



Transdermal properties of pet deworming thermosensitive sustained-release drops enhanced by hydroxypropyl methyl cellulose E5

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ARTICLE INFO

Keywords:

Sustained-release temperature-sensitive drop
Hydroxypropyl methyl cellulose E5
Cumulative drug penetration

ABSTRACT

Using hydroxypropyl methyl cellulose (HPMC E5) as a key excipient, a thermosensitive sustained-release drop formulation of imidacloprid (IMD) and moxidectin (MOX) was prepared. The effects of HPMC E5 on the thermosensitivity, rheology and transdermal behavior were investigated. Poloxamer 407 and 188 were used as thermosensitive matrices, and HPMC E5 served as a stabilizer and penetration auxiliary. 1,2-Propanediol, polyethylene glycol 400 and azone were used as penetration enhancers. The formulation was optimized via in vitro rat skin transdermal experiments, and the optimal ratios of P407, P188 and HPMC E5 were 12.0%, 3.5% and 0.5%, respectively. Infrared spectroscopy indicated hydrogen bonding between HPMC E5, the drug and the matrix. Rheological studies showed that HPMC E5 improved shear-thinning and thermosensitive gelation, enabling rapid film formation at body temperature and sustained drug release. Compared with the formulation without HPMC E5, addition of 0.5% HPMC E5 increased cumulative transdermal amounts of IMD and MOX to 0.62 and 0.45 mg cm⁻² ($P < 0.01$), with good sustained-release characteristics. The skin irritation test revealed no redness or edema. HPMC E5 enhances transdermal absorption, sustained release, rheological adaptability and skin adhesion. The prepared drops avoid drug loss, reduce dosing frequency, and offer a safe, effective transdermal option for pet deworming.

1. Introduction

Compared with oral and injection routes, local administration can effectively reduce the toxic side effects of drugs[1]. A novel drug delivery system based on temperature sensitive can respond to changes in temperature, so that the release of drugs can be located and controlled, and the local absorption of drugs can be improved, thus improving the therapeutic effect[1–3]. In the treatment of hemorrhagic blood loss due to trauma, quickclot and dry fibrin sealer dressings have limitations in slowing blood loss. However, temperature-sensitive drops may have the potential to improve hemostasis and wound closure in trauma treatment. Temperature-sensitive triblock copolymers (PEO-PPO-PEO) can be protected by forming a drop at body temperature to promote blood clotting and cover wounds Jun et al., 2020[4]. Another study Yi et al., 2023 [5] showed that the combined application of IL-36Ra and PLGA-PLGA temperature sensitive hydrodrop designed and prepared by the drug could extend the duration of the drug and achieve the effect of slow release of the drug, thus effectively delaying the

progression of osteoarthritis degeneration. Thermosensitive hydrodrops can undergo phase transitions or reversible sol-drop transitions with changes in ambient temperature[6–10], which can enhance the local penetration and time control of drugs, and improve the bioavailability of drugs[8–10]. As known, poloxamer as the commonly applied material to form the drop is a (PEO-PO-PEO) triblock copolymer, and poloxamer series drops are widely recognized for their good fluidity and short gelation time[6]. It has reported that P407 was used in a checkpoint antibody delivery system[7]. The results showed that after the antibody was added into the drop and injected subcutaneously, the antibody showed sustained release effect in vitro[2].

Pet ownership has been shown to mitigate the risk of mental illness and coronary heart disease by alleviating blood pressure, stress, and anxiety. However, it is also pertinent to note that pet ownership could potentially elevate the risk of human infection with parasitic pathogens Massetti et al., 2023 [11]. In the context of extensive socioeconomic and urban transitions, the uneven distribution of wealth exerts a profound influence on life expectancy and the prevalence of diseases among

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<https://doi.org/10.1016/j.mtadv.2026.100973>

Received 18 May 2026; Received in revised form 30 August 2026; Accepted 8 September 2026

Available online 21 September 2026

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populations in disadvantaged countries Colella et al., 2022 [12]. Zoonotic parasites pose a chronic and substantial impediment to vulnerable communities Colella et al., 2022 [12]. Organisms such as fleas and worms, commonly carried by animals like cats and dogs, can result in chronic or/and severe illnesses in those who are afflicted Colella et al., 2022 [12], [13]. Toxocariasis infection, in particular, can incur substantial socio-economic burdens on impoverished communities and may result in visual impairment and other neurological disorders in children Amoah et al., 2023 [14]. Consequently, it is imperative to administer deworming treatments to pets harboring parasites Amoah et al., 2023 [14].

