution. Mannitol, PEG, and benzalkonium chloride were added to the medication solution mentioned above. The aforementioned mixture was thoroughly mixed with the polymeric solutions of HPMC K 100 and xanthan gum, which were made

Table 1: Formulation data of different Oxymetazoline Hydrochloride *in situ* Nasal gels

S. No.	Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Oxymetazoline hydrochloride (% w/v)	7	7	7	7	7	7	7	7	7	7
2	HPMC K-100 (% w/v)	0.2	0.4	0.6	0.8	0.2	0.4	0.6	0.8	0.2	0.4
3	Mannitol (% w/v)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
4	Xanthan gum (% w/v)	0.10	0.10	0.10	0.15	0.15	0.15	0.20	0.20	0.20	0.25
5	PEG (%)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
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
7	Methanol (ml)	5	5	5	5	5	5	5	5	5	5
8	PBS (pH 6.4) (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9	Distilled water (ml; QS)	25	25	25	25	25	25	25	25	25	25

independently in distilled water. After 15 min of magnetic stirring, the mixture was added to the phosphate buffer solution (PBS). Distilled water was added to the final volume to achieve the necessary amount (Nandgude *et al.*, 2008; Sherafudeen and Vasantha, 2015). Table 1 describes the different formulation (F1-F10) of Oxymetazoline Hydrochloride *in situ* gel.

Characterization of in-situ gel:

FT-IR studies for drug and excipients compatibilities: The pre-formulation investigation was completed before the dosage forms were developed (Ramesh *et al.*, 2018). IR spectrum investigations are primarily used to identify chemicals qualitatively, whether they are in their pure form or in combination with polymers and excipients. They also serve as a tool for determining the nature of chemical interactions. I.R. is associated with covalent bonding; hence, the spectra can provide intricate details about the composition of molecules. Comparisons between the compounds' spectra and the pure compound were done to prove this conclusion.

Gelling temperature and gelling time: The term "gelling temperature" describes the temperature at which, at 90 °, the formulation's meniscus would no longer move. The method developed by Miller and Donovan was applied to ascertain the gelation investigations. By setting the test tube, which contained an adequate amount of the produced solutions, in a water bath at 4°C, the gelling temperature was ascertained. Every two minutes, the water bath's temperature was gradually raised by 1°C. Gelling time of formulations was calculated by applying the methods Miller and Donovan described (Miller and Donovan, 1982). Prior to administration, the delivery systems are in the sol form; however, after administration, they go through gelation to become a gel. The moment at which gelation was initially detected was noted as the gelling time. By adding 2 ml of the manufactured formulation to a 10 ml test tube with a 1 cm diameter, the sol-gel transition temperature of the *in situ* gel formulations was measured. The tube was kept in a water bath with circulation set at 37 °C after being sealed with parafilm. Ten minutes were given for equilibration after each temperature setting. In order to assess the gelation and gauge the sample's condition, the test tube was lastly positioned horizontally (Sabale *et al.*, 2020).

Viscosity of solution: Using a Brookfield viscometer DV-II+ Pro connected to an S-94 spindle (Brookfield Engineering Laboratories Inc., MA, and USA), the viscosity of the *in situ* gel systems was measured. The beaker was filled with the created gel compositions. The temperature was maintained at 37 ± 0.5 °C while the spindle was lowered perpendicularly into the gel at a speed of l00 rpm. When the system was cooling, the viscosity was measured. Each measurement was carried out three times (Shah *et al.*, 2011).

Rheological properties of in situ gels: Using a Brookfield LVDV-E Viscometer (Brookfield Engineering Laboratories, Inc., USA), the rheological characteristics of *in situ* gel compositions were examined. At first, the temperature was kept above 40 °C. By increasing the spindle rotational speed from 0.3 to 100 rpm, the rheological parameters were examined and the viscosity (h), shear rate (g), and shear stress (t) were noted. Each measurement was carried out three times (Khatri *et al*., 2021).

Determination of pH: A 10 ml volumetric flask was filled with 1 ml of the produced gels, and the solution was thinned with distilled water. A digital pH meter (Shambhavi Impex, India) that had been previously calibrated using phosphate buffers at pH 4 and pH 7 was used to measure the pH of the resultant solution (Vijay *et al.*, 2012).

Drug content: 1 ml of the formulation was added to 10 ml of volumetric flask, and it was then diluted with up to mark with distilled water. Once more, 10 ml of distilled water were used to dilute 1 ml of this solution. Finally, using a UV visible spectrophotometer (Shimadzu 1800), the absorbance of the produced solution was measured at 217 nm against a blank reagent. The tests were conducted in triplicate and the average data were recorded. (Majithiya *et al.*, 2006; Sherafudeen and Vasantha, 2015).

Gel strength: Sample (50 g) was put into graduated cylinder (100 ml). The formulations were gelled by placing them in a thermostat set to 37 °C. The time it took for a 35 g weight to sink 5 cm in the gel was used to gauge the gel's strength (Saudagar and Khandbahale, 2017; Trupa *et al.*, 2019).

Spreadability: A rectangular glass slide measuring 10 x 4 cm was used to assess spreadability. A thread was used to secure the sheep's nasal mucosa from the serosal side to the slide's surface. The slide was maintained at 37 °C in a hot air oven (Navyug Udyog, India), with a single gel drop positioned at a 120° on the mucosa. The spreadability of a liquid gel drop was measured in relation to its travel distance prior to gelation. Three readings on average were noted (Choi I *et al.*, 1998). The spredability was measured by using the following formula:

$$S = ML/T$$

Where S = Spreadability' M = Weight tide to upper slide, L = Length moved on the glass slide, T = Time taken to separate the slide completely from each other.

