International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 9, Issue 6, 2017

Original Article

THERMOREVERSIBLE *IN-SITU* NASAL GEL FORMULATIONS AND THEIR PHARMACEUTICAL EVALUATION FOR THE TREATMENT OF ALLERGIC RHINITIS CONTAINING EXTRACTS OF *MORINGA OLIFERA* AND *EMBELIA RIBES*

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Received: 30 Mar 2017, Revised and Accepted: 10 Oct 2017

ABSTRACT

Objective: The present study was planned to develop thermo-reversible *in-situ* gel for the treatment of allergic rhinitis (AR). The objective of the present investigation was to develop a mucoadhesive *in-situ* gel with reduced nasal mucocilliary clearance to improve the local effect of the polyherbal extract in the treatment of allergic rhinitis (AR). The prolonged residence of drug formulation in the nasal cavity is one of utmost importance for intranasal drug delivery. The prepared formulations were subjected for gelling temperature, gelling time, viscosity, gel strength, pH, drug content, mucoadhesive strength, spread ability and irritancy studies.

Methods: In the study the pluronic F127 (PF127) based mucoadhesive *in-situ* nasal gels containing *Moringa olifera* (MO) and *Embelia ribes (ER) extracts* were used having antioxidant and anti-inflammatory effect. A polyherbal thermosensitive *in-situ* hydrogel was designed and evaluated by the mixing of pluronic F127, poly (ethylene glycol) (PEG400) and Xanthan gum with a small amount of (hydroxypropyl methylcellulose) HPMC K4M and Carbopol 934. Total 13 thermosensitive *in-situ* gels of extracts were prepared through combination of HPMC K4M or Carbopol or xanthan gum and PF127. All the preparations were investigated, and the selected method for gel formation underwent the thermal transition from sol to hydrogel.

Results: The mucoadhesive gel after being administered into the nasal cavity, get transformed into the viscous hydrogel at body temperature, which diminished nasal mucociliary clearance and prolonged the duration of action. The *in-situ* nasal herbal gel prepared by combination of different concentration of to HPMC K4M or carbopol or xanthan gum with PF127 (10% w/v) produces the better and effective gel. The findings of evaluation parameter indicate that the in-situ gel prepared by combination with corbopol were better quality compared to HPMC K4M and xanthan gum.

Conclusion: From these findings, it can be concluded that *in-situ* herbal nasal gels may be potential drug delivery systems for *Moringa olifera* and *Embelia ribes* extracts to overcome first-pass metabolism and thereby to improve the bioavailability. The mucoadhesive *in-situ* gel system is a promising approach for the intranasal delivery of polyherbal extracts for the therapeutic effects improvement of Allergic rhinitis.

Keywords: *Moringa olifera*, *Embelia ribes*, HPMC, Carbopol, *In-situ*, Pluronic F127

DOI: http://dx.doi.org/10.22159/ijap.2017v9i6.18780

INTRODUCTION

Allergic rhinitis (AR) is a heterogeneous disorder, which is often characterized by mucosal infiltration and actions of eosinophils, plasma cells, and mast cells. This disorder is extremely widespread but its diagnosis and prevention is very poor. Presently, various types of drug formulations for Allergic rhinitis are available. The practices of nasal formulation are limited due to associate constraints with drug delivery systems poses a major drawback. The factors affecting the drug delivery system comprise volume of the nasal cavity for the drug volume (<0.2 ml), mucociliary clearance, and anterior discharge [1-3].

Generally synthetic antihistamines are used to provide symptomatic relief to allergic symptoms due to histamine release. The synthetic drugs are associated with various types of side effects [4]. Herbal medicines have been widely used all over the world since ancient times and have been recognized by physicians and patients for their better therapeutic value as they have fewer adverse effects as compared with modern medicines. Natural molecules derived from plant extracts offer a particularly exciting avenue for further research. Plant extracts, however, are often ill-defined as to the method of extraction, plant-to-solvent ratio and the content of active ingredients. Moreover, the stability of the colour, odour, transparency and/or active ingredients with time is also often a limiting factor [5, 6]. Plant extracts are different in several respects from purified therapeutic agents. Firstly, they are more dilute than the pure chemicals that are familiar to us; secondly herbs often contain additional active principles that may be closely related both chemically and therapeutically to the constituent primarily responsible for its effects. Phytotherapeutics need a scientific approach to deliver the components in a sustained manner to increase patient compliance and avoid repeated administration [7].

