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Formulation and Evaluation of Meclizine Hydrochloride Cyclodextrin-Based Mucoadhesive Thermosensitive Nasal *In-Situ* Gel

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Abstract

Meclizine Hydrochloride (MCZ) is an effective antihistamine for the prevention and treatment of nausea and vomiting, with low oral bioavailability (about 30 to 40%) due to low water solubility. The purpose of the current study was to develop and characterize a thermo-responsive nasal *in-situ* gel for MCZ. To enhance the solubility of MCZ, an inclusion complex with Hydroxypropyl-β-Cyclodextrin (HP-β-CD) was prepared and characterized. The prepared complex was utilized in the preparation of thermosensitive *in situ* gels using the cold method. Twelve formulations were developed by employing various concentrations of Poloxamer 407, either alone or in combination with Poloxamer 188. Additionally, hydroxypropyl methylcellulose K4M (HPMC K4M) was incorporated as a mucoadhesive polymer. The prepared formulations were characterized by their appearance, pH value, gelation temperature, mucoadhesive force, gel strength, drug content, and drug release rate. The results showed that as the concentration of poloxamer 188 and HPMC K4M were increased, there was a decrease in gelation temperature, an increase in mucoadhesive strength, and a decrease in the percent drug released. The *in-situ* gel formulation (F 9) with 19 % P407, 3 % P188 and 1% HPMC K4M was identified as the optimum formula with gelation temperature of (32.62±0.1 °C), pH value (6.13±0.05), gel strength (39.3 ±0.57 sec), mucoadhesive force (3389.30±0.46 dyne/cm^2), and *in-vitro* drug release of (75.7%) over 6 hours by non-Fickian diffusion mechanism. Owing to these properties the prepared formulation may be used as an effective nasal delivery system for management of nausea and vomiting.

Keywords: Meclizine HCl, *in situ* nasal gel, poloxamers, mucoadhesive polymer, hydroxypropyl-β-Cyclodextrin.

Introduction

Nasal drug delivery has become a well-established option for systemic drug delivery, offering an attractive alternative to traditional drug delivery methods. This is mainly due to several advantages of this route of administration, including self-administration, non-invasiveness, painless therapy, and rapid onset of action [(1)]. In addition, rapid drug absorption and avoidance of first-pass metabolism by this route are particularly valuable in managing critical conditions like severe nausea and vomiting [(2)]. Thermosensitive *in situ* gels are fluid-like before nasal administration and are easily instilled into the nose as drops assuring dose accuracy. They transform into gels at body temperature [(3, 4)]. Poloxamer (P 407) is a thermosensitive triblock copolymer composed of two hydrophilic polyethylene oxide (PEO) blocks surrounding a central hydrophobic polypropylene oxide (PPO) unit [(5)]. The combined use of *in situ* gel-forming polymers and mucoadhesive polymers has been reported in the literature and demonstrated to be effective at overcoming the problem of rapid mucociliary clearance, hence enhancing the contact time of the drug delivery system at the administration site and subsequently enhancing drug bioavailability [(6,7)]. Meclizine hydrochloride (MCZ) is a first-generation antihistamine (H1 receptor antagonist) widely used for the prevention and treatment of nausea and vomiting associated with a variety of conditions such as motion sickness, post-operation, and pregnancy [(8-10)]. MCZ has a short half-life of 5-6 h and belongs to a class II drug in the biopharmaceutics classification system (BCS) due to low water solubility a slow rate of absorption, and low oral bioavailability of about 30 to 40% [(11,12)]. Formulation of MCZ in the form of thermosensitive, mucoadhesive nasal *in situ* gel would provide an attractive way to overcome the problems of first-pass metabolism. However, sufficient drug solubility is important for the development of an effective intranasal delivery system. Cyclodextrins (CDs) have been used extensively to improve drug solubility. The ability of CDs to complex with drugs and increase their solubility belongs to their unique molecular structure which resembles a truncated cone, with a hydrophilic outer surface and a

hydrophobic inner chamber. Natural cyclodextrins, especially β-CD, have limited water solubility in aqueous solutions; therefore, the more water-soluble derivative, 2-hydroxypropyl--β-CD (HP -β-CD) is preferred for aqueous pharmaceutical solutions [13, 14]. The use of different kinds of cyclodextrins for enhancement of solubility of MCZ has been previously investigated and hydroxypropyl β-cyclodextrin (HP-β-CD) emerged as the most efficient one. [15,16]. Thermosensitive nasal *in situ* gels of some antiemetics such as metoclopramide [17, 18] and domperidone [19] have been already reported. Malviya V [20] reported the formulation of nasal *in situ* gels of MCZ using sulfobutyl ether -β-CD as a complexing agent. The purpose of this study is the formulation of mucoadhesive, nasal *in situ* gels of MCZ based on P 407 as thermoreversible polymer, HPMC K 4M as mucoadhesive polymer utilizing HP-β-CD as drug complexing/solubilizing agent with the potential of ease of administration, enhanced nasal residence and improved drug bioavailability.

Material and Methods

Materials

Meclizine hydrochloride was supplied by Shanghai Macklin Biochemical Co. Ltd. (China). HPMC K4M, Poloxamer 407, Poloxamer 188, and Hydroxypropyl-β-Cyclodextrin (HP-β-CD) were purchased from Xian Sonwu Biotech Co., Ltd (China). Sodium chloride, calcium chloride, and potassium chloride were purchased from Central Drug House (India). Benzalkonium chloride was supplied by Pioneer Company for pharmaceutical industries (Iraq). All chemicals and reagents used were of analytical grade.

Preparation of Meclizine Hydrochloride/ HP-β-CD Inclusion Complex

MCZ/ HP-β-CD inclusion complex was prepared by kneading method at(1:1) MCZ: HP-β-CD molar ratio. The mixture of MCZ and HP-β-CD was triturated in a mortar with a small volume of water-methanol solution (50:50 by volume) for 60 minutes. The formed slurry was oven-dried at a temperature of 45°C. The dried mass was ground into a powder and then sieved through sieve no.60. A physical mixture (PM) was also prepared for comparison by mixing the drug, with the required amount of cyclodextrin in a mortar for few minutes to get homogenous mixture and then sieved with sieve no 60. The prepared samples were stored in a well-sealed container till use. [21]

Characterization of Meclizine Hydrochloride/HP-β-CD Inclusion Complex

The dried powder of MCZ/ HP-β-CD inclusion complex was characterized using the following tests:

Drug Content of Meclizine Hydrochloride/ HP-β-CD Inclusion Complex

Complexes equivalent to 10 mg of MCZ were accurately weighed and dissolved in 50 ml methanol. The solution was sonicated for 15 minutes and its volume was completed to 100 ml. The solution was filtered using a 0.45 µm syringe filter, suitably diluted, and the absorbance of MCZ was determined spectrophotometrically by measurement at 230 nm [22]. The drug concentration was calculated from a previously constructed calibration curve. All experiments were performed in triplicate.

Fourier Transform Infrared (FTIR) Spectroscopy

To confirm complex formation, FTIR spectra of MCZ, HP-β-CD, PMs, and the prepared complex were acquired using an FTIR spectrometer (Biotech Engineering Management, UK) in the scanning range of 4000 to 400 cm^{-1} [23].

Differential Scanning Calorimetry (DSC)

DSC study was conducted on MCZ, HP-β-CD, PM, and MCZ/HP-β-CD complex using DSC 60 plus (Shimadzu, Japan). A sample of 4 to 5 mg was sealed in an aluminum pan and heated at 100 ml/min nitrogen flow rate, at a scanning rate of 10 °C/min, at a temperature range of 30 to 300 °C [21].

Scanning Electron Microscopy (SEM)

The morphology of pure MCZ, HP-β-CD, PM, and MCZ/HP-β-CD complex was evaluated using SEM (Inspect F50, Holland). To enhance conductivity, the samples were made electrically a thin layer of gold was applied within a vacuum environment. Subsequently, the samples were examined and photographed at various magnifications, with direct data capture of the images [24].