Mucoadhesive strength: The force needed to separate the formulation from goat nasal mucosal tissue that was taken from the slaughterhouse was used to calculate the mucoadhesive potential of the created preparation. A portion of the goat nasal mucosa was placed in an inverted beaker, and one of the pans of the modified mucoadhesion test equipment was filled with the formulation to be tested. On the other side, the weight was increased until the two-mucosa separated from one another (Nirmal *et al.*, 2010).

$$\mathrm{M} = \mathrm{m} * \mathrm{g}/\mathrm{A}$$

Where, M= mucoadhesive strength in dyne/cm^2, m= weight in grams, g= gravitational force

A= area in cm^2.

In vitro drug release: Xylometazoline hydrochloride *in situ* nasal gel drug release was accomplished by employing a Franz diffusion cell with a dialysis membrane (mol. wt. 12000 D) as a barrier. The dialysis membrane separated the donor compartment from the receptor compartment, which was filled with 2 ml of nasal *in situ* xylometazoline hydrochloride gel after the assembly was assembled and the temperature was kept at 37±1°C. The pH 6.8 phosphate buffer was placed inside the receptor compartment. At regular intervals, 1 ml aliquots of the material were removed and replaced with a fresh receptor media of the same volume of phosphate buffer. The samples underwent spectrophotometric analysis at 217 nm after being suitably diluted with phosphate buffer (Khandagale *et al.*, 2018; Valavi *et al.*, 1019).

Accelerated stability studies: *In situ* gel formulation

stability tests were conducted in compliance with the principles set forth by the International Conference on Harmonization. Enough *in situ* gel in nasal spray bottles was kept in a desiccator (Sabar Scientific, India) with a saturated sodium chloride solution (75 ± 5% relative humidity (RH)). The samples were taken out of the desiccator after 1, 2, 3, 5, and 6 months of being kept in a hot air oven at 40 ± 2 °C. Investigations were conducted into alterations in the preserved formulations' appearance, drug content, gelling strength, and *in vitro* drug release. The three decisions' mean values were noted.

Differential scanning calorimetry: Thermograms of a particular formulation (F4) using differential scanning calorimetry (DSC) were acquired after it was kept for two months at 40 ± 2 °C and 75 ± 5% relative humidity. The samples were put in airtight aluminium pans and heated at a rate of 10 °C per minute while being scanned between 30 and 200 °C.

X-Ray diffraction studies: Using a copper target at a voltage of 40 kV and a current of 30 mA, the Jeol JDX 8030 X-ray diffract meter (MTI Corporation, USA) was used to record the X-Ray diffraction studies (XRD) pattern of the chosen formulation (F4) for a defined quantity of pure medication. A range of 10–80 º in °2 θ was scanned (Kohda *et al*., 1997; Jug and Bećirević-Laćan, 2004).

Results

Compatibility studies:

FTIR spectral analysis was used to characterize the drug and polymers to look for any physical or chemical changes to the drug's properties. The primary peaks of the Oxymetazoline Hydrochloride were found to be unchanged in the spectra of the drug-polymer mixture, indicating that there was no interference in the functional groups, according to the data. IR spectra of the pure drug (Oxymetazoline Hydrochloride) and mixture of drug and polymer are shown in Figures 1 and 2, respectively and Table 2. FTIR was used to identify the specific functional groups found in pure drug and mixture of drug and polymer. The presence of IR bands at 2359.80 cm^{-1}, 2341.45 cm^{-1} and 1447.94 cm^{-1} 1361.25 cm^{-1} in FTIR spectrum of pure drug were assigned to C=C stretching vibration, NO_2 stretching vibration as shown in Figure 1. The presence of IR bands at 3248.34 cm^{-1}, 22.53.23 cm^{-1} and 22169.79 cm^{-1}, 2147.67 cm^{-1} in FTIR spectrum of mixture of drug and polymer were assigned to C=C stretching vibration, as shown in Figure 2.

Gelling temperature, gelling time, viscosity of solution, drug content and gel strength:

In this study, 2^4 factorial designs were used to generate 10 formulations of *in situ* nasal gels. The basis polymers that were used were xanthan gum and HPMC K-100. Table 3 displays the gel strength, drug content, viscosity of solution, gelling temperature, and gelling time of the produced formulation.

In the solubility form, every formulation was visible. The *in situ* nasal gel that was generated had a gelling temperature that varied from 33.2 ± 0.41 °C to 34.8 ± 0.36 °C. For thermo reversible nasal gel, the ideal gelling temperature is between 30 and 36 °C. The term "gelation point" describes the temperature at which, after gradually raising the temperature to 90 °, the formulation's meniscus would no longer move (Majithiya *et al.*, 2006). Every formulation in the current analysis displayed a gelling temperature that fell within the range.

On the other hand, when the temperature rises, the gelation does not occur at the nasal mucosa region, which results in rapid nasal clearance. The formulation's gelling time varied from 4.0 ± 0.41 sec to 10.1 ± 0.16 sec. The gelling times for formulas F2, F4, F5 and F8 were found to be sufficient. The produced formulation's drug content varied from 97.54 ± 0.43% to 99.68 ± 0.83%. The formulation's viscosity varied from 130.34 ± 0.57 to 211.75 ± 1.35cP. When 0.8% of HPMC K-100 was added to the formulations together with concentrations of 0.10%, 0.15%, 0.20%, and 0.25% of xanthan gum, the viscosity increased.