In recent years, the novel *in-situ* gelling formulations are progressing rapidly especially in the field of nasal drug delivery. There is an increase in the number of *in-situ* forming systems has been formulated and developed for the various biomedical parameters out of the different preparations the thermally induced gelling systems had to be the most challenging one, for the development of nasal drug delivery systems. The nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery. In addition, intranasal absorption avoids the gastrointestinal and hepatic presystemic metabolism, enhancing drug [8].

Among the different nasal drug delivery systems, *in-situ* gel formulations have been explored for both local and systemic drug delivery. These drug delivery systems exist in sol form before their administration; however, once administered, they undergo gelation to form a gel. The factors regulating the in-situ gel formation process include microenvironment temperature, changes in pH, presence of ions, ultraviolet irradiation, and polymers. Rheological properties of gels, which are critical to their efficacy, are important in retaining the gel at the site of application or absorption [9]. The plant used in formulation was selected based on scientifically reported property. In the present study we have selected *Moringa olifera (MO)* and *Embelia ribes (ER)* for the formulation of herbal nasal gel. Therefore,

an attempt has been made to formulate pluronic F127 (PF127) based mucoadhesive *in-situ* nasal gels containing *Moringa olifera* and *Embelia ribes* to enhance its therapeutic effect.

MATERIALS AND METHODS

Materials

Moringa olifera fresh leaves were collected and dried; *Embelia ribes* fruit (dreid) were brought from local market. The leaves and seeds were authenticated by State Ayurvedic College Lucknow with specimen no. 17 and 19 respectively. Pluronic F127 (PF127) 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 *Moringa olifera* leaves and *Embelia ribes* fruits, 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 thermorevresible *in-situ* nasal polyherbal gel by cold method

The thermorevresible nasal *in-situ* gel formulation was prepared by cold method [10]. For preparation of PF127 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 PF127. The carbopol 934/pluronic F127 mixed solutions, hydroxypropyl methylcellulose K4M/PF127 and xanthan gum/PF127 mixed solutions were prepared by dispersing the required amount of PF127in 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 *Moringa olifera* (2%w/w) and *Embelia ribes* (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).

Table 1: Composition of different thermoreversible *in-situ* nasal polyherbal gels

Ingredients	Formulations												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
MO (%w/v)	2	2	2	2	2	2	2	2	2	2	2	2	2
ER (%w/v)	2	2	2	2	2	2	2	2	2	2	2	2	2
Pluronic F127 (%w/v)	16	14	12	10	10	10	10	10	10	10	10	10	10
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	0.01	0.01	0.01	0.01
Distilled water (ml)	q. s.	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

MO: *Moringa olifera* extract %w/v, ER: *Embelia ribes* extract %w/v

Evaluation of thermoreversible *in-situ* nasal polyherbal gels

Gelling temperature and gelling time

Gelling temperature refers to the temperature when the meniscus of the formulation would no longer move upon slanting the test tubes at 90 ° angle. The gelling temperature was determined by placing the test tube, containing sufficient quantity of the prepared solutions, in a water bath at 4 °C. The temperature of water bath was increased slowly at a constant rate of 1 °C in every 2 min.

Gelling time was recorded as the time for first detection of gelation. The sol-gel transition temperature (Tsol-gel) of the prepared *in-situ* gel formulations was evaluated by transferring 2 ml of the prepared formulation to a test tube (10 ml), with a diameter of 1.0 cm. After sealing with a parafilm, the tube was kept in a circulation water bath at 37 °C. Following each temperature setting, equilibration was allowed for 10 min. Finally, the test tube was placed horizontally to observe the state of the sample and to examine the gelation. All the measurements were performed in triplicates.

