Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 44 No. 05 (2023)

In-Situ Nasal Gel Formulations and Their Pharmaceutical Evaluation for the Treatment of Allergic Rhinitis Containing Extracts of *Tagetes Erecta Linn and Similax Zeylanica*

Archana Gautam[1*], Divya Pathak[2]

[1]Research Scholar, Department of Pharmacy, IIMT University, Meerut, Uttar Pradesh*
[2]Associate Professor, Department of Pharmacy, IIMT University, Meerut, Uttar Pradesh

Corresponding Author: Archana Gautam[1*]
[1]Research Scholar, Department of Pharmacy, IIMT University, Meerut, Uttar Pradesh*
Email: [1]Archana.gautam909@gmail.com*

Abstract: The goal of this study was to create a thermo-reversible in-situ gel for the treatment of allergic rhinitis (AR). The goal of this study was to create a mucoadhesive in-situ gel with decreased nasal mucocilliary clearance in order to increase the local impact of a polyherbal extract in the treatment of allergic rhinitis (AR). The extended residency of the drug formulation in the nasal cavity is critical for intranasal medication administration. Gelling temperature, gelling duration, viscosity, gel strength, pH, drug content, mucoadhesive strength, spread ability, and irritancy tests were performed on the produced formulations.
Methods: In this investigation, pluronic F8 (PF8)-based mucoadhesive in-situ nasal gels containing Tagetes erecta Linn and Similax zeylanica extracts with antioxidant and anti-inflammatory properties were employed. By combining pluronic F8, poly (ethylene glycol) (PEG400), and Xanthan gum with a tiny quantity of (hydroxypropyl methylcellulose) HPMC K4M and Carbopol 934, a polyherbal thermosensitive in-situ hydrogel was created and assessed. A total of 9 in-situ extract gels were created using a mix of HPMC K4M, Carbopol, xanthan gum, and PF8. All of the preparations were evaluated, and the gel formation technique chosen underwent the temperature transition from sol to hydrogel.
After being injected into the nasal cavity, the mucoadhesive gel transforms into a viscous hydrogel at body temperature, reducing nasal mucociliary clearance and extending the duration of action. The best and most effective nasal herbal gel is made by combining varying concentrations of HPMC K4M, carbopol, or xanthan gum with PF8 (10% w/v). The results of the assessment parameters show that the in-situ gel made with corbopol was of higher quality than HPMC K4M and xanthan gum**.**
Conclusion: Based on these findings, in-situ herbal nasal gels may be promising drug delivery vehicles for Tagetes erecta Linn and Similax zeylanica extracts to circumvent first-pass metabolism and hence boost bioavailability. The mucoadhesive in-situ gel system is a potential technique for intranasal administration of polyherbal extracts for the enhancement of allergic rhinitis therapeutic effects**.**

Keywords: Tagetes Erecta Linn, Similax Zeylanica , HPMC, Carbopol, *In-Situ*, Pluronic.

1. INTRODUCTION

Allergic rhinitis (AR) is a diverse condition marked by mucosal infiltration and the activities of eosinophils, plasma cells, and mast cells. This condition is highly common, yet diagnosis and prevention are inadequate. There are now several medication formulations available for Allergic Rhinitis. Nasal formulation procedures are constrained due to associated limits with drug delivery systems, which is a major disadvantage. The medication delivery mechanism is influenced by parameters such as nasal cavity capacity for drug volume (0.2 ml), mucociliary clearance, and anterior discharge [1-3].

