FORMULATION AND EVALUATION OF THERMORESPONSIVE IN SITU NASAL GEL CONTAINING BERBERINE AND ONION EXTRACT

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Abstract

The aim of present work was to develop the in-situ thermos-responsive nasal gel by cold technique and evaluate its efficacy against congestion due to allergic rhinitis. Berberine, onion extracts and Pluronic PF127 was characterized by FTIR. The berberine, onion extract and Pluronic PF127 was fabricated by using the cool technique, using the berberine and (Pluronic) PF127 blend in separate ratio to optimize these influences on the medication deliver profile. Nasal gels were evaluated through the various parameter namely gel time, gelling temperature, viscosity, gel strength, mucoadhesive strength, in vitro drug release study and in vivo study of the drug formulation. The improved preparation that passed the aforementioned examinations was then put through an expedited stability investigation. Over the course of the 28 days, it maintained a decent level of stability. This in situ gel appears to be a successful nasal administration method based on overall effectiveness.

Keyword: In situ nasal gel, Berberine, Onion extract, Pluronic PF127.

1. INTRODUCTION

Nasal medication delivery methods have the ability to bypass the first pass effect and prevent GIT pre-systemic excretion. A certain medication's therapeutic benefit could be obtained with a lower dosage **(Kumar et.al 2011)[1]**. Intranasal delivery system were preferred nasal route for administering medications since it offers all the benefits mentioned above, as well as a sizable absorptive surface area and high vascularity **(Mishra Set.al 2013, Arora P et.al 2002)[2]** and is regarded as the iv's replacement route. However, the nasal route has the drawback of the medication being quickly eliminated from the nasal passages by mucociliary beating. A mucoadhesive method can be used to slow down fast muco-ciliary clearance and increase bioavailability. These systems stick to the mucus and prolong its stay inside the nasal cavity. This increases the amount of medicine that comes into touch with the nasal mucosa and makes it easier for the drug to be absorbed, increasing its bioavailability. **(Basu S et.al 2010)[3].**

The word "in situ," which comes from the Latin for "in place," refers to a liquid formulation. The early 1980s saw the initial formulation of this unique idea. The cross-linking of polymer chains, which may be performed by creating covalent bonds or non-covalent bond formation, results in gel formation. Both organic and synthetic polymers were used to make in situ gels. Over an extended length of time, in situ gel devices can provide rather constant plasma profiles. **(Abbas, 2012)[4]**Because of its wide surface area, permeable endothelium membranes, increased total blood circulation, and minimization of first-pass metabolism, the nasal route has demonstrated improved systemic bioavailability. A beta blocker called timolol maleate is typically used to treat high blood pressure. Considerable hepatic medication absorption during first pass. Jag dale et al. (2016)[5] claim that the medication has a 4 hr half-life. 601 percent of timolol maleate is bioavailable when taken orally. Optimizing the controlled release in situ nasal injection of timolol maleate was the goal of the current experiment and HPMC. The thermo-reversible in situ nasal gel was made with the polymer Poloxamer 407.**(Altunta & Yener, 2017)[6]** Innovative intranasal aqua-triggered in-situ gels are micro-emulsions that instantly gel when in touch with minute amounts of water to create mucoadhesive gels. They are devoid of polymers. The study's goals were to create ATIS diazepam (ATIS-diazepam) as a non-injectable treatment for epileptic situations and assess the effectiveness.**(Bachhav et al., 2020)[7]** Due to their numerous limitations, oral drug delivery techniques are unable to effectively transfer a variety of therapeutic agents to the brain, including their sluggish beginning of action. Also, oral preparations have a short half-life of 1-2 hours, with the medication being swiftly removed by the hepatic and renal systems after going through hepatic first-pass metabolism.**(Mittal et al., 2013)[8]** By extending the duration of the medication's residence nasal drug administration is primarily designed to increase drug absorption rate and bioavailability. As a consequence of the controlled drug release and extended drug contact time provided by the thermoreversible gel formulation, local and systemic bioavailability are enhanced, dosage needs are decreased, and patient safety and acceptability are increased.**(Shelke et al., 2015)[9]**

2. MATERIALS AND METHOD

2.1 DRUGS AND CHEMICAL USED

Berberine was purchased from Johnlee Pharmaceuticals Pvt. Ltd. Mumbai India. Poloxamer, Na CMC, hydroxy propyl cellulose, HPMC K15, PVA were obtained from the laboratory of Hygia Institute of Pharmaceutical Education and Research, Lucknow. Onion extract was gifted from the Garon Dehydrates PVT Ltd Indore Madhya Pradesh.

2.2 METHODS OF FORMULATION

2.2.1 Cold Method:

This procedure involves stirring the medication with enough double-distilled water and storing it in a refrigerator overnight at 4°C. After that, the gelling agent PF127 gently added while being stirred. The distribution kept in the fridge until it becomes a clear solution, and then the volume is adjusted with purified water. When using pluronic, or carbopol as a gelling polymer, this approach is adopted. The polymeric dispersion of poloxamer is in solution at lower temperatures and turns into a gel at higher nasal temperatures because the solubility of the polypropylene oxide chain in the poloxamer decreases at high temperatures, causing a polymer to precipitate or salt out. (**Ban MM .et, al 2018)**[10]

2.2.2. Identification of drug:

One of the most crucial preliminary tests to carry out for the verification and verification of the purity of the sample prior to formulation formation is drug identification. The identification test is offered as a Pharmacopeial analysis to help in verifying the stated identity of the substance.

