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Research Article

Development and Characterization of Hyaluronic Acid Incorporated Thermosensitive Nasal *in Situ* Gel of Meclizine Hydrochloride

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Abstract

Background: Meclizine hydrochloride (MCZ) is an antihistamine that is used as an antiemetic to prevent and cure nausea and vomiting. Because of its limited water solubility and first-pass metabolism, it exhibits variable absorption. ***Objective***: To formulate and evaluate MCZ as an intranasal *in situ* gel with increased residence time and permeability. ***Methods***: We made an inclusion complex of MCZ using various cyclodextrins as a complexing agent to help the drug dissolve better. The complexes were studied, and the ones that were better at dissolving were chosen to be used in the creation of an in situ gel with poloxamer 407 (17–20% w/v) and hyaluronic acid (0.25–0.75% w/v). Prepared formulas were subjected to various evaluation tests, and the optimum formula was subjected to an *ex vivo* permeation study. ***Results***: Hydroxypropyl-cyclodextrin (HP-CD) complexation increased the solubility of MCZ. A prepared complex (10 mg of MCZ) was used for nasal *in situ* gel preparation. Formula (F3) containing 17% poloxamer 407 and 0.75% hyaluronic acid exhibited favorable characteristics, including optimal gelation temperature (33.33°C), drug content (100.51%), gel strength (35.0 seconds), spreadability (4.2 cm), and 98.52% *in vitro* drug release over 5 hours in simulated nasal fluid (pH 6.8), and provided considerably high permeability. ***Conclusions***: A mucoadhesive *in situ* gel formulation of MCZ (HP-β-CD) is a promising nasal formulation for the management of nausea and vomiting.

Keywords: Hyaluronic acid, *In situ* gels**,** Meclizine hydrochloride, Poloxamer, Thermo-sensitivity.

تطوير وتوصيف هلام أنفي حراري حساس يحتوي على حامض الهيالورونيك وميكليزين هيدروكلوريد

الخلاصة

الخلفية: ميكليزين هيدروكلوريد (MCZ) هو مضاد للهستامين يستخدم كمضاد للقيء لمنع وعلاج الغثيان والقيء. بسبب قابليته المحدودة للذوبان في الماء والتمثيل الغذائي للمرور الأول، فإنه يظهر امتصاصا متغيرا. **الهدف**: لصياغة وتقييم MCZ كهلام موضعي في الأنف مع زيادة وقت الإقامة والنفاذية. **الطرق:** تم تحضير مركب مشتمل من ميكليزين هيدروكلوريد باستخدام أنواع مختلفة من الدكسترين الحلقي كعامل معقد. تم تشخيص المعقدات المحضرة وتم اختيار المعقد الذي يظهر تأثير إذابة أفضل لتحضير الهلام الموضعي باستخدام بولوكسامير 407 (17-20% وزن/حجم) وحمض الهيالورونيك (0.25-0.75% وزن/حجم). تم إخضاع الصيغ المحضرة لاختبارات تقييمية مختلفة لتحديد الصيغة المثلى، والتي تم إخضاعها لدراسة التخلل. **النتائج:** تم تعزيز قابلية ذوبان هيدروكلوريد الميكليزين باستخدام هيدروكسي بروبيل- بيتا- سيكلودكسترين. تم استخدام مركب محضر يعادل 10 ملغ من ميكليزين هيدروكلوريد لتحضير هلام الأنف موضعي التكوين. أظهرت الصيغة (F3) التي تحتوي على 17% بولوكسامير 407 و0.75% حمض الهيالورونيك خصائص إيجابية، بما في ذلك درجة حرارة الهلام المثالية (33.33 درجة مئوية)، ومحتوى الدواء (100.51%)، وقوة الهلام (35.0 ثانية)، وقابلية الانتشار (4.2 سم)، و 98.52 ٪ تحرر الدواء في المختبر على مدى 5 ساعات في السائل الأنفي المحاكى (الرقم الهيدروجيني 6.8) وتوفير نفاذية عالية إلى حد كبير. **الاستنتاجات** : التركيبة الهلامية المخاطية ذاتية التكوين من ميكليزين هيدروكلوريد وبعد تعزيز قابلية الذوبان باستخدام هيدروكسي بروبيل –بيتا –سيكلودكسترين كعامل معقد بنسبة 1:1 تعتبر واعدة لعلاج الغثيان والقيء.