Synthetic antihistamines are commonly used to treat allergy symptoms caused by histamine release. Synthetic medications are connected with a wide range of adverse effects [4]. Herbal remedies have been widely utilized around the world from ancient times and have been acknowledged by physicians and patients for their superior therapeutic value due to less side effects when compared to contemporary pharmaceuticals. Natural compounds obtained from plant extracts provide a very intriguing route for future research. Plant extracts, on the other hand, are frequently ill-defined in terms of extraction process, plant-to-solvent ratio, and active component level. Furthermore, the color, odor, transparency, and/or active substances' stability over time is frequently a limiting issue [5, 6]. Plant extracts differ from refined medicinal substances in numerous ways. For starters, they are more dilute than the pure substances we are acquainted with; second, herbs frequently include other active principles that may be chemically and therapeutically connected to the ingredient principally responsible for its effects. To maximize patient compliance and minimize recurrent administration, phytotherapeutics require a scientific strategy to distribute the components in a sustained way [7].

Novel in-situ gelling formulations have advanced quickly in recent years, particularly in the field of nasal medication administration. There has been a rise in the number of in-situ forming systems that have been designed and developed for various biomedical parameters, with thermally induced gelling systems being the most difficult to produce for nasal drug delivery systems. The nasal mucosa has emerged as a clinically feasible route for systemic medication administration. Furthermore, intranasal absorption bypasses gastrointestinal and hepatic presystemic metabolism, which improves medication absorption [8].

In-situ gel formulations for both local and systemic drug administration have been investigated among the many nasal drug delivery techniques. Before administration, these drug delivery systems exist in sol form; however, once delivered, they undergo gelation to form a gel. Microenvironment temperature, pH fluctuations, the presence of ions, UV irradiation, and polymers are all elements that influence the in-situ gel formation process. Gel rheological characteristics, which are key to its effectiveness, play a role in keeping the gel at the site of application or absorption [9]. The plant included in the mixture was chosen based on scientifically documented properties. We used Tagetes erecta Linn and Similax zeylanica for the formulation of herbal nasal gel in this investigation. To improve the therapeutic impact of pluronic F8 (PF8)-based mucoadhesive in-situ nasal gels including Tagetes erecta Linn and Similax zeylanica, an attempt was undertaken.

2. MATERIALS AND METHODS

Materials

Tagetes erecta Linn fresh leaves were collected and dried; *Similax zeylanica* (dreid) were brought from local market. The leaves and seeds were authenticated by Forest Research Institute Dehradun U.K. Pluronic was supplied from Sigma Aldrich Pvt. Ltd India, hydroxypropyl methylcellulose K4M, Xanthan gum, and Carbopol 934 were from SDFCL Pvt Ltd. India. All the other chemicals and reagents used in this study were of analytical grade.

Methods

Preparation of extracts

Air dried and coarsely powdered (500 gm) of *Tagetes erecta Linn* leaves and *Similax zeylanica* were weighed and their hydroalcoholic extracts were prepared separately, by using distilled water and ethanol. The extracts were then concentrated to dryness under reduced pressure and controlled temperature, respectively and they were preserved in a refrigerator.

Preparation of *in-situ* nasal polyherbal gel by cold method

The thermorevresible nasal *in-situ* gel formulation was prepared by cold method [10]. For preparation of PF8 solutions, the required amount of polymer was dispersed in distilled, deionized water with continuous stirring for 1 h. The partially dissolved pluronic solutions were stored in the refrigerator until the polymer was completely dissolved (approximately 24 h). The preparation of hydroxypropyl methylcellulose K4M solution is the same as that of PF8. The carbopol 934/pluronic F8 mixed solutions, hydroxypropyl methylcellulose K4M/PF127 and xanthan gum/PF8 mixed solutions were prepared by dispersing the required amount of PF8in the desired concentration of carbopol 934 or HPMC K4M with continuous stirring for 1 h, respectively. Different isotonicity agents, benzalkonium chloride (Fisher Scientific. India.) (as preservative) and the desired amount of *Tagetes erecta Linn* (2%w/w) and *Similax zeylanica* (2%w/w) were added in the solution. The samples were then allowed to equilibrate at 4 °C overnight (24 h at least) [11]. The composition of nasal gel is given in (**table 1).**

