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## Formulation Development and Evaluation of *In-Situ* Nasal Gel of Phenylephrine Hydrochloride

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### ABSTRACT

*pH-sensitive development It was intended to increase absorption with phenylephrine hydrochloride in-situ nasal gel. Carbopol-934 and sodium alginate were combined in the current research work to benefit the pH-sensitive gelation property. Sodium alginate and carbopol-934 were prepared in various amounts to create several formulations. Carbopol-934 and sodium alginate concentrations determine the release profile in this formulation. The formulations underwent testing for factors like pH, drug content, viscosity, mucoadhesive strength, gel strength, in-vitro drug release, and excipient compatibility. To examine how different amounts of Carbopol-934 (X<sub>1</sub>) and Sodium alginate (X<sub>2</sub>) might affect various models of a certain drug release kinetic, a 3<sup>2</sup> factorial design was used. For dependent variables, regression analysis and variance analysis were used. In-vitro drug release and mucoadhesive formulation were both successfully provided by the formulation, according to the study. This study aimed to create an intranasal gel for drug delivery to the brain via the olfactorylobe pathway.*

**Keywords:** *In-Situ Gelling System, Sodium alginate, Nasal Decongestant, Carbopol-934, and pH Sensitive*

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### INTRODUCTION

The creation of innovative medicine delivery methods has received a lot of attention lately. By giving pharmaceuticals a more accurate spatial and temporal location within the body through a controlled drug administration, the therapeutic efficacy and safety of medications given by conventional techniques can be increased. In the pharmaceutical sciences as well as the pharmaceutical industry, the utilization of the nasal route for drug delivery is a developing area. While the vast majority of nasal formulations are created and utilized for local administration to treat allergies, infections, or congestion in the nose, other nasal delivery uses have grown in significance in recent years.[1] Due to the lack of pancreatic and gastric enzymatic activity, the neutral pH of the nasal mucus, and less dilution by gastrointestinal contents, the nasal mucosa has been considered as a potential administration route to achieve faster and higher levels of drug absorption.[2,3] The process of creating a new medicinal molecule is costly and time-consuming. As a result, by delivering medications to the intended site in a controlled or sustained manner, the safety and efficacy ratio of "old" drugs can be enhanced. As a result, in situ gelling nasal medication delivery systems are created. Drug delivery systems known as in situ gels initially take the form of a solution before being injected into the body, but once there, they go through a gelation process to become a rigid gel. In the early 1980s, this novel idea was originally proposed. In contrast to liquid formulations, nasal in situ gels are administered as low viscosity solutions into the nasal cavity, but they also release the medicine gradually and continuously, making them particularly helpful for medications used on a regular basis. Numerous factors, including solvent exchange, ultraviolet light, ionic cross-linking, temperature alteration, pH change, and ionization, cause in situ gels to develop, allowing for the gradual and controlled release of drugs. The in situ gel technique is more dependable since the medication releases slowly and consistently, it is reproducible, has high stability, is biocompatible, and can be administered in precisely the right amounts. It is advised to use phenylephrine hydrochloride to treat community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and acute exacerbations of chronic bronchitis (AECB). By stabilizing the complex produced between DNA and topoisomerases, it prevents the replication and transcription of bacterial DNA. The goal of this work is to create a nasal in situ gel of phenylephrine hydrochloride for the treatment of respiratory tract infections, particularly sinusitis and bronchitis, in order to achieve site-

specific action and to sustain the drug release for a longer period of time, which reduces the frequency of dosage administration and increases patient compliance[4].

## MATERIAL AND METHODS

Phenylephrine Hydrochloride was obtained from Yarrow chem. Products , Mumbai; Sodium alginate was obtained from Loba chemie, Mumbai. and Carbopol-934 was obtained from ModernIndustries, Nashik, Propylene Glycol, Bezalkonium Chloride and Triethanolamine used were ARGrade.

