Development of Drug Delivery System for Sinus Mucosal Tissues with Mucoadhesive Thermosensitive Sol-Gel Components: Analysis of Evidence from Laboratory to Animal Research

Muhammad Ilham Dhiya Rakasiwi*, Ahmad Fadhil Ilham, Natan Kevin Partogu Siagian

Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
Corresponding author e-mail: muhammad.ilham65@gmail.com

DOI: https://10.46496/medula.v10i2.13

Received 20 January 2023
Accepted 14 April 2023
Available online 28 July 2023

ABSTRACT

Background: *Chronic rhinosinusitis (CRS) is a chronic inflammation of the nasal cavity (12 weeks or more). Until now, the pharmacological treatment for CRS using a nasal drug delivery system (DDS) has been frequently chosen due to the convenience of the administration. However, nasal DDS shows several disadvantages, such as the vulnerability of sinus mucosa to irritation and medication.* ***Purpose:*** *To assess available literature evidence regarding nasal DDS based on sol-gel using P407 and HPMC for CRS therapy.* ***Methods:*** *A literature search on nasal DDS development using sol-gel thermosensitive mucoadhesive P407 and HPMC was conducted through Pubmed and Proquest journal databases. The supporting articles were searched using specific keywords with inclusion criteria.* ***Results:*** *Sol-gel with P407 (15,5% w/w) and HPMC (0,4% w/w and 0,7% w/w) shows gelation temperature 34.18±0.06°C and 32.76±0.45°C respectively, and virtually clear gel. Rheological evaluation of sol-gel DDS shows modulus G'>G" at 8°C (solution form), while at 32°C shows modulus G'<G" (elastic gel form). In vitro test of dexamethasone release shows velocity 70-81 µg/cm² h−1/2 after 72 hours of administration. Ex vivo test shows slow permeation of dexamethasone at sinus mucosa for 8 hours.* ***Conclusion:*** *Based on the in vitro and ex vivo models, the thermosensitive mucoadhesive gel composed of p407 and HPMC produced extended drug release profiles in conditions mimicking the human nasal cavity, which indicated their suitability for treating a range of conditions affecting the nasal cavity/sinuses.*

Keywords: *chronic rhinosinusitis; drug delivery system; gel; HPMC; P407*

INTRODUCTION

Rhinosinusitis is an inflammatory process of the paranasal sinuses and respiratory tract. Rhinosinusitis that lasts 12 weeks or more can be categorized as a chronic condition or chronic rhinosinusitis (CRS). (Battisti, Modi and Pangia, 2021; Kwon and O'Rourke, 2021) Globally, CRS is a common disease with a prevalence that varies by region. Research in Asia shows that the prevalence of CRS is around 2.7 to 8% (Beule, 2015; Hussain et al., 2018).

Pharmacological therapy is a type of management that is commonly used to treat CRS. Administration of drugs such as antibiotics, decongestants, saline irrigation, and corticosteroids aims to eliminate infection, reduce sinonasal inflammation, and maintain drainage of the sinonasal tract. These drugs can be administered through oral or systemic routes (Suh, Ramakrishnan and Chiu, 2011; Liang and Lane, 2013;

Piromchai et al., 2013; Barshak and Durand, 2017).

Developing a nasal drug delivery system (DDS) is a promising method to get a better drug effect with minimum side effects. Nasal DDS is a method of administering drugs through the nasal route and is the treatment of choice for some diseases of the nose and paranasal sinuses, including CRS. The abundant blood vessels in the nasal mucosa allow systemic drug absorption (Albu, 2012; Djupesland, 2013; Ghori et al., 2015).

However, nasal DDS still has several drawbacks, one of which is the susceptibility of the nasal mucosa to local irritation caused by drugs (Djupesland, 2013). In addition, drug bioavailability can also be reduced due to the mucociliary clearance mechanism, which sweeps the drug down to the nasopharynx and digestive tract so that the contact time for the drug to be absorbed is reduced (Djupesland, 2013; Ghori et al., 2015). The requirement to overcome this problem is the development of an in situ gelling system that will contact the epithelial layer and immediately turn into a gel in situ. The gel will remain attached to the mucosal epithelial layer where it is administered, extending the residence time. (Boddupalli et al., 2010).