X-Ray Powder Diffraction (X-RPD)

The X-ray diffraction patterns were recorded for pure MCZ, HP-β-CD, PM, and MCZ/ HP-β-CD inclusion complex using an X-ray diffractor (XRD, DX 2700 BH, Haoyuan, China) with copper target X-ray tube set at 40 kV and 30 mA, utilizing Cu Kα as incident radiation (λ_{Cu} = 1.5406˚A). The (2θ) scan range was between 5˚- 80 ˚, at a scanning rate of 0.05˚/min [25].

Preparation of Thermosensitive Nasal in Situ Gelling Formulations

Thermosensitive nasal *in situ* gels were prepared by the cold method using poloxamers as gelling polymers. Initially, to identify the most suitable concentration ratio between the gelling polymers P 407 and P 188, plain formulations were prepared and screened for their gelation temperature (Table 1). Different concentrations of P 407 (17-20% w/v) and P188 (0-4 % w/v) were solubilized in distilled water at 4 ºC using a magnetic stirrer (Stuart, England) at 50 rpm, then formulations were stored refrigerated (4 ºC) for 24 h to obtain a clear and uniform solution [26]. Formulations having

suitable gelation temperature (i.e., 32–35 °C) were chosen for inclusion of MCZ/ HP-β-CD complex and mucoadhesive polymer (HPMC K4M) to prepare *in situ* gelling nasal formulation (Table 2).

Various concentrations of HPMC K4M (0.5-1% w/v) were added to the poloxamer solution at (4°C) and stirred until fully dissolved. Subsequently, the required amount of MCZ/HP-β-CD complex (1% w/v) was dissolved in a small volume of cold water (4°C) containing benzalkonium chloride (BKC) (0.05 % w/v) as a preservative and stirred gently with the poloxamer solution. The final volume was adjusted using cold distilled water and formulations were refrigerated overnight (4°C) to ensure complete solubilization [27].

Characterization of Thermosensitive Nasal in Situ Gelling Formulations

Measurement of Gelation temperature

To estimate the gelation temperature of formulations, a 2 ml formulation was transferred into a 10 ml transparent tube and was covered. The tube was then immersed in a water bath at room temperature and the temperature was gradually raised from 20 to 40 °C in increments of 1°C every minute and left to equilibrate for 5 min at each new setting. The temperature rise was accompanied by test tube slanting at 90° and observation to check the occurrence of gelation, which was thought to have happened when the meniscus stopped moving upon tilting [6].

Appearance and pH determination

The prepared formulations were visually inspected under a black-and-white background for their clarity. The clarity of formulation was graded as follows: turbid (+), clear (++), and very clear (+++) [28]. The pH of formulations was measured using a calibrated digital pH meter (PHS-100, Germany). Formulation (10 ml) was added in a glass beaker and the probe of pH meter probe was inserted into the liquid-state formulation to record its pH [29].

Drug Content

One ml formulation was pipetted into a volumetric flask. Methanol was added and the final volume was completed to 100 ml. After suitable dilution, the absorbance of the solution was measured spectrophotometrically at 230 nm. The mean of three readings was used to calculate the percentage of drug content in the formulation. [22, 30]

Gel Strength Determination

Gel strength was determined by placing a 50-ml formulation into a 100-ml graduated cylinder and letting it for 5 minutes to equilibrate in a water bath maintained at 34°C to allow for gel formation. After gelation, a weight of 35 grams was placed onto the gel and the time it took to penetrate 5 cm through the gel was recorded as a measure of gel strength [31].

Table 1. Plain formulations for selection of proper gelling polymer concentration

Code	Poloxamer 407 (%w/v)	Poloxamer 188 (%w/v)	Distilled water up to (ml)
P1	17	0	10
P2	17	1.5	10
P3	17	3	10
P4	17	4	10
P5	18	0	10
P6	18	1.5	10
P7	18	3	10
P8	18	4	10
P9	19	0	10
P10	19	1.5	10
P11	19	3	10
P12	19	4	10
P13	20	0	10
P14	20	3	10
P15	20	4	10

Table 2. Composition of MCZ/HP-β-CD nasal *in situ* gel formulations

Code	MCZ equivalent (mg)	Poloxamer 407 (%w/v)	Poloxamer 188 (%w/v)	HPMC K4M (%w/v)	BKC (%w/v)	Distilled Water up to (ml)
F1	100	17	0	0.5	0.05	50
F2	100	17	0	0.75	0.05	50
F3	100	17	0	1.0	0.05	50
F4	100	18	3	0.5	0.05	50
F5	100	18	3	0.75	0.05	50
F6	100	18	3	1.0	0.05	50
F7	100	19	3	0.5	0.05	50
F8	100	19	3	0.75	0.05	50
F9	100	19	3	1.0	0.05	50
F10	100	19	4	0.5	0.05	50
F11	100	19	4	0.75	0.05	50
F12	100	19	4	1.0	0.05	50

Ex-vivo Mucoadhesive Strength

A modified balance method using *ex-vivo* sheep nasal mucosa was used to measure the mucoadhesive strength of formulations. Animal mucosal nasal tissue was obtained from a local slaughterhouse. Specimens were prepared from sheep's nasal cavity by excision from nasal turbinates and detached from the adhering cartilaginous tissue using forceps and scalpel. The obtained specimens were washed with 0.9% (w/v) NaCl solution and stored at -20 °C until use. The mucosal membrane was soaked in phosphate buffer (pH 6.5) prior starting the experiment [32].

For the experimental setting, both sides of the two-pan balance were equilibrated by placing one plastic beaker on the left pan and a weight (5 g) on the right pan. The nasal mucosal section was glued with cyanoacrylate to a glass vial with the mucosal side out, and stored at 35°C for 10 min. The vial was connected below the right-side pan of the balance in an inverted position, the mucosal tissue was wetted with phosphate buffer (pH 6.5). One millilitre of the prepared formulation was poured and allowed to spread as a thin film over a watch glass positioned below the vial with mucosal tissue at the right-side pan of the balance. The nose tissue-equipped vial was forced down onto the gel (by adding extra weight in the right pan) with one minute allowed as preliminary contact time. Water was slowly added into the beaker at the left side pan of the balance, and the process was continued until the mucosa was completely detached from the formula. The weight of water required to detach the nasal *in-situ* gel from the nasal mucosa was recorded and used to calculate the mucoadhesive force using the following equation:

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

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 [33].

In-vitro Drug Release Study

In-vitro drug release studies of selected mucoadhesive *in situ* gel formulations were carried out using a Franz diffusion cell. Dialysis membrane (Molecular weight 12,000–14,000 k Da) previously soaked in release media for 2 hours was clamped between the donor and the receiving compartments. The receptor compartment was filled with (11 ml) of simulated nasal fluid (SNF) at pH 6.5 thermostated at 35 ± 1°C and maintained under constant magnetic stirring at 50 rpm as release medium, whereas the donor compartment was filled with 1 ml of the formulation (containing drug equivalent to 10 mg). Aliquots of 1 ml were withdrawn from the receptor compartment and replenished with fresh volume of release medium at predetermined time intervals until 6 hours. After adequate dilutions, withdrawn samples were filtered through a 0.45 µm syringe filter, and the absorbance was measured spectrophotometrically at 230 nm using SNF of pH 6.5 as a blank and the cumulative percentage of MCZ released was estimated using a previously constructed calibration curve [6,23].

Analysis of drug release kinetics

To have insight into the drug release mechanism, the data obtained from the *in vitro* release study were fitted to various kinetic models, including the zero-order, first-order, Higuchi model, and Korsmeyer Peppas model whereby (*n*) is the diffusion exponent indicates the nature of the release mechanism. The model that shows the highest regression (R^2) value was chosen as the best-fit model. The mathematical calculations were performed using a DDSolver Excel Microsoft add-in program [34].