### Pre-formulation Study Compatibility Study-

#### Fourier Transform Infra-Red (FT-IR) analysis

The samples were tested using an FT-IR spectrophotometer. Dry potassium bromide was mixed with the test sample, which weighed between 4 to 5 mg. The sample was then analyzed using a transmission mode with a wave number range of 4000 to 400 cm<sup>-1</sup> [5, 6]

#### Ultraviolet-Visible Spectroscopy Study

The UV-visible spectrophotometer Shimadzu 1800 series was used to get the UV spectrum of phenylephrine hydrochloride. The medication, which was precisely weighed at 10 mg, was dissolved in enough water to make a volume of 10 ml. 100 g/ml of the stock solution's concentration was achieved by diluting it. To get a concentration of 10 g/ml, an aliquot volume of 1 ml was taken out and diluted with water to make a volume of 10 ml. To determine the maximum wavelength, the spectra of the resulting solution was scanned from 200 to 400 nm.[7-12]

#### Method

The formulas were created using the cold approach. The medication was hydrated individually in a determined amount of distilled water at room temperature, chilled, and stored at 4 °C for the mucoadhesive and gelling polymers. On an ice bath, the two polymeric solutions were slowly combined. The polymer solution was then gradually added with constant stirring. Drug and polymer solutions were combined by gently swirling them together. The finished dispersion was then kept in a fridge until a clear solution was made.

The materials listed in (Table-1) were used to create various gel formulizes. Carbopol-934 content in this formulation ranged from 0.1% to 0.3%, and sodium alginate concentration was between 0.1% and 0.2%. Drug was dissolved in a mixture of distilled water and propylene glycol; each polymer was hydrated separately. Overnight, the solution was left out at room temperature. In the polymeric solution, preservative was added. The polymeric solution and medication were combined under cold conditions.[13-24]

**Table No.1 Composition of formulation batches as per 3<sup>2</sup> factorial designs**

F.C. Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Phenylephrine Hydrochloride	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Carbopl-934	0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
Sodium Alginate	0.1	0.1	0.1	0.15	0.15	0.15	0.2	0.2	0.2
Propylene Glycol	1	1	1	1	1	1	1	1	1
Benzoalkoniumchloride	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Distilled Water(ml)	100	100	100	100	100	100	100	100	100

### Evaluation of Nasal Gel [25-36]

#### Physical parameter

##### Clarity

The formulation were examined visually for clarity.

##### pH

A digital pH meter (Digital pH meter 335) was used to calculate the pH of each composition. Previously, pH 4 and pH 7 were used to calibrate this. The pH readings were taken right away after preparation.<sup>23</sup>

##### Rheological study Viscosity

The Brookfield viscometer, model DV-II + PRO, and spindle no. LV-3<sup>20</sup>, were used to measure the rheological characteristics of gels. The formulations' viscosities were measured at pH 7.4 and their respective pHs, along with varied shear rates.

##### Measurement of Gelling capacity

By adding 1 drop of the created formulations into a vial containing 2 mL of freshly made SNF, the gelling capabilities of the formulations were ascertained. Visual evaluation of gelation and timing of gelation were

both used.

### Measurement of the gel strength

A 50 mL graduated cylinder was filled with a sample of 25 mL of the gel. On the gel surface, 14.33 g of weight were applied. The time in seconds needed for a weight to pierce 5 cm of gel—a measurement of the ophthalmic gel's strength at physiological temperature—was recorded. Each measurement was made three times (n=3). The equipment for determining gel strength at different pH levels, including pH 7.4

### Spreadability

The gel formulation's spreadability is measured in square metres per minute (cm<sup>2</sup>/min). The spreadability of solution formulations F1 through F9 was evaluated using Whatmanns filter paper (0.45mm). The tip of a 1-ml graduated pipette with a rubber bulb was secured vertically to the stand so that it was 2 cm above the horizontal surface of the filter paper in a round shape. On the filter paper's middle, 0.1 ml of the sol formulation was dropped. The surface area that the formulation covered at each 20-second interval was measured.

### Drug Content

Shimadzu UV-1800 double beam UV-visible spectrophotometer was used to determine the drug content of the formulation. Formulation volume modified to 10 millilitres after being diluted with double-distilled water. Using 10ml of double-distilled water, one millilitre of this solution was once more diluted. Using a UV-visible spectrophotometer, the produced solution's absorbance was finally determined at 272 nm.