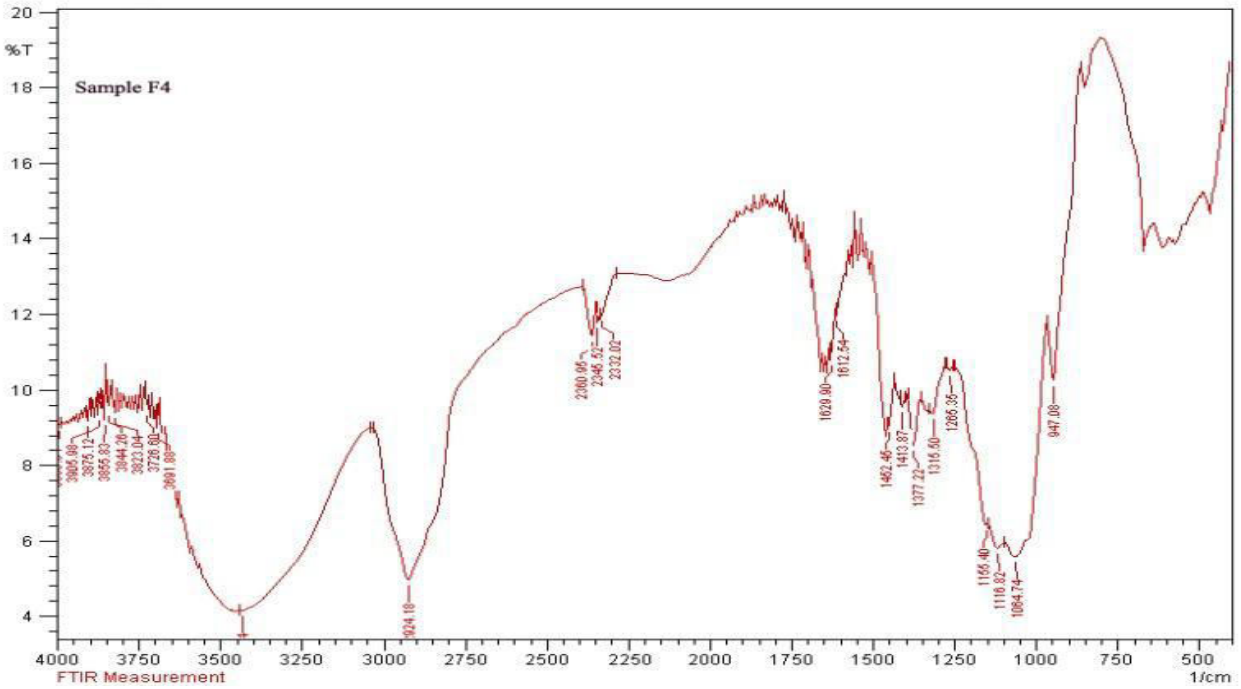

Fig. 1: FTIR spectrum of Oxymetazoline Hydrochloride.