Statistical analysis

The experimental outcomes were presented as the mean of three experiments ± standard deviation (SD). Data were subjected to analysis using a one-way analysis of variance (ANOVA) test at a significance level of ($p < 0.05$).

Results

Characterization of meclizine hydrochloride/HP-β-CD Inclusion Complex

Drug Content of meclizine hydrochloride/ HP-β-CD Inclusion Complex

The percent drug content of the prepared complex was found to be 96.4%± 0.15 w/w, which indicates uniform distribution of the drug [16].

Fourier Transform Infrared (FTIR) Spectroscopy

The main characteristic peaks of pure MCZ at 3394.72 cm^{-1} (secondary amine N-H stretching), 3047.53 cm^{-1}(aromatic C–H stretching), multiple sharp bands between 1,600 and 1,400 cm^{-1} (aromatic C=C stretching), 1276.88 cm^{-1} (C–N stretching), and 698.23 cm^{-1} (C–Cl stretching) are illustrated in (Figure 1A). The FTIR spectrum of HP-β-CD as a pure (Figure 1B) is characterized by intense broad peaks at 3402.43 cm^{-1} (O–H stretching), 2966.52 and 2927.94 cm^{-1} (C–H asymmetrical/symmetrical stretching), 1647.21 cm^{-1} (H–O–H bending), 1029.99 cm^{-1} (C–O stretching). The results of this analysis are consistent with literature data [35]. Comparative analysis of the FTIR spectra of MCZ and HP-β-CD and the spectrum of PM (Figure 1C) shows the superposition of the absorption spectra of both components since there was no interaction in the physical mixture. However, the (N-H stretching) band of MCZ disappeared due to the (O-H stretching) masking effect of HP-β-CD. In addition, certain peaks of MCZ underwent slight shifts and displayed a reduction in intensity. This is believed to be primarily due to dilution resulting from the mixing process. In (Figure 1D), the peak associated with water crystallization with HP-β-CD at 1647.21 cm^{-1} appeared somewhat diminished. This reduction could potentially be attributed to the replacement of water molecules by MCZ within the cavity of HP-β-CD, indicating the formation of the inclusion complex in its solid state [21]. MCZ peaks related to relevant groups exhibited a smoothing effect but there were no additional peaks in the MCZ-HP-β-CD complex, indicating a non-covalent interaction in the inclusion complex.

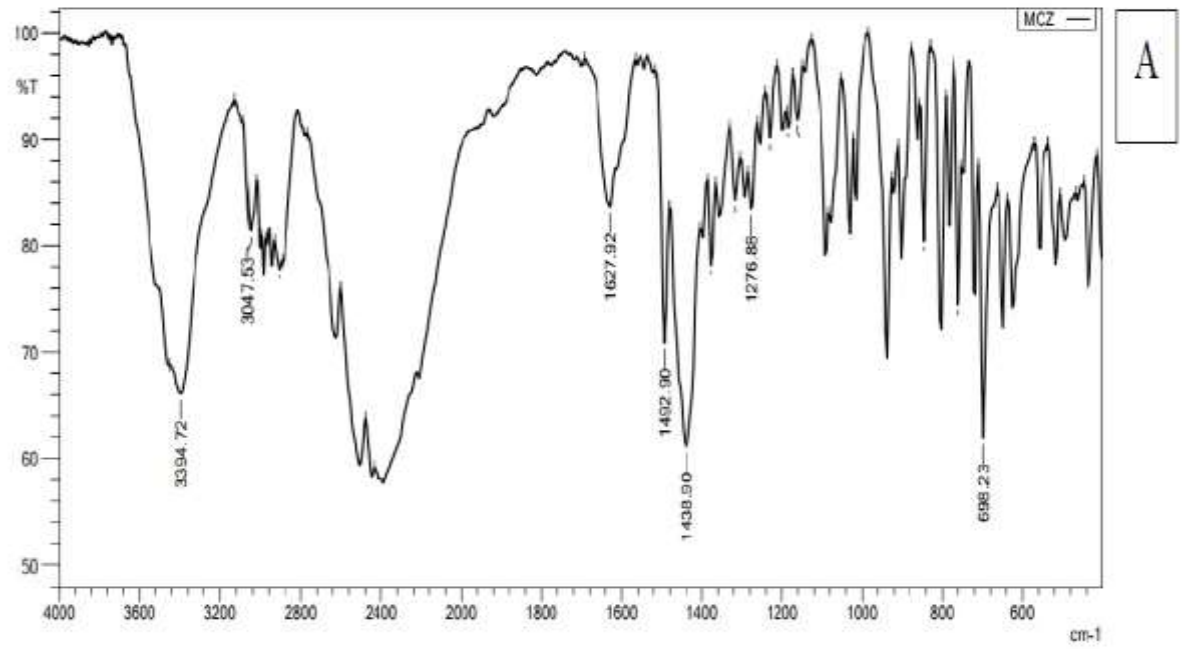
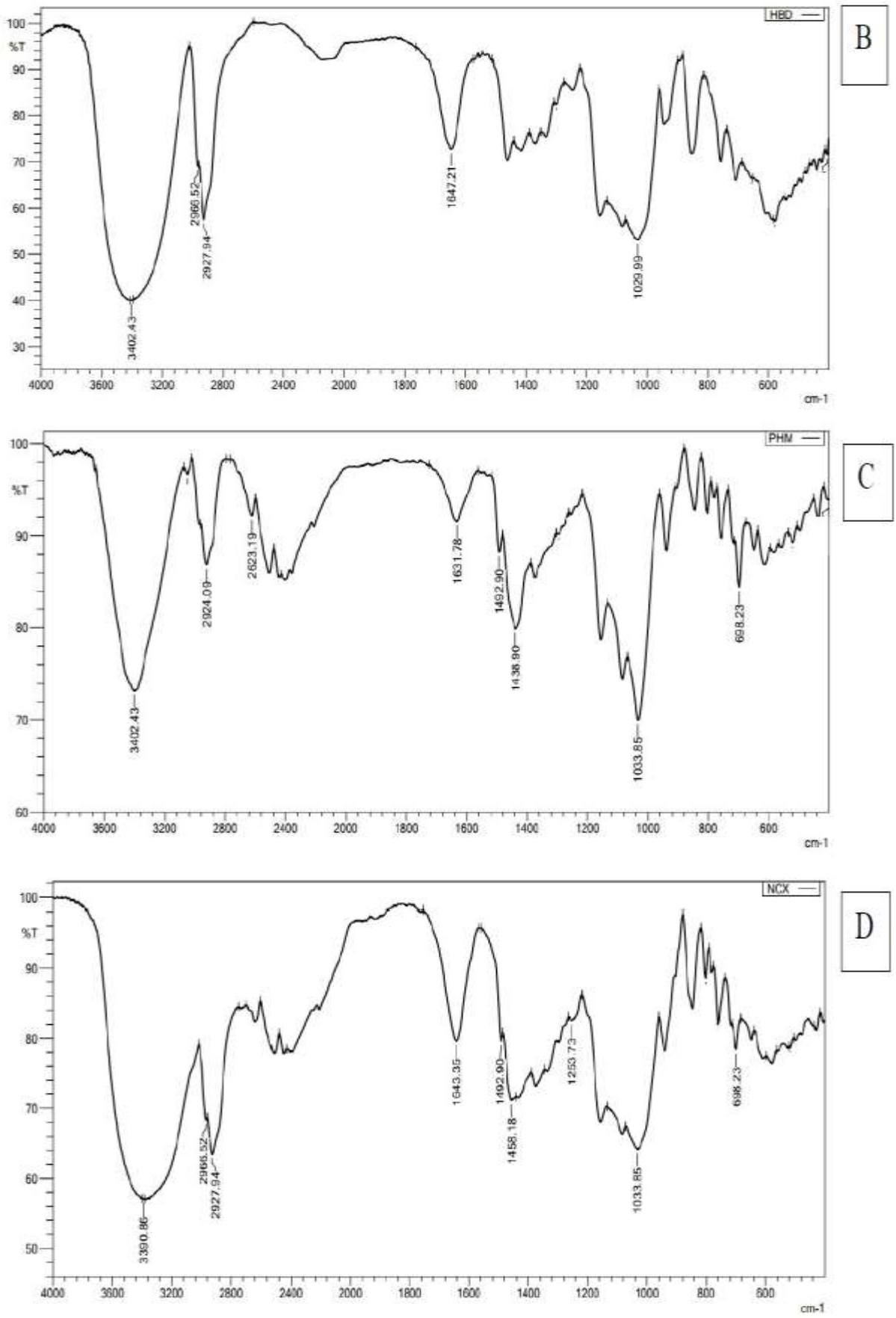


Figure 1. FTIR spectrum of (A) MCZ, (B) HP-β-CD, (C) PM, and (D) MCZ/ HP-β-CD Complex.



