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Original Research Article

Nasal *In-situ* Gel of Inert Cellulose for Allergic Rhinitis

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ABSTRACT

Allergic rhinitis is a very common disease that is treated with a variety of systemic and locally applied drugs. The advantage of nasal route of avoiding the systemic side effect of drug is outweighed by the low effectiveness of the intranasal formulations due to the rapid cleaning mechanisms of the nose. This work aims to produce nasal in-situ gel using hydroxypropyl methyl cellulose (HPMC) as the active ingredient. HPMC is an inert cellulosic material that will provide a natural barrier against the allergens and will aid in treatment and preventing the allergic rhinitis. In addition, a pH sensitive polymer (Carbopol) had been added to this formula, to provide in-situ gelling of the solution upon contact with nasal mucosa. In this work, two concentrations of HPMC (namely 0.8% and 1.6%) have been studied. All the prepared formulas were characterized by different techniques. In addition, the muco-adhesiveness, the in-vivo retention time and the safety of the selected formula were studied. Results indicated that hydroxypropyl methyl cellulose in-situ gel can be produced with very good characteristics using 1.6% HPMC with 0.9% carbopol. The in-vitro study confirmed the moderate gelling capacity with high muco-adhesiveness. This is supported by the *in-vivo* retention time study which is conducted on live sheep and the recorded retention time was prolonged. The histopathology study confirmed the absence of any toxic or necrotic effect on nasal tissue. To conclude, this study succeeded in formulating a new promising, comfortable and safe treatment of allergic rhinitis.

Keywords: Smart gel, Nasal in-situ gel, Allergic rhinitis, HPMC, Inert cellulose, pH-sensitive.

Introduction

Allergic rhinitis is characterized by inflammatory changes in the nasal mucosa caused by exposure to inhaled allergens. It is a common disease, affecting between 20 to 40 % of the world population. There may be co-morbidities with other organs being involved, commonly allergic conjunctivitis and allergic asthma. Indeed, these diseases are increasingly considered to be a single entity, with a spectrum of respiratory allergic response, termed the unified allergic airway.[1] There is an increasing evidence that inhibition of antigen-antibody reaction at the nasal mucosa, not only causes local improvement of nasal allergic symptoms, but also causes significant improvement at the level of lower airways.[1,2]

Being immunoglobulin E (IgE) mediated disease, prevention and modification of allergen exposure represents an essential part in the management of allergic rhinitis.[3] There is abundant allergen specific IgE in these patients. When an inhaled allergen binds to IgE, it triggers mast cell degranulation causing release of histamine and other mediators, which will initiate an inflammatory cascade leading to classical allergy symptoms.[4] Formation of a contact barrier between the allergens and the IgE will prevent the consequent inflammatory cascade. An inert cellulose powder has been used for this purpose one decade ago, where protective barrier on the nasal mucosa may prevent contact between inhaled allergen and mucosal cells.[5] This cellulose material, named hydroxypropyl methyl cellulose (HPMC), has been applied as dry powder and demonstrated good safety profile. HPMC has been introduced into the market as nasal spray of dry powder called Nasaleze®. This system of micronized powder was licensed in the European Union as Class I medical device.[6] HPMC is an odorless and tasteless powder accepted as food additives in Europe and it is widely used as an excipient in different pharmaceutical preparations including oral, nasal, ophthalmic and topical formulations. It is also used very extensively in cosmetics products. HPMC is generally regarded as safe material (GRAS) and it is FDA approved as inactive ingredient.[7] In addition, HPMC is well tolerated and its safety as food ingredients is well documented.[8] A clinical trial conducted on volunteers indicated that HPMC powder was as effective as budesonide, a potent corticosteroid, in preventing allergic rhinitis.[9] HPMC is regarded as a barrier, not only against inhaled allergens, but also against noxious agents and environmental dust that may irritate the nasal mucosa.[9] Nasal mucocilliary clearance is a fundamental function required to maintain the health and defense of the nose. About 20–40 mL of mucus are secreted from the nose at resting condition. It forms a blanket over the nasal mucosa that, together with the cilliary action of the epithelial layer, act to " wash out" any foreign substance entering the nose posteriorly to the nasopharynx where they can be swallowed or expectorated.[10] For any material to act as a barrier against allergen contact, it has to stay on the mucosa for a while, and to resist the continuous washing effect of the beating cilia.[4] Indeed, in addition to barrier action of this nasal application, there is increasing consideration to nasal route utilization for immunization.[11] The nasal application of liquid dosage form is more comfortable than powder dosage form, however there is a limitation of rapid mucocilliary clearance. This obstacle can be overcome by using gel. Indeed, there is no way to apply consistent and precise dose by gel. In-situ gel takes both advantages of precise dose of liquid and long contact time of gel. In situ gels are smart hydrogels, known as stimuli-sensitive hydrogels, that altered from liquid into gel in response to alterations in the environment. The stimuli could be change in temperature, pH or ionic strength.[12]