2.2.3. Appearance: -

When compared to the claimed appearance of the drug sample, the appearance of the acquired sample was distinguishable in terms of hue.

2.2.4. Solubility

The weighted excess of the drug sample was dissolved in acetone, methol, and water to determine its solubility. The drug sample was vigorously mixed to dissolve it, and any remaining drug material was filtered out. The medication was filtered, allowed to dry, and then weighed. Subtracting the amount of dissolving weighted excess from the drug sample's solubility.

2.2.5. Melting point

One quantitative analysis for the identification of organic compounds is the determination of melting point. A tiny amount of the material was placed within a capillary to determine the results of this capillary technique. Capillary should be put in a melting point apparatus with one end shut. The temperature at which the medication totally melts was measured to determine the drug sample's melting point.

2.2.6. UV Spectroscopic Estimation

One of the analytical methods for identifying drug samples is UV spectroscopy. The drug sample's UV spectroscopy was used to estimate the maximum concentration and compare it to the maximum concentration of the drug that has already been published.

2. 3. FORMULATION: -

Preparation of Berberine:

Table 1: PF127 blend by hot melt process

S. No.	Batch and Ratio	Berberine Drug	Polymer PF127(32%w/v)
1.	B_1 (1:1)	200mg	200mg
2.	B_2 (1:2)	200mg	400mg
3.	B_3 (1:4)	200mg	800mg
4.	B_4 (1:6)	200mg	1200mg
5.	B_5 (1:8)	200mg	1600mg

2.3.1. Procedure for B1 Batch: -

In this process, weigh 200mg of berberine and 200mg of PF127 and transfer them into the china disc and melt them by using the water bath. The melted formulation is mixed, dried, and converted into the powder form and collected in the glass vials.

2.3.2. B2 Batch: -

In this batch, weigh 200mg of berberine and 400mg of PF127 and transfer them into the china disc, melt the formulation in the water bath, and collect the formulation in the powder form in the glass vials.

2.3.3. B3 Batch: -

In this process weigh 200mg of berberine and 800mg of PF127 and transfer them into the china disc and melt them using the water bath. The melted formulation mixed, dried and converted into the powder form and collected in the glass vials.

2.3.4. B4 Batch: -In this process weigh 200mg of berberine and 1200mg of PF127 and transfer them into the china disc and melt them by using the water bath. The melted formulation mixed and dried and converted into the powder form and collected in the glass vials.

2.3.5. B5 Batch: In this process weigh 200mg of berberine and 1600mg of PF127 and transfer into the china disc and melt them by using the water bath. The melted formulation mixed and dried and converted into the powder form and collected in the glass vials. All formulations were prepared using the hot and cold method in this process, and the B2 batch was chosen for further investigation because the other formulations did not gel at body temperature or room temperature.

Table 2: Formulation of drug and polymer Composition

Composition	F1	F2	F3	F4	F5
Berberine	100mg	100mg	100mg	100mg	100mg
Onion extract	1gm	1gm	1gm	1gm	1gm
PF127(32% w/v Stock solution)	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
1% w/v PVA solution	1ml				
1% w/v HPMCK15		1ml			
1% w/v Na CMC			1ml		
1% w/v HPC				1ml	
1% w/v HEC					1ml

2.4. Preparation of In-situ nasal gel: -

The thermo reversible in situ nasal was prepared by using the cold method. A plain and drug-loaded PF-127 gels were prepared with a sufficient quantity of distilled water and stirred, while for plain PF-127 gels, without drug, they were kept overnight at 4 ^{0}C in the refrigerator until the clear solution was obtained and finally volume was adjusted.

Formulation 1 and formulation 2 is used to further investigation for the formulation of in situ nasal gel and their evaluation parameter.

Table No 3: Formulation of HPMC K15 And PVA

INGREDIENT	F1	F2
Onion extract	1gm	1gm
Berberine	50mg	50mg
HPMC K15		2ml
PVA	2ml	
WATER	2ml	2ml
PF127(32% w/v Stock solution)	5.25ml	5.25

2.5. ANALYTICAL METHODOLOGY-

2.5.1. Preparation of the calibration curve:

- **Preparation of 1st standard stock solution**

In order to create a 100 ml stock solution, 10 mg of berberine were weighed, combined, and added to a 100 ml volumetric flask.

- **Preparation of 2st standard stock solution (100µg/ml)**

- A additional 1ml of a berberine stock solution concentration in distilled water diluted with water to generate a solution with a 100 g/ml concentration.
- A further 2ml of a berberine stock solution concentration in pure water was 200 g/ml concentration solution was diluted with water.