Continuted Figure 1.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was utilized to investigate the formation of the inclusion complex between MCZ and HP-β-CD. In the DSC thermogram of MCZ (Figure 2A), a prominent endothermic peak was observed at 220.6 °C, which corresponds to its melting point and confirms its crystalline nature, consistent with what has been reported in the literature [16].

For HP-β-CD (Figure 2B), a relatively broad endothermic peak centered at 134.24 °C was observed. The DSC analysis of the physical mixture of MCZ and HP-β-CD (Figure 2C) displayed an additive thermogram, with peaks for both MCZ and HP-β-CD still present. However, there was a slight shift towards lower temperatures, with MCZ at 198.59 °C and HP-β-CD at 99.01 °C, as a result of the mixing of these two components. In contrast, the DSC curve of the MCZ/HP-β-CD complex (Figure 2D) showed a distinct change. The absorption peak of HP-β-CD appeared at 125.01°C and the characteristic endothermic peak of MCZ at 220.6 °C was replaced by two lower-intensity peaks at 193.08 °C and 188.26 °C. This change suggests a reduction in the crystalline nature of MCZ and partial amorphization due to the formation of the complex.

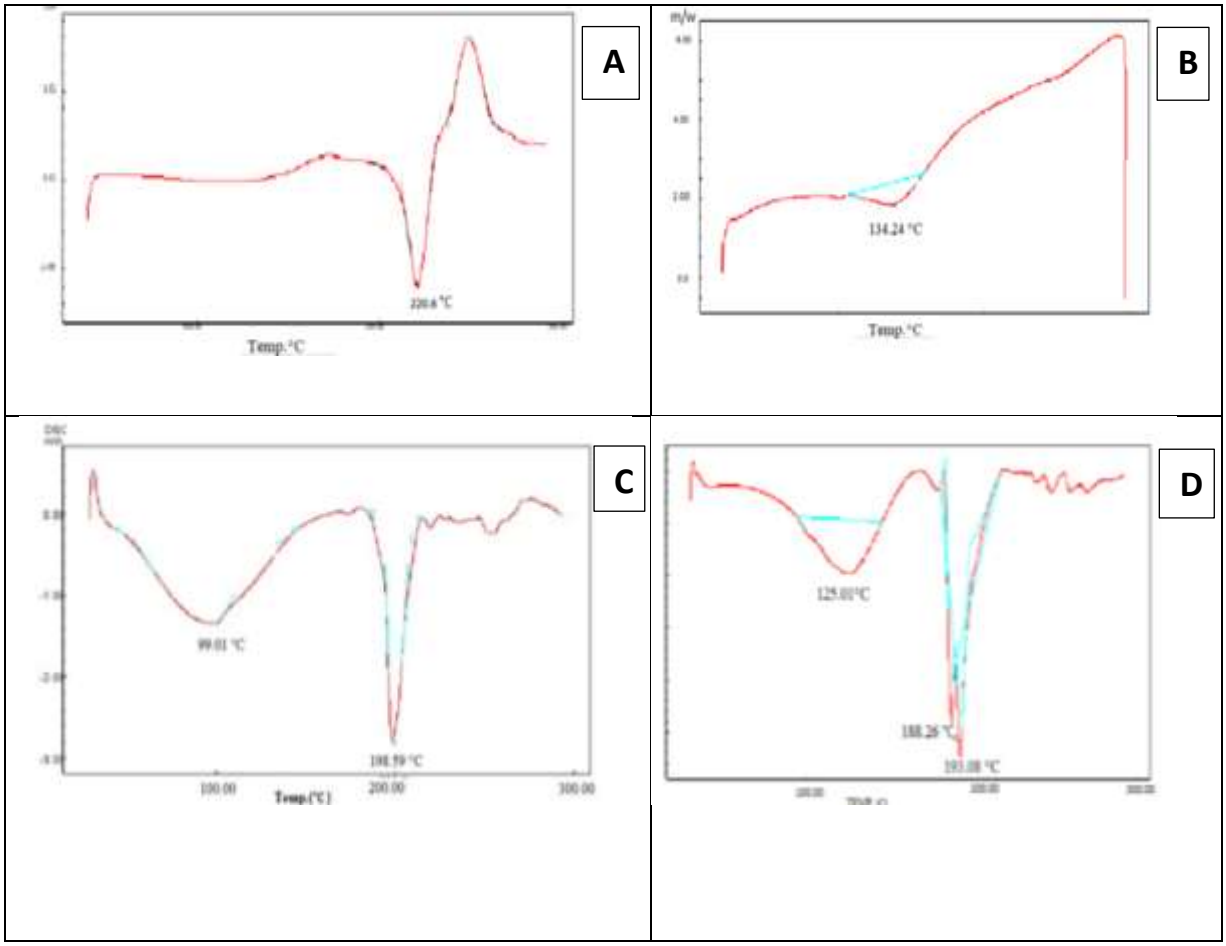


Figure 2. DSC thermograms of (A) pure MCZ, (B) HP-β-CD, (C) PM and (D) MCZ/HP-β-CD Complex.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy images of MCZ, HP-β-CD, PM, and MCZ/HP-β-CD inclusion complexes are shown in (Figure 3). The pure MCZ exhibited a typical appearance characterized by rod-like crystals with a smooth surface, as depicted in (Figure 3A). Conversely, HP-β-CD presented as rounded, compact solid particles with a rough, porous surface texture, as shown in (Figure 3B). When MCZ and HP-β-CD were physically mixed, two distinct entities representing MCZ and HP-β-CD separately were evident (Figure 3C). However, in the MCZ/HP-β-CD complex, as illustrated in (Figure 3D), the original morphology of both individual components was no longer discernible and the MCZ/HPβCD inclusion complex had almost no regular crystal morphology indicating the formation of the inclusion complex. Similar observations were reported by Sing *et al* [36] for mucoadhesive nasal *in situ* gel of loratadine.