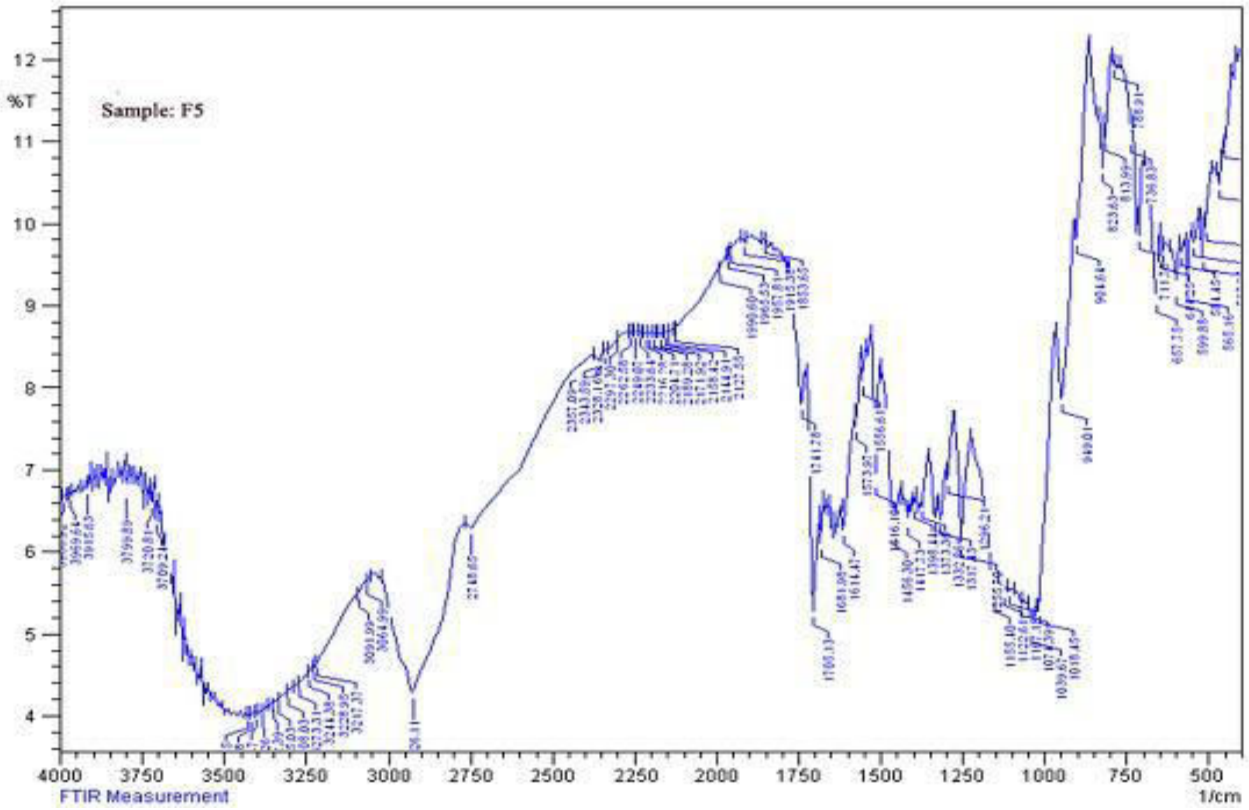

Fig. 2: FTIR spectra of mixture.

Table 2: FTIR spectrum of observed and characteristic peak of pure Drug and Mixture of compounds

FTIR Spectrum	IR absorption bands (cm-1)		Bond	Functional group
	Observed Peak	Characteristic Peak		
Oxymetazoline Hydrochloride	2359.80	2100-2660	C=C	Alkynes
	2341.45	2100-2660	C=C	Alkynes
	1447.94	1330-1540	NO_2	Nitro compounds
	1361.25	1220-1540	NO_2	Nitro compounds
Mixture	3248.34	3010-3300	C≡H	Alkynes
	2253.23	2100-2660	C=C	Alkynes
	2169.79	2100-2660	C=C	Alkynes
	2147.67	2100-2660	C=C	Alkynes

When HPMC K-100 was used in the formulations at concentrations of 0.2%, 0.4%, and 0.6%, a difference in viscosity was noted. The gel strength of formulation ranges from 51.16 ± 0.66 to 62.14 ± 0.58 sec. The range of the mucoadhesive strength was 3010.89 ± 1.21 to 6678.89 ± 0.45. The strength of mucoadhesive material was directly correlated with the HPMC K-100 content. Figure 3 shows the relationship between the viscosity of the gels and the polymer ratios (xanthan gum and HPMC ratios).

Spreadability, pH, and mucoadhesive strength:

Table 4 displays the physicochemical characteristics, including pH, mucoadhesive strength, and Spreadability. The formulation's Spreadability varied from 10.1±0.24 to 6.7±0.67 cm. The formulation's pH varied from 5.5 ± 0.008 to 6.0 ± 0.002. These results showed that the formulations' pH values were within an acceptable range. The formulations' mucoadhesive strengths ranged from 3004.45 ± 1.65to 6548.54 ± 0.59 dyne/cm^2.

Mucoadhesive drug delivery techniques extend the dosage's residence time at the application or absorption site by enabling quick drug dissipation in the circulatory system, which inhibits first-pass metabolism. In the current investigation, formulations made with a high HPMC K-100 concentration showed greater macro adhesion strength than formulations made with a lower concentration. Consequently, HPMC K-100's high concentration is more important to the formulation than xanthan gum.

In vitro drug release:

The produced formulations' *in vitro* drug release is displayed in (Figs. 4, 5). Maximum drug release was seen in the formulations F1 (99.91%), F2 (99.97%), F3 (99.85%), and F9 (99.98%) after 6 h. Then, after 8 h, the formulations F5 (99.75%), F6 (99.75%), F7 (99.93%) and F10 (99.81%) showed maximum drug release. After 10 h, the medication was released from the remaining formulations, F4 (99.88%) and F8 (99.76%).

The manufactured nasal gels may be

Table 3: Gelling temperature, gelling time, viscosity of solution, drug content, and gel strength of *in situ* nasal gel of Oxymetazoline Hydrochloride

Formulation code	Appearance	Gelling temperature (°C) *	Gelling time (s)*	Viscosity of solution (cP)*	Drug content (%)*	Gel strength (s)*
F1		33.2 ± 0.41	10.1 ± 0.16	164.56 ± 0.68	99.35 ± 0.33	51.16 ± 0.66
F2		33.7 ± 0.34	4.1 ± 0.45	174.85 ± 0.36	98.10 ± 0.47	55.56 ± 0.73
F3		33.4 ± 0.45	6.2 ± 0.73	130.34 ± 0.57	98.27 ± 0.84	58.57 ± 0.45
F4		34.3 ± 0.79	4.5 ± 0.40	187.57 ± 0.96	99.37 ± 0.95	61.45 ± 0.76
F5	**Transparent**	34.8 ± 0.36	4.8 ± 0.30	186.68 ± 1.27	97.54 ± 0.43	57.57 ± 0.87
F6		33.6 ± 0.65	5.3 ± 0.54	195.47 ± 0.84	99.63 ± 0.28	54.46 ± 0.75
F7		34.4 ± 0.59	6.6 ± 0.36	192.47 ± 1.13	99.68 ± 0.83	58.26 ± 0.85
F8		33.9 ± 0.57	4.0 ± 0.41	211.75 ± 1.35	98.28 ± 0.75	62.14 ± 0.58
F9		34.5 ± 0.45	4.9 ± 0.76	175.55 ± 0.47	98.12 ± 0.23	55.16 ± 0.37
F10		33.6 ± 0.37	4.5 ± 0.37	156.32 ± 0.25	99.10 ± 0.87	54.37 ± 0.68