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INTRODUCTION

The intranasal route of drug delivery is becoming a reliable and viable alternative to oral and parenteral routes. It can be used to deliver drugs locally as well as to target and deliver a wide range of therapeutic compounds throughout the body [1]. This might be because of the special structure of the nasal mucosa, which has a large surface area, a porous endothelial membrane, and a lot of blood flow. This keeps the substance from going through the liver's first-pass elimination and gut wall metabolism, which could cause damage in the digestive tract. Because of these qualities, the nasal mucosal membrane is a place where drugs can quickly enter the bloodstream and start working. This makes the nasal route especially useful for treating serious conditions like severe nausea and vomiting [2]. Meclizine hydrochloride (MCZ), a first-generation antihistamine, is an antiemetic widely used for the prevention and treatment of nausea and vomiting associated with a variety of conditions, such as pregnancy and motion sickness [3,4]. However, it has a short half-life and poor water solubility, leading to low oral bioavailability [5]. Nasal mucoadhesive in situ gel is a promising way to deliver meclizine HCl because it keeps the drug concentration high at the site of action, avoids first-pass metabolism, and improves drug delivery throughout the body. It has an appealing characteristic as it remains fluid-like before nasal administration, allowing precise dosing and easy application as a drop. After being injected, *in situ* gelation happens at the body temperature of the nose. This is possible with the help of different thermosensitive polymers [6]. Poloxamer 407 is a thermosensitive polymer that is often used. It is not harmful or irritating, dissolves easily in water, releases drugs well, and mixes well with other chemicals. It has been extensively investigated for developing *in situ* gel systems for nasal drug delivery [7,8]. To ensure longer residence time at the application site and to have a better opportunity for enhanced absorption, in situ gel-forming polymers are usually combined with mucoadhesive polymers. Hyaluronic acid (HA) is a naturally occurring polymer that is biocompatible and biodegradable. It was found to strengthen the gel structure of P-407 without changing its ability to respond to changes in temperature [9]. Having a sufficient amount of drug solubility is essential for creating an effective intranasal delivery system, especially with the limited volume of solution within the nasal cavity. A variety of methods have been utilized to increase the solubility of poorly water-soluble drugs, and the use of different kinds of cyclodextrins (CD) represents one of these approaches [10]. The aim of this study was to formulate mucoadhesive *in situ* nasal gels of meclizine hydrochloride with enhanced solubility using the HP-β-CD complex for effective management of nausea and vomiting.

METHODS

Materials

Meclizine hydrochloride was supplied by Shanghai Macklin Biochemical Co. Ltd. (China), hyaluronic acid, Poloxamer 407, Poloxamer 188, Hydroxypropyl-β-Cyclodextrin (HP-β-CD) and β-Cyclodextrin (β-CD) were purchased from Xian Sonwu Biotech Co., Ltd. (China), sodium chloride, calcium chloride, and potassium chloride were supplied from Central Drug House (India), and benzalkonium chloride was provided by Pioneer Co. for pharmaceutical industries, Iraq.

Preparation of inclusion complex

An inclusion complex of MCZ and β-CD or HP-β-CD in a (1:1) molar ratio was prepared by the kneading method. Equimolar quantities of MCZ and the complexing agent were triturated in a mortar with a small volume of water-methanol (1:1 v/v) solution. The formed slurry was kneaded for 45 minutes and then oven-dried at 45 °C. The dried mass was pulverized by passing through sieve no. 60 [11].