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This work hypothesizes that HPMC can be prepared as in-situ gel to act as a protective barrier in treatment of allergic rhinitis. Accordingly, this work aims to formulate the inert cellulose, HPMC, as in-situ gel that is administered as liquid and converted to gel upon contact with the nasal mucosa. Different concentrations of the pH-sensitive polymer, carbopol, will be used and investigated for achieving the required gelling property. The novelty of this work is in providing a new dosage form (in-situ gel) for allergic rhinitis. This dosage form will be more convenient to patients than nasal powder dosage form. It will be administered very easily as liquid with precise dose and due to gelation, it will provide prolong contact. The presence of carbopol in the formula will further prolong the contact time due to its mucoadhesive property which will result in less frequent administration.

Materials and Methods

Preparation of in-situ gel

Nasal in-situ gel was formulated using HPMC (molecular mass 1261.4) as the active ingredient. Two concentrations of HPMC (namely 0.8% and 1.6%) were chosen on the basis of the marketed product, Nasaleze®, which contains 0.8% of cellulose powder for prevention of allergic rhinitis. Carbopol 934 (molecular mass 72.0626) (56 and 68% w/w carboxylic acid content) was used as in-situ gel forming agent. Different concentrations (0.4% - 1%) of Carbopol were tested in order to find the optimum formula. Phosphate buffer solution (PBS) (pH 5.8) was used as a solvent for the two polymers, while phosphate buffer (pH 7.4) was the medium selected to study the in-vitro gelation properties.

The required weight of HPMC was dissolved in PBS (pH 5.8) and mixed until no visible clumps are seen. Carbopol 934 was weighed and added to HPMC solution. The mixture was left over night to ensure complete wetting and swelling of Carbopol 934. Next morning, the mixture undergoes stirring to ensure uniform mixing of the two polymers and the volume was completed using the same solvent. The prepared formulas were kept refrigerated. Table.1 shows the composition of the prepared formulas.

In-vitro gelling capacity:

This study was performed using phosphate buffer (PH 7.4) as a neutralizing medium in order to transform formulas from solution to gel state. One drop of the tested sample was placed in a vial containing 2 mL of neutralization solution. Visual assessment of gel formation and the time required for the gel formed to be dissolved was studied.[9] The gelling capacity was ranked according to the visual assessment into (+ for weak gel, ++ for acceptable gel, +++ for medium gel, ++++ for strong gel). where the sign of (+) indicates gelling time >20 sec., (++) indicates gelling time is <20 sec., (+++) indicates gelling time is <10 sec. and (++++) indicates gelling time in <5 sec.

pH and clarity:

pH measurement was conducted by diluting 1 mL of formulas in gel state up to 25 mL using D.W and then pH was measured using digital pH meter (Mettler/Germany). Clarity was tested by visual inspection of all the prepared formulas against white-colored paper.

Gel strength:

Formulas undergone this rest after being transitioned into gel state using PBS (pH 7,4) as a neutralizing agent. Gel strength was tested by placing 50 g of the neutralized gel sample in 100mL glass cylinder and to calculate the time (in seconds) required for a 35g weight to pass 5cm through the gel sample. All the formulas were converted into gel using phosphate buffer solution (pH 7.4) before performing the test.[13,14]

Viscosity

The viscosity of nasal product has a documented effect on the nasal clearance of the products .[15] In addition, viscosity of the preparation is very important during the application to achieve a uniform dose with an easy and applicable form. The viscosity measurements of samples in gel state were carried out by using Brookfield viscometer (Brookfield Engineering Laboratories Inc., RVDV-IIþ pro model, USA). The measurement was conducted at room temperature and repeated for three times.

Mucoadhesive strength

This test was performed using method described by Bagul et al using samples of tested formulas after being transformed into gel state.[15] A physical balance was modified in a way described in Figure (1) in order to measure mucoadhesion force. Fresh Sheep intestinal mucosa was used; it is obtained from local slaughter. After applying the transitioned gel, fixed force was applied for 3 minutes, then the force was removed and water was dropped inside the cup attached to the opposite arm. The weight of water (in grams) needed to detach the two mucosal pieces from each other was considered as the mucoadhesion strength. The following formula was used to calculate mucoadhesion force:

Force of adhesion (N) =Mucoadhesion strength (gm)/1000 × 9.81
Mucoadhesive Strength (dynes / cm^2) = mg /A

Where m is weight required for detachment in grams, g is acceleration due to gravity (980 cm/s^2) and A is surface area of mucosa exposed (cm^2).

FTIR study:

Samples of HPMC, Carbopol 934 and a 1:1 mixture of the two polymers were studied by FTIR spectroscopy to find out whether there is any chemical interaction (incompatibility) between the used polymers.