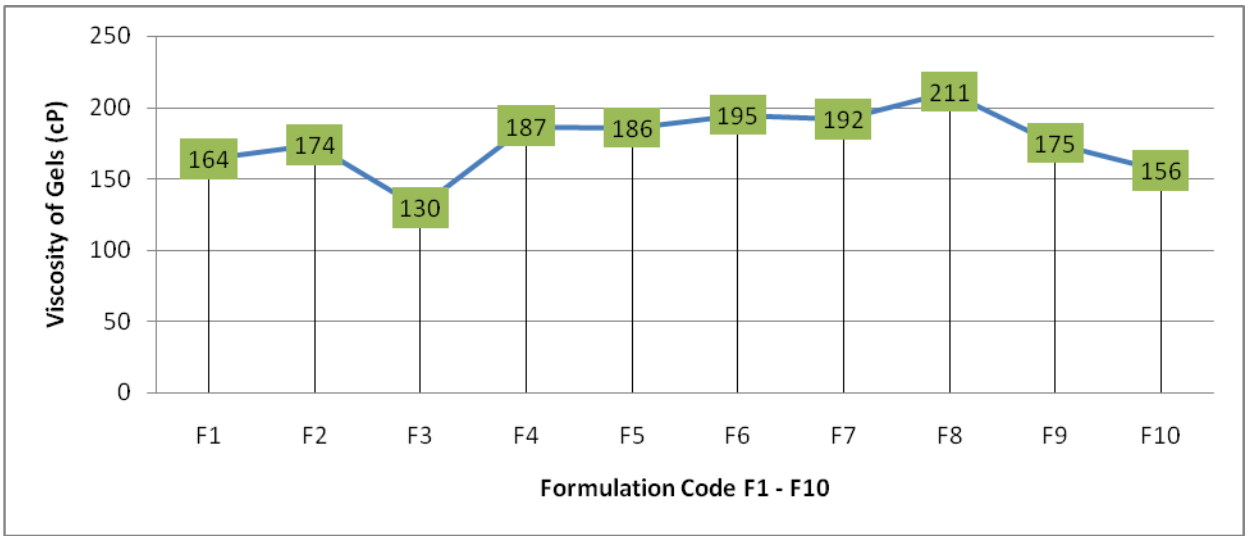

Fig. 3: The relation between the polymer ratios and the viscosity of the formulations (F1-F10).

Table 4: Mucoadhesive strength, Spreadability, and pH of different formulations of in situ nasal gel of oxymetazoline hydrochloride

Formulation code strength	Mucoadhesive strength	Spreadability (cm)*	pH*
F1	3004.45 ± 1.65	10.1 ± 0.24	5.6 ± 0.018
F2	4275.65 ± 0.55	8.9 ± 0.83	5.5 ± 0.008
F3	5877.93 ± 0.75	6.7 ± 0.67	5.9 ± 0.002
F4	6548.54 ± 0.59	7.6 ± 0.38	6.0 ± 0.002
F5	3248.53 ± 0.84	9.8 ± 0.57	5.9 ± 0.011
F6	4343.89 ± 0.67	8.3 ± 0.59	5.8 ± 0.001
F7	5846.94 ± 0.04	6.9 ± 0.38	5.9 ± 0.002
F8	6436.96 ± 0.24	7.8 ± 0.86	6.0 ± 0.001
F9	3456.65 ± 0.67	9.5 ± 0.46	5.8 ± 0.003
F10	4596.46 ± 0.98	8.8 ± 0.74	5.9 ± 0.003

*Averages of six determinations

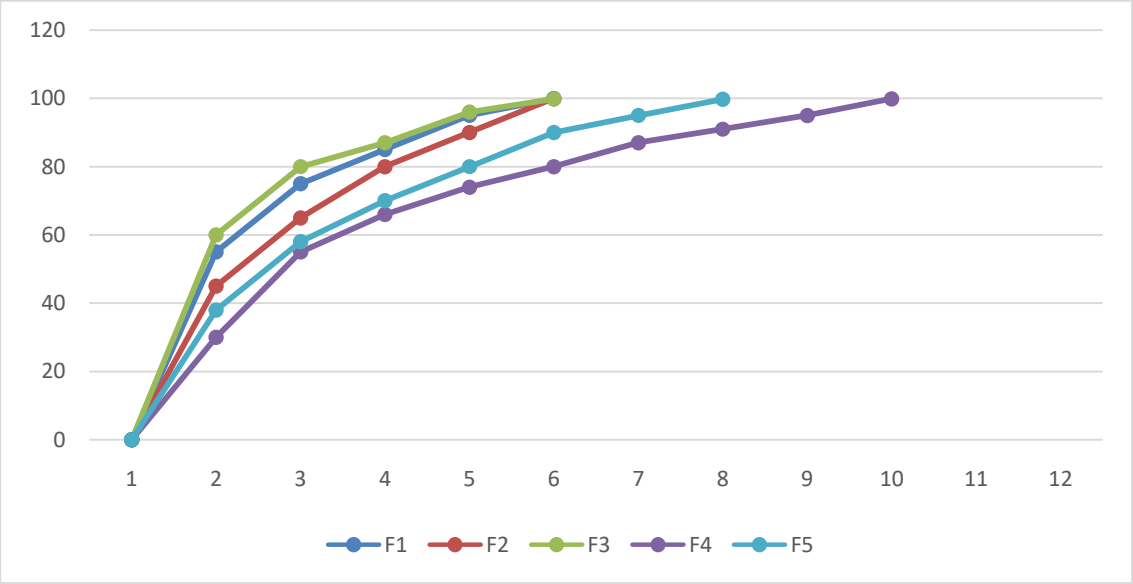

Fig. 4: *In vitro* drug release of *in situ* nasal gel (F1-F5).