Phase solubility studies

We studied how well MCZ dissolves in water when β-CD or HP-β-CD is present, following the steps described by Higuchi and Connors [12]. Aqueous solutions (50 ml) of different concentrations (2.5–12.5 mM) of β-CD or HP-β-CD were prepared in 100-ml screw-capped bottles. To these solutions, an excess amount of MCZ (100 mg) was added to form saturated solutions. These bottles were positioned in a shaking water bath (Karl Kolb, Germany) at 37 °C for 72 hours. After 72 h, samples were withdrawn, filtered through a 0.45-µm syringe filter, appropriately diluted, and the concentration of the dissolved drug was spectroscopically analyzed at 230 nm [13]. A phase solubility diagram was constructed by plotting the molar concentration of β-CD or HPβCD vs. the molar concentration of MCZ dissolved, and the stability constant (K_c) for the prepared complex was determined using the following equation [14]:

$$K_c = \frac{slope}{S0\ (1 - slope)} \quad \ldots \text{Eq. 1}$$

The slope was found by looking at the first straight line on the graph. S0 is the solubility of MCZ in water when there is no complexing agent present, and it can be found by finding the point where the straight line meets the y-axis in the phase solubility diagram.

Preparation of thermosensitive nasal in situ gels

The optimized complex was developed as *an in situ* nasal gel by the cold method described by Schmolka [15]. Various concentrations of poloxamer 407 (17–20% w/v) and poloxamer 188 (0–4% w/v) were solubilized using cold distilled water and stored in a

refrigerator at 4°C for 24 hours to yield a clear solution. The solutions were screened for their gelation temperature, and those exhibiting suitable nasal *in situ* gelation temperatures (within the range of 30-36°C) were selected for incorporation of the drug and mucoadhesive polymer. Different concentrations of hyaluronic acid (0.25–0.75% w/v) as a mucoadhesive polymer were introduced into the poloxamer solutions (Table 1).

Table 1: Composition of MCZ/HP-β-CD nasal *in situ* gel formulations*

Code	Poloxamer 407 (% w/v)	Poloxamer 188 (% w/v)	Hyaluronic acid (% w/v)
F1	17	0	0.25
F2	17	0	0.50
F3	17	0	0.75
F4	18	3	0.25
F5	18	3	0.50
F6	18	3	0.75
F7	19	3	0.25
F8	19	3	0.50
F9	19	3	0.75
F10	19	4	0.25
F11	19	4	0.50
F12	19	4	0.75

*Each formula contained MCZ/H-P-β-CD inclusion complex (equivalent to 10 mg/ml of meclizine hydrochloride) and 0.05% w/v of benzalkonium chloride.

The mixture was magnetically stirred at 50 rpm. Subsequently, a weighed amount of MCZ/H-P-β-CD inclusion complex (equivalent to 10 mg/ml of meclizine hydrochloride) and 0.05% w/v of benzalkonium chloride as preservative were gradually added under continuous stirring of the mixture. Formulations were stored at a temperature of 4°C until use [16] (Table 1).

Measurement of gelation temperature

The gelation temperature was determined by placing 2 ml of the formulation into a test tube. The test tube was sealed and immersed in a water bath, and the temperature of the water bath was gradually increased. When the meniscus stopped moving after tilting the test tube to a 90-degree angle, gelation had occurred [17].

Drug content

One ml of the formulation was placed into a volumetric flask and diluted with methanol. The solution was gently shaken, and its volume was made up to 100 ml. One ml of the solution was taken and diluted with 10 ml of methanol, and the absorbance was measured at a maximum wavelength of 230 nm using a UV-VIS spectrophotometer [18].

pH determination

The pH of the formulations was determined by placing 10 ml of each formula into a glass beaker and immersing the probe of a calibrated pH meter (PHS-100, Germany) into it. Each measurement was repeated three times [19].