- A further 3ml of a berberine stock solution concentration in pure water which was then 300 g/ml concentration solution was diluted with water.
- A additional 4ml of a berberine stock solution concentration in pure water in 10ml), which was then 400 g/ml concentrated with water.
- A 500g/ml concentration solution was created by diluting a 5ml berberine stock solution in deionised water (5ml in 10ml) with water.

2.6. Identification of Drug Samples

Both drugs namely berberine and onion extract were identified by UV & IR spectroscopy which confers by previous research published reports. Other identification tools were also used to confer their identity like appearance, solubility and melting point.

3. RESULTS AND DISCUSSION AND CONCLUSION

3.1. Viscosity:

The viscosity of the preparations ranges from 217136 to 2564693.

Table No 4: Viscosity of the drug formulation of HPMC k15

Time (Minute)	Viscosity (centripoise)
2	217136
4	323135
6	508454
8	1888672
10	1948330
12	2315661
14	2432921
16	2540662
18	2564693
20	2563810

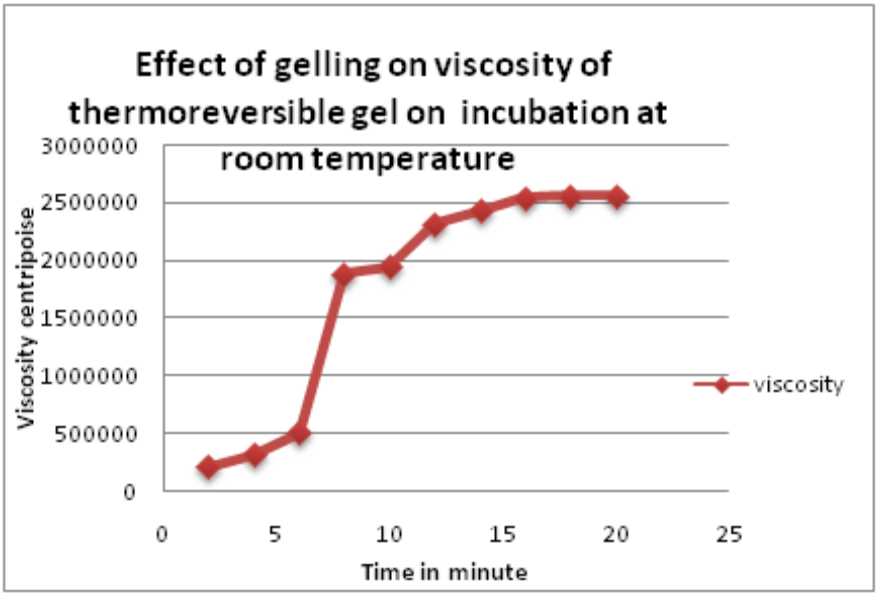


Figure 1: Viscosity of the drug formulation of HPMC k15

Table 5: Viscosity of the drug formulation of PVA

Time (Minute)	Viscosity (Centripoise)
3	277196
6	513861
9	2564704
12	2563855
15	2565643
18	2564570
21	2565643
24	2564257
27	2565240
30	2564034

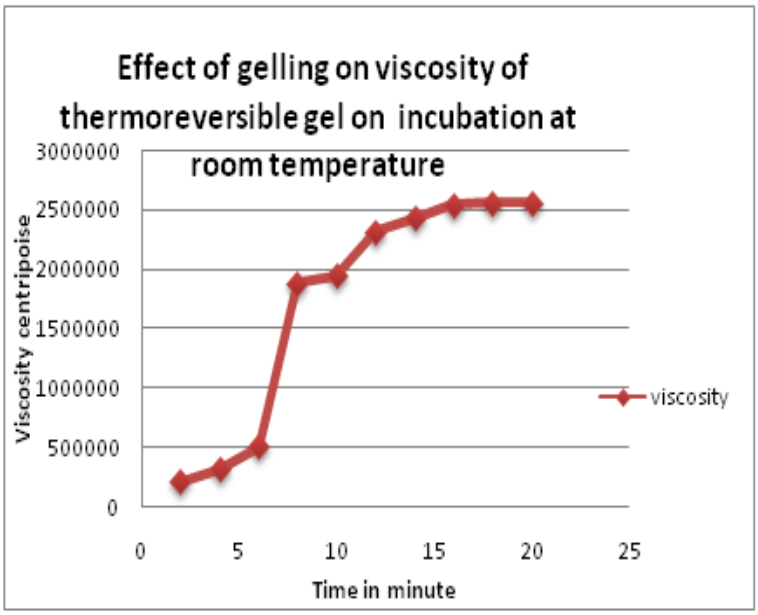


Figure 2: Viscosity of the drug formulation of PVA

3.2. Determination of residence time in case of allergic rhinitis

Table 6: Removal timing of the gel

Drop per minute	**Volume per minute**	**Removal of gel time**	**Removal of gel time**
21	1.8 ml	12min 4sec	18min 28sec
42	2.4 ml	11min	12min 2sec
84	5.1 ml	10min	10min 28sec
126	8.6 ml	8min	5min 4sec
168	13 ml	2min	2min 5sec
	PVA	PVA	HPMC K_{15}