From these considerations, it is necessary to develop nasal DDS. The gel material used is poloxamer 407 (P407) which is widely used in mucoadhesive gel research for nasal drug delivery systems. P407 is known to have suitable thermo-sensitive gelling properties, low toxicity and irritation, excellent water solubility, and good drug release characteristics. (Zhang et al., 2002; Majitjiya et al., 2006). Hydroxypropyl Methyl Cellulose (HPMC) is commonly used with poloxamer for intranasal gel development and shows increased drug strength and bioavailability. (Mehta, Surve and Menon, 2009; Jagdale, Shewale and Kuchekar, 2016; Pandey et al., 2017). Based on their characteristics, P407 and HPMC can be used as a sol-gel in nasal DDS to treat CRS in the presence of thermosensitive and mucoadhesive properties (Pandey et al., 2017; Wang et al., 2017; Giuliano et al., 2018). We analyzed the available literature evidence regarding the development of DDS for application to CRS.

METHOD

A systematic literature review on DDS Development with Mucoadhesive Thermosensitive Sol-Gels was prepared using a comprehensive literature analysis. A search for main and supporting articles was conducted on the Pubmed journal database, Proquest and the Google Scholar search engine with specific keywords. The inclusion criteria for the main article literature search were English articles published for less than 10 years (except basic knowledge). Three researchers systematically analyzed the literature from the main article to supporting articles. We did not utilize Boolean operators other than AND/OR to broaden the search results. All keywords and a generated search flowchart are shown in Figure 1. Before we discussed the findings, we assessed the validity of all selected articles. A full assessment of their validity can be read in

Supplementary Table 1. We have used tools to assess preclinical studies by the Office of Health Assessment and Translation (OHAT) to assess the validity of the relevant studies.

RESULT

From the results of the literature search, the authors obtained six journals that were analyzed (Supplementary Table 2) (Zaki et al., 2007; Baloglu et al., 2011; Yuan et al., 2012; Lee et al., 2017; Pandey et al., 2017; Su et al., 2020). After understanding the research outlines of all these journals, the authors collected 28 supporting pieces of literature to strengthen the review compiled. The points discussed in this literature topic are the ability of the gel to change shape, strength or ability to stick to the mucosa and in vitro and ex vivo tests on tissues.

DISCUSSION

Optimization of Sol-Gel Phase Changes in Nasal Cavity Temperature

An ideal drug delivery system for the mucosal cavity must meet the criteria of being a solution at room temperature and a sol-gel in the mucosal cavity. The concentration of constituents such as P407 and HPMC determines the transition temperature from solution to gel (gelation temperature). The regression analysis results with an R2 of 0.967 showed a significant correlation between the concentrations of P407 and HPMC and the gelation temperature. These results are supported by experiments from Pandey P et al. which showed a decrease in gelation temperature according to the increase in HPMC concentration when the concentration of P407 was constant (Pandey et al., 2017; Wang et al., 2017).

Pandey P et al.'s experiment used 32.7(±0.45)°C to 35.9(±0.23)°C as the optimal gelation temperature. Meanwhile, Wang Y et al.'s experiment uses a temperature of 30°C to 32°C as the optimal temperature. This optimal temperature difference was caused by the addition of glycerol in the experiment by Pandey P et al., which changed the gelation rate (Pandey et al., 2017; Wang et al., 2017). Experiments by Su et al. found the optimal gelation time of about 3.8 minutes at 34°C (Su et al., 2020).

Experiment Pandey P et al. using P407 concentration of 15.5% w/w as optimal concentration because it can consistently achieve gelation temperature of 32-35°C. Experiment Wang Y et al. requires a greater concentration of P407 (Pandey et al., 2017; Wang et al., 2017). Based on the evidence that has been described, the administration of drug delivery systems using P407 and HPMC will change the phase to a specific gel at the temperature of the nasal mucosa. It will not change the phase when in storage (room temperature).