Gel strength determination

Gel strength was measured by placing a sample (50 ml) of formulation in a 100-ml graduated cylinder. The cylinders were equilibrated in a water bath at 37 °C. A weight of 35 mg was placed in a small plastic circular cup and positioned on top of the gelled formulations. Gel strength was determined by measuring the time taken by the weight to sink 5 cm in the gel [20].

Spreadability

To evaluate spreadability, 1g of fully gelled formulation was placed at the center of a 20 × 20 cm glass plate and covered with another glass plate of the same size. A weight of 1 kilogram was gently applied to the glass plate for one minute. Upon weight removal, the final diameter was measured in centimeters [21].

Viscosity and rheological behavior studies

The rheological properties of selected formulations were analyzed using a Myr digital rheometer (Model VR 3000, Spain). Viscosity was determined at room temperature (25 °C) and the temperature of the nasal cavity (34°C). During the initial phase before gelation, samples were subjected to shear at a constant rate of 10 rpm using spindle types R4 and R5. The rheological properties of the gelled formulations were measured at rotational speeds ranging from 10 to 200 rpm using spindle number R7. Each sample underwent shearing for 2 minutes before the measurements were recorded. All the measurements were performed in triplicate [22].

Ex-vivo mucoadhesive strength

The mucoadhesive strength of formulations was measured using a modified balance technique using sheep nasal mucosa obtained from a local slaughterhouse. Tissue specimens were prepared by excising nasal turbinates and separating them from adhering cartilaginous tissue using forceps and a scalpel. The tissue was washed with a 0.9% NaCl solution and stored at -20°C until use [23]. The experimental setup involved balancing both sides of a two-pan balance using a plastic beaker on the left pan and a 5 g weight on the right pan. Using cyanoacrylate glue, the nasal mucosal section was attached to a glass vial such that the mucosal side faced outward and left at 35°C for 10 minutes. The mucosal tissue was moistened with phosphate buffer (pH 6.5), and the vial was placed in an inverted position under the right-side pan of the balance. One milliliter of the prepared formulation was spread as a thin film on a watch glass

and positioned beneath the vial with the mucosal tissue on the right side of the balance. The vial was pressed onto the gel by adding weight to the right pan. A contact time of one minute was maintained. On the left side pan, water was gradually added to the beaker positioned above it until complete detachment of the mucosa from the formula was observed. The amount of water needed to detach the formulation from the nasal mucosa was recorded and utilized to calculate the mucoadhesive force using the following equation [24]:

$$Detachment\ force\ (dyne/cm^2) = m \text{ x } G/A \ldots \text{ Eq. 2}$$

where *m* is the weight required for detachment (in gm), *G* is the acceleration due to gravity (980 cm/s^2), and *A* is the area (cm^2) of the exposed mucosal membrane.

In-vitro drug release study

Drug release studies of selected formulations were conducted using a Franz diffusion cell and a dialysis membrane (molecular weight cutoff of 12,000–14,000 kDa). The acceptor compartment was filled with the release medium, which was 11 ml of simulated nasal fluid (SNF) with a pH of 6.5 at 35 ± 1°C and a magnetic stirring rate of 50 rpm that stayed the same. The dialysis membrane was pre-soaked in SNF for 2 hours before being securely clamped between the donor and acceptor compartments. The donor compartment was filled with 1 ml of the tested formulation. Samples of 1 ml were withdrawn from the acceptor compartment at specified time intervals (5, 10, 15, and 30 minutes), followed by one-hour intervals up to a total of 6 hours. Withdrawn samples were replaced with an equal volume of fresh SNF (pH 6.5) at each time interval to maintain sink conditions. Samples were properly diluted, put through a 0.45-µm syringe filter, and diluted with 10 ml of SNF. They were then analyzed spectrophotometrically at 230 nm, with SNF (pH 6.5) serving as a blank. The amount of MCZ released was determined using a preconstructed calibration curve, and the cumulative percent drug release curve was plotted as a function of time [25]. The *ex-vivo* permeation study for the most suitable formulation (F3) and control containing MCZ/HP-β-CD aqueous solution (drug concentration 10 mg/ml) was carried out using a Franz-type diffusion cell in a similar way as in the drug release study, except that a sheep nasal mucosal membrane obtained from a local butcher shop was used in the diffusion cell instead of the dialysis membrane. The mucosal area available for diffusion was 1.76 cm^2. Withdrawn samples were analyzed for their drug content at various time intervals, and the cumulative permeation of drugs versus time graph was plotted. The permeability coefficient was calculated at steady-state conditions by using the following equation [26]:

$$P_{eff} = J_{ss} / C_0 \ldots\ldots\ldots \text{ Eq. 3}$$

Where J_{ss} is the flux at steady state and is calculated as the slope of the linear portion of the plot between the cumulative amount of drug permeated per unit area versus time; C_0 represents the initial concentration of the drug.

RESULTS AND DISCUSSION

Phase solubility studies are useful to predict not only the solubilizing capacity of different cyclodextrins but also the stability constant and stoichiometric ratio of the complex. Figure 1 shows phase solubility profiles that show a positive relationship between how well MCZ dissolves in water and the concentrations of β-CD or HP-β-CD.

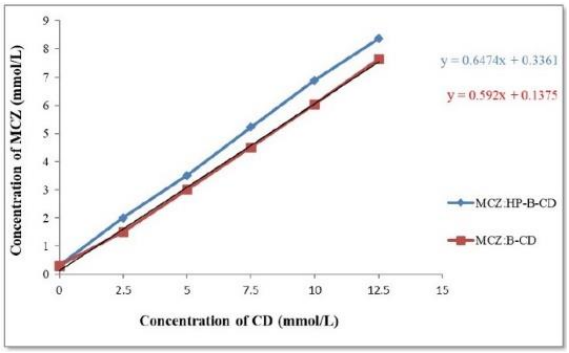

Figure 1: Phase solubility diagram of MCZ in aqueous solutions of β-CD or HP-β-CD at 37°C.

These profiles reveal a linear relationship between the typical AL-type as per Higuchi Connors classification, indicating the formation of a soluble 1:1 inclusion complex of MCZ and β-CD or HP-β-CD at the concentration ranges investigated. The highest solubility of MCZ in the presence of HP-β-CD was reached at 8.419±0.054 mmol/L when using 12.5 mmol/L HP-β-CD, demonstrating a nearly 27-fold increase in MCZ solubility compared to the equilibrium solubility of MCZ (0.308±0.002 mmol/L, 37°C). The stability constant (Kc) values calculated utilizing equation (1) were found to be 469.84 M-1 and 594.18 M-1 for β-CD and HP-β-CD, respectively. These values were within the range of 50 to 5000 M−1, which is considered suitable for the formation of stable complexes [27]. When you use HP-²-CD, you get higher values. This means that MCZ/HP²CD forms a more stable inclusion complex than MCZ/CD. This can be attributed to the larger contact surface and more spread-out configuration of HP-β-CD as compared to β-CD [12]. Consequently, HP-β-CD has been chosen for subsequent formulation and evaluation studies (Figure 1). The gelation temperature of screened poloxamer gels was found to be in the range of 24.8 to 44.2 °C (data not shown). Among these gels, only four formulations exhibited optimal gelation temperatures as those of the nasal cavity and were utilized for the incorporation of hyaluronic acid as a mucoadhesive polymer and the MCZ/HP-β-CD complex to form nasal *in situ* gels. As shown in Table 2, the gelation temperature of formulations (F1–F12) was found to be

in the range of 31.43 to 41.23°C. Increasing the concentration of P407 from 18% to 19% significantly decreased the gelation temperature (p<0.05). This was clear in formulations (F4-F6) as compared to formulations (F7-F9) containing 18 and 19% P407, respectively.