Ingredients	**Formulations**								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
MO (%w/v)	2	2	2	2	2	2	2	2	2
ER (%w/v)	2	2	2	2	2	2	2	2	2
Pluronic F127 (%w/v)	16	12	10	10	8	8	8	8	8
Carbopol 934 (%w/v)				0.5	1.0	1.5			
Hydroxypropyl methylcellulose K4M(%w/v)	-	-	-	-	-	-	0.5	1.0	1.5
Xanthan gum (%w/v)		-	-	-	-	-	0.5	1.0	1.5
Benzalkonium chloride (%v/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled water (ml)	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

Figure No 01 Polyherbal Gel

Evaluation of *in-situ* nasal polyherbal gels

Gelling temperature and gelling time

The gelling temperature is the temperature at which the meniscus of the formulation no longer moves when the test tubes are slanted at a 90-degree angle. The gelling temperature was established by immersing a test tube holding a sufficient amount of the prepared solutions in a 4 °C water bath. The temperature of the water bath was gradually increased at a consistent rate of 1 °C every 2 minutes.
Gelling time was recorded as the time when gelation was first detected. The obtained in-situ gel formulations' sol-gel transition temperature (Tsol-gel) was determined by transferring 2 ml of the prepared formulation to a test tube (10 ml) with a diameter of 1.0 cm. The tube was placed in a 37 °C circulating water bath after being sealed with parafilm. Equilibration was permitted for 10 minutes after each temperature setting. Finally, the test tube was put horizontally to check the sample's condition and gelation. All measurements were taken in triplicate.

Viscosity of solution

Viscosity of the *in-situ* gel systems was determined using Brookfield viscometer coupled with S-94 spindle (Brookfield Engineering Laboratories Inc., MA, USA). The prepared gel formulations were transferred to the beaker. The spindle was lowered perpendicularly into the gel at l00 rpm and temperature was maintained at 37±0.5 °C. The viscosity was determined during the cooling of the system. All the measurements were performed in triplicates.

Determination of pH

One ml of the prepared gels was transferred to a 10 ml volumetric flask, and the solution was diluted with distilled water. The pH of resulting solution was determined using a digital pH meter (Elico LI120, India), which was previously calibrated using phosphate buffers at pH 4 and pH7.

Drug content assay

One ml of the prepared formulation was dispersed in 10 ml of methanol for 2–3 min with occasional shaking. The resulting solution was filtered through a 0.45 µm filter paper and was diluted with methanol. The amount of flavonoids present in the formulation was determined spectrophotometrically at 275 nm (Shimadzu UV1800, Japan).

Gel strength and Mucoadhesive strength

Fresh sheep nasal mucosa was used to measure ex vivo mucoadhesive strength. By eliminating the underlying fat and loose tissues, the mucosal membrane was separated. Three washes of distilled water and phosphate buffer (pH 6.4) were performed on the membrane. The experiment was designed using the modified balancing approach.

By placing one beaker on the left pan and a weight (5 g) on the opposite pan, the balance was equilibrated on both sides. The sheep nasal mucosa was cut into 1 cm2 pieces and cyanoacrylate bonded to the glass support, allowing the smooth surface of the nasal mucosa to face the upper side of the glass. The bonded sheep nasal mucosa was soaked with phosphate buffer (pH 6.4) by filling the beaker on the right-hand side of the balance with the buffer and lowering the glass support. The configuration seen above was put on the right side of the pan.

On the lower surface of the right pan, a thin coating of the produced gel (1 g) was applied. By removing the beaker from the left pan, the right pan was lowered and spread with gel. To achieve appropriate contact between the nasal mucosa and the gel, the pan was kept undisturbed for 2 minutes. Following that, using a burette, water was progressively introduced to the left pan until the nasal mucosa was detached from the gel film. The weight necessary to separate the mucosa was used to compute the mucoadhesive force. The magnitude of the force was measured in dynes per square centimeter (dyne/cm2).