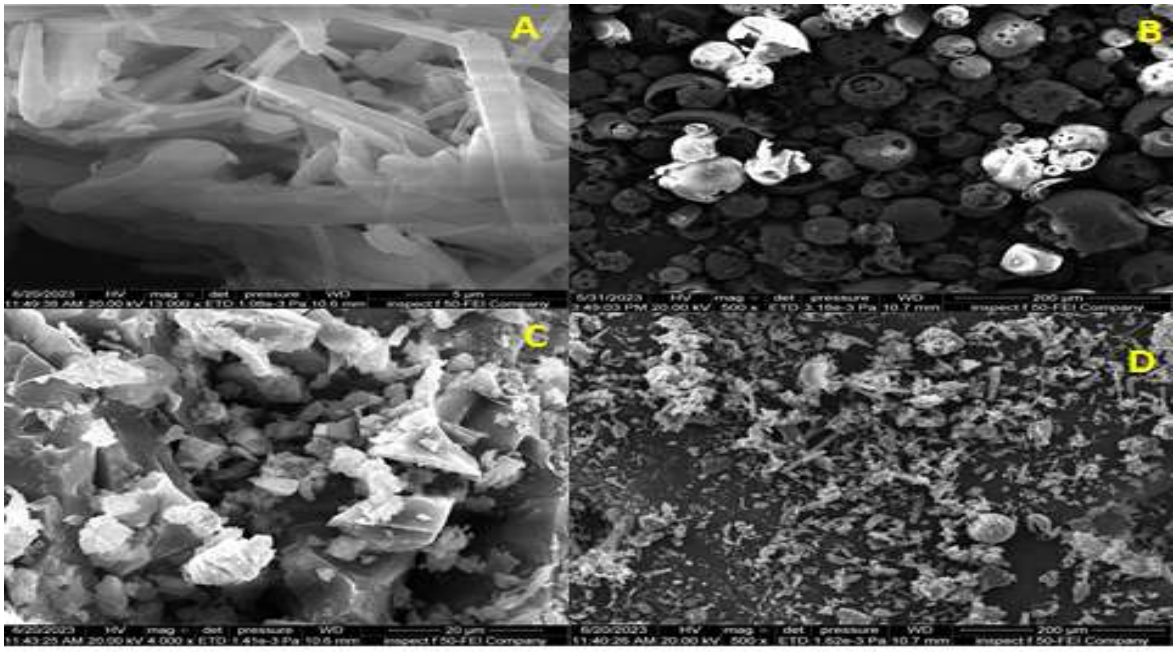


Figure 3. SEM of pure (A) MCZ, (B) HP-β-CD, (C) PM and (D) MCZ/ HP-β-CD Complex.

X-Ray Powder Diffraction (X-RPD)

The results of the XRD analysis are shown in (Figure 4). According to the X-ray diffractograms of pure MCZ (Figure 4A), sharp characteristics peak at diffraction angle 6.4°, 7.2°, 14.6°, 21.4°, 23.2, 26° and 29.4° with approximate intensities of 721, 1483, 1069, 953, 810, 873 and 508, respectively, were evident and is similar to that reported in the literature indicating the crystalline nature of the drug [23]. The X-ray diffraction patterns of the HP-β-CD (Figure 4B), show broad hallow peaks that confirmed its amorphous form. The X-ray diffraction pattern of PM (Figure 4C) showed both MCZ and HP-β-CD peaks indicating the presence of both species. The X-ray diffraction pattern of the MCZ/ HP-β-CD inclusion complex (Figure 4D) exhibited a change in peak positions and widening of existing peaks with lower intensity, indicating that the drug was in a moderately amorphous or disarranged crystalline phase during complexation.

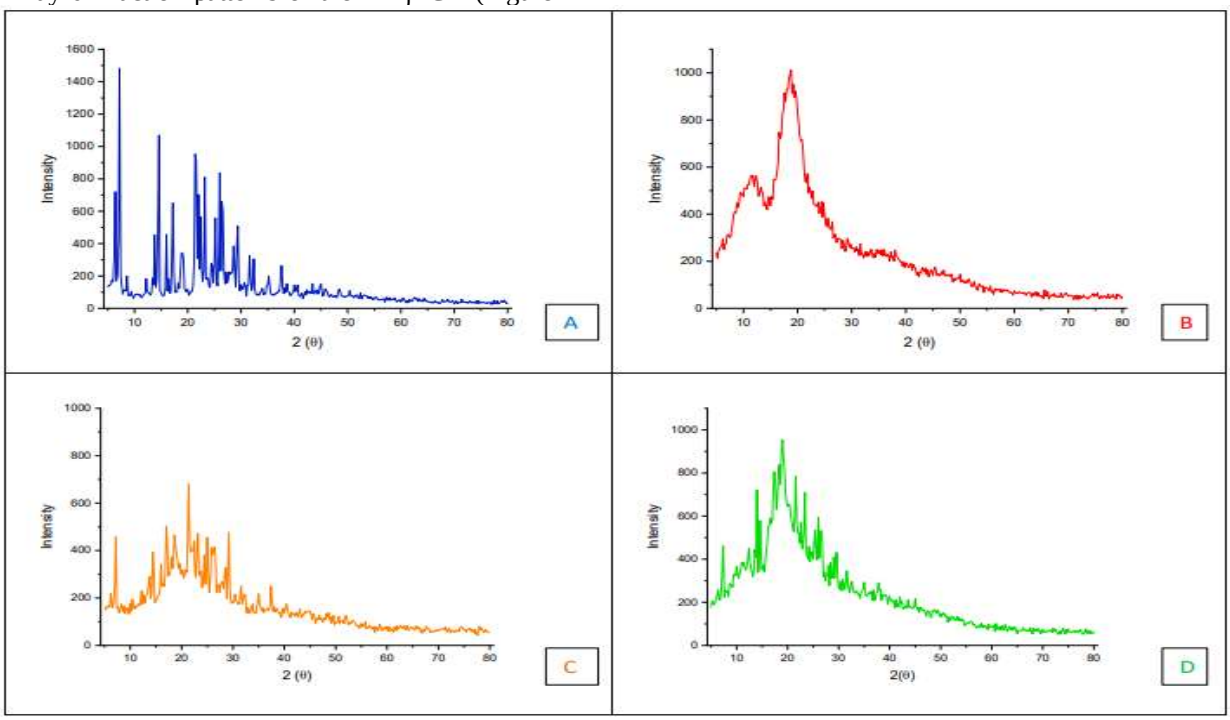


Figure 4. XRPD diffractograms of (A) MCZ, (B) HP-β-CD and (C) PM, and (D) MCZ/ HP-β-CD Complex.

Characterization of Thermosensitive Nasal *in Situ* Gelling Formulations

Measurement of Gelation temperature

The gelation temperature of plain poloxamer gels was observed for the screened poloxamer gels and was found to be in the range of 24.8 ± 0.1 to 44.2 ± 0.4 °C (Table 3). There was a significant decrease ($p < 0.05$) in gelation temperature as the concentration of P407 was increased, whereas the opposite behaviour was observed when the concentration of P188 was increased. Such phenomena can be explained by the packaging of micelles and micelle entanglements and the fact that increasing P 407 concentration leads to a higher ratio of polypropylene oxide (PPO) units leading to dehydration and formation of larger numbers of micelles at a lower temperature and greater ease of gelation. As for the addition of P188, there will be an increase in the ratio of polyethylene oxide (PEO) leading to less entangled micelles thereby raising the critical micelle temperature [37, 38]. Similar observations have been reported in the literature [32]. Among these gels, only four formulations P1 and P7 (comprising 17% P 407 with 0 and 3% P 188) and formulations P11 and P12 (comprising 19% P 407 with 3 and 4% P 188) exhibited a Sol-Gel temperature within the acceptable range of (32 to 35 °C) for use within the nasal cavity and were selected for incorporation of MCZ/ HP-β-CD complex and HPMC K 4M as mucoadhesive polymer, and were used for further studies. By increasing the concentrations of the mucoadhesive polymer HPMC K4 (0.5, 0.75, and 1%) in formulations F1-F3, F4-F6, F7-F9, and F10-F12 containing P407/P188 in a ratio of (17/0, 18/3, 19/3 and 19/4) % w/v, respectively, the gelation temperature was reduced. This may be explained by the capacity of HPMC K4 to interact with polyethylene oxide (PEO) chains within poloxamer molecules, leading to dehydration and enhanced entanglement of neighbouring molecules through increased intermolecular hydrogen bonding [39]. This was in a good agreement with observations reported by Raheema *et al* [40].