Table 2: Evaluation parameters of meclizine hydrochloride nasal *in situ* gel formulations

Code No.	Gelation Temperature (ºC)	pH	Drug content (%)	Gel strength (seconds)	Mucoadhesion strength (dynes/cm^2)	Spreadability (cm)
F1	41.23±0.05	-	-	-	-	-
F2	37.46±0.15	-	-	-	-	-
F3	33.33±0.05	5.8±0.1	100.51±0.02	35.0±1.5	2646.94±14.5	4.2±0.15
F4	36.56±0.15	-	-	-	-	-
F5	38.06±0.05	-	-	-	-	-
F6	35.36±0.05	-	-	-	-	-
F7	32.80±0.1	5.7±0.1	102.14±0.03	46.0±1.0	3540.63±39.1	4.1±0.1
F8	34.03±0.1	5.6±0.05	100.20±0.02	45.0±1.0	3655.81±30.87	3.8±0.15
F9	33.76±0.1	5.7±0.1	101.80±0.01	47.3±0.57	4059.86±66.8	3.9±0.15
F10	31.43±0.15	-	-	-	-	-
F11	34.80±0.15	5.8±0.05	99.31±0.02	46.0±0.52	4881.14±90.4	3.7±0.15
F12	36.50±0.1	-	-	-	-	-

Data are expressed as mean±SD, n= 3.

Conversely, an opposite behavior is observed with increasing the concentration of P 188. This is evident in formulations (F10–F12) as compared to formulations (F4–F6) containing 3% and 4% P 188, respectively. The reduction in gelation temperature of *in situ* gel formulations with an increase in the concentration of P 407 can be elucidated by a higher proportion of polypropylene oxide (PPO) units, leading to dehydration and the formation of a greater number of micelles at a lower temperature, facilitating easier gelation, whereas the addition of P188 leads to an increase in the ratio of polyethylene oxide (PEO), resulting in less entangled micelles and subsequently raising the critical micelle temperature. Similar observations have been documented in the literature [28]. The mucoadhesive polymer hyaluronic acid also decreases the gelation temperature; this could be due to its ability to interact with polyethylene oxide (PEO) chains within poloxamer molecules. Such interaction results in a more compact structure and entangled molecules through an increase in intermolecular hydrogen bonding [25]. Only formulations (F3, F7, F8, F9, and F11) showed sol-gel transition temperatures in the nasal physiological range, and other combinations were excluded from further evaluations (Table 2). The percent drug content of all formulations was found to be within the range of 99.31±0.02 to 102.14±0.03%, as shown in Table 2, indicating uniform distribution of drug throughout the gel and suggesting that the process used in this study was effective in producing gels with consistent drug content and minimal variability. The pH range of selected formulations was in the range of 5.6–5.8 (Table 2), is considered suitable for intranasal use, and is within the nasal pH range of 4.5–6.5 [29]. The gel strengths of the formulations ranged from 35.0±1.5 to 47.3±0.57 sec (Table 2) and were considered appropriate for nasal administration as they were within the acceptable range of 25 to 50 seconds [30]. For nasal *in situ* gel to be used on nasal mucosa without leaking after administration, it must have proper spreadability. Table 2 shows acceptable data for the spreadability of formulations, as values were in the range of 2.5-7 cm, indicating easy application [31]. A formulation should ideally have a low viscosity when administered to the nasal cavity; nevertheless, following administration, it should have enough viscosity to remain at the site of application. The viscosity of formulations both in sol and gel states is illustrated in Figure 2 and ranges from 832 to 1314 cPs before gelation at 25 °C and 9734 to 13140 cPs after gelation at 34°C. Formula F11 showed significantly higher viscosity as compared to other formulations. As the temperature increases, the polymers undergo dehydration, and polymer-polymer association occurs, increasing viscosity [32].