Spreadability
Spreadability was determined using a 10 × 4 cm rectangular glass slide. The sheep nasal mucosa from serosal side was tied on the surface of slide with a thread. The slide was kept in a hot air oven, at 37 °C and one drop of gel was placed on the mucosa at an angle of 120 °. Spreadability was determined relative to the distance travelled by the drop of gel (liquid) before its gelation. Average of three readings was recorded [12-16].

Irritancy study
Mark an area (5 cm^2) on the left hand dorsal surface. The cream was applied to the specified area and time was noted. Irritancy, erythema, edema, was checked if any for regular intervals up to 24 h and reported.
It is done by using swiss mice. The back skin of area of 5 cm^2 is used. If the formulation produced scores of 2 or less they are considered to have no skin irritation [5, 6].

- Erythemia scale: none-0, slight-1, well defined-2, moderate-3, scar formulation-4.
- Edema scale: none-0, slight-1, well defined-2, moderate-3, severe-4.

3. RESULTS AND DISCUSSION

Gelling temperature, gelling time and viscosity of *in-situ* nasal herbal gels
The basis polymers for the nine distinct in-situ nasal herbal gels were HPMC, carbopol, and xanthan gum. Table 2 shows the findings of gelling temperature, gelling time, and viscosity of herbal gels.
The in-situ nasal herbal gel gelling temperature ranged between 26.14 °C and 36.17 °C. The gelling temperature of generated gel results show that it is acceptable for thermo reversible nasal gel.
Herbal gel gelling times ranged from 5.2 to 11.3 seconds (table 2). The formulation's gelling temperature was confirmed to be within the range. The gelling period rises as the concentration of F4 decreases.
The in-situ nasal herbal gels had viscosities ranging from 30.2 to 40.3 Pa•s. The viscosity of in-situ nasal herbal gels increases as the concentration of PF8 increases. Similarly, increasing the concentration of HPMC K4M/carbopol/xanthan gum improves formulation viscosity.

Formulation	Gelation temperature (°C)	Gelling time (sec)	Viscosity/(Pa·s)
F1	36.17±0.43	8.1±0.02	32.3±0.37
F2	32.52±0.63	9.1±0.07	35.7±0.15
F3	30.83±0.51	8.5±0.02	32.2±0.84
F4	31.38±0.43	9.7±0.17	32.4±0.39
F5	32.52±0.17	8.1±0.02	31.5±0.53
F6	29.35±0.47	7.5±0.08	32.1±0.68
F7	26.14±0.25	9.7±0.17	30.4±0.92
F8	31.61±0.58	9.3±0.09	30.5±0.48
F9	31.52±0.17	7.6±0.11	32.2±0.84

Gel strength, ph and drug content of *in-situ* nasal herbal gel
The outcomes of gel strength, pH and drug content of *in-situ* nasal herbal gel are displayed in (table 3). The gel strength of *in-situ* nasal herbal gel was ranged between 53.1 to 63.7s. It was observed on higher concentration of Carbopol 934 exhibited maximum gel strength. The addition of HPMC K4M/Carbopol/Xanthan gum in PF8 resulted to increase the gel strength.
Gel pH was in the range of 5.2 to 5.9 which was in the range of pH at the absorption site (4.5-6.5). The drug content of the *in-situ* nasal herbal gels ranged between 90.4% and 93.4%.

Formulation	pH	Gel strength (s)	Drug content
F1	5.4±0.07	55.8±0.28	91.8±0.82
F2	5.6±0.02	58.3±0.63	93.4±0.63
F3	5.5±0.05	58.3±0.63	92.7±0.49
F4	5.5±0.08	59.6±0.58	92.6±0.67
F5	5.6±0.07	57.5±0.09	92.7±0.49
F6	5.8±0.02	59.6±0.58	91.6±0.26
F7	5.2±0.01	55.8±0.34	92.3±0.34
F8	5.6±0.02	57.2±0.19	91.6±0.26
F9	5.5±0.05	59.6±0.58	92.3±0.34