### In-Vitro Drug Release Study

In-vitro release study of the formulated in-situ gel was carried out by using diffusion cell through Cellophane membrane. The formulation 1 ml were placed in donor compartment and Freshly prepared 100 ml simulated nasal electrolyte solution (sodium chloride 0.745gm, potassium chloride 0.129 gm, calcium chloride dehydrated 0.005gm, distilled water q.s. 100ml in receptor compartment. Cellophane membrane were mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that Cellophane membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C 0.5°C. 2ml of sample is withdrawn from receiver compartment after 30 min, 1, 2, 3, 4, 5, 6, 7 & 8 hrs and same volume of fresh medium is replaced. The withdrawn samples was diluted to 10ml in a volumetric flask with phosphate buffer pH 6.8 and analyzed by UV spectrophotometer at 272nm

## RESULT AND DISCUSSION

### Clarity:

All of the developed nasal gel formulations were discovered to be devoid of dispersed particle matter upon thorough visual inspection against a dark and white backdrop. It was determined that each formulation was clear.

### pH

The pH of all formulations from F1 through F9 was discovered to be between 6.0 and 6.4. (Table 2)

**Table 2: Evaluation Parameter**

Formulation Code	Observed pH (±S.D)	Gel Strength (±S.D)	Detachment Force (±S.D)	Drug Content (±S.D)	Cumulative drug released (±S.D)
F1	6.4± 0.2	0.49±0.2	0.04285±0.0058	95.30±0.04	94.02
F2	6.1±0.4	0.72±0.03	0.05546±0.056	94.88±0.46	95.30
F3	6.4±0.3	0.55±0.01	0.06540±0.056	95.91 ±0.59	95.80
F4	6.1±0.2	0.61±0.14	0.06600±0.056	94.41±0.44	97.62
F5	6.4±0.3	0.49±0.01	0.04660 ±0.057	98.41 ±0.44	98.22
F6	6.4±0.3	0.75±0.03	0.04578 ±0.057	99.44±0.51	99.22
F7	6.0±0.2	0.57±0.02	0.05578±0.0056	96.44±0.41	91.55
F8	6.1±0.1	0.46±0.02	0.04478±0.0055	99.51±0.51	90.23
F9	6.4±0.1	0.44±0.07	0.0671±0.00565	93.41 ±0.45	89.68

### Gel Strength-

Gelling and mucoadhesive polymer concentrations were discovered to have an impact on gel strength. The best mucoadhesive gel should have the right gel strengths to be conveniently delivered and to be held at the nasal mucosal region without leaking after administration. The results for viscosity and gel strength for all formulations were comparable.

### Drug Content-

All manufactured nasal formulations were found to contain between 95.30 and 99.44% of their total drug

content. As a result, consistency of content was seen across all formulations.

**Spreadability**

In situ gel must have the proper spreadability to be administered with ease and to spread readily on nasal mucosa without leaking after application. The spreadability measurement data are shown in Table 2. Due to increased in situ gel surface area being covered after being placed on filter paper, Formulation F6 exhibits the greatest spreadability.

**Viscosity**

Tables 3 and 4 display the formulations' viscosities at their respective pH values of and 7.4. Figures 4 and 5 depict the formulation's viscosities at their different pH levels and at pH 7.4. Plots of viscosity vs shear rate (rpm) for all formulations demonstrate a reduction in viscosity as rpm was raised, indicating that gel has a pseudoplastic flow. Viscosity increased as pH level was raised, as well. The main element impacting formulation viscosity was carbopol concentration. Carbopol has demonstrated significant increases in viscosity when Sodium alginate content is 0.1% w/v to 0.2% w/v.

**Table no.3 Viscosity Of Formulations**

RPM	Viscosity (cp) of Formulation								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	412.6	460.3	570.2	432.1	462.1	615.3	460.5	460.3	738.2
10	254.4	210.2	360.1	265.1	297.5	395.3	279.9	276.2	440.1
15	180.6	280.2	300.3	197.3	266.3	335.4	212.2	220.3	350.1
20	160.1	235.3	290.1	177.2	243.2	280.3	185.4	198.2	285.1
25	141.2	252.2	236.5	170.2	225.2	245.3	178.3	164.3	247.1
30	111.2	162.1	180.1	130.2	178.1	230.3	137.2	149.3	296.1