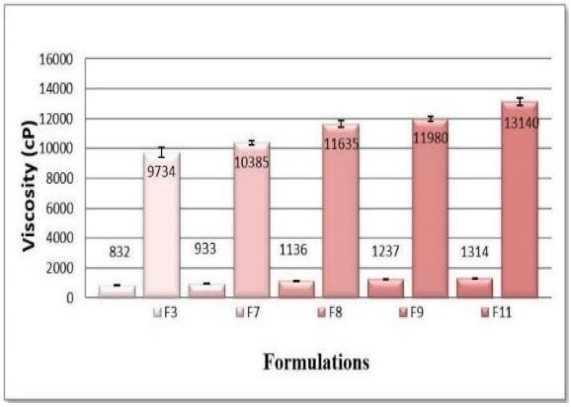

Figure 2: Viscosity values of selected *in situ* gel formulations of MCZ (A) before gelation at 25 ºC, (B) after gelation at 34 ºC.

Increasing the concentration of poloxamer increased the viscosity of formulations both in solution and in gel state. This can be attributed to the rise in both the number and size of micelles, which increased the micelle count per unit volume and led to a greater number of cross-links among adjacent micelles [33]. Moreover, increasing the concentration of hyaluronic acid from 0.25% to 0.75% (F7 to F9) increased the viscosity of formulations. Such an effect can be related to the increasing crosslinking of the polymers and is consistent with those observations reported in earlier studies [25] (Figure 2). We measured the

viscosity of gelled formulations at 35 °C with different shear rates (10–200 rpm) to see how they changed the viscosity of the formulations. As shown in Figure 3, viscosities decreased as the shear rate increased. All gel formulations exhibited non-Newtonian flow and shear-thinning properties. Shear-thinning features are considered advantageous for thermosensitive hydrogels destined for nasal administration since they will increase the spreadability of the gels and their ability to remain at the site of application [30]. (Figure 3).

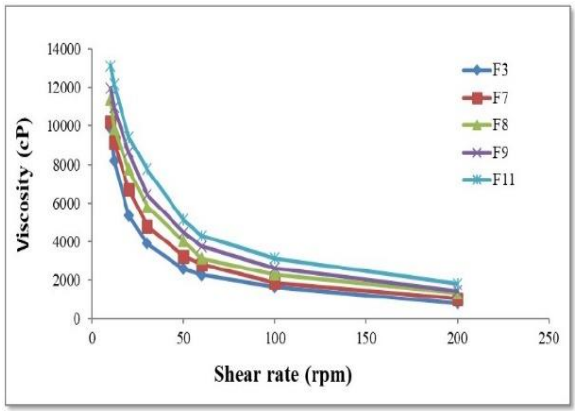

Figure 3: Viscosity profiles of selected *in situ* gel formulations of MCZ at 34 ºC.

The mucoadhesion force is an important factor for in situ gelling nasal formulations because it affects how well the gel goes through the nose and how quickly the drug gets into the body. Despite their gelling properties, poloxamers have been reported to have a short residence time. This hurdle can be overcome by using bioadhesive polymers [34]. Results in Table 2 indicate that the mucoadhesive strength was in the range of 2646.94 to 4881.14 dyne/cm^2. None of the formulations exceeded the upper limit (i.e., greater than 10,000 dyne/cm^2) [35] and therefore can be considered to have optimum mucoadhesion properties. An increase in the concentration of P 188 produced an increase in mucoadhesive properties, as is evident in formulations F8 and F11 containing 3 and 4% HA, respectively. Moreover, increasing the concentrations of the mucoadhesive polymer (HA) produced a significant increase (p<0.05) in mucoadhesive strength, as is evident in formulations (F7–F9). This result is similar to what Cirri et al. [10] found, and it's because the hydroxyl and carboxyl groups of the polymer and the amino groups in mucin are more closely connected through hydrogen bonds [36]. The *in vitro* drug release profiles from formulations suitable for nasal drug delivery (F3, F7, F8, F9, and F11) are shown in Figure 4. The cumulative drug release from all the formulations after 5 hours was found to be more than 65%. Formulation F3, comprising 17% w/v P 407 and 0.75% HA, exhibited the highest drug release of 99.88% after 5 hours. On comparing the drug release profiles, it is evident that the release of MCZ was reduced with an increasing concentration of poloxamer as well as the concentration of mucoadhesive polymer.