3.3. pH of Nasal gel

Utilizing pH buffers of 4 and 7, a digital pH meter was calibrated. Each formulation sample contained 20 millilitres, which were taken in a beaker and appropriately dipped in glass electrode. The solution's pH was then measured three times **(Nisha et al., 2012)[11].**

Table 7: pH of the polymer and drug such as:

S. No.	Polymer and Drug	pH level of polymer and drug
1.	HPMC K15	6.78
2.	PVA	5.86
3.	Berberine	6.55
4.	Onion extract	3.87

3.4. Gelling Temperature

Table 8: Gelling time of different Formulation solution

S. No.	Formulation No	Temperature	Time (Gelling)
1	F1	37◦C	35 sec
2	F2	37◦C	1 min 19 sec
3	F3	37◦C	27 sec
4	F4	37◦C	48 sec
5	F5	37◦C	45 sec

Table 9: Gel Strength determination

S.No.	Formulation Code	Gel strength (sec)
1.	F1	40
2.	F2	55
3.	F3	70
4.	F4	82
5.	F5	91

3.5 Spreadability: -

Formulation F1 and F2 showed good Spreadability as compare to other formulation.

3.6 In vitro drug release study: -

Table 10: Cumulative % release of the drug formulation berberine, Pluronic PF127, Onion extract and HPMC K15

Time	Absorbance	Conc	Drug cont.	CPR
0.25	0.096	9	0.18	10.40
0.5	0.133	13.11	0.29	16.72
1	0.233	24.22	0.52	30.28
2	0.282	29.67	0.67	38.50
3	0.343	36.44	0.82	47.28
4	0.395	42.22	0.95	55.13
6	0.486	50.33	1.13	65.51
8	0.468	52.33	1.20	69.23

Table 11: Cumulative % release of the drug formulation berberine, Pluronic PF127, Onion extract and PVA

Time	Absorbance	Conc	Drug cont.	CPR
0.25	0.181	18.44	0.37	23.95
0.5	0.155	20.56	0.47	30.29
1	0.214	22.11	0.50	32.72
2	0.270	28.33	0.63	41.10
3	0.304	32.11	0.73	47.22
4	0.238	34.44	0.79	50.99
6	0.325	42.22	0.95	61.54
8	0.446	47.89	1.08	70.42

Table 12: Cumulative Percentage Drug Release Studies of PVA and HPMC K15

Time	CPR NGHPF127	CPR NGPPF127
0.25	23.95382395	10.40462428
0.5	30.28860029	16.71804753
1	32.72005772	30.27617213
2	41.1038961	38.49710983
3	47.22222222	47.27681439
4	50.98845599	55.13166346
6	61.54401154	65.5105973
8	70.41847042	69.22928709

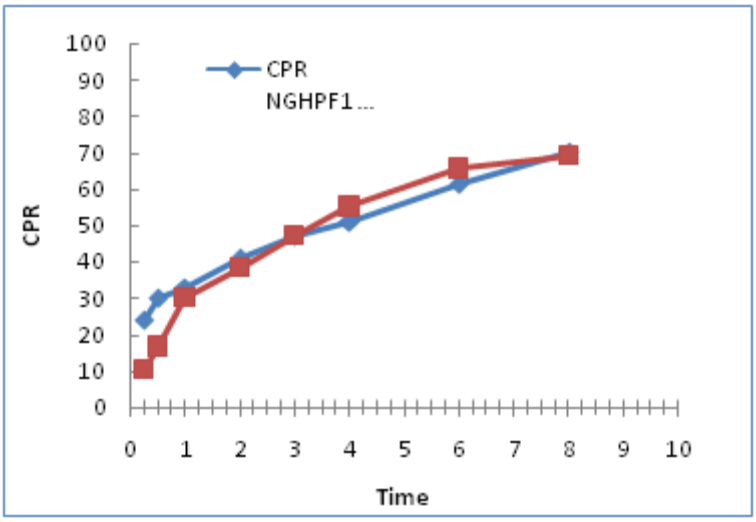


Figure 3: Comparative effects on drug release of formulation (HPMC K15 and PVA)

3.7 Pharmacological study:

Table 13: Grouping of animals

S.No.	Group	Treatment	Route	No. of animals
1.	N. CONT	Normal saline	Intranasal	4
2.	Negative CONT	OVA	Intranasal	4
3.	Test1	OVA, PVA	Intranasal	4
4.	Test 2	OVA, HPMC	Intranasal	4
5.	Standard	Dexamethasone	Intranasal	4
		Total		24

3.8 Experimental Animals requirements

Swiss albino mice, weight (25-30g) of either gender (male or female) was obtained from Animal House of HIPER-Lucknow. A rodent was allowing acclimatizing for 1 week and housed in standard polypropylene cages with standard pellet diet. Animal was maintained under controlled room temperature (23±2˚C) and relative humidity (60±5%) with 12h light/12h dark cycle. **(Aswar. et, al 2015)[12]**