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

Mucoadhesive strength

Ex vivo mucoadhesive strength was determined using fresh sheep nasal mucosa. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed thrice with distilled water and phosphate buffer (pH 6.4). Modified balance method was used to design the experiment.

The balance was equilibrated on both sides by placing one beaker on the left pan and a weight (5 g) on the opposite pan. The sheep nasal mucosa was cleaved into 1 cm^2 and glued with cyanoacrylate over the glass support to allow the smooth surface of nasal mucosa face the upper side of the glass. The glued sheep nasal mucosa was wetted with phosphate buffer (pH 6.4) by filling the beaker with the buffer on the right-hand side of the balance by lowering the glass support. The above setup was placed under the right side of the pan.

A thin film of the prepared gel (1 g) was spread on the lower surface of the right pan. The right pan was lowered and was spread with gel by removing the beaker from the left pan. The pan was left undisturbed for 2 min to ensure proper contact between the nasal mucosa and the gel. Following this, water was slowly added to the left pan using a burette until the nasal mucosa was separated from

the gel film. The mucoadhesive force was calculated by determining the weight required to separate the mucosa. The force was expressed in dynes per square centimeter (dyne/cm^2).

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].

Animals

Healthy swiss mice (20-25 g), were obtained from the Centarl drug research institute (Lucknow, India). Prior to experimentation, the animals were quarantine for at least one week to a 12-h light/dark cycle All experimental protocols were from the CPCSEA (AUUP/AIP/ PhD/006/2017) and approved by Institutional Animal Ethics Committee.

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.

RESULTS AND DISCUSSION

Gelling temperature, gelling time and viscosity of *in-situ* nasal herbal gels

The thirteen different *in-situ* nasal herbal gels were formulated using HPMC, carbopol and xanthan gum as the base polymers. The results of gelling temperature, gelling time and viscosity of herbal gels are demonstrated in (table 2).

The gelling temperature of the *in-situ* nasal herbal gel ranged between 26.14 °C and 36.17 °C. The findings of the gelling temperature of prepared gel indicate that suitable for thermo reversible nasal gel.

The gelling time of herbal gel ranged between 5.2 and 11.3 sec (table 2). The gelling temperature of formulation was found to be within the range. The gelling time increases on decreasing the concentration of F4.

The viscosity of the *in-situ* nasal herbal gels ranged between 30.2 and 40.3 Pa·s. The viscosity of *in-situ* nasal herbal gels enhance on higher concentration of PF127. Similarly, on increasing the concentration of HPMC K4M/carbopol/xanthan gum, it enhances the viscosity of formulation.

Table 2: Gelling temperature, gelling time and viscosity of solution thermo reversible *in-situ* nasal polyherbal gel formulations

Formulation	Gelation temperature (°C)	Gelling time (sec)	Viscosity/(Pa·s)
F1	26.14±0.25	5.2±0.05	40.3±0.82
F2	29.35±0.47	7.5±0.08	35.7±0.15
F3	32.52±0.63	8.1±0.02	32.3±0.37
F4	36.17±0.43	11.3±0.6	29.5±0.64
F5	31.24±0.81	9.1±0.07	32.2±0.84
F6	30.83±0.51	8.5±0.02	32.4±0.39
F7	29.45±0.64	6.2±0.04	32.9±0.67
F8	32.18±0.38	10.5±0.14	31.5±0.53
F9	31.38±0.43	9.3±0.09	31.8±0.45
F10	31.02±0.37	7.6±0.11	32.1±0.68
F11	33.41±0.95	10.8±0.04	30.2±0.47
F12	32.52±0.17	9.7±0.17	30.4±0.92
F13	31.61±0.58	8.5±0.13	30.5±0.48

Values are mean±SD of three determinations

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 PF127 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%.