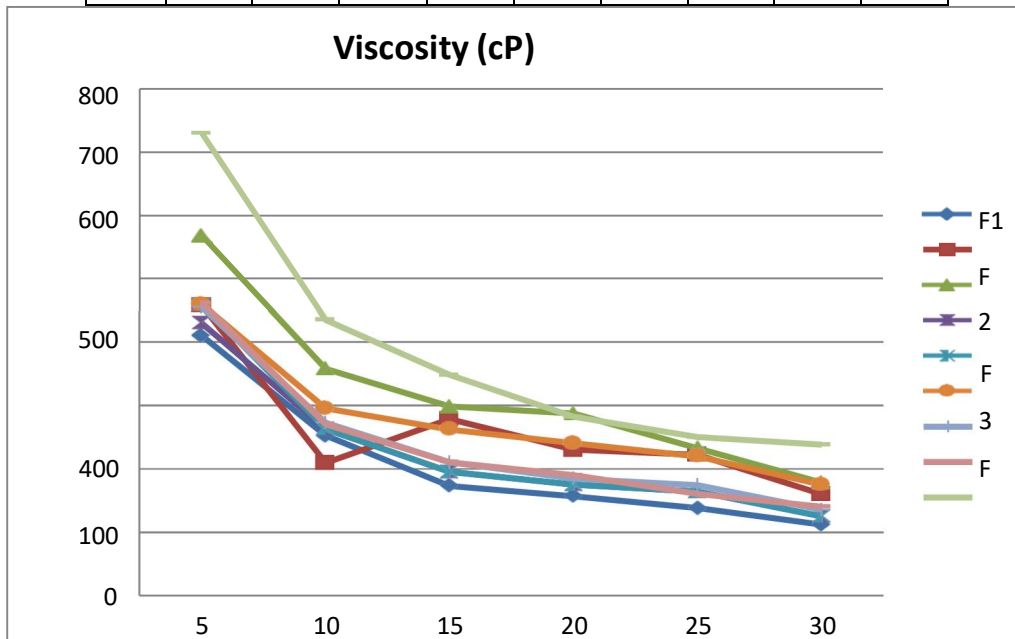


Figure no. 1 Viscosity Of Formulations

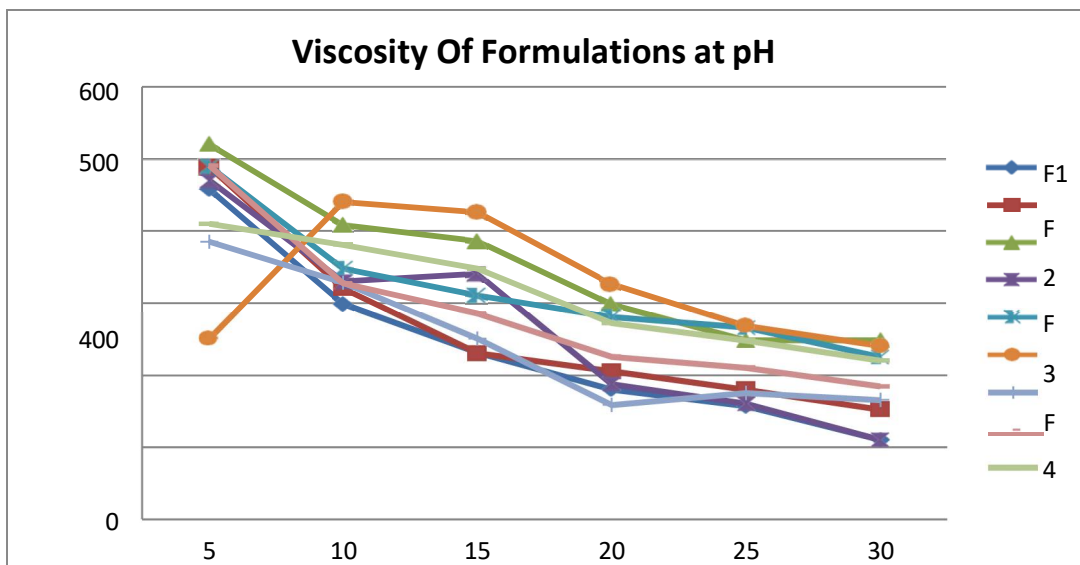


Figure no 2.Viscosity Of Formulations at pH 7.4

Table no 4 Viscosity of Formulation at pH 7.4

RPM	Viscosity (cp) of Formulation								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	459	492.5	521.1	472.2	492.2	253.2	387.2	493.8	415.2
10	300.1	322.2	410.5	332.1	350.3	443.2	329.1	330.2	383.9
15	232.5	239	375.5	341.7	313.2	429.5	255.3	290.1	351.1
20	158	205	280.8	180	225.3	298	187.3	272.1	325.8
25	159.5	183	250	169.2	271.7	270.3	180.2	235.3	249.1
30	112	154.1	250.3	112.2	227.1	243.3	168.5	189.3	225.2