3.9 Methodology

To establish the allergic rhinitis in mice Intraperitonial injections of 0.2ml mixed suspension of ovalbumin (0.5mg/ml) plus aluminum hydroxide (20mg/ml) on day 1, 8, and 15, respectively was performed to sensitize mice. Then, on days 22-29, 20µl OVA was instilled into the nose of allergic rhinitis mice to trigger challenge. Additionally, on days 22-29, mice were administered intranasally with optimized formulations of onion extracts and berberine in combination (20 µl) 1 hour prior to OVA challenge. Dexamethasone 5mg/kg Sigma-Aldrich dissolved in 30µl distilled water was instilled into the nose of allergic rhinitis mice 1 hour prior to OVA challenge as positive control. The mice was observed for sneezing and nose rubbing assessment. **(Zhang et, al. 2021, Rahman et, al 2011)[3]**

3.9.1 Body weight

Animals were frequently weighed on the first, eighth, fifteenth, and twenty-second days to track how the test medication affected body weight. The number of times a person rubbed their eyes or sneezed per unit time was tallied continuously in a randomized blind manner immediately after a nasal challenge for 40 minutes. These physiological characteristics were examined and graded as follows. When someone sneezes, they exhale explosively after taking a big breath in, and when they massage their nose, they graze their external paranasal region with one or both of their forelimbs (Zhao et al., 2005). The intensity of the nostrils' redness was used to gauge the nose's level of redness **(Suleimani et al.., 2008)[14].**

Table 14: Nasal rubbing per unit time and sneezing per unit time

Group	Treatment	Nasal rubbing /unit time	Sneezing/unit time	Nasal redness
Normal control	Normal saline	16.21±1.2	12.38±1.4	0.48±0.03
AR Control (N.C)	OVA Albumin	102.32±2.3	64.76±1.6	2.43±0.09
T1	OVA Albumin+PVA	39.32±1.6	52.12±2.3	1.58±0.06
T2	OVA + HPMC	32.63±1.5	36.73±2.1	0.94±0.04
Dexamethasone (Std)	Dexamethasone	22.38±1.7	23.92±1.8	0.59±0.07

3.9.2 Spleen weight:

Animals were slaughtered, their spleens were removed, the wetness was blotted utilizing filter paper to eliminate any remaining moisture, and the organ weight was calculated to use an electronic weight machine after 24 hours following the last intranasal challenge.

3.9.3 Lung weight:

Animals had been slaughtered and their lungs had been split, moisture had been separated by blotting with filter paper and measured utilizing a electronic weighing scale after 24 hours after the last intranasal challenge.

Table 15: Assessment of the weight of spleen and lung of the mice

S. No.	Group	Treatment	wt. of spleen (g)	wt. of lung (g)
1	Normal control	Normal saline	0.14±0.02	0.25±0.06
2	AR Control (N.C)	OVA Albumin	0.26±0.01	0.56±0.03
3	T1	OVA Albumin+PVA	0.21±0.02	0.47±0.03
4	T2	OVA + HPMC	0.17±0.02	0.39±0.04
5	Dexamethasone (Std)	Dexamethasone	0.15±0.02	0.31±0.04