Table 1: The different formulas of HPMC in-situ gel

Formula code	HPMC conc. (w/w %)	Carbopol 934 conc. (w/w %)
F1	0.8	0.4
F2	0.8	0.5
F3	0.8	0.6
F4	0.8	0.7
F5	0.8	0.8
F6	0.8	0.9
F7	0.8	1
F8	1.6	0.9
F9	1.6	0.6
F10	1.6	0.3

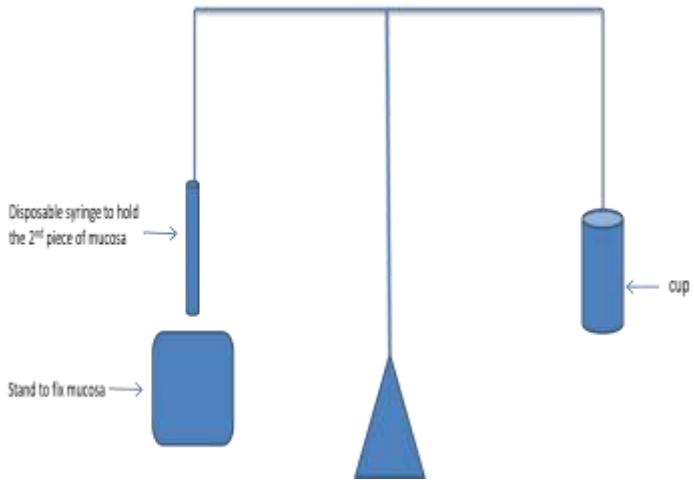

Figure 1: Modified balance to measure mucoadhesion force

In vivo retention time measurement (animal study)
Contact time or retention time of the selected formula was studied by comparing the retention time of the selected formula of in-situ gel with the retention time of normal saline as a control. One mL of the selected formula (1.6% HPMC with 0.9% carbopol) was applied as a solution into a nostril of the nose of live sheep. For comparison, one mL of normal saline was applied in another nostril as a negative control. Then the retention time was monitored visually by using medical endoscope (Nasal Endoscope, Karl-Storz 4mm, zero degree, Germany). The work on animal was authorized by the medical research ethics committee at University of Mosul (MREC), document number 20/21 (39) and the work was conducted by an otolaryngologist. The retention of the formula was visualized after different time intervals (5,10,15, 20 and every 10 minutes) until the disappearance of the gel. The time required for the disappearance of the formula was considered as the retention time. The experiment was repeated three times and the mean and standard deviation were calculated. The washing out period after each application was one week (i.e. there was a week time interval between each experiment). In order to confirm the result, the experiment was repeated using fluorescent substance (Fluorescein sodium ophthalmic strips, OptiGlo, India). One fluorescein strip was immersed into 5mL of each solution for one minute then the two samples were pumped through a one mL disposable syringe (without needle) into each nostril of the sheep. Then the retention time was followed up after different time interval. This sort of using Fluorescin strips have been used before in tracking the retention time of in-situ gel after ophthalmic administration of ciprofloxacin in-situ gel to rabbits.[13]

Irritancy test
The irritancy test was applied by monitoring of any sign of redness, developing of edema or any signs of inflammation. This is conducted through endoscopy imaging of nasal tissue after the application of selected formula of in-situ gel in comparison to the application of normal saline as a negative control. The endoscopy procedure conducted three times on three different occasions.

Histopathological evaluation of nasal mucosa
Nasal sheep mucosa was obtained freshly from a local slaughter, the removal of the mucosa of nose was performed by ENT surgeon (the third author is otolaryngologist) and then the selected formula was applied on mucosa for 5 hours. Similarly, the mucosa was treated with phosphate buffer pH 7.4 as negative control .[17] After the treatment, the tissues were stored in 10% of formalin solution and then the tissue were stained with hematoxylin and eosin staining (H and E). The specimens were examined using a light microscope to explore the safety of the treatment on mucosal tissue during the application.

Statistical analysis
Unpaired student *t-test* were employed for the statistical analysis and a p-value of ≤ 0.05 was considered to be statistically significant.

Results and Discussion

In-vitro gelling capacity
Gelling capacity indicates the time required to convert solution to gel. Optimal gelling time is less than 10 seconds.[18] Results presented in Table 2 demonstrated the gelling capacity of the different formulas. F1 resulted in a very weak gel after neutralization. F2, F3 and F9 exhibited mild gelling capacity while F4, F5, F6 and F8 formulas showed moderate gelling capacity in comparison to F7, which showed the highest gelling capacity. Carbopol produced a gel, that expands up to 1000 folds of its initial volume with semisolid consistency that will prolong the contact time. The gelling capacity is correlated well with the concentration of carbopol; as the carbopol increased the gelling capacity is increased and this is in agreement with similar works used carbopol as a gelling agent.[19,20] The gelling capacity is related to the strength of crosslinking and more ionization leads to more crosslinks with stronger bonds. The nasal application of liquid is preferred upon nasal gel as the patient can install the required dose precisely. However, the nasal clearance of liquid is fast. Nasal in-situ gel offers double advantages of accurate dosing and long contact with the nasal mucosa. The formulas with good gelling capacity will be further investigated through different tests.