Rheological Evaluation

Rheological observations were carried out using the flow characteristics and viscoelastic properties. The ratio of shear stress and shear rate measures flow characteristics. In gel conditions, an increase in shear stress will be followed by an increase in the shear rate (the tendency of the substance to flow).

Meanwhile, in solution, shear stress is not related to shear rate. With a P407 concentration of 15.5% w/w, liquid properties appear at the storage temperature (8°C) and gel properties at the target mucosal temperature (34°C) (Chang et al., 2002; Baloglu et al., 2011; Pandey et al., 2017).

The viscoelasticity of the P407 gel was tested using an oscillation test as a P407 sol-gel simulation under daily activity conditions. This test uses a comparison between G' (elasticity) and G" (viscosity component) under oscillatory conditions with different frequencies. If G'>G", the elasticity is greater than the viscosity so that the substance tends not to flow (sol-gel). Meanwhile, if G'<G", then the viscoelasticity shifts to flow (solution). At 8oC, the ratio of the two properties is always G'<G" (solute). Meanwhile, at 32oC, oscillation triggers G' to increase (G'>G") so that elasticity increases and gel properties appear so that it supports the ability of sol-gel to stick to the nasal mucosa during daily activities (Baloglu et al., 2011; Pandey et al., 2017). Rheological assessment is important to ensure that the gel in the nasal mucosa will remain attached to the mucosa and not move/shift into the surrounding space. At the temperature of the nasal mucosa, P407 gel exhibited the ability to adhere to the nasal mucosa.

Gel Strength Evaluation

After knowing that the components of the drug delivery system can experience gelation and remain attached to the temperature of the nasal cavity, the gel strength was assessed. To measure gel strength, research by Pandey P et al. used a pressure gauge (Pascal). In contrast, research by Wang Y et al. used viscosity measured by placing a load on the gel and calculating the duration of time the load entered 5 cm into the gel and counted in seconds. Both experiments had the same result increasing the HPMC concentration led to an increase in gel strength (Pandey et al., 2017; Wang et al., 2017).

Pandey P et al. proved that the gel strength increased from 1,509.41 (±0.93) Pa (HPMC 0% w/w) to 10,983.31 (± 0.21) Pa (HPMC 1% w/w) with a concentration P407 fixed (15.5% w/w). In Wang Y's experiment, et al., it showed that the gel strength increased according to the increase in HPMC even though there was a change in P407 concentration. Gel strength is targeted at 25-50 seconds. Because the strength of the gel <25s is considered too small to hold the sol-gel form, and the strength of the gel> 50s can cause discomfort to the nasal mucosa. Therefore, an HPMC concentration of >0.6% w/w is not optimal (Pandey et al., 2017; Wang et al., 2017). HPMC is known to play a role in increasing the strength of the gel so that the gel can maintain its shape. The two studies above demonstrated the maximum concentration of HPMC that can be used to develop a nasal drug delivery system.

Mucoadhesion Character

Mucoadhesion is the ability of the gel to adhere to the mucosa against mucociliary clearance. The greater the mucoadhesion of the gel, the longer the gel can stay on the mucosa. Nevertheless, if the mucoadhesion is too great, the gel can cause damage to the

mucosa. Experiments by Pandey P et al. concluded that at a standard concentration of P407 (15.5% w/w), mucoadhesion increased as the HPMC concentration increased. However, in contrast to the gel strength, changes in P407 concentration had a negative impact on mucoadhesion (Boddupalli et al., 2010; Pandey et al., 2017; Wang et al., 2017). The character of mucoadhesion is important in developing drug delivery systems considering that the purpose of developing such a system is to extend the residence time of the drug. P407 and HPMC concentrations determine these characteristics.

Mechanical Character

Three main mechanical characteristics are used to assess the performance of the sol-gel: hardness, cohesiveness and adhesion. Hardness is defined as the effort to move the sol-gel from the container to the desired location. A good gel has low hardness, so it is easy to apply. Cohesiveness assesses the strength of the sol-gel to return to its initial shape after being given an external force. Stickiness is the last important character because it measures the effort of the gel to adhere to the mucosa (Schmolka, 1972; Tan, Peh and Al-Hanbali, 2000; Zaki et al., 2007; Baloğlu et al., 2010; Baloglu et al., 2011).