Table 16: Assessment of the Hematological parameters

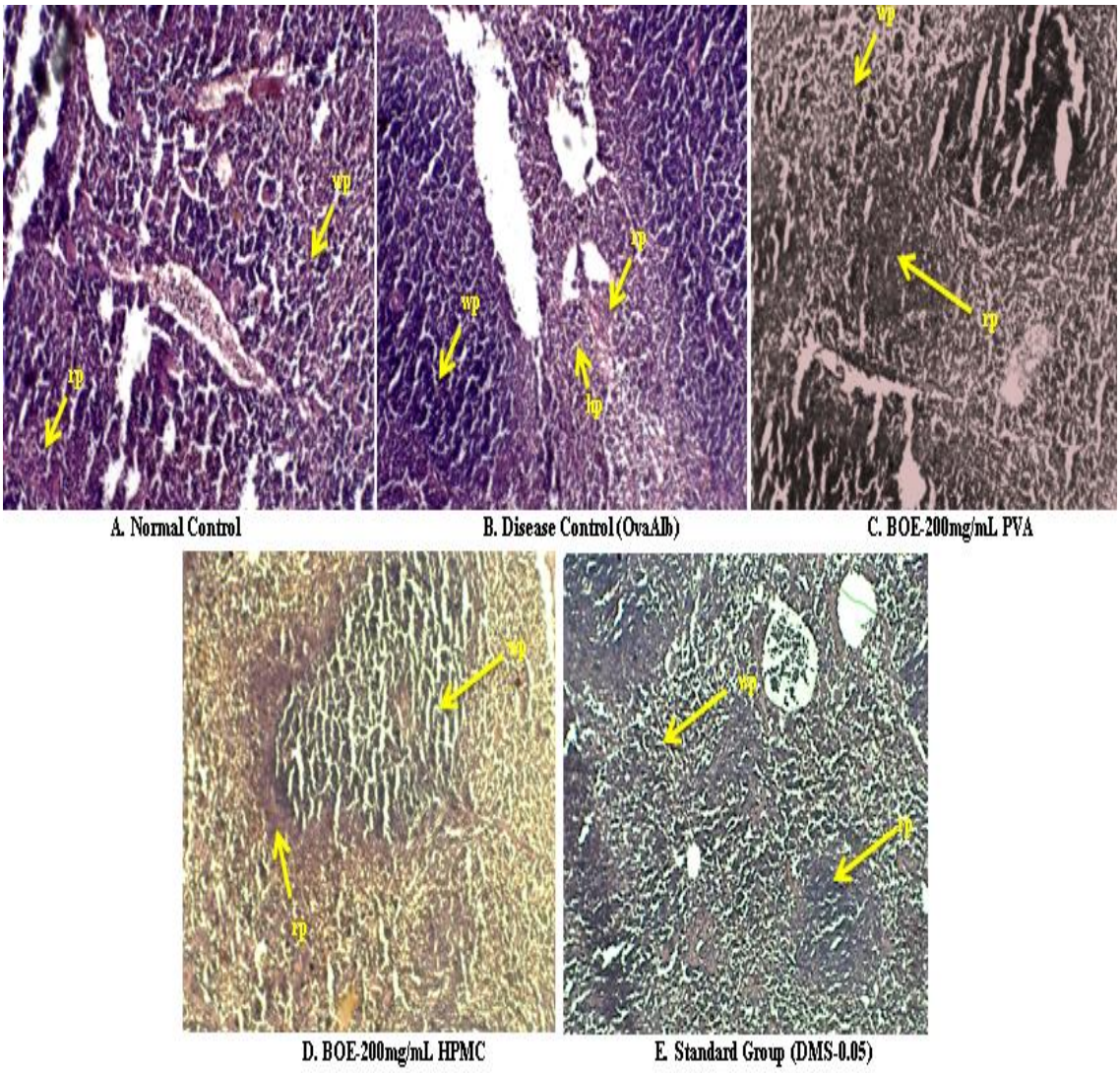
		Hematological Parameters					
Group	**Treatment**	**Total Leucocytes count (WBC)10^3 /µL**	**Neutrophils (%)**	**Lymphocyte (%)**	**Monocytes (%)**	**Eosinophils (%)**	**Basophils (%)**
Normal	Normal saline and	5.3±0.02	70.5±1.2	24.3±0.3	1.2±0.8	3.2±0.02	0.9±0.03
Negative control	OVA Albumin (20 µL)	10.3±0.03†	60.5±1.6†	32.6±0.4†	6.3±0.4†	4.7±0.06†	1.9±0.07†
T1	BOE, PVA (20 µL)	8.2 ±0.04^{a}	63.5±1.7^{a}	29.8±0.7^{a}	3.2±0.6^{a}	5.3±0.04^{a}	1.3±0.04^{a}
T2	BOE, HPMC (20 µL)	7.1±0.05^{c}	64.5 ±1.6^{c}	26.7±0.6^{b}	2.1±0.3^{b}	4.7±0.03^{b}	1.1±0.06^{b}
Standard	Dexamethasone 0.05%w/v	6.2 ±0.06^{c}	68.3 ±1.3^{c}	25.2±0.3^{c}	1.8±0.7^{c}	5.3±0.01^{c}	0.6±0.02^{c}

All values were expressed as Mean ± SEM, n=5, Data was analyzed using one way ANOVA (Analysis of variations) by Graph Pad Prism Software (Version 5.) via Newman-Keuls $p<0.05$a, $p<0.01$b, $p<0.001$c compared to Group II (Disease control) rodents.

3.9.4 Histopathological study spleen and lung of the Swiss albino mice (Greiner et al.2012, Wang et al.2007)

The histology of the spleen is shown in Figure 4.8. The typical group had red and white pulps that were completely undamaged. White pulp includes white blood cells and triggers an immune response via humoral cell-mediated pathways, whereas red pulp contains Monocytes and generates an innate response. White and red pulps completely degenerated in the AR control group, while all treatment groups provided dose-dependent protection.

Figure 4 depicts a photomicrograph of representative lung slices. The alveoli, bronchioles, and epithelial cell linings were all intact in the normal group. Treatment with tests and regular medications provided protection. In situ nasal gel (200 mg/kg) produced noticeable results.



Histological alteration of spleen in mice:

A. The normal group shows intact white and red cell pulps.
B. The AR control group shows the wide-ranging disruption in white and red pulp cells, hyperplasia is observed.
C. BOE-200mg/mL PVA shows protective effect on red and white pulp cells.
D. BOE-200mg/mL HPMC shows more protection of both cells and intact structure with less hyperplasia.
E. Standard Group (DMS-0.05) group shows more protective effect on red and white pulps and less hyperplasia were observed.