Table 3: Gel strength, pH and drug content of thermo reversible *in-situ* nasal polyherbal gel formulations

Formulation	pH	Gel strength (s)	Drug content
F1	5.2±0.05	62.1±0.14	91.5±0.68
F2	5.2±0.01	57.5±0.09	92.7±0.49
F3	5.4±0.07	55.8±0.28	90.4±0.24
F4	5.6±0.02	53.1±0.04	93.4±0.63
F5	5.4±0.09	55.4±0.42	91.8±0.82
F6	5.5±0.05	58.3±0.63	92.6±0.67
F7	5.7±0.04	63.7±0.18	92.5±0.43
F8	5.5±0.08	54.5±0.34	91.7±0.54
F9	5.8±0.03	56.2±0.61	92.3±0.28
F10	5.9±0.02	59.6±0.58	90.7±0.17
F11	5.4±0.09	54.1±0.47	92.3±0.34
F12	5.6±0.07	55.8±0.34	93.1±0.49
F13	5.8±0.02	57.2±0.19	91.6±0.26

Values are mean±SD of three determinations

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

The findings of mucoadhesive strength and spreadability of *in-situ* nasal herbal gel are exhibited (table 4). The mucoadhesive strength was ranged between 6317.2 to 4236.7±0.61 dyne/cm^2. The higher concentration of Carbopol 934 produced greater mucoadhesive strength. Mucoadhesive drug delivery systems allows rapid dissipation of drug in the circulatory system, thereby preventing the first-pass metabolism and prolonging the residence time of the dosage at the site of application or absorption. In the present study, the formulations prepared with high concentration of HPMC/ carbopol/xanthan gum exhibited more mucoadhesion strength as compared to PF127 (10%). The spreadability of *in-situ* nasal herbal gel ranged between 7.6±0.21 to 11.7±0.65 cm.

Table 4: Mucoadhesive strength and spreadability of thermoreversible *in-situ* nasal polyherbal gel formulations

Formulation	Mucoadhesive strength (dyne/cm^2)	Spreadability (cm)
F1	6154.2±0.53	7.6±0.21
F2	5236.8±0.29	9.2±0.53
F3	4914.5±0.73	10.8±0.43
F4	4236.7±0.61	12.3±0.17
F5	4862.9±0.38	11.7±0.65
F6	5543.4±0.92	11.1±0.34
F7	6317.2±0.68	10.2±0.41
F8	4567.5±0.51	10.7±0.57
F9	5247.9±0.36	9.3±0.83
F10	6153.3±0.18	8.8±0.19
F11	4365.7±0.54	11.2±0.32
F12	4739.2±0.32	10.5±0.48
F13	5934.8±0.47	9.1±0.56

Values are mean±SD of three determinations

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, F12 and F13 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

Formulations	Irritant	Erythema	Edema
F1	0	0	0
F2	0	0	0
F3	0	1	0
F4	1	0	0
F5	0	0	0
F6	0	1	0
F7	1	0	1
F8	0	0	0
F9	0	0	0
F10	0	0	0
F11	0	0	1
F12	1	0	0
F13	0	1	0

In the past few years, an increasing number of *in-situ* gel forming systems have been reported for various biomedical applications, including drug delivery, cell encapsulation, and tissue repair. These were in the form of solutions, but gelation could occur *in-situ* by ionic cross-linking or a change of ph or temperature. The latter approach is based on temperature induced phase transition. The pluronics are made from ABA-type triblock copolymers containing PEO (A) and PPO units (B). Further the concentrated aqueous solutions of pluronic form thermo reversible gels.

The gel containing pluronic produces weak mechanical strength, rapid erosion, and the non-biodegradability of PEO-PPO-PEO, which prevented the use of high molecular weight polymers. Hence, to minimize the associated drawback, it is required to formulate the pluronic with other bioadhesive polymers namely carboxymethyl-cellulose (CMC), hydroxypropylmethyl cellulose (HPMC K4M), carbopol, xanthan gum, methyl methacrylate etc. We planned to restrain the viscoelastic properties and the bioadhesive characteristics of PF127 by forming dual systems with a high molecular weight HPMC K4M/Carbopol/xanthan gum [17, 18]. The object of the present study to formulate *in-situ* nasal herbal gel, modulating the viscoelastic properties and the bioadhesive characteristics of PF127by forming dual systems with a high molecular weight HPMC K4M or carbopol.