Table 3. Gelation temperatures of thermosensitive polymer gels

Code	Poloxamer 407 (%w/v)	Poloxamer 188 (%w/v)	Sol-Gel Temperature (Mean ±SD, n=3)
P 1	17	0	33.46 ± 0.20
P 2	17	1.5	36.90 ± 0.10
P 3	17	3	37.46 ±0.15
P 4	17	4	44.20 ± 0.40
P 5	18	0	28.80 ± 0.15
P 6	18	1.5	29.93 ± 0.15
P 7	18	3	32.46 ± 0.05
P 8	18	4	36.73 ± 0.40
P9	19	0	27.10 ± 0.15
P10	19	1.5	28.56 ± 0.15
P11	19	3	33.52 ± 0.05
P12	19	4	34.66± 0.20
P13	20	0	24.80 ± 0.10
P14	20	3	27.80 ± 0.17
P15	20	4	29.40 ± 0.15

Appearance and pH determination

All prepared formulations were transparent and clear. The pH of formulations is an essential parameter for its intranasal administration and to minimize nasal mucosal irritation. The pH of the formulation was found to be from 5.83 ± 0.05 to 6.13 ± 0.05 (Table 4) and is within the acceptable pH range of (4.5–6.5) reported for nasal formulations [41].

Drug Content

The percent drug content of all formulations was discovered to be in the range of 98.50 ± 0.020 to 101.28 ±0.15% as shown in (Table 4) indicating uniform distribution of drug throughout the gel [26].

Gel Strength Determination

Gel strength values within the range of 25 to 50 seconds are considered adequate. If the gel strength falls below 25 seconds, it may lose its structure and break apart rapidly, whereas if it exceeds 50 seconds, it could become excessively rigid and potentially cause irritation to the mucous membranes [42]. The gel strengths of the formulations ranged from 36.4 ± 0.25 to 39.5 ± 0.11 sec (Table 4) and were considered appropriate for nasal administration. An increase in gel strength with increasing the concentration of poloxamer 188 from 3% (formulations F8) to 4% (formulations F11) was observed. Gel strength was also found to increase with the increase in concentration of HPMC K4M at the three concentrations tested as it is

evident with formulation (F7- F9). This might be related to increased packing in the poloxamer lattice because of hydrogen bonding between poloxamer and HPMC K4M in the nasal gel [43].

Ex-vivo Mucoadhesive Strength

Results of the mucoadhesive strength measurement shown in Table (4) indicate that the mucoadhesive strength increases significantly ($p < 0.05$) with an increase in the concentration of mucoadhesive polymer. Mucoadhesive strength is dependent on the nature of polymer bonding with membranes, and a higher mucoadhesive strength prolongs the retention time. HPMC is a polar polymer containing numerous hydrophilic functional groups. When the polymeric chains of HPMC are hydrated and wetted, they swell and become entangled with the creation of weak chemical interactions between entangled chains and with the glycoprotein chains of nasal tissue mucin, resulting in adhesion and longer retention time in the nasal cavity [40]. Such observations were consistent with those reported in the literature [7].

Table 4. Characterization of mucoadhesive MCZ/ HP-β-CD nasal *in situ* gel formulations (Data are expressed as means ± SD, n = 3)

Code	P 407 (%)	P 188 (%)	HPMC K4M (%)	Sol-Gel Temperature (◦C)	Appearance	pH	% Drug content	Gel strength (sec)	Mucoadhesive strength (dynes/cm^2)
F1	17	-	0.5	33.2 ± 0.15	+++	6.10 ± 0.1	99.29 ± 0.047	36.40 ± 0.25	2059.95± 0.40
F2	17	-	0.75	32.53 ± 0.15	++	6.10 ± 0.1	101.28 ±0.15	36.7 ± 0.15	2128.17 ± 0.32
F3	17	-	1	29.56 ± 0.15	NA	NA	NA	NA	NA
F4	18	3	0.5	37.60 ± 0.1	NA	NA	NA	NA	NA
F5	18	3	0.75	36.86 ± 0.15	NA	NA	NA	NA	NA
F6	18	3	1	35.81 ± 0.1	NA	NA	NA	NA	NA
F7	19	3	0.5	33.63 ± 0.05	+++	6.10 ± 0.1	99.63 ± 0.035	37.40 ± 0.2	2730.13 ± 0.75
F8	19	3	0.75	33.17 ± 0.1	++	5.90 ± 0.05	99.90 ± 0.030	38.50 ± 0.05	2849.43 ± 0.70
F9	19	3	1	32.62 ± 0.1	++	6.13 ± 0.05	99.72 ± 0.015	39.30 ± 0.057	3389.30 ± 0.46
F10	19	4	0.5	36.0 ± 0.05	NA	NA	NA	NA	NA
F11	19	4	0.75	34.16 ± 0.1	++	5.83 ± 0.05	98.50 ± 0.020	39.50 ± 0.11	2915.3 ± 0.45
F12	19	4	1	31.30 ± 0.1	NA	NA	NA	NA	NA

NA: non- available

In-vitro Drug Release Study

In vitro, drug release profiles from F1, F2, F7, F8, F9, and F11 formulations are shown in Figure 5. There was a rapid initial release rate from all formulations, this may be due to incomplete gel formation in the earlier time, but later it became slower due to gel formation. There was a statistically significant ($p < 0.05$) lower drug release rate upon increasing the concentration of mucoadhesive polymer (HPMC K4M) which is observed in formulations F1 and F2 exhibiting 98.60 and 79.17% of drug release in 4 hrs, respectively. Similar behaviour was also observed for formulations F7-F9 exhibiting 86.8, 72.7, and 55.8% of the drug in 4 hrs, respectively. This effect may be attributed to an increase in the viscosity of the gel layer seen with increasing the polymer concentration resulting in higher retardation of the drug in gel [42]. Furthermore, formulations F8 and F11 containing increased concentrations of P 188 exhibited a significant reduction in the % of drug released. This might be due to the increased viscosity of the gel, which created limitations in the aqueous pathways through which drug dispersion occurred between the poloxamer micelles, and is in accordance with observations of El Shagea *et al* [44].