Figure 4: Histological alteration in spleen tissue of mice

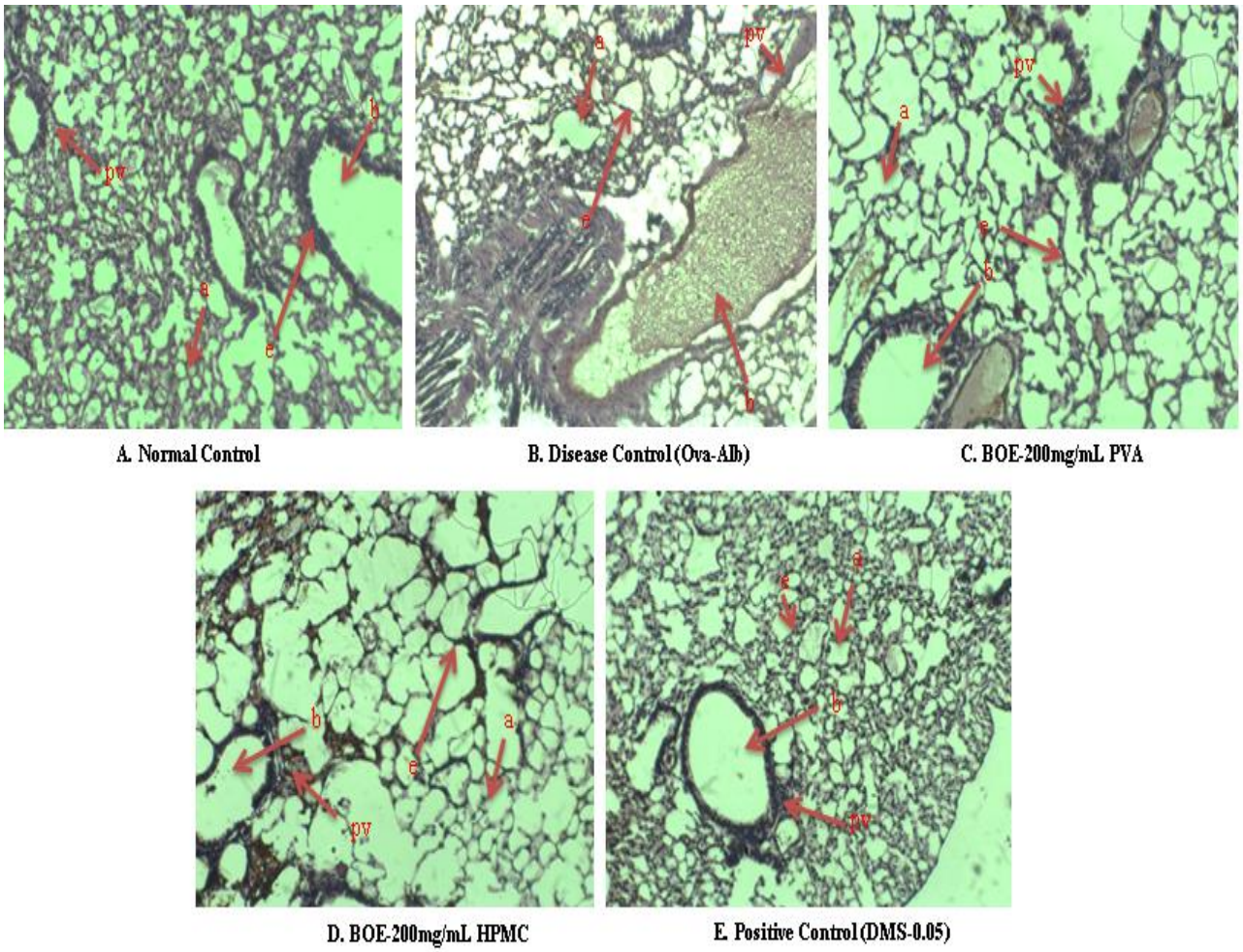


Figure. Histological alteration in lung tissue of mice:
photomicrograph of lung sections stained with hematoxylin and eosin:

A. The normal group shows alveoli and bronchioles having normal architecture. Epithelial cells linings are intact with absent in inflammation and prominent pulmonary veins were seen.
B. The AR control group section shows abnormal bronchiole epithelium and degenerated alveolar sacs.
C. Animals treated with BOE-200mg/mL PVA demonstrates intact epithelial cell linings; partial protection of bronchioles and alveoli, with minimum Inflammation.
D. Animals treated with BOE-200mg/mL HPMC shows moderate intact alveoli and bronchiolar structures.
E. Animals treated with DMS-0.05 shows partial cell disruption in alveoli and bronchioles. The epithelial cell linings show less damage.

Figure 5: Histological alteration in lung tissue of mice

4. DISCUSSION

The present work describes the development of the in situ thermoresponsive nasal gel by the cold technique and evaluates its efficacy against congestion due to allergic rhinitis. Berberine, onion extracts, and Pluronic PF127. The berberine, onion extract and Pluronic PF127 were manufactured by using the cold method, utilizing the berberine and Pluronic PF127 blend in different ratios to optimize their influence on the drug release profile. In situ nasal gel was evaluated by the various parameters, namely pH of the gel. Gowda et al. (2011) conducted an in vitro drug release study as well as an in vivo study of the drug formulation. The improved formulation that passed the aforementioned tests was then put through an expedited stability investigation. Based on its overall effectiveness, this in situ gel appears to be a reliable nasal delivery strategy for the treatment of allergic rhinitis. Multiple mediators generated by mast

cells and other inflammatory cells are thought to be the cause (Al Suleimani & Walker, 2007). There are two stages to an allergic reaction (AR). In the first stage, mast cells and basophiles are activated. Eosinophils, mast cell, and basophile migration into the nasal tissue occurs in the final stage. The existing therapies aim to either lessen the impact of mediators generated by activated cells or stop their effects on organs. According to Wang et al. (2007), OVA albumin induced in mice exhibits nasal allergy symptoms similar to those seen in people. By using OVA-induced AR, the current study aimed to evaluate berberine anti-allergic characteristics. To sensitize animals, OVA albumin will be administered intraperitonial over the course of 1, 8, and 15 days, respectively. The drug's nasal formulation including an onion extract and berberine was then administered intravenously. For the treatment of allergic rhinitis, the drug formulation was administered to the test groups T1 and T2. The first group of mice received the formulation containing a combination of berberine, onion extract PF127, and PVA, and the second group of mice received the formulation containing a combination of berberine, onion extract PF127, and HPMC K15.