pH and clarity
The measured pH values are presented in Table 2. It is obvious that the pH is decreased with the increment in carbopol concentration. This is due to the acidic nature of acrylic acid derivative, that contains anionic carboxylic group .[21]

However, the formulator should be aware that highly acidic value is not suitable for nasal application. Data in Table 2 demonstrated that all formulas exhibited acceptable pH values as the nasal mucosa can tolerate pH value between 3 and 10.[20] In addition, Table 2 demonstrated the results of clarity, where the clarity of all formulas are acceptable except formula 7 (F7). Formula (F7) showed insoluble polymer particles, which might be due to the high concentration of Carbopol. This with the low pH characteristic represents a good reason to exclude this formula from further studies.

Viscosity
The measurement of viscosity was conducted at what is called ambient or room temperature. This is conducted to ensure that the product viscosity is within the acceptable limit and the product can be applied easily and the dose for the liquid dosage form can be measured accurately. Table 3 demonstrates the viscosities of the three selected formulas, where the viscosity is increased as the percentage of carbopol polymer is increased. F8 demonstrated significant difference ($p<0.05$) from F9.

Table 2: The results of pH measurement, gelling capacity and gel strength test

Formula code	pH	Clarity	Gelling capacity	Gel strength (sec.)
F1	4.29	Clear	+	1
F2	4.22	Clear	++	1.2
F3	3.95	Clear	++	1.5
F4	3.87	Clear	+++	1.6
F5	3.79	Clear	+++	1.8
F6	3.76	Clear	+++	2
F7	3.07	Not clear	++++	4
F8	3.70	Clear	+++	5
F9	4.15	Clear	++	2
F10	4.64	Clear	+	1

Table 3: Viscosity, mucoadhesion strength and mucoadhesion force for the selected formulas

Formula Code	Carbopol concentration (w/w %)	Viscosity (cp)	Mucoadhesion strength (gm)	Mucoadhesion force (N)
F8	0.9	13.303± 0.523*	7.285	0.071
F9	0.6	9.433± 0.522*	5.32	0.052
F10	0.3	3.946± 0.924*	4.766	0.046

*: Mean ± S.D.; n =3

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In addition, F9 demonstrated highly significant difference ($p<0.05$) from F10. However, all the measured viscosities are within acceptable limits. It is worthy to mention that HPMC contributes to the viscosity of the system as it is a known thickening agent.[8] F6 with high carbopol concentration demonstrated very high viscosity that cannot be measured through the available device and the result is not included in Table 3.

Mucoadhesion test

The mucoadhesive properties of carbopol has been documented before in a study involved preparation of the antidiabetic drug, Glipizide, as microbeads.[21] The mucoadhesion property, which is mainly due to the crosslinking with the mucin of mucous membrane, is very essential in prolongation of the contact time. The results of mucoadhesive properties are in accordance with the results obtained when teriflunomide was developed as nanoformulation for nasal to brain delivery where carbopol was used as mucoadhesive agents.[22]

In our results, which is presented in table 3, it is obvious that the highest muco-adhesiveness is recorded with formula 8 (F8).

It is clear that mucoadhesion strength is increased as the concentration of carbopol is increased. This is consistent with work of Shah *et al* who investigated the effect of different carbopol concentrations (0.25, 0.5 and 0.75%) on the muco-adhesiveness of different formula of nasal in-situ gel of the mast cell stabilizer drug, the sodium cromoglycate, which is used for allergic rhinitis.[23] Accordingly, the formula with the highest mucoadhesion force, formula 8 (F8) was selected for further study on live animal.

Chemical compatibility

The FTIR spectrum demonstrated in Figure 2 showed the characteristic peaks of HPMC as follows: a peak above 3450, which reveals the presence of hydroxyl group (OH) stretching, a peak at 2867, which reveals C-H group stretching and a peak at 1048, which reveals the C-O group stretching. Figure 3 represents the FTIR spectra of carbopol 934. FTIR spectra showed a peak between 3000 and 2940, which represents OH stretching vibration. There is a noticeable peak near 1700 (1701) cm^{-1}, which reveals the carbonyl stretching (C=O stretching band).

The FTIR spectra of the HPMC/Carbopol mixture is shown in Figure 4. It is very clear that Carbopol retains its characteristic peak at 1702 cm^{-1} while HPMC retains its peak at 1048 cm^{-1}. The absence of new peaks or shifting of the prominent characteristic peaks indicated that there is no notable chemical incompatibility between HPMC and carbopol and they can be formulated into one formula.