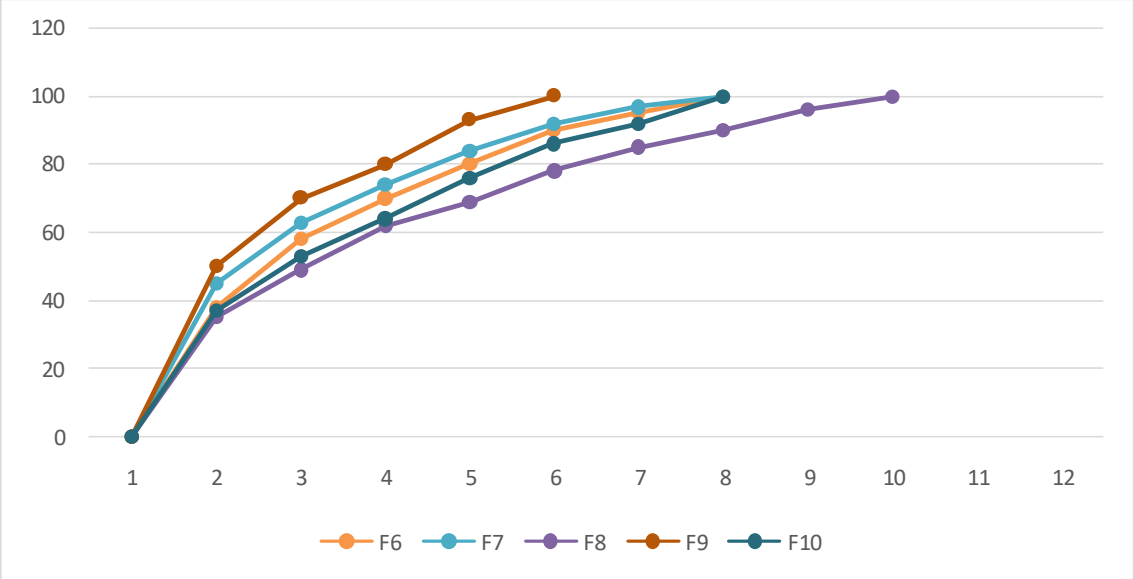

Fig. 5: *In vitro* drug release of *in situ* nasal gel (F5-F10).

preserving the drug in the matrix network and inhibit early release of the medication, according to *in vitro* drug release data. This allows the nasal gels to remain intact during the study time. Table 5 depicts the R2, k, and n values.

Accelerated stability studies:

Table 6 displays information from the accelerated stability experiments of the chosen *in situ* gel formulations. The medication content of the chosen *in situ* gel formulations was consistent with the initial observations made at the start of the trial and continued to be so throughout the accelerated stability analysis. By the end of the expedited research period, these formulations showed acceptable *in vitro* drug release and gelling strength. There were no discernible variations in texture or colour.

Differential scanning calorimetry:

Figure 6 shows the temperature curves of the chosen formulation (F5). The DSC shows a

Table 5: Coefficient values of different formulations of nasal *in situ* gel of oxymetazoline hydrochloride

Formulation Code	Higuchi			Korsmeyer-Peppas		
	r^2	*Y*	*k*	r^2	*y*	*n*
FI	0.938	45.26x + 7.656	39.29	0.227	0.894x + 1.317	0.867
F2	0.937	43.76x + 7.37	40.78	0.234	0.904x + 1.315	0.906
F3	0.939	47.37x + 6.683	45.36	0.246	0.924x + 1.307	0.924
F4	0.956	28.95x + 9.635	25.99	0.329	0.775x + 1.2537	0.775
F5	0.974	36.98x + 6.825	33.98	0.287	0.825x + 1.255	0.824
F6	0.978	39.45x + 7.254	35.46	0.284	0.836x + 1.267	0.836
F7	0.986	35.26x + 4.904	37.27	0.303	0.853x + 1.248	0.854
F8	0.979	25.37x + 9.257	28.67	0.327	0.774x + 1.254	0.778
F9	0.945	44.05x + 8.175	42.07	0.228	0.885x + 1.315	0.856
F10	0.979	37.37x + 4.507	38.36	0.313	0.875x + 1.243	0.878

Table 6: Accelerated stability studies of different formulations of *in situ* gel of oxymetazoline hydrochloride