Based on research by Pandey P et al., formulation of HPMC 0,5% w/w showed a hardness value of 0.692 ± 0.53 N, a solidity of 0.98 ± 0.17 and a stickiness of 2.01 ± 0.01 N mm (Pandey et al., 2017). This result shows that the sol-gel with poloxamer, HPMC and chitosan has mechanical properties that can be tolerated when intranasal application.

In Vitro Drug Release Test

Experiments by Lee et al. used resveratrol (RSV) as an anti-inflammatory agent, and the results showed that RSV contained in a mucoadhesive vehicle that reduced the number of polyps in the nasal tissues of rats more than RSV solution without a mucoadhesive vehicle (Lee et al., 2017)

Formulation of HPMC 0,3% w/w and HPMC 0,5% w/w sol-gel drug release assay used dexamethasone (DXN) samples for the treatment of CRS. The cumulative release from the DXN solution was 91% after 8 hours of administration. This result is inversely proportional to the drug release from the sol-gel, where there is a slow and continuous release of HPMC 0,3% (73%) and HPMC 0,5% w/w (62%) after 72 hours(Martino, Church and Seiberling, 2015; Pandey et al., 2017). Using the sol-gel can increase the duration of drug release (DXN) and facilitate continuous release.

Ex Vivo Test of Nasal Drug Release

In vivo test results can be predicted with ex vivo tests using human tissue excision results. Human sinus mucosal tissue was used for ex vivo HPMC 0,3% w/w and HPMC 0,5% w/w tests to predict in vivo test results. The ex vivo absorption profile showed that the DXN solution experienced significant release in the initial 2-4 hours, and then the absorption rate decreased. Testing the ex vivo absorption profile of both formulations

conducted by Pandey P et al., do not show absorption in the first 1 hour, followed by slow absorption for 8 hours (Fluhr, Feingold and Elias, 2006; Pandey et al., 2017).

Another study using a poloxamer- and HPMC-based formulation showed promising results for the delivery of geniposide for neurodegenerative diseases (Pandey et al., 2017; Wang et al., 2017). Using a sol-gel containing 0.1% DXN demonstrates the potential of a poloxamer-based formulation for controlled drug release and should be developed into the clinical trial stage.

CONCLUSION

Nasal drug delivery systems (DDS) using mucoadhesive thermosensitive sol-gels (P407 and HPMC) have shown several advantages in terms of intranasal drug administration for chronic rhinosinusitis. The sol-gel will be aqueous at room temperature, it make easier to store and administer. At the temperature of the nasal cavity, the sol-gel will tend to be a gel, thus it allows increased drug retention in the nasal cavity, which is assisted by mucoadhesive properties, gel strength and rheological characteristics which counteract the physiological clearance mechanisms of the respiratory cavity. The use of Nasal DDS also facilitates slow and continuous drug release; it is proved by ex vivo and in vitro tests. In the future, biomechanical research and in vitro sol-gel P407-HPMC research can be deepened to obtain a more comprehensive picture of the potential application of drug delivery systems.

REFERENCES

Albu, S., 2012. Novel drug-delivery systems for patients with chronic rhinosinusitis. Drug Design, Development and Therapy, 6, p. 125. doi: 10.2147/DDDT.S25199.

Baloglu, E. et al., 2011. Rheological and mechanical properties of poloxamer mixtures as a mucoadhesive gel base', Pharmaceutical development and technology, 16(6), pp. 627–636. doi: 10.3109/10837450.2010.508074.

Baloğlu, E. et al., 2010. Design and formulation of mebeverine HCl semisolid formulations for intraorally administration. AAPS PharmSciTech, 11(1), pp. 181–188. doi: 10.1208/S12249-009-9374-3.

Barshak, M. B. and Durand, M. L., 2017. The role of infection and antibiotics in chronic rhinosinusitis. Laryngoscope Investigative Otolaryngology, 2(1), p. 36. doi: 10.1002/LIO2.61.