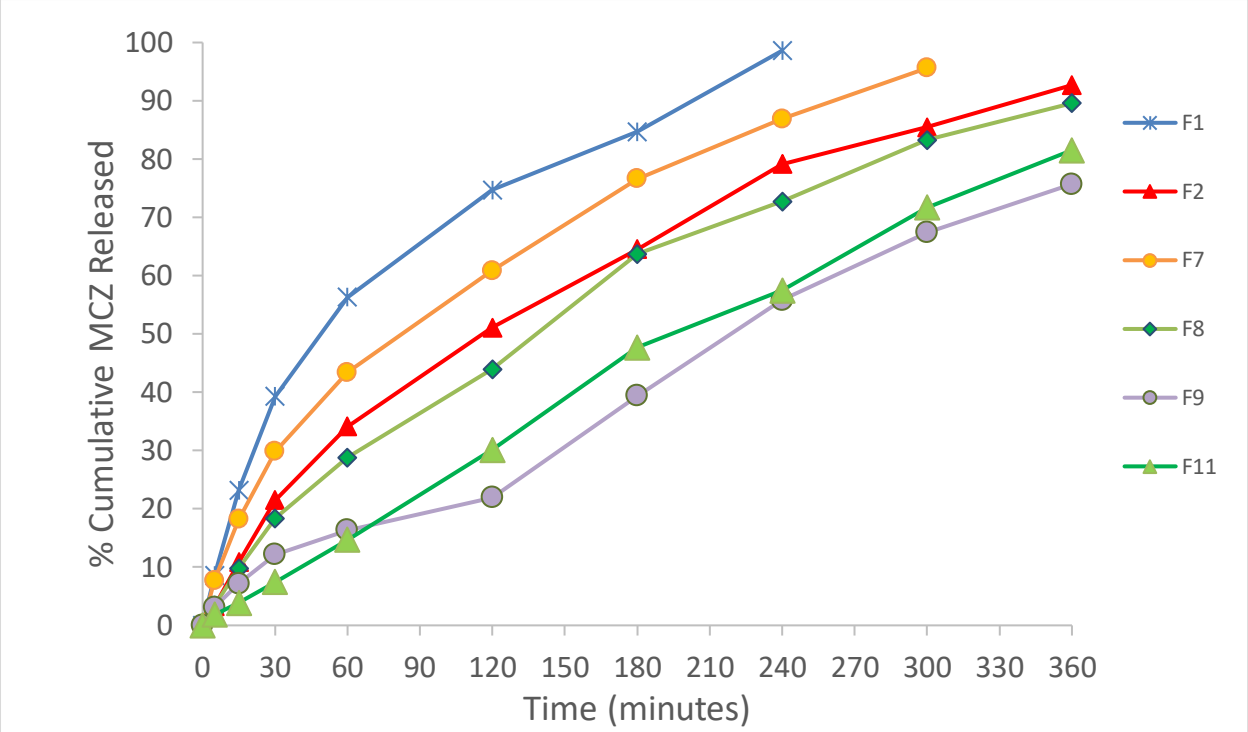


Figure 5. *In vitro* release profiles of MCZ from mucoadhesive *in-situ* nasal gels.

Analysis of drug release kinetics

The results of the *in vitro* drug release data fitting to various mathematical models with their regression coefficient (R^2) values are compiled in Table 5. Formulations best fitted Peppas model for drug release among others as the *n* values were in the range of 0.5–1.0 displaying anomalous or non-Fickian diffusion mechanism release of drug [45].

Table 5. Kinetic evaluation of drug release data for different nasal in situ gel formulations using several models

Formula	Kinetic models				
	Zero	First	Higuchi	Korsmeyer-Peppas	
	Regression coefficient (R^2)				*n*
F 1	0.8264	0.9927	0.9802	0.9969	0.542
F 2	0.9902	0.9621	0.9165	0.9963	0.866
F 7	0.8818	0.9891	0.9897	0.9963	0.574
F 8	0.9882	0.9756	0.9285	0.9949	0.837
F 9	0.9904	0.9513	0.8521	0.9934	0.806
F 11	0.9905	0.9452	0.8587	0.9926	0.8099

Conclusion

In conclusion, this study suggests that using HP-β-CD was an effective technique for enhancing MCZ solubility. The formulated *in situ* gelling formulations of MCZ/ HP-β-CD can be promising for nasal administration in liquid form which transfers into gel on contact with nasal mucosa, and provides an easy-to-use alternative to traditional dosage forms with prolonged residence time in the nasal cavity, leading to lower administration frequency and reduction in the associated side effects.

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Conflicts of Interest

None.

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Ethics Statements

No ethical statement is required (no *in vivo* study was conducted).

Author Contributions

The authors confirm contribution to the paper as follows: study conception and design L.M, K.K; data collection, K.K; analysis and interpretation of results: L.M, K.K; draft manuscript preparation: L.M, K.K. All authors reviewed the results and approved the final version of the manuscript.

References

1. Laffleur F, Bauer B. Progress in nasal drug delivery systems. Int J Pharm. 2021;607:120994.
2. 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. Eur J Pharm Sci. 2007;32(4–5):296–307.
3. Palhal AP. In-situ nasal gel: Modernistic advancement in drug delivery. World J Pharm Res. 2017;6:566–77.
4. Wang Q, Zuo Z, Cheung CKC, Leung SSY. Updates on thermosensitive hydrogel for nasal, ocular and cutaneous delivery. Int J Pharm. 2019;559:86–101.
5. Karavasili C, Fatouros DG. Smart materials: In situ gel-forming systems for nasal delivery. Drug Discov Today. 2016;21(1):157–66
6. Alkufi HK, Kassab HJ. Formulation and evaluation of sustained release sumatriptan mucoadhesive intranasal *in-situ* gel. Iraqi J Pharm Sci. 2019;28(2):95–104.
7. Marzouk MA, Osman DA, Abd El-Fattah AI. Formulation and *in vitro* evaluation of a thermoreversible mucoadhesive nasal gel of itopride hydrochloride. Drug Dev Ind Pharm. 2018;44(11):1857–67.
8. Wibble T, Engström J, Verrecchia L, Pansell T. The effects of meclizine on motion sickness revisited. Br J Clin Pharmacol. 2020;86(8):1510–8.
9. Maltepe C, Koren G. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum-a 2013 update. J Popul Ther Clin Pharmacol. 2013;20(2):184-92
10. Tateosian VS, Champagne K, Gan TJ. What is new in the battle against postoperative nausea and vomiting? Best Pract Res Clin Anaesthesiol. 2018;32(2):137-48.
11. Darwesh AY, El-Dahhan MS, Meshali MM. A new dual function orodissolvable/dispersible meclizine HCL tablet to challenge patient inconvenience: in vitro evaluation and in vivo assessment in human volunteers. Drug Deliv Transl Res. 2021;11(5):2209–23.
12. Qazi F, Shoaib MH, Yousuf RI, Siddiqui F, Nasiri MI, Ahmed K, et al. QbD-based Eudragit coated Meclizine HCl immediate and extended release multiparticulates: formulation, characterization and pharmacokinetic evaluation using HPLC-Fluorescence detection method. Sci Rep. 2020;10(1): 1476-65
13. Saokham P, Muankaew C, Jansook P, Loftsson T. Solubility of cyclodextrins and drug/cyclodextrin complexes. Molecules. 2018;23(5):1–15.
14. Hadi BM, Al-Khedairy EBH. Preparation and Characterization of Atorvastatin Calcium Trihydrate -cyclodextrin Inclusion Complex. Int J Drug Deliv Technol. 2022;12(3):1171–9.
15. Gupta MM, Patel Mitul G, Kedawat M. Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of meclizine hydrochloride with β-cyclodextrine. J Appl Pharm Sci. 2011;1(9):150–3.
16. Sharma, Sanjay Kumar, Patel RP. Enhancing the solubility and dissolution rate of meclizine hydrochloride by inclusion complex. J Drug Deliv Ther. 2019;9(4):57–64.
17. Upendra C Galgatte, Pravin D Chaudhari. Development of Metoclopramide hydrochloride in situ gel: nasal delivery and pharmacokinetics in New Zealand rabbits. Asian J Pharm Clin Res. 2019;12(4):280–5.
18. Mahajan HS, Gattani S. *In situ* gels of metoclopramide hydrochloride for intranasal delivery: *In vitro* evaluation and *in vivo* pharmacokinetic study in rabbits. Drug Deliv. 2010;17(1):19–27.
19. Agrawal A, Maheshwari RK. Formulation development and evaluation of in situ nasal gel of poorly water soluble drug using mixed solvency concept. Asian J Pharm. 2011;5(3):131–40.
20. Malviya V. Design and characterization of thermosensitive mucoadhesive nasal gel for meclizine hydrochloride. International Journal of Pharmaceutical Sciences and Nanotechnology. 2022;15(1):5782-93.
21. George SJ, Vasudevan DT. Studies on the preparation, characterization, and solubility of 2-HP-β-cyclodextrin-meclizine HCl inclusion complexes. J Young Pharm. 2012;4(4):220–7.
22. Vemula SK, Vangala M. Formulation development and characterization of meclizine hydrochloride sublimated fast dissolving tablets. Int Sch Res Not. 2014;2014:1–8.
23. Palakurthi S, Kolluru S, Mehra N, Hidau M. Cyclodextrin complexation of meclizine hydrochloride and its influence on the solubility for its repurposing. Drug Deliv Lett. 2017;7(1):54–61.
24. Yang J, Ma Y, Luo Q, Liang Z, Lu P, Song F, et al. Improving the solubility of vorinostat using

cyclodextrin inclusion complexes: The physicochemical characteristics, corneal permeability and ocular pharmacokinetics of the drug after topical application. Eur. J. Pharm. Sci. 2022;168:106078.