5. CONCLUSION

Nasal medication delivery is an unique platform that offers an alternative to injection administration. More medications in the form of nasal formulations designed for systemic treatment may be introduced into the market in the near future. Several factors influence the development of a medicine with a drug delivery system. Novel nasal treatments are also expected to be commercialized for the treatment of long-term ailments such as diabetes, osteoporosis, and fertility treatment. One of the key issues in nasal product development is the bioavailability of nasal medicinal formulations. In contrast, pharmaceutical companies are investing heavily in the development of nasal products due to the increased demand for nasal medicine products. One of the primary obstacles in the development of nasal medication products is their bioavailability. In contrast, pharmaceutical companies are investing heavily in the development of nasal products due to the increased demand for nasal medicine products in the worldwide pharmaceutical industry. So, in order to reduce side effects and improve the effectiveness of nasal products, we need focus on basic research in nasal drug delivery.

In this study the influence of the in situ nasal gel formulation and evaluation study for the treatment of the allergic rhinitis disease.

REFERENCES:

1. Kumar M, Chaturvedi M, Pathak M. A review on mucoadhesive polymer used in nasal drug delivery system. J Adv Pharm Technol Res. 2011;2(4):215–22.
2. Mishra S, Patel NS, Kumar M, Pathak K. Cross-linked mucoa d h e s i v e m i c r o s p h e r e s b a s e d o n a n i o n icheteropolysaccharide for nasal delivery of felodipine: optimization and in vitro evaluation. Drug Delivery Letters. 2013;3:136–48.
3. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today. 2002;7: 967–75.

4. Basu S, Bandyopadhyay AK. Nasal drug delivery. AAPSPharmSciTech. 2010;11(3):1223–36.
5. Sherafudeen, S.P. and Vasantha, P.V., 2015. Development and evaluation of in situ nasal gel formulations of loratadine. *Research in pharmaceutical sciences*, *10*(6), p.466.
6. Kaur, P., Garg, T., Rath, G. and Goyal, A.K., 2016. In situ nasal gel drug delivery: A novel approach for brain targeting through the mucosal membrane. *Artificial cells, nanomedicine, and biotechnology*, *44*(4), pp.1167-1176.
7. Rao, M., Agrawal, D.K. and Shirsath, C., 2017. Thermoreversible mucoadhesive in situ nasal gel for treatment of Parkinson's disease. *Drug development and industrial pharmacy*, *43*(1), pp.142-150.
8. Basu, S. and Bandyopadhyay, A.K., 2010. Development and characterization of mucoadhesive in situ nasal gel of midazolam prepared with Ficus carica mucilage. *AapsPharmscitech*, *11*(3), pp.1223-1231.
9. Altuntaş, E. and Yener, G., 2017. Formulation and evaluation of thermoreversible in situ nasal gels containing mometasone furoate for allergic rhinitis. *AAPS PharmSciTech*, *18*(7), pp.2673-2682.
10. Chelladurai, S., Mishra, M. and Mishra, B., 2008. Design and evaluation of bioadhesive in-situ nasal gel of ketorolac tromethamine. *Chemical and Pharmaceutical Bulletin*, *56*(11), pp.1596-1599.
11. Fahmy, U.A., Ahmed, O.A., Badr-Eldin, S.M., Aldawsari, H.M., Okbazghi, S.Z., Awan, Z.A., Bakhrebah, M.A., Alomary, M.N., Abdulaal, W.H., Medina, C. and Alhakamy, N.A., 2020. Optimized nanostructured lipid carriers integrated into in situ nasal gel for enhancing brain delivery of flibanserin. *International Journal of Nanomedicine*, *15*, p.5253.
12. Sabale, A.S., Kulkarni, A.D. and Sabale, A.S., 2020. Nasal in situ gel: Novel approach for nasal drug delivery. *Journal of Drug Delivery and Therapeutics*, *10*(2-s), pp.183-197.
13. Ban, M.M., Chakote, V.R., Dhembre, G.N., Rajguru, J.R. and Joshi, D.A., 2018. In-situ gel for nasal drug delivery. *Int. J. Dev. Res*, *8*, pp.18763-18769.
14. Bhandwalkar, M.J., Inamdar, I.K., Kalbhare, S.B., Changan, A.D. and Mandrupkar, S.N., 2020. A review on in situ Nasal Gels for Nasal drug delivery system. *Journal of Pharmaceutical Advanced Research*, *3*(12), pp.1062-73.