Evaluation Parameter	Formulation	1st month	2nd month	3rd month	5th month	6th month
Drug content (mg)*	F2	99.12 ± 0.19	98.97 ± 0.11	98.62 ± 0.8	98.32 ± 0.13	97.89 ± 0.11
	F5	98.32 ± 0.12	98.12 ± 0.14	97.87 ± 0.22	97.36 ± 0.13	97.11 ± 0.12
	F7	98.56 ± 0.16	98.12 ± 0.15	97.98 ± 0.12	97.46 ± 0.18	96.99 ± 0.14
	F9	99.38 ± 0.32	99.12 ± 0.14	98.28 ± 0.13	98.12 ± 0.13	97.89 ± 0.13
Gelling strength (s)*	F2	60.12 ± 0.19	59.92 ± 0.32	59.42 ± 0.12	59.12 ± 0.32	58.22 ± 0.12
	F5	62.05 ± 0.12	61.76 ± 0.16	61.28 ± 0.32	61.14 ± 0.12	60.89 ± 0.18
	F7	64.14 ± 0.21	63.98 ± 0.14	63.48 ± 0.11	63.16 ± 0.21	62.99 ± 0.17
	F9	62.99 ± 0.16	62.67 ± 0.21	62.38 ± 0.18	62.14 ± 0.12	61.97 ± 0.16
***In vitro* drug release (%) ***	F2	99.68 ± 1.4	99.12 ± 1.1	98.86 ± 2.1	98.98 ± 1.3	98.76 ± 1.4
	F5	99.52 ± 2.1	99.18 ± 1.8	98.92 ± 1.1	98.69 ± 1.1	98.18 ± 2.1
	F7	99.32 ± 2.2	99.08 ± 1.4	98.89 ± 1.2	98.47 ± 2.1	98.12 ± 2.2
	F9	99.12 ± 1.6	98.99 ± 2.1	98.62 ± 1.4	98.32 ± 2.1	98.12 ± 1.8
Appearance	F2	No change occurs	No change occurs	No change occurs	No change occurs	No change occurs
	F5	No change occurs	No change occurs	No change occurs	No change occurs	No change occurs
	F7	No change occurs	No change occurs	No change occurs	No change occurs	No change occurs
	F9	No change occurs	No change occurs	No change occurs	No change occurs	No change occurs

*****Averages of six determinations

potential interaction between the medication and the polymers in the formulations and offers helpful information about the physical characteristics of the sample, such as whether it is crystalline or amorphous. Determining the melting point of xanthan gum and HPMC K-100 gets challenging because it depends on molecules. Furthermore, there were no endothermic or exothermic peaks visible in the 50–280 ºC range on the thermograms of xanthan gum and HPMC. Because of its melting process, oxymetazoline HCl's thermal curve had a profile typical of a pure, crystalline, anhydrous drug, with a prominent exothermic peak (T peak=137.31 ºC). In contrast, the mannitol thermal profile had endothermic and exothermic maxima at 114.90 °C and 172.50 °C,

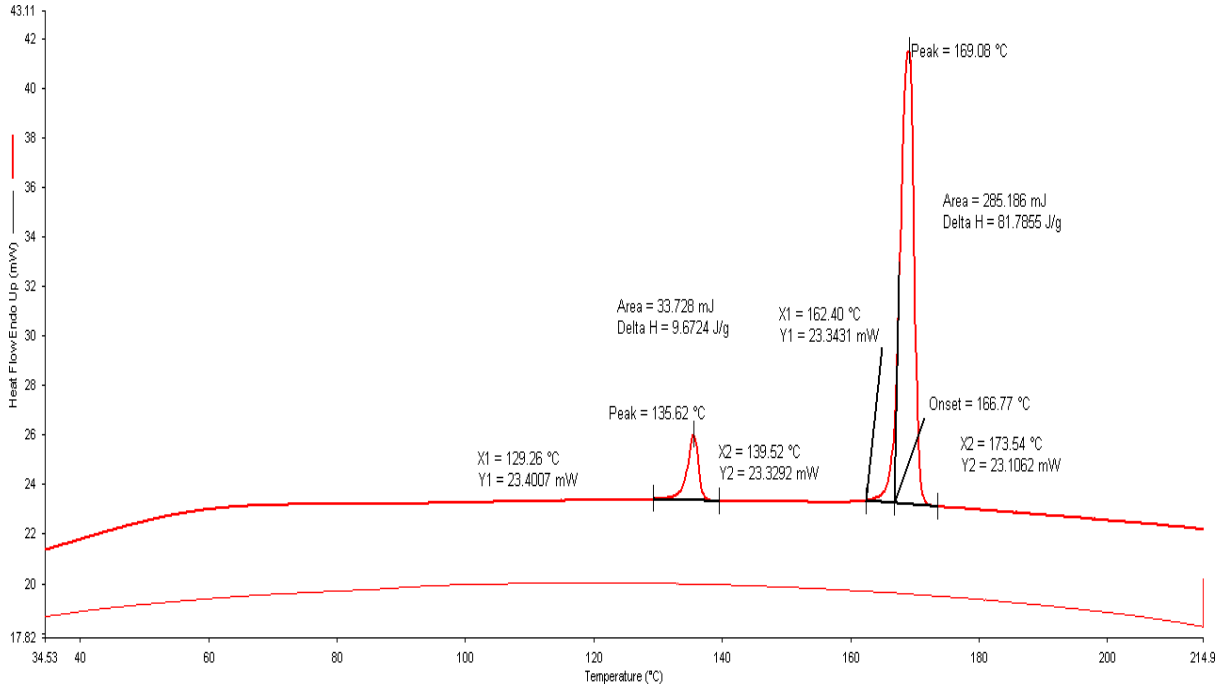

Fig. 6: DSC of selected *in situ* gel formulation (F5).