Battisti, A. S., Modi, P. and Pangia, J., 2021. Sinusitis, StatPearls.

Beule, A., 2015. Epidemiology of chronic rhinosinusitis, selected risk factors, comorbidities, and economic burden. GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery, 14, p. Doc11. doi: 10.3205/CTO000126.

Boddupalli, B. M. et al., 2010. Mucoadhesive drug delivery system: An overview. Journal of Advanced Pharmaceutical Technology & Research, 1(4), p. 381. doi: 10.4103/0110-5558.76436.

Chang, J. Y. et al., 2002. Rheological evaluation of thermosensitive and mucoadhesive vaginal gels in

physiological conditions. International journal of pharmaceutics, 241(1), pp. 155–163. doi: 10.1016/S0378-5173(02)00232-6.

Djupesland, P. G., 2013. Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review. Drug Delivery and Translational Research, 3(1), p. 42. doi: 10.1007/S13346-012-0108-9.

Fluhr, J. W., Feingold, K. R. and Elias, P. M., 2006. Transepidermal water loss reflects permeability barrier status: validation in human and rodent in vivo and ex vivo models. Experimental dermatology, 15(7), pp. 483–492. doi: 10.1111/J.1600-0625.2006.00437.X.

Ghori, M. U. et al., 2015. Nasal Drug Delivery Systems: An Overview. American Journal of Pharmacological Sciences, 3(5), pp. 110–119. doi: 10.12691/AJPS-3-5-2.

Giuliano, E. et al., 2018. Mucosal Applications of Poloxamer 407-Based Hydrogels: An Overview. Pharmaceutics, 10(3). doi: 10.3390/PHARMACEUTICS10030159.

Health Assessment and Translation Group of the National Toxicology Program, 2019. OHAT Risk of Bias Rating Tool for Human and Animal Studies. Durham, NC: Health Assessment and Translation Group; National Toxicology Program.

Hussain, S. et al., 2018. Management of rhinosinusitis in adults in primary care. Malaysian Family Physician : the Official Journal of the Academy of Family Physicians of Malaysia, 13(1), p. 28.

Jagdale, S., Shewale, N. and Kuchekar, B. S., 2016. Optimization of Thermoreversible In Situ Nasal Gel of Timolol Maleate. Scientifica, 2016, p. 6401267. doi: 10.1155/2016/6401267.

Kwon, E. and O'Rourke, M. C., 2021. Chronic Sinusitis', StatPearls.

Lee, M. et al., 2017. Sinonasal Delivery of Resveratrol via Mucoadhesive Nanostructured Microparticles in a Nasal Polyp Mouse Model. Sci Rep, 7, p. 40249. doi: 10.1038/srep40249.

Liang, J. and Lane, A. P., 2013. Topical Drug Delivery for Chronic Rhinosinusitis. Current otorhinolaryngology reports, 1(1), pp. 51–60. doi: 10.1007/S40136-012-0003-4.

Majitjiya, R. J. et al., 2006. Thermoreversible-mucoadhesive gel for nasal delivery of sumatriptan. AAPS PharmSciTech, 7(3), p. 67. doi: 10.1208/pt070367.

Martino, B. J., Church, C. A. and Seiberling, K. A., 2015. Effect of intranasal dexamethasone on endogenous cortisol level and intraocular pressure. International forum of allergy & rhinology, 5(7), pp. 605–609. doi: 10.1002/ALR.21514.

Mehta, M. R., Surve, S. A. and Menon, M. D., 2009. Novel Nasal in situ Gelling System for Treatment of Sinusitis. Indian J Pharm Sci, 71(6), pp. 721–2.

Pandey, P. et al., 2017. Formulation, functional evaluation and ex vivo performance of thermoresponsive soluble gels - A platform for therapeutic delivery to mucosal sinus

tissue. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 96, pp. 499–507. doi: 10.1016/J.EJPS.2016.10.017.

Piromchai, P. et al., 2013. Chronic rhinosinusitis and emerging treatment options. International Journal of General Medicine, 6, p. 453. doi: 10.2147/IJGM.S29977.