Mucoadhesive strength and spreadability of *in-situ* nasal herbal gel

Table 4 shows the results of mucoadhesive strength and spreadability of in-situ nasal herbal gel. The mucoadhesive strength was measured in the range of 6317.2 to 4236.70.61 dyne/cm2. The higher the concentration of Carbopol 934, the stronger the mucoadhesive strength. Mucoadhesive drug delivery techniques allow for quick drug dissipation in the circulatory system, avoiding first-pass metabolism and extending dose residence duration at the site of application or absorption. In the current investigation, formulations with a high concentration of HPMC/carbopol/xanthan gum demonstrated higher mucoadhesion strength than PF8 (10%). In-situ nasal herbal gel spreadability varied from 9.20.21 to 11.70.65 cm.

Formulation	Mucoadhesive strength (dyne/cm^2)	Spreadability (cm)
F1	5236.8±0.29	10.8±0.43
F2	4236.7±0.61	11.7±0.65
F3	5247.9±0.36	11.1±0.34
F4	4365.7±0.54	10.7±0.57
F5	4739.2±0.32	10.2±0.41
F6	5934.8±0.47	11.2±0.32
F7	5236.8±0.29	10.5±0.48
F8	4862.9±0.38	9.2±0.53
F9	4365.7±0.54	10.7±0.57

Adverse effect of *in-situ* nasal herbal gel

The *in-situ* nasal herbal gel show no redness, edema, inflammation and irritation during irritancy studies (table 5). The F3, F4, F6, F7, F8 and F9 produced slight irritation, edema and erythema, but it is acceptable.

The prepared *in-situ* nasal herbal gels were safe to use.

Table 5: Adverse effect thermo reversible *in-situ* nasal polyherbal gel formulations

Formulation	Irritant	Erythema	Edema
F1	0	0	0
F2	0	0	0
F3	0	0	1
F4	1	1	1
F5	0	1	0
F6	1	0	0
F7	0	0	0
F8	0	1	1
F9	1	1	0

In-situ gel forming devices have been described for a variety of biomedical applications, including drug delivery, cell encapsulation, and tissue healing, in recent years. These were solutions, however gelation might happen in-situ due to ionic cross-linking or a change in ph or temperature. The latter method relies on temperature-induced phase transitions. The pluronics are comprised of ABA-type triblock copolymers with PEO (A) and PPO (B) units. Furthermore, pluronic concentrated aqueous solutions create thermally reversible gels.
The pluronic gel exhibits low mechanical strength, quick erosion, and non-biodegradability of PEO-PPO-PEO, preventing the usage of large molecular weight polymers. To reduce the related disadvantage, the pluronic must be combined with other bioadhesive polymers such as carboxymethyl-cellulose (CMC), hydroxypropylmethyl cellulose (HPMC K4M), carbopol, xanthan gum, methyl methacrylate, and so on. We intended to limit the viscoelastic and bioadhesive qualities of PF8 by constructing dual systems with high molecular weight HPMC K4M/Carbopol/xanthan gum [17, 18]. The goal of this work is to create an in-situ nasal herbal gel that modulates the viscoelastic properties and bioadhesive capabilities of PF8 by building dual systems with high molecular weight HPMC K4M or carbopol.
The formulation of in-situ gels is highly appealing since it is fluid-like prior to nasal administration and therefore readily implanted as a drop, allowing precise dosage, but settles into a gel with enhanced residence length at body temperature.