Formulation of *in-situ* gels appears very attractive since it is fluid like prior to nasal administration and can thus easily be instilled as a drop allowing accurate dosing, but sets into a gel with increased residence time at body temperature.

PF127 has excellent thermo sensitive gelling properties, low toxicity and irritation, excellent water solubility, good release characteristics and compatibility with other excipients. HPMC K4M/carbopol/ xanthan gum was selected as mucoadhesive agent. PF127 is more soluble in cold water than in hot water therefore gels were prepared by cold technique.

Table 2 demonstrated with the increase of concentration of HPMC K4M or carbopol or xanthan gum, temperature was lessened and viscosity was raised moderately. Thus, packing of micelles and micelle entanglements might be the possible mechanisms of pluronic solution gelation with increase of temperature. PF127 solution behaves as a mobile viscous liquid at room temperature (25 °C), and transformed into a semi-solid transparent gel at body temperature (37 °C). Pluronic formulations generally increase drug residence time at application

sites through gelling, resulting in improved bioavailability and efficacy. Block copolymer PF127gels were thought to be formed 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, which contributed to the aggregation [17]. The desired gel strength may be achieved by combination of 2 polymers, so, PF127 concentration could be reduced to lower toxicity of huge PF127content.

The experiments about effect of combination of bioadhesive agents and PF127 on gelation temperature and rheology behavior demonstrated that the packing and entanglements of micelles were promoted by adding either HPMC K4M or carbopol or xanthan gum, which accordingly lead to decrease of gelation temperature. There was some optimization about gelation temperature to ensure a solution at room temperature (25 °C), and a semi-solid transparent gel at body temperature (37 °C) [17]. These results suggested that the optimum concentration for HPMC K4M or carbopol or xanthan gum solution used *in-situ* gel forming system was 0.5%–1.5% (w/v), and that of pluronic F127 was below 10% (w/v).

The viscosity of the formulated herbal gels was increased with the increment in the amount of hydroxypropylmethyl cellulose HPMC K4M or carbopol or xanthan gum. The viscosity was directly dependent on the bioadhesive content of the formulations. The hydroxypropylmethyl cellulose HPMC K4M or carbopol or xanthan gum can markedly prolong the residence time of the drugs in the nasal cavity because of their desirable mucoadhesive property. This can facilitate the sustained release of the drug can be maintained due to the high viscosity of the cellulose following hydration in the nasal cavity. Consequently, it increases the intranasal bioavailability of both small hydrophobic and hydrophilic macromolecular drugs [10, 19].

The presence of combination of HPMC K4M or carbopol or xanthan gum significantly increased the viscosity as well as gel strength. In addition, the formulations prepared with high concentration of HPMC K4M were associated less spread ability. This was attributed to the high viscous nature of HPMC K4M. The results of ph of the formulations did not show any mucosal irritation because all the formulations ph was within in the acceptable range. Formulation should possess mild acidic ph for activation of lysozyme (A natural antibacterial enzyme important for controlling nasal microbial count which becomes inactive at alkaline pH) [13].

Mucoadhesion involves 3 stages: wetting; interpenetration; and mechanical interlocking between mucin and polymer. Owing to the characteristic anatomy and physiology of the nasal passage, i.e., large surface area, highly vascularized epithelium, porous endothelial membrane, nasal drug delivery has emerged as a promising route of drug administration for the systemic therapy. The combination of HPMC K4M or carbopol or xanthan gum increases the mucoadhesive strength resulting to enhance the retention of drug in endothelial membrane [20]. The *in-situ* nasal herbal gel show no redness, edema, inflammation and irritation during irritancy studies, and it was safe to use. The *in-situ* nasal herbal gel prepared by combination of different concentration of to HPMC K4M or carbopol or xanthan gum with PF127 (10% w/v) produces the better and effective gel. The findings of evaluation parameter indicate that the in-situ gel prepared by combination with corbopol were better quality compared to HPMC K4M and xanthan gum.

CONCLUSION

The outcomes of the present study indicate that extract of *Moringa olifera* and *Embelia ribes* 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

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