**In-Vitro Drug Release-  
Cumulative Drug Release Of Formulation**

Cumulative Drug Release (%) (±S.D.)									
Timein (sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
30 (mi n)	29.68±0.14	16.15±0.14	6.53±0.20	26.15±0.22	11.60±0.21	12.90±0.34	23.10±0.13	10.27±0.30	10.40±0.40
1	38.85±0.15	29.35±0.44	18.97±0.28	36.42±0.17	22.87±0.35	15.20±0.37	30.20±0.20	16.17±0.22	18.35±0.27
2	50.55±0.17	42.70±0.22	38.10±0.11	56.65±0.19	32.40±0.17	28.28±0.47	56.45±0.10	29.52±0.10	25.60±0.15
3	78.82±0.12	56.68±0.11	47.59±0.41	72.89±0.29	48.09±0.19	40.80±0.37s	68.09±0.33	42.80±0.12	36.10±0.35
4	95.07±0.15	68.10±0.13	56.40±0.20	96.12±0.42	58.20±0.07	50.10±0.28	78.90±0.38	53.48±0.18	45.45±0.45
5	94.35±0.23	84.55±0.18	66.79±0.16	96.35±0.56	64.17±0.01	62.80±0.24	96.39±0.41	63.20±0.21	57.15±0.40
6	95.55±0.11	95.10±0.19	75.10±0.17	96.70±0.32	78.45±0.34	71.59±0.12	96.41±0.06	75.42±0.34	67.64±0.24
7	95.75±0.02	95.55±0.08	85.84±0.45	96.80±0.17	86.24±0.33	84.05±0.19	96.66±0.11	83.77±0.46	81.79±0.36
8	94.02±0.08	95.30±0.18	95.80±0.11	97.62±0.13	98.22±0.14	99.22±0.15	91.55±0.15	90.23±0.47	89.68±0.49

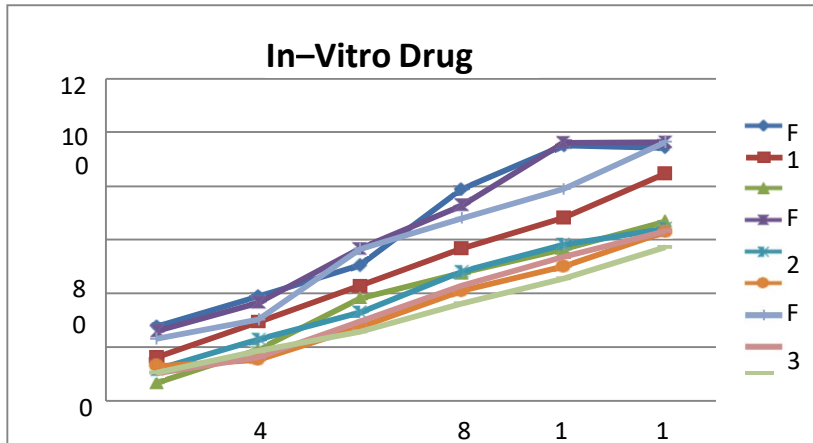


Figure no. 4 In-vitro Drug Release

Out of the nine formulations, the largest release was discovered for F6 formulation, according to the result. This shows that 99.22% of the medication has been released and is now active in decongesting the nasal passages. The steady state release of the F6 formulation for up to 8 hours suggests that this formulation would have good contact with biological membranes.

**OPTIMIZATION**

Software called Design Expert 7.0 was used to investigate how independent variables affected answers. The table below displays the experimental design arrangement created for 9 potential batches of phenylephrine HCl in situ gel. ANOVA testing was done on the software-suggested models, such as linear, 2FI, quadratic, and cubic, that fit the data the best. In order to obtain one factor and perturbation graphs for each individual dependent variable, regression polynomials were first computed for each individual dependent variable. For each distinct dependent variable or response (R), mathematical models were created and stated as equations.