PF8 has excellent thermosensitive gelling capabilities, is low in toxicity and irritation, has high water solubility, has acceptable release characteristics, and is compatible with various excipients. As a mucoadhesive agent, HPMC K4M/carbopol/xanthan gum was used. Because PF8 is more soluble in cold water than in hot water, gels were created using the cold approach.
Table 2 showed that increasing the content of HPMC K4M, carbopol, or xanthan gum reduced temperature while increasing viscosity somewhat. Thus, micelle packing and micelle entanglements might be plausible processes of pluronic solution gelation as temperature rises. At ambient temperature (25 °C), PF8 solution acts as a mobile viscous liquid, and at body temperature (37 °C), it transforms into a semi-solid translucent gel. Pluronic formulations often improve bioavailability and effectiveness by increasing drug residence time at application sites by gelling. The aggregation of block copolymer PF8gels was thought to be caused by hydrogen bonding in aqueous systems, caused by the attraction of the pluronic ether oxygen atom of the ethyleneoxide chain with protons of the carbopol carboxylic groups or hydroxypropylmethyl cellulose hydroxyl groups [17]. The appropriate gel strength may be produced by combining two polymers, therefore the PF8 concentration can be lowered to lessen the toxicity of the high PF8 content.

The experiments on the effect of combining bioadhesive agents and PF8 on gelation temperature and rheology behavior revealed that adding either HPMC K4M or carbopol or xanthan gum promoted micelle packing and entanglements, resulting in a decrease in gelation temperature. The gelation temperature was tweaked to provide a solution at ambient temperature (25 °C) and a semi-solid clear gel at body temperature (37 °C) [17]. According to these findings, the best concentration for HPMC K4M, carbopol, or xanthan gum solution employed in-situ gel forming system was 0.5%-1.5% (w/v), whereas pluronic F127 was less than 10% (w/v).

The viscosity of the manufactured herbal gels rose when the amount of hydroxypropylmethyl cellulose HPMC K4M, carbopol, or xanthan gum increased. The viscosity of the formulations was directly proportional to their bioadhesive concentration. Because of their desired mucoadhesive characteristic, hydroxypropylmethyl cellulose HPMC K4M, carbopol, or xanthan gum can significantly lengthen the residence period of medications in the nasal cavity. Because of the high viscosity of the cellulose after hydration in the nasal cavity, this can allow prolonged drug release. As a result, both small hydrophobic and hydrophilic macromolecular medicines have increased intranasal bioavailability [10, 19].

The inclusion of a mixture of HPMC K4M, carbopol, or xanthan gum enhanced viscosity and gel strength substantially. Furthermore, formulations developed with a high concentration of HPMC K4M had a lower spread ability. This was due to HPMC K4M's high viscosity. The ph of the formulations did not produce mucosal irritation since the ph of all formulations was within an acceptable range. Lysozyme (a natural antibacterial enzyme helpful for regulating nasal microbial count that becomes inactive at alkaline pH) should be activated in the formulation [13].

Mucoadhesion occurs in three stages: wetting, interpenetration, and mechanical interlocking of mucin and polymer. Because of the nose passage's unique architecture and physiology, such as its enormous surface area, highly vascularized epithelium, and porous endothelium membrane, nasal drug delivery has emerged as a viable route of drug administration for systemic treatment. The combination of HPMC K4M, carbopol, or xanthan gum enhances mucoadhesive strength, which improves medication retention in endothelium membranes [20]. During irritancy trials, the in-situ nasal herbal gel showed no redness, edema, inflammation, or irritation, and it was safe to use. The best and most effective nasal herbal gel is made by combining varying concentrations of HPMC K4M, carbopol, or xanthan gum with PF8(10% w/v). The results of the assessment parameters show that the in-situ gel made with corbopol was of higher quality than HPMC K4M and xanthan gum.

4. CONCLUSION

The outcomes of the present study indicate that extract of *Tagetes erecta Linn* and *Similax zeylanica* was successfully incorporated into the formulation to obtain *in-situ* nasal gel. The formulated *in-situ* nasal herbal gel showed good gelling temperature, gelling time, viscosity, gel strength, ph, drug content, mucoadhesive strength and spreadability. The novel mucoadhesive *in-situ* gels containing plant extract was developed to overcome the first-pass metabolism and enhance the subsequent low bioavailability of the drug. However, future *in vivo* studies are required to confirm these results.