Heartworm is a principal parasite affecting cats, and active macrocyclics such as MOX and ivermectin are included in the preventative products currently available on the market [13]. MOX has been suggested as a viable option for the chemoprophylaxis of nematodiasis due to its extended half-life and commendable safety profile [15]. It [15] has demonstrated that formulations containing 10% IMD and 1% MOX can mitigate the shedding of *C. felis* larvae and alleviate the associated clinical manifestations. The application of 10% w/v IMD and 2.5% w/v MOX (Advocate, Advantage® Multi®, Bayer) in conjunction with doxycycline (Ronaxan, Merial®) formulations have been demonstrated to effectively eradicate both microfilaria and adult heartworm infections [16,17].

IMD is a colorless, crystalline insecticide belonging to the neonicotinoid class, which disrupts the normal functioning of the central nervous system in insects and exhibits selective binding to the nicotinic acetylcholine receptors, thereby causing desensitization of these receptors Brambilla et al., 2022 [18]. MOX belongs to macrolide antibiotic with a broad spectrum of activity James et al., 2023 [19]. Derived from the fermentation broth of *Streptomyces cyaneogriseus*, the chemical structure of moxiconin closely resembles that of naemistin, save for the presence of methoxime group at position C-23 [20]. Its mode of action involves binding to glutamate-gated chloride ion channels. For the prevention and control of heartworm, hookworm, roundworm, and other internal/external parasites, various dosage forms have been developed for oral, topical, and injectable administration Savadelis et al., 2022 [21].

Products of IMD and MOX drops (Advocate, Bayer) with once a month frequency are easy to stick to hair and cause drug loss while pet shaking. To avoid the limitations of IMD and MOX drops for pet deworming, sustained-release temperature-sensitive drop of IMD and MOX was studied to avoid the loss of pet drops in the process of medication and reduce dosing frequency to improve the overall application effects. The sustain-release temperature-sensitive drop was sol at room temperature and can effectively adhere to the skin at body temperature by drop state, which avoided drug loss and sustained drug release.

2. Materials and methods

2.1. Materials

High-purity IMD ($\geq 97\%$) and MOX (96%) were procured from Shanghai Maclin Biochemical Technology Co., Ltd. Anhydrous ethanol (AR) and DMSO (AR) were sourced from Tianjin Fuyu Fine Chemical Co., Ltd. 1,2-propylene glycol (AR) was acquired from Tianjin Damao Chemical Reagent Factory. Peppermint oil and laurazone (98%) were provided by Shandong West Asia Chemical Industry Co., Ltd. (West Asia Reagent). P407 was obtained from meilunbio® while P188 was sourced from Solarbio. Sodium chloride (AR) was obtained from Tianjin Hengxing Chemical Reagent Manufacturing Co., Ltd. Ulatan (ethyl carbamate) was sourced from Tianjin Guangfu Technology Development Co., Ltd. Ethyl paraben (99%) was obtained from RON's reagent. HPMC E5 (molecular weight of 50000) and HPMC E50 (molecular weight of 10000-1500000) were provided by Anhui Shanhe

Pharmaceutical Accessories Co., Ltd.

Instrument	Manufacturer
UV-1801 UV-Visible spectrophotometer	Beijing Beifenrayleigh Analytical Instrument (Group) Co., LTD.
WQF-530 Fourier transform infrared spectrometer	Beijing Beifen Rayleigh Analytical Instrument (Group) Co., LTD.
Hsc-differential Scanning calorimeter	Beijing Hengjiu Experimental Equipment Co., LTD
BSA124S-CW One-thousandth electronic balance	Sartorius Scientific Instruments (Beijing) Co., LTD.
KQ-100V Ultrasonic cleaner	Kunshan Ultrasonic Instrument Co., LTD.
W-201B digital constant temperature water bath	Changzhou Macono Instrument Co., LTD
SYT-101 multifunctional transdermal diffuser	Yanji Aidi Zhu Technology Co., LTD.