25. Aloisio C, de Oliveira AG, Longhi M. Solubility and release modulation effect of sulfamerazine ternary complexes with cyclodextrins and meglumine. J. Pharm. Biomed. Anal. 2014;100:64-73.

26. Rao M, Agrawal DK, Shirsath C. Thermoreversible mucoadhesive in situ nasal gel for treatment of Parkinson's disease. Drug Dev Ind Pharm. 2017;43(1):142–50.

27. Gu F, Fan H, Cong Z, Li S, Wang Y, Wu C. Preparation, characterization, and in vivo pharmaclokinetics of thermosensitive in situ nasal gel of donepezil hydrochloride. Acta Pharm. 2020;70(3):411–22.

28. Yurtdaş-Kırımlıoğlu G. A promising approach to design thermosensitive in situ gel based on solid dispersions of desloratadine with Kolliphor® 188 and Pluronic® F127. J Therm Anal Calorim. 2022;147(2):1307–27.

29. Naresh WR, Dilip DV, Sunil KP. Xyloglucan based Nasal in situ gel formulation of mirtazapine for treatment of depression. Indian J Pharm Educ Res. 2020;54(2):S210–9.

30. Thakkar H, Vaghela D, Patel BP. Brain targeted intranasal in-situ gelling spray of paroxetine: Formulation, characterization and in-vivo evaluation. J Drug Deliv Sci Technol. 2021;62:102317

31. Bhuva F, Patel LD. In-Situ Gelling for Prolonged Drug Delivery: Formulation and in-vitro evaluation of imidazole class drug. J Pharm Chem Biol Sci. 2018;6(4):292–304.

32. Corazza E, di Cagno MP, Bauer-Brandl A, Abruzzo A, Cerchiara T, Bigucci F, et al. Drug delivery to the brain: In situ gelling formulation enhances carbamazepine diffusion through nasal mucosa models with mucin. Eur J Pharm Sci. 2022;179:106294.

33. Thomas LM, Khasraghi AH, Saihood AH. Preparation and evaluation of lornoxicam in situ gelling liquid suppository. Drug Inven Today. 2018;10:1556–63.

34. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. The AAPS journal. 2010 Sep;12:263-71.

35. Nikolić VD, Ilić-Stojanović SS, Nikolić LB, Cakić MD, Zdravković AS, Kapor AJ, Popsavin MM. Photostability of piroxicam in the inclusion complex with 2-hydroxypropyl-β-cyclodextrin. Hem ind. 2014;68(1):107-16.

36. Singh RMP, Kumar A, Pathak K. Thermally triggered mucoadhesive in situ gel of loratadine: β-Cyclodextrin complex for nasal delivery. AAPS PharmSciTech. 2013;14(1):412–24.

37. Zarrintaj P, Jouyandeh M, Ganjali MR, Hadavand BS, Mozafari M, Sheiko SS, et al. Thermo-sensitive polymers in medicine: A review. Eur Polym J. 2019;117:402–23.

38. Abdel Bary G. Preparation and characterization of thermosensitive mucoadhesive in situ gels for nasal delivery of ondansetron hydrochloride. Al-Azhar J Pharm Sci. 2014;50(2):191–207.

39. Lakshmi P, Harini K. Design and optimization of thermo-reversible nasal in situ gel of atomoxetine hydrochloride using Taguchi orthogonal array design. Dhaka Univ J Pharm Sci. 2019;18(2):183–93.

40. Raheema DA, Kassab HJ. Preparation and in-vitro evaluation of secnidazole as periodontal in-situ gel for treatment of periodontal disease. Iraqi J. Pharm. Sci.. 2022;31(2):50-61.

41. Wang Y, Jiang S, Wang H, Bie H. A mucoadhesive, thermoreversible in situ nasal gel of geniposide for neurodegenerative diseases. PLoS One. 2017;12(12):1–17.

42. Pathan IB, More B. Formulation and characterization of intra nasal delivery of nortriptyline hydrochloride thermoreversible gelling system in treatment of depression. Acta Pharm Sci. 2017;55(2):35–44.

43. Godbole MD, There PW, Dangre P V. Formulation and optimization of prolonged release nasal in situ gel for treatment of migraine. Indo Am J Pharm Res. 2014;4(02):1320–32.

44. El Shagea HN, Makar RR, Salama AH, Elkasabgy NA, Basalious EB. Investigating the targeting power to brain tissues of intranasal rasagiline mesylate-loaded transferosomal in situ gel for efficient treatment of Parkinson's disease. Pharmaceutics. 2023;15(2):533

45. Salunke SR, Patil SB. Ion activated in situ gel of gellan gum containing salbutamol sulphate for nasal administration. Int J Biol Macromol. 2016;87:41–7.

صياغة وتقييم هلام الأنف الحراري اللاصق للمخاط القائم على سيكلودكسترين للميكليزين هيدروكلوريد

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الخلاصة

ميكليزين هيدروكلوريد هو مضاد هيستامين فعال للوقاية من الغثيان والقيء وعلاجه ، مع انخفاض التوافر البيولوجي الفموي (حوالي ٣٠ إلى ٤٠٪) بسبب انخفاض الذوبان في الماء. كان الغرض من الدراسة الحالية تطوير وتوصيف هلام أنفي موضعي حساس للحرارة للمكلزين لتعزيز الذوبان, تم تحضير معقد تضمين مع هيدروكسي بروبيل بيتا سيكلودكسترين وتوصيفه. تم استخدام المركب المحضر في تحضير هلامات حساسة للحرارة في الموقع باستخدام الطريقة الباردة .

تم تطوير اثني عشر تركيبة باستخدام تراكيز مختلفة من بولاكسمر ٤٠٧ اما بشكل منفرد او مدمج مع بولاكسمر ١٨٨ .بالإضافة إلى ذلك ، تم دمج هيدروكسي بروبيل ميثيل سلولوز K4M كبوليمر التصاق مخاطي. تم تمييز التركيبات المحضرة من حيث مظهرها وقيمة درجة الحموضة ودرجة حرارة تكوين الهلام وقوة التصاق المخاط وقوة الهلام ومحتوى الدواء ومعدل تحرر الدواء. أظهرت النتائج أنه مع زيادة تركيز بولاكسمر ١٨٨ و هيدروكسي بروبيل ميثيل سلولوز K4M ، كان هناك انخفاض في درجة حرارة تكوين الهلام ، وزيادة في قوة التصاق المخاط ، وانخفاض في النسبة المئوية للدواء المتحرر. تم تحديد تركيبة الهلام الموضعي (F9) مع ١٩٪ بولاكسمر ٤٠٧ و ٣٪ بولاكسمر١٨٨ و ٠,٥٪ هيدروكسي بروبيل ميثيل سلولوز K4M على أنها الصيغة المثلى بدرجة حرارة تكوين هلام تبلغ (٣٢,٦٢ ± ٠,١ درجة مئوية) ، وقيمة درجة الحموضة (٦,١٣ ± ٠,٠٥) ، وقوة الهلام (٣٩,٣ ± ٠,٥٧ ثانية) ، وقوة التصاق المخاط (٣٣٨٩,٣٠ ± ٠,٤٦ داين / سم ٢) ، وتحرر الدواء في المختبر بنسبة (٧٥,٧٪) على مدار ٦ ساعات عن طريق آلية الانتشار غير الفيكية. نظرًا لهذه الخصائص ، يمكن استخدام التركيبة المحضرة كنظام توصيل أنفي فعال لمعالجة الغثيان والقيء.

الكلمات المفتاحية: ميكليزين هيدروكلوريد، هلام أنفي، بولاكسمر، بوليمر لاصق ، هيدروكسي بروبيل بيتا-سيكلودكسترين