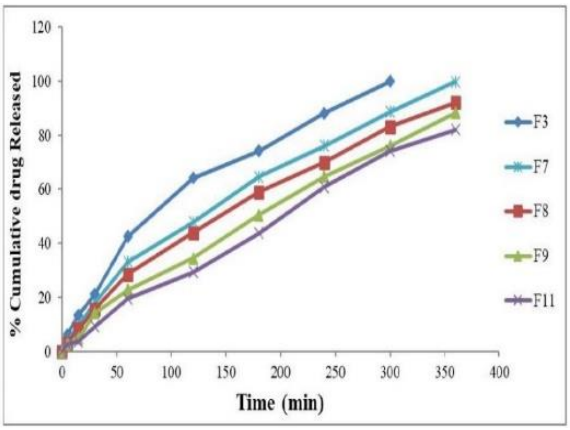

Figure 4: *In vitro* release profile of MCZ from thermosensitive gel formulations.

This can be attributed to the decreased number and dimensions of channels in the micellar structure at higher poloxamer and creating a higher viscosity gel network with mucoadhesive polymer, trapping the drug and hindering its release [37] (Figure 4). Based on the results of the characterization and release studies, formulation F3 had the best gelation temperature, gel strength, and mucoadhesive strength. It was also chosen to have the highest drug release rate so that the drug could be seen moving through the nasal mucosa. The permeation study was also conducted for the drug solution for comparison prepared using the MCZ/H-P-β-CD inclusion complex (equivalent to 10 mg/ml of meclizine hydrochloride). Cumulative amounts over time profiles were presented in Figure 5, and effective permeability coefficients and flux values are listed in Table 3.

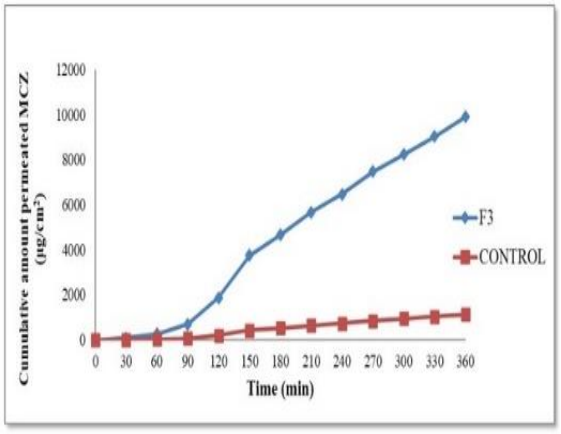

Figure 5: *Ex vivo* permeation of MCZ from F3 versus control through the nasal mucosa.

This study found that the MCZ flux was significantly higher (p<0.05) from formula F3 to a drug solution in water within 5 hours. It is reported in the literature that P-407 gels are viscous, isotropic liquid crystals consisting of micelles, and the drug is released by diffusion through channels of the gel matrix [38]. The addition of hyaluronic acid increases the permeation coefficient; this is attributed to the permeation-enhancing effect of HA [39] (Table 3, Figure 5).

Table 3: *Ex-vivo* permeation parameters of MCZ

Formula No.	Flux (J_{ss}) ($mg/cm^2/min$)	P_{eff} (cm/min)
F3	$2.918x10^{-2}$	$2.918x10^{-3}$
Control	$3.35x10^{-3}$	$3.35x10^{-4}$

Conclusion

In terms of gelation temperature, drug concentration, viscosity, and mucoadhesive strength, formulation F3 (poloxamer 407: 17% and HA: 0.75%) was shown to be excellent. Ex vivo tests on sheep nasal mucosa revealed increased permeability. The results indicate that the suggested formulation is suitable for nasal delivery, with a good retention period and a controlled release effect.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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