2.2. Preparation of IMD and MOX temperature-sensitive drop

P407 and P188 with designed weight was dissolved using 20 mL of distilled water. The mixture was subsequently resealed and stored in a refrigerated environment at 4°C. If the formulation involves the addition of a stabilizer, such as HPMC E5, it is recommended to add the stabilizing agent subsequent to the weighing of P407 and P188. Thereafter, P407, P188, and the stabilizing agent were combined and immersed in distilled water, the entire mixture being refrigerated at 4°C to facilitate swelling. The preservative (ethyl paraben) and permeation enhancers, including 1, 2-propylene glycol, polyethylene glycol 400, laurazone, anhydrous ethanol, any suitable combination were incorporated. Subsequently, thorough mixing was employed to ensure complete swelling, following which the solution was hermetically sealed. The sealed solution was then allowed to stand at room temperature (not exceeding 25°C) for 30 min to facilitate the formation of the matrix solution. IMD (10% by weight) and MOX (1% by weight) were dissolved in dimethyl sulfoxide (DMSO) solution via ultrasound for 30 min. After cooling, these substances were incorporated into the matrix solution, and the mixture was ultrasonicated for approximately 4 h while being stirred continuously. Subsequently, distilled water was added to reach an ultimate volume of 0.4 mL, and the solution was thoroughly mixed.

2.3. Determination of gelling temperature and gelling time

0.4 mL of the prepared temperature-sensitive drop was transferred into a test tube at ambient temperature (not exceeding 25°C), and the drop was found to be in a sol state. Subsequently, the test tube was placed within a water bath, and the temperature at which the sol converted to a drop was monitored under varying temperature conditions (with a heating rate of 1 min/°C). This temperature was designed as the gelation temperature, which was determined and recorded in parallel trials for three times, subsequent to which the average value was calculated.

At ambient temperature (not exceeding 25°C), 0.4 mL temperature-sensitive drop remained in a sol state. Subsequently, the test tube was placed within a 32°C constant-temperature water bath for 10 min, at which point the timing was initiated. Throughout the process, the tube was inverted at irregular intervals to facilitate observation and record the gelation time [6]. This process was replicated in triplicate for parallel measurements, following which the mean gelation time was computed.

2.4. Design expert

The three independent variables examined were P407, P188, and DMSO, each measured in grams. P407 was in the range of 4.4 g to 8.8 g, while P188 exhibited a weight range of 0.4 to 3.6 g, and DMSO changed from 4.4 to 14.08 g. The gelation temperature was designated as the dependent variable. Please refer to the attached table for detailed formulations. Data analysis was conducted utilizing Design Expert software

(version 13).

2.5. Transdermal test in rats

The skin, stratum corneum and dermis of rats are relatively thin, the barrier function of the active layer is weak, the hair follicle density is high and densely distributed, the sweat glands are underdeveloped, and they mainly dissipate heat by licking. The barrier of rat skin is relatively weak and the permeability is high. The hairy areas of a cat or dog's skin are thinner, while the hairless areas (such as the paw pads and the tip of the nose) are thicker. The dermis is thicker, with more collagen and elastic fibers, and a stronger barrier function. The sweat glands have limited function and mainly rely on respiration and paw pads for heat dissipation. The sebaceous glands secrete more actively, the barrier function is stronger, and the permeability is relatively lower. Rats can be used as preliminary screening models, but subsequent validation with skin that is closer to the target species is required.

The rat were rendered unconscious through the administration of a 20% urtane solution via intraperitoneal injection and secured to a fixation platform with their abdomens facing upwards. The progression of rat fur growth was monitored and the direction of shaving being opposite to the direction of fur growth. Initially, a robust utility wool shears should be employed to remove the terminal hair, during this phase, gentle manipulation of the skin is imperative to prevent the blade's edge from puncturing the epidermis. Subsequently, a fine-toothed razor was used to eliminate the finer hair. Prior to its use, the integrity of the mesh on the fine razor was verified to avert skin injury. Repeated back-and-forth shaving was prohibited. Any sections of injured skin were delineated with a marker to prevent subsequent invisibility during handling. Euthanasia was achieved through cervical dislocation. An incision was meticulously made with sharp surgical scissors along the upper and lower abdomen, exercising caution to avoid damaging the muscle fibres. The shaved skin was clamped with forceps and a incision was executed along one side of the skin using the surgical scissors, followed by the removal of subcutaneous tissue with ophthalmic curved scissors and the final skin incision. The epidermal layer of the specimen was positioned downward, with the skin extended and affixed to the dissecting table using a thumbtack. Subcutaneous tissue was removed with small forceps and ophthalmic bending scissors, washed with normal saline, and bagged.