Schmolka, I. R., 1972. Artificial skin. I. Preparation and properties of pluronic F-127 gels for treatment of burns', Journal of biomedical materials research, 6(6), pp. 571–582. doi: 10.1002/JBM.820060609.

Su, Y. et al., 2020. Chitosan Hydrogel Doped with PEG-PLA Nanoparticles for the Local Delivery of miRNA-146a to Treat Allergic Rhinitis. Pharmaceutics, 12(10), p. 907. doi: 10.3390/pharmaceutics12100907.

Suh, J. D., Ramakrishnan, V. and Chiu, A. G., 2011. The role of topical therapies in the treatment of chronic rhinosinusitis - PubMed. Braz J Otorhinolaryngol, 77(6), pp. 680–681.

Tan, Y. T. F., Peh, K. K. and Al-Hanbali, O., 2000. Effect of Carbopol and polyvinylpyrrolidone on the mechanical, rheological, and release properties of bioadhesive polyethylene glycol gels. AAPS PharmSciTech, 1(3). doi: 10.1208/PT010324.

Wang, Y. et al., 2017. A mucoadhesive, thermoreversible in situ nasal gel of geniposide for neurodegenerative diseases. PLoS ONE, 12(12). doi: 10.1371/JOURNAL.PONE.0189478.

Yuan, Y. et al., 2012. Thermosensitive and mucoadhesive in situ gel based on poloxamer as new carrier for rectal administration of nimesulide. International journal of pharmaceutics, 430(1–2), pp. 114–119. doi: 10.1016/J.IJPHARM.2012.03.054.

Zaki, N. M. et al., 2007. Enhanced bioavailability of metoclopramide HCl by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. Eur J Pharm Sci , 32(4–5), pp. 296–307. doi: 10.1016/J.EJPS.2007.08.006.

Zhang, L. et al., 2002. Development and in-vitro evaluation of sustained release poloxamer 407 (P407) gel formulations of ceftiofur. J Control Release, 85(1–3), pp. 73–81. doi: 10.1016/s0168-3659(02)00273-0.