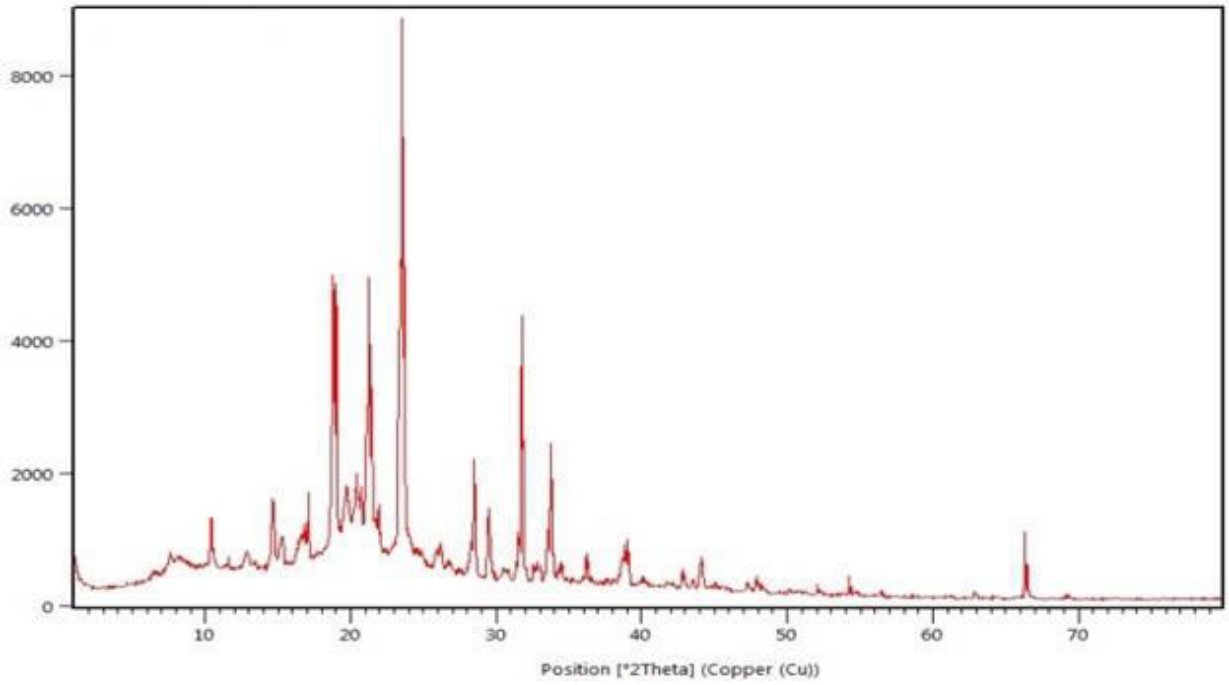

Fig. 7: X-ray diffraction pattern of selected F5 formulation.

respectively.

X-Ray diffraction studies:

Figure 7 displays the XRD pattern of the chosen formulation (F5). Using an X-Ray diffractometer with Cu at 10-800/2θ intervals, the XRD patterns were found. At a scanning speed of 40/min, voltage of 40.0 (kV), and current of 30.0 (mA), the degree of diffraction was measured.

Discussion

A total of ten formulations of oxymetazoline hydrochloride *in situ* nasal gels were created for this study, and their gelling temperatures and times, viscosities, drug contents, gel strengths, spreadabilities, pH, mucoadhesive strengths, *in vitro* drug release, differential scanning calorimetry, and X-ray diffraction studies were all assessed. The experiment was designed using 2^4 factorial designs, with the basis polymers being xanthan gum and HPMC K-100.

The amount of polymers present determined the type of gel that was produced. The term "gelling temperature" refers to the temperature at which the liquid phase changes into gel. If the gelling temperature is lower than the specified period, a gel can form at ambient temperature. On the other hand, when the temperature rises, the nasal mucosa does not gel, which results in rapid nasal clearance. All of the formulations, however, demonstrated rapid gelation upon contact with the solution and maintained their integrity over a prolonged length of time for the drug's sustained release. The term "gelling time" refers to how long it takes a sol form to form a gel.

As the concentration of HPMC K-100 increased, the test gels' viscosity also increased. The polymeric content of the formulations had a direct bearing on the viscosity. The *in situ* gels formed an elastic and viscous gel instantly when they were combined with phosphate buffer solution (pH 6.4). The formulations made with a high HPMC K-100 content, however, had a lower spreadability. This was explained by the fact that HPMC K-100 has a high viscosity. Because every formulation's pH was within an acceptable range, the pH values did not indicate any mucosal discomfort.

Throughout the course of the trial, the drug release was extended in the formulations made with more viscous polymers. The concentration and viscosity of the polymer utilised in the formulations were associated with the medication release. The concentration of HPMC K-100 determined the release rate at fixed medication concentrations. The higher the concentration of HPMC K-100, the lesser the drug release. Stability tests' findings showed that there was no impact on the formulations' physical and chemical stability during the testing phase.

The drug melting peak was recorded at 135.59 ºC, indicating that there were no interactions between oxymetazoline hydrochloride and the other excipients in the formulation that was chosen. However, in the chosen formulation (79.7696 J/g), there was no discernible decrease in the heat of fusion (ΔH; 82.5385 J/g) with respect to crystalline nature.

These results showed that the crystalline form of oxymetazoline hydrochloride may be preserved by the chosen excipients. It should be noted, though, that the drug's physical state changes to an amorphous or partially amorphous state, which causes a high energy state and high disorder. This leads to increased solubility and a quicker rate of dissolution. There was less of a shift from the drug's crystalline to amorphous form, as evidenced by the almost identical number of strong peaks that formed the XRD pattern in the chosen formulation. Additionally, the peak in the physical mixture showed that the medicine and certain excipients did not interact.

Conclusion

A novel formulation of mucoadhesive *in situ* gels containing oxymetazoline hydrochloride was created to address the issue of first-pass metabolism and improve the drug's limited bioavailability. Laboratory experiments have demonstrated that *in situ* gels have the potential to

function as a drug delivery method for oxymetazoline hydrochloride, with improved stability and release characteristics. Nevertheless, it is necessary to conduct future *in vivo* investigations in order to validate these findings.

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