In vivo retention time measurement (animal study)

Usually, the retention time is measured by a sophisticated technique, called gamma scintigraphy, that depends on labeling the drug with a radioactive substance such as ^{99m}Tc.[24] However, in this work a simple endoscopy technique was used. Sheep was selected as a model in the measurement due to two reasons: First, the large nasal space available for the endoscopy and second, the similarity to human nose that reported the feasibility of nasal sheep as a model for research in endoscopy.[25] The main advantage of in-situ gel upon other liquid nasal preparations is the long contact time. Results showed that the retention time of the selected formula after three experiments was 55±5 minutes while the normal saline retention time was 8±1 minutes. This is in accordance with an experiment conducted on rats and showed that carbopol prolonged the mucociliary transport up to 52 min for mucoadhesive gel.[26] Figure 5 represents the endoscopy images after application of the selected formula in comparison to normal saline, which is used as negative control. Image in column B at the top showed clearly the accumulation of fluorescent gel in comparison to the image in column A, that represents the nostril treated with the fluorescin-normal saline as a control treatment. The mucociliary clearance is the mechanism responsible for the short contact time of nasal preparations. Usually, sophisticated procedure is used to follow the contact time and deposition of nasal dosage form like a gamma deposition studies, which depend on using radiopaque contrast with its known limitations. According to our knowledge, this is the first time where the nasal endoscopy, which is used mainly in diagnostic field in medicine, is used to follow the contact time of nasal drug delivery system.

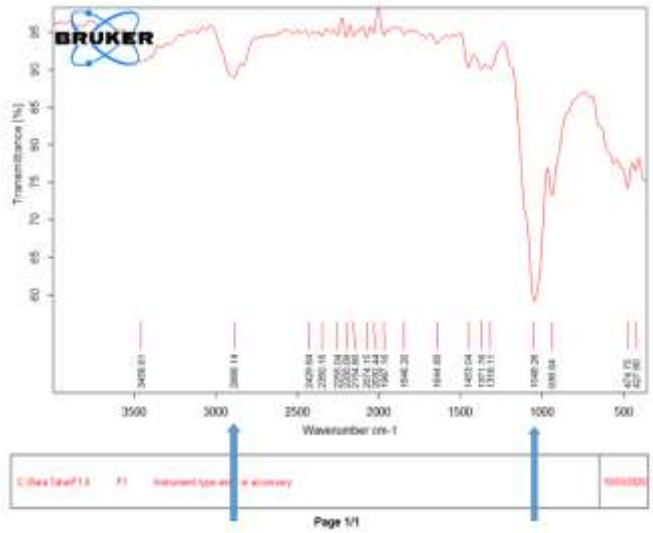

Figure 2: FTIR spectra of HPMC

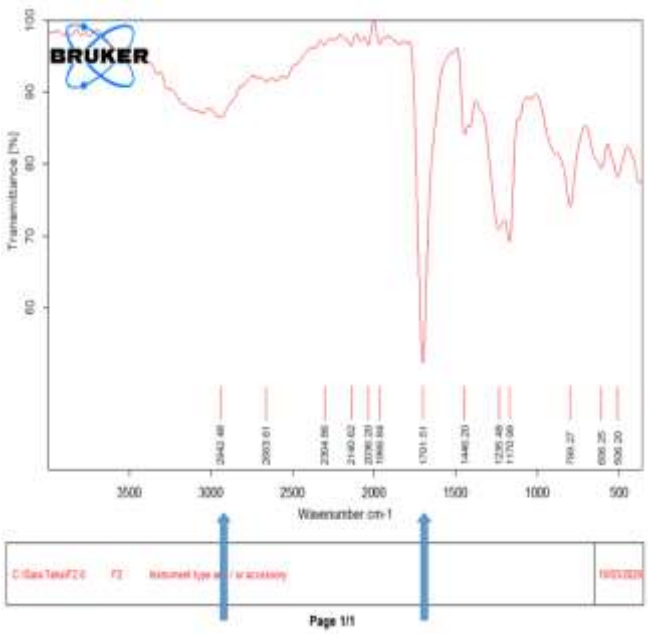

Figure 3: FTIR spectra of carbopol 934

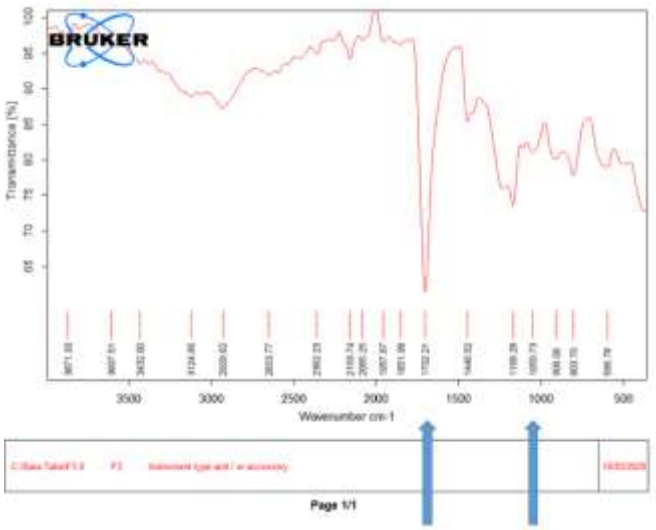

Figure 4: FTIR spectra of HPMC/Carbopol admixture.