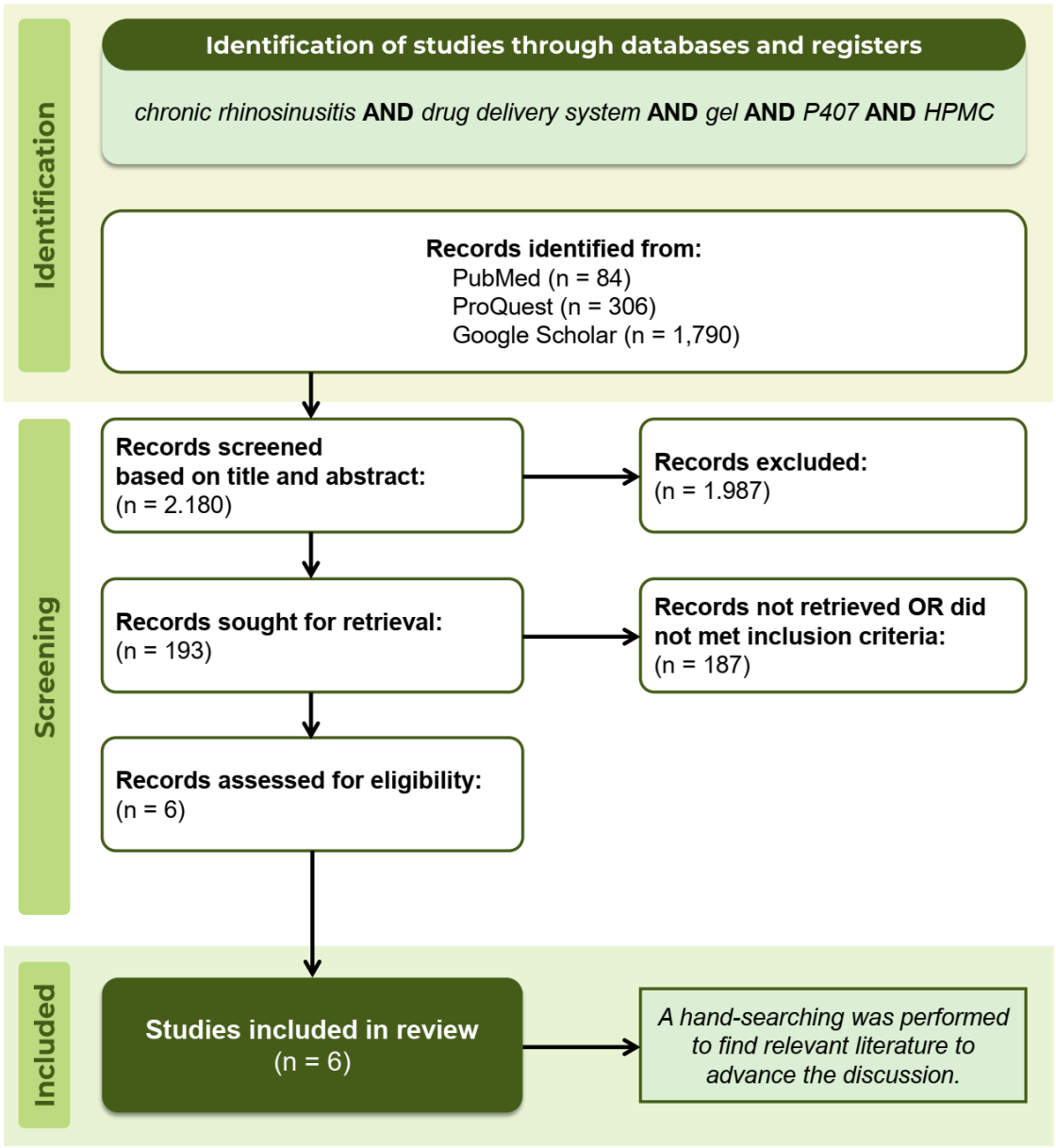

Figure 1. Literature Search Flow

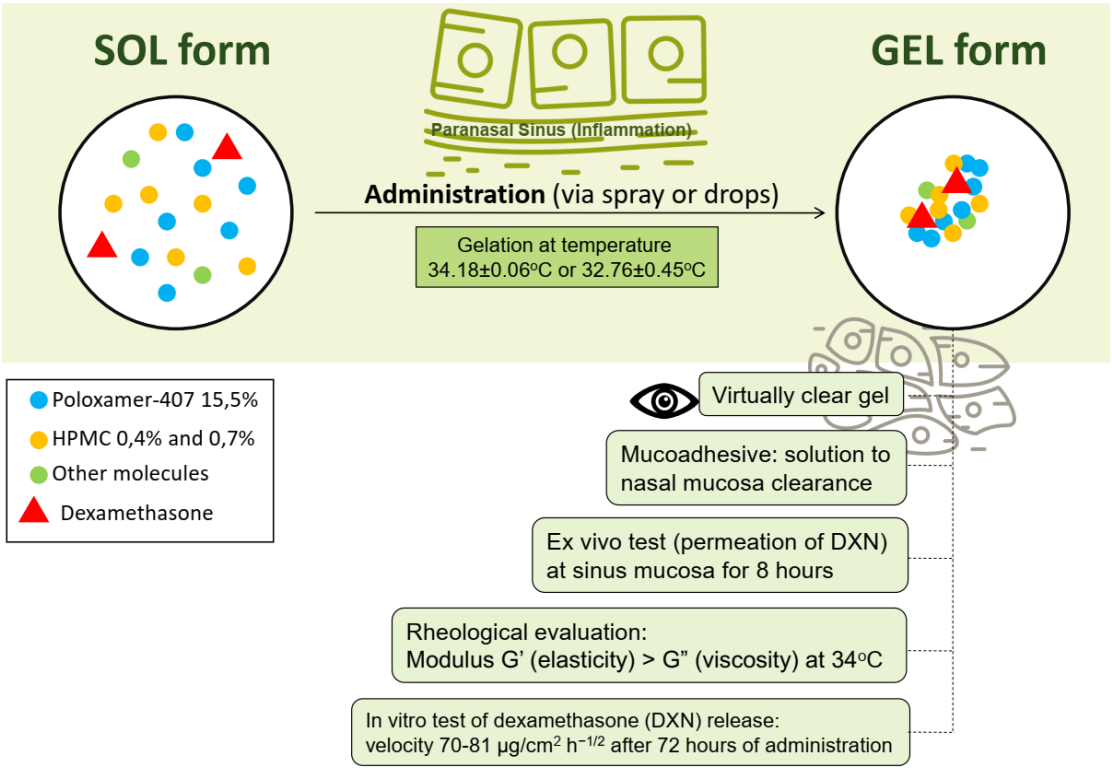

Figure 2. Application of P407 and HPMC Thermosensitive Thermosensitive Sol-Gel on the paranasal sinus mucosa

Supplementary Table 1. Summary of critical review of validity aspect for included in-vitro/in-vivo studies.(Health Assessment and Translation Group of the National Toxicology Program, 2019)

Studies, Year	Appraisal criteria								
	Selection bias		Performance bias		Exclusion bias	Detection bias		Selective reporting bias	Other potential threats to internal validity
	Randomization	Concealment	Identical experimental condition	Blinding of research personnel	Minimal and rational attrition/ exclusion	Confidence in exposure characterization	Confidence in outcome assessment	All measured outcomes reported	
Zaki et al, 2007 (Zaki et al., 2007)	🟤	⚪	🟢	⚪	🟤	🟢	🟤	🟢	🟢
Baloglu et al, 2011 (Baloglu et al., 2011)	🟤	⚪	🟢	⚪	🟤	🟢	🟤	🟢	🟢
Wang et al, 2017 (Wang et al., 2017)	🟤	⚪	🟢	⚪	🟤	🟢	⚪	🟢	🟢
Lee et al, 2017 (Lee et al., 2017)	🟤	⚪	🟢	⚪	⚪	🟢	🟤	🟢	🟢
Su et al, 2020 (Su et al., 2020)	🟤	⚪	🟢	⚪	🟤	🟢	🟤	🟢	🟢
Pandey et al, 2017 (Pandey et al., 2017)	🟤	⚪	🟢	⚪	🟤	🟢	🟤	🟢	🟢