The Franz vertical diffusion cell (SYT-101 multifunctional transdermal diffuser, Yanji Aidi Zhu Technology Co., LTD.) was utilized to immobilize the skin of the treated rats between the donor and receiver cells, ensuring that the epidermis faced the donor cell and the dermis faced the receiver cell. The designated diffusion area was 1.54 cm². In vitro transdermal assay was conducted using temperature-sensitive drop, utilizing a commercial product as the control and 30% anhydrous ethanol-normal saline serving as the receiver solution. Subsequently, 0.4 mL of the test preparation or control was instilled into the drug delivery compartment and uniformly applied to the rat's skin. Additional 4 mL of 30% anhydrous ethanol-normal saline was then added to the receiver compartment to expel any bubbles and ensure the rat's skin was immersed at the same level as the liquid. Following continuous mixing at a temperature of 32°C and a speed of 500 rpm, 4 mL of the receiver solution was collected at various time intervals post-administration. Afterwards, 4 mL of fresh receiver solution at 32°C were added to replace the collected samples. The withdrawn receiver solution was passed through a 0.45 µm organic microporous filter membrane, and the filtrate was collected to measure drug content using UV absorbance (UV-1801 Beijing Beifen rayleigh Analytical Instrument (Group) Co., LTD.) at wavelengths of 269 nm and 244 nm. The cumulative permeability was calculated accordingly. Cumulative osmotic concentrations at each time point and the corresponding cumulative osmotic quantities for the test preparation were computed using the established cumulative osmotic concentration formula. The sampling time was plotted along the x-axis and the cumulative osmotic quantity on the y-

axis. Statistical analysis of the cumulative permeability aided in the selection of the optimal formulation for enhancing drug permeation. The formula for calculating cumulative permeability was as follows:

$$Q = \frac{C_n \times V + \sum_{i=1}^{n-1} C_i \times V_i}{s} \quad (1)$$

$$Q_s = \frac{Q}{h} \quad (2)$$

Q: Cumulative drug penetration, Qs: Cumulative penetration of drugs per hour, Cn: The concentration of the drug in the sample at n times of sampling, V: The volume of the receiving liquid in the receiving tank (4 mL), Ci: The concentration of the drug in the sample at time i sampling, Vi: each sampling volume (0.4 mL), S is the effective penetration area (1.54 cm²), h: Penetration time.

2.6. Infrared spectroscopy and differential scanning calorimetry (DSC)

IMD, MOX, and the prepared control samples for formulation 1, 8, 55, 56, and 1, 8, 55, 56 were subjected to infrared spectroscopy analysis (WQF-530 Fourier transform infrared spectrometer, Beijing Beifen Rayleigh Analytical Instrument (Group) Co., LTD.) using an infrared spectrometer, resulting in corresponding spectral data. The specific working conditions for FTIR measurement was KBr mode, spectral range of 400 to 4000 cm⁻¹, spectral resolution of 1 cm⁻¹, 4 times of scans, background acquisition procedure of background than transmittance, spectral preprocessing applied included smoothing and removal the carbon dioxide peak.

The heat flow diagram of optimal formulation was measured by DSC (HSC-4). The sample was placed in an aluminum dish and heated from 60°C to 170°C at a rate of 5 °C/min under the protection of nitrogen.

2.7. Rheometry

Rheological research primarily investigated the correlations between viscosity and temperature, as well as viscosity and shear rate using TA (Discovery HR-20, USA). The temperature scope for constructing viscosity and temperature curves extended from room temperature to 50°C, incorporating the modal temperature profiles of formulations 1, 8, 45, 47, 48, 55, and 56, which were conducted at frequencies of 0.1 Hz and heating rates of 1 °C/min within the temperature range of 25°C to 50°C. Additionally, the viscometer-shear rate relationships for these formulations were tested at temperatures of 25°C, 30°C, 32°C, and 37°C, shear rates were recorded in the range from 1 to 100 s⁻¹.

2.8. Skin irritation

A piece of skin on the back of one healthy rabbit (3 cm × 3 cm) was selected and shaved. Each piece of skin was administered the optimal prescription, commercial available product (Advocate) and normal saline respectively. The skin conditions of the rabbits were observed.