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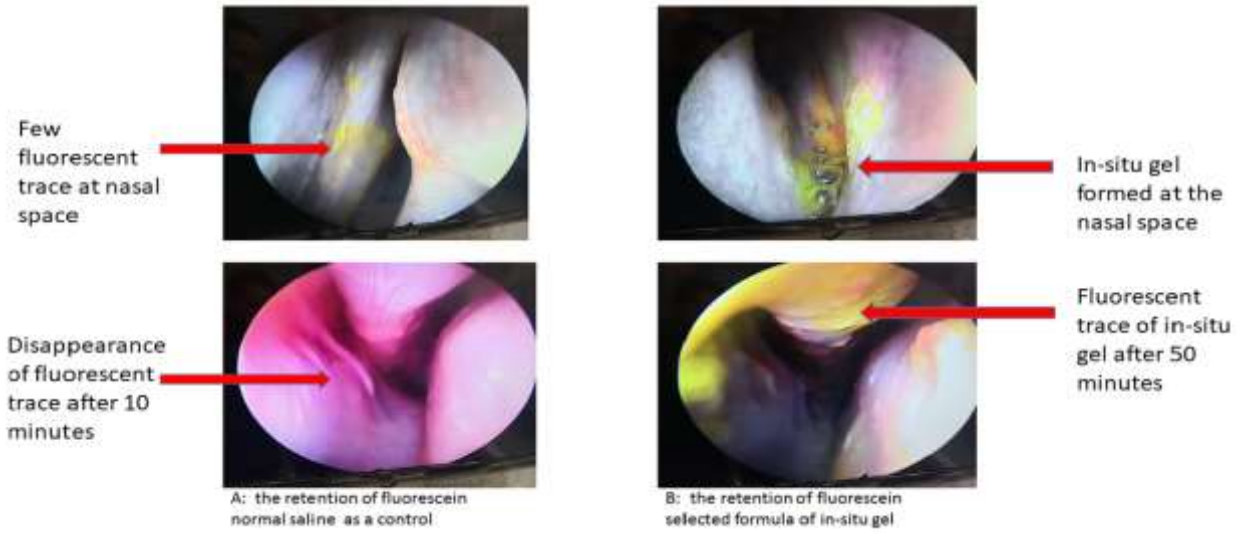

Figure 5: The endoscopy images of nasal passage after administration of fluorescin-formula (selected formula) (B) in comparison to fluorescin-normal saline as a control (A).

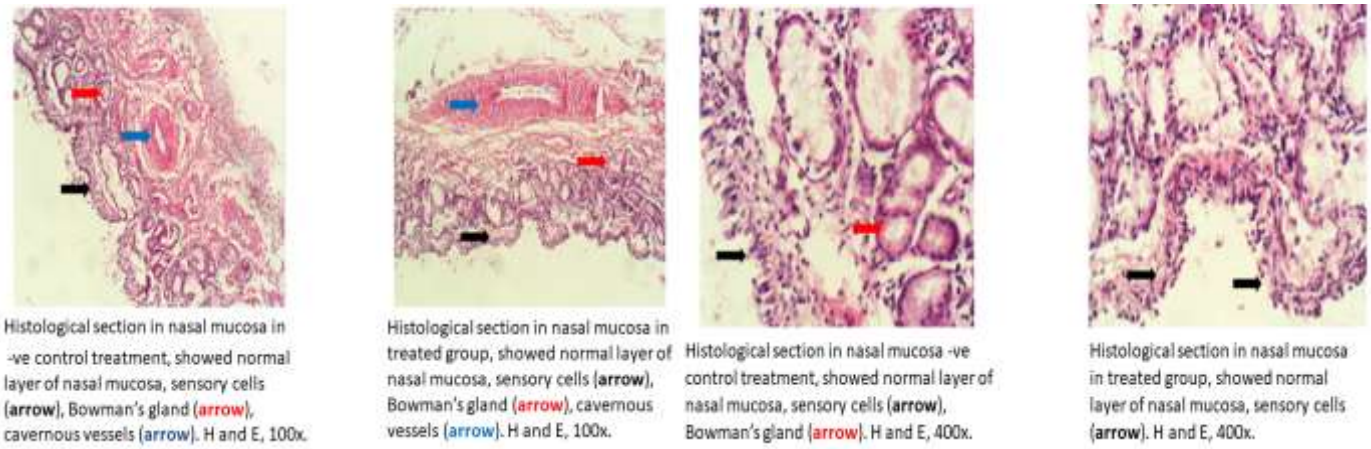

Figure 6: The histopathology of nasal mucosal tissue after treatment with nasal in-situ gel in comparison with treatment with normal saline as negative control.