Notes: Definitely low risk of bias (🟢); probably low risk of bias (🟤); probably high risk of bias/insufficient information (⚪); definitely high risk of bias (🔴)
Criteria summarised from appraisal sheets available at https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

Supplementary Table 2. Characteristic of Study

Studies, Year	Testing Method	Gel Material	Active Component	Indication
Zaki et al, 2007 (Zaki et al., 2007)	Laboratory, *In Vitro, In Vivo*	Poloxamer 407, Polyethylene glycol (PEG)	Metoclopramide	Nausea and vomiting associated with cancer therapy, pregnancy, and migraine
Baloglu et al, 2011 (Baloglu et al., 2011)	Laboratory, *In Vitro, Ex Vivo*	Poloxamer 407, Poloxamer 188	N/A	N/A
Wang et al, 2017 (Wang et al., 2017)	Laboratory, *In Vitro, Ex Vivo*	Poloxamer 407, Poloxamer 188, Hydroxypropyl methylcellulose (HPMC)	Geniposide	Neurodegenerative diseases
Lee et al, 2017 (Lee et al., 2017)	Laboratory, *In Vitro, In Vivo*	Poly (lactic-co-glycolic acid) (PLGA), Polyethylene glycol (PEG)	Resveratrol	Chronic rhinosinusitis
Su et al, 2020 (Su et al., 2020)	Laboratory, *In Vitro, In Vivo*	Chitosan	miRNA-146	Allergic rhinitis
Pandey et el, 2017 (Pandey et al., 2017)	Laboratory, *In Vitro, Ex Vivo*	Poloxamer 407, Chitosan, Hydroxypropyl methylcellulose (HPMC)	Dexamethasone	Chronic rhinosinusitis