3. Results and discussion

3.1. Transdermal test in rats

Formulation procedure was schematic illustrated in Fig. 1. According to Fig. 2A, it illustrated the cumulative penetration curve for IMD within the commercially available product (Advocate, Bayer), as well as for formulation 1, 8, 43, 54, 55, and 56. The result illustrated that the cumulative permeability of IMD in commercial product (Advocate, Bayer) underwent substantial fluctuations over time, whereas the cumulative permeability of IMD in formulations 1, 8, 43, 54, 55, and 56 exhibited minimal variance with respect to time, suggesting that the alteration in cumulative permeability was dose-form dependent. The temperature-

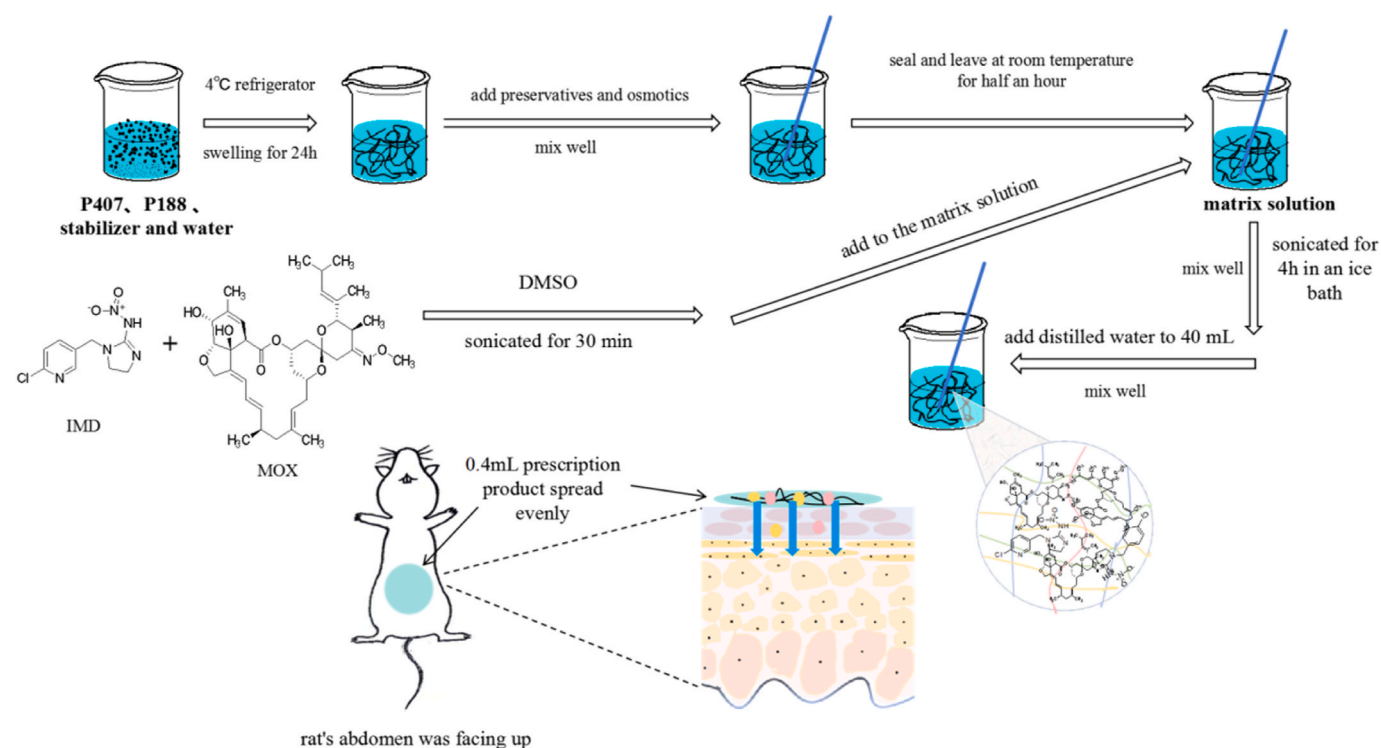


Fig. 1. Schematic diagram of the form process and transdermal application of IMD and MOX temperature-sensitive drop.

sensitive drop enabled a sustained release of the medication.

Fig. 2B described the IMD drug cumulative penetration curve of the temperature-sensitive drop composite of IMD and MOX with different dosages of DMSO and 1,2-propylene glycol. It can be seen that the cumulative penetration of IMD in formulation 43 was the smallest when the time exceeded 20 h. Osmotic enhancer of 1,2-propylene glycol was added to formulation 8, while no osmotic enhancer existed in formulation 43. The results showed that the cumulative permeability of IMD in formulation 43 was less than that of