The procedure is simple to conduct, gave clear image and, interestingly, it can be considered as a simple in vivo study to be conducted on live animals, where the ciliary clearance is intact.

Irritancy test

The nasal endoscopy study, which conducted on live sheep, reveals no redness, edema or any signs of inflammation in nasal tissue after the application of the selected formula of nasal in-situ gel.

Histopathological study

This test is conducted to investigate the safety of the applied formula of nasal in-situ gel when applied to sheep nasal mucosa. This study demonstrated the shape and architecture of nasal tissue through using the light microscope. Figure 6 demonstrated the histopathology of treated tissue in comparison with tissue treated with negative control. It is obvious that the application of Formula 8 nasal in-situ gel did not cause notable changes in histological architecture, which is represented by similar normal histological structure of both the treated group and the negative control-treated group. The images in Figure 6 shows normal mucosa with normal sensory cells, normal Bowmans gland and normal cavernous vessels. This is in consistent with similar work conducted by Alkufi and Kassab,[27] who prepared nasal in-situ gel of sumatriptan and investigated the effect of their formulas that incorporated carbopol as a gelling agent.[27] These results are expected as all the used excipients are safe materials and used widely in different pharmaceutical applications.

Conclusion

The inert cellulose, HPMC can be formulated as nasal in-situ gel with the aid of the pH sensitive polymer, Carbopol 934. This novel delivery of HPMC will provide in-situ gel with long contact time. This work demonstrated several advantages of this formulation of HPMC including the followings: The transition to gel is prominent and confirmed through *in-vitro* and *in-vivo* experiments. The formula is clear, with suitable pH, suitable viscosity and free from chemical incompatibilities. In addition, it is safe and assures long contact time with nasal mucosa of live animal.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Small P, Keith PK, Kim H. Allergic rhinitis. Allergy, Asthma Clin Immunol [Internet]. 2018; 14(s2):1–11.
2. Watts AM, Cripps AW, West NP, Cox AJ. Modulation of Allergic Inflammation in the Nasal Mucosa of Allergic Rhinitis Sufferers with Topical Pharmaceutical Agents. Front Pharmacol. 2019 Mar; 29(10):294.
3. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, Brignardello-Petersen R, Canonica GW, Casale T, Chavannes NH, Correia de Sousa J, Cruz AA, Cuello-Garcia CA, Demoly P, Dykewicz M, Etxeandia-Ikobaltzeta I, Florez ID, Fokkens W, Fonseca J, Hellings PW, Klimek L, Kowalski S, Kuna P, Laisaar KT, Larenas-Linnemann DE, Lødrup Carlsen KC, Manning PJ, Meltzer E, Mullol J, Muraro A, O'Hehir R, Ohta K, Panzner P, Papadopoulos N, Park HS, Passalacqua G, Pawankar R, Price D, Riva JJ, Roldán Y, Ryan D, Sadeghirad B, Samolinski B, Schmid-Grendelmeier P, Sheikh A, Togias A, Valero A, Valiulis A, Valovirta E, Ventresca M, Wallace D, Waserman S, Wickman M, Wiercioch W, Yepes-Nuñez JJ, Zhang L, Zhang Y, Zidarn M, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017; 140(4):950-958.
4. Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Walter Canonica G, Melén E, Palomares O, Scadding GK, Togias A, Toppila-Salmi S. Allergic rhinitis. Nat Rev Dis Primers. 2020 Dec 3;6(1):95. Åberg N, Dahl Å, Benson MA. nasally applied cellulose powder in seasonal allergic rhinitis (SAR) in children and adolescents; reduction of symptoms and relation to pollen load. Pediatr Allergy Immunol. 2011; 22(6):594–9.
5. Popov TA, Emberlin J, Josling P, Seifalian A. In vitro and in vivo Evaluation of the Efficacy and Safety of Powder Hydroxypropylmethylcellulose as Nasal Mucosal Barrier. Medical Devices: Eviden Res. 2020; 13:107–13. Product general information. Available from: https://www.nasaleze.com/. Accessed 9-9-2021
6. Rowe RC, Shesky PJ, Quinn ME. (2009). Handbook of pharmaceutical excipients, Sixth edition, Pharmaceutical press, London.
7. George A Burdock. Safety assessment of hydroxypropyl methylcellulose as a food ingredient. Food and Chem Toxicol. 2007;(45):2341–51
8. Chen X, Guan W, Sun S, Zheng P, Sun L, Chen D, Douglas Zhang X. Effects of Intranasal Cellulose Powder on Asthma Control in Children with Mild-to-Moderate Perennial Allergic Rhinitis: A Randomized, Placebo-Controlled Trial. American J Rhinology & Allergy. 2019; Mar;33(2):184-193.
9. Bustamante-Marin XM, Ostrowski LE. Cilia and Mucociliary Clearance. Cold Spring Harb Perspect Biol. 2017; 9(4):a028241.
10. Ali ZA, Alkotaji M. Nose to brain delivery of drugs for CNS diseases Iraqi Journal of Pharmacy, 2021; 18(1):93-107.
11. Ali ZH and Alkotaji M. Smart hydrogel polymers for drug delivery. Military medical science letters. 2021; 90:1-14.
12. Ramadan AA, Elbakry AM, Esmaeil AH, Khaleel SA. Pharmaceutical and pharmacokinetic evaluation of novel rectal mucoadhesive hydrogels containing tolmetin sodium. J Pharm Investig. 2018; 48(6):673-683.
13. Al-bazzaz FY and Al-kotaji M. Ophthalmic in-situ sustained gel of ciprofloxacin, preparation and evaluation study. Int J Appl Pharmaceut. 2018; 10(4):153.
14. Saito S, Ainai A, Suzuki T, Harada N, Ami Y, Yuki Y, Takeyama H, Kiyono H, Tsukada H, Hasegawa H. The effect of mucoadhesive excipient on the nasal retention time of and the antibody responses induced by an intranasal influenza vaccine. Vaccine. 2016; 34(9):1201-7.
15. Bagul U, Gujar K, Dhat S, Aphale S, Bhavsar M. *In vitro* study of mucoadhesive strength of polymers for mucoadhesive drug delivery systems. International Journal of Current Pharmaceutical Research. 2009; 1(1):43-5.
16. Majithiya RJ, Ghosh PK, Umrethia ML, Murthy RSR. Thermoreversible-mucoadhesive Gel for nasal delivery of sumatriptan. AAPS PharmSciTech. 2006; 7(3):E80–E86.
17. Bhalerao H, Koteshwara K, Chandran, S. Design, optimisation and evaluation of in situ gelling nanoemulsion formulations of brinzolamide. Drug Deliv. and Transl. Res. 2019; 9:7-9.
18. Gupta S. Carbopol/Chitosan Based pH Triggered In-situ Gelling System for Ocular Delivery of Timolol Maleate. Scientia Pharmaceutica. 2010; 78(4):959–76.
19. WU C, QI H, CHEN W, HUANG C, SU C, LI W, & HOU S. Preparation and Evaluation of a Carbopol®/HPMC-based In-situ Gelling Ophthalmic System for Puerarin. YAKUGAKU ZASSHI. 2007; 127(1):183–191.
20. Magbool FF, Elnima EI, Shayoub ME, Hamedelniel EI. Design, Formulation, and Evaluation of Carbopol 940 and Xanthan Gum as Gel Bases for Oral Local Drug Delivery for Oral Mucosal Infectious Diseases. EJBPS. 2018; 5(10):9-21.
21. Bera K, Mazumder B, Khanam J. Study of the Mucoadhesive Potential of Carbopol Polymer in the Preparation of Microbeads Containing the Antidiabetic Drug Glipizide. AAPS PharmSciTech. 2015; 17(3):743–56.
22. Gadhave D, Rasal N, Sonawane R, Sekar M, Kokare C. Nose-to-brain delivery of teriflunomide-loaded lipid-based carbopol-gellan gum nanogel for glioma: Pharmacological and in vitro cytotoxicity studies. Int J Biol Macromol. 2021; 167:906-20.
23. Shah R, Patel D, Mehta M, Patel C. Design and optimization of mucoadhesive nasal in-situ gel containing sodium cromoglycate using factorial design. Asian J Pharmaceut. 2011; 5(2):65.
24. Tyagi S, Sharma N, Gupta SK, Sharma A, Bhatnagar A, Kumar N, Kulkarni GT. (2015). Development and gamma scintigraphical clearance study of novel *Hibiscus rosasinensis* polysaccharide based mucoadhesive nasal gel of rizatriptan benzoate. J Drug Delivery Sci Technol 2015; 30:100–106.
25. Macias-Valle L, Finkelstein-Kulka A, Manji J, Okpaleke C, Al-Salihi S, Javer AR. Evaluation of sheep sinonasal endoscopic anatomy as a model for rhinologic research. World J Otorhinolaryngol - Head and Neck Surgery. (2018) Dec; 4(4): 268–272
26. Zaki NM, Awad GA, Mortada ND, Abd ElHady SS. Enhanced bioavailability of metoclopramide HCl by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. EJBPS. 2007 32(4-5):296–307.
27. Alkufi HK and Kassab HJ. Formulation and Evaluation of Sustained Release Sumatriptan Mucoadhesive Intranasal in-situ gel. Iraqi J Pharmaceut Sci. 2019; 28(2):95-104.