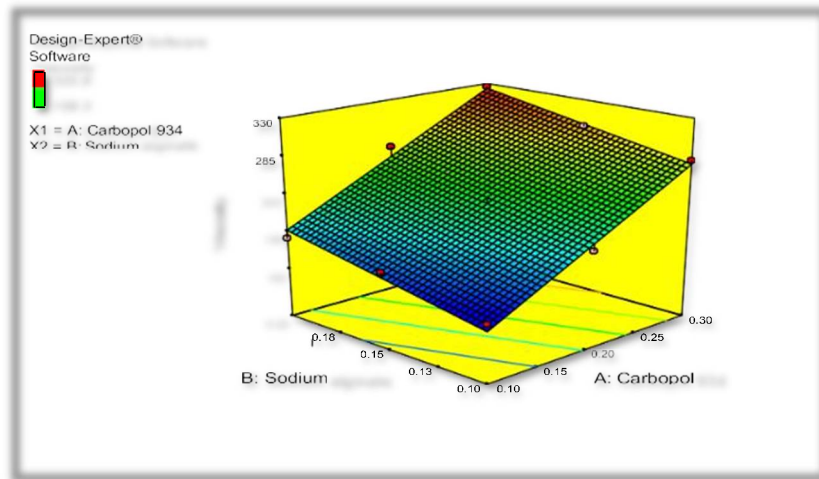
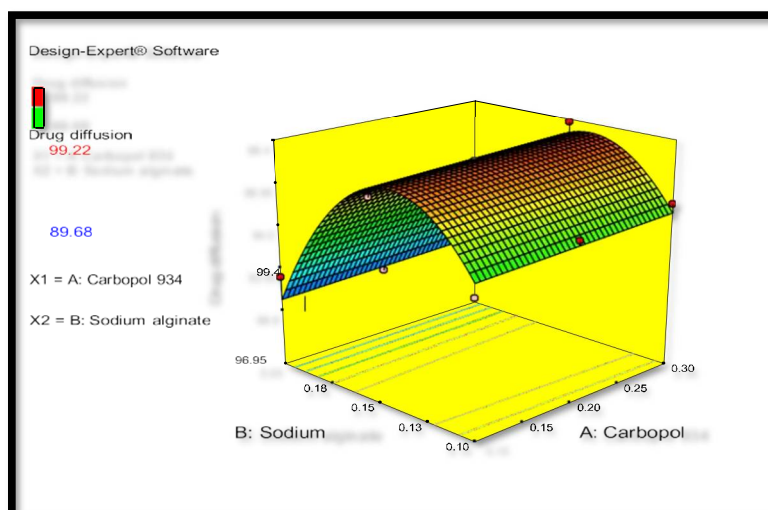


Figure no.5 3D plot for Viscosity



**Figure no.6 3D plot for Drug Release**

## CONCLUSION

Phenylephrine hydrochloride in-situ gel was successfully developed. pH-dependent polymer is carbopol. Mucoadhesive polymers include sodium alginate. The nasal gel's clarity, pH, viscosity, gel strength, bioadhesive drug content, drug release, and stability research were all noted. The drug and excipient pre-formulation study was completed, and all of the results were compared to the requirements to determine which results passed the test. The results of the investigation on the compatibility between drugs and excipients demonstrate that the drug was compatible with the excipients employed in formulation. The entire formulation was inspected for visual appearance, and it was discovered to be a translucent gel, respectively. All of the formulations' pH levels were found to be within the acceptable mucosal region pH range, which is between 6.5 and 8.5 for the nasal cavity. Carbopol 934 and sodium alginate percentages in the formulation that affect the drug's viscosity. Viscosity increases when carbopol 934 and sodium alginate content in the formulation rises. When compared to sodium alginate, carbopol 934 had a far higher impact on viscosity because of its much lower P value. Formulations' gel and bio adhesive strengths reflect the findings regarding viscosity. The permissible range for drug content for all of the formulations was found to be 95.30-99.44%.

Over a period of three months at 25°C, the improved formulation F6 displayed good stability and no change in any physical properties. Carbopol 934 and sodium alginate percentages in the formulation have an effect on medication diffusion. Diffusion exhibits a curvature impact as sodium alginate in the formulation and carbopol 934 in the formulation rise. Since sodium alginate's P value was much lower than that of carbopol 934, it had a much greater impact on diffusion. Good nasal mucosal permeability was observed in the permeation investigation up to 8 hours after the formulation was optimized.

This phenylephrine hydrochloride nasal in-situ gel formulation satisfies all prerequisite requirements for usage on nasal mucosa. The bioavailability of Phenylephrine Hydrochloride in gel form when supplied nasally may be increased by this optimized formulation, which also offers an alternative to the formulation that is often taken orally. It has improved viscosity and mucoadhesive properties.

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