Conflict of Interests
The authors declare no conflict of interests

5. REFERENCES

1. Togias AG. Systemic immunologic and inflammatory aspects of allergic rhinitis. J Allergy Clin Immunol 2000;106:S247–S250.
2. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol 2001;108:S2–S8.
3. Capkova Z, Vitkova Z, Subova M. Formulation of loratadine into hydrogels. Acta Fac Pharm Univ Comenianae 2005;52:73–8.
4. Kisan RJ, Manoj NG, Ishaque MS, Vilarsrao JK, Sambjahi SP. Nasal drug delivery system-factors affecting and applicatins. Curr Drug Ther 2007;2:27–38.
5. Basu S, Bandyopadhyay AK. Development and characterization of mucoadhesive *in-situ* nasal gel of midazolam prepared with Ficus carica mucilage. AAPS PharmSciTech 2010;11:1223-31.
6. Swathi S. Phytochemical screening and TLC studies of *Moringa oleifera* extract: their antibacterial and anti-oxidant activities Int Curr Pharm Res 2015;1:46-9.
7. Pratibha N, Saxena VS, Amit A, D'souza P, Bagchi M, Bagchi D. Anti-inflammatory activities of Aller-7, a novel polyherbal formulation for allergic rhinitis. Int J Tissue Reactions 2003;26:43-51.
8. Krishnamoorthy R, Mitra AK. Prodrugs for nasal drug delivery. Adv Drug Delivery Rev 1998;29:135–46.
9. Hu G, Walls RS, Bass D, Bullock R, Grayson D, Jones M, *et al*. The Chinese herbal formulation biminne in management of perennial allergic rhinitis: a randomized, double-blind, placebo-controlled, 12-week clinical trial. Annals of Allergy, Asthma Immunol 2002;88:478-87.

10. Schmolka IR. Artificial skin: preparation and properties of pluronic F-127 gels for treatment of burns. J Biomed Mater Res 1972;6:571–82.
11. Sherafudeen SP, Vasantha PV. Development and evaluation of *in-situ* nasal gel formulations of loratadine. Res Pharm Sci 2015;10:466–76.
12. Gizurarson Sveinbjorn. Anatomical and histological factors affecting intranasal drug and vaccine delivery. Curr Drug Delivery 2012;9:566–82.
13. Bhalerao AV, Lonkar SL, Deshkar SS, Shirolkar SV, Deshpande AD. Nasal mucoadhesive *in-situ* gel of ondansetron hydrochloride. Indian J Pharm Sci 2009;71:711–3.
14. Miller SC, Donovan MD. Effect of poloxamer 407 gels on the miotic activity of pilocarpine nitrate in rabbits. Int J Pharm 1982;12:142–52.
15. Kumar MV, Aravindram AS, Rohitash K, Gowda DV, Parjanya K. Formulation and evaluation of in-situ gel of bromhexine hydrochloride for nasal delivery. Der Pharm Sinica 2012;3:699–707.
16. Shinde JV, Mali KR, Dias RJ, Havaldar VD, Mahajan NS. *In-situ* mucoadhesive nasal gels of metaclopramide hydrochloride: preformulation and formulation studies. J Pham Res 2008;1:88–96.
17. Li GL, Li M. Preparation and evaluation of ophthalmic thermosensitive *in-situ* gels of penciclovir. J Chin Pharm Sci 2007;16:90–5.
18. Schille´n K, Glatter O, Brown W. Characterization of a PEO-PPO-PEO block copolymer system. Progr Colloid Polym Sci 1993;93:66–71.
19. Mainardes RM, Urban MC, Cinto PO, Chaud MV, Evangelista RC, Gremiao MP. Liposomes and micro/nanoparticles as colloidal carriers for nasal drug delivery. Curr Drug Delivery 2006;3:275–85.
20. Rana Abu-Huwaij, Rana M Obaidat, Kamal Sweidan, Yusuf Al-Hiari. Formulation and *in vitro* evaluation of xanthan gum or carbopol 934-based mucoadhesive patches, loaded with nicotine. AAPS PharmSciTech 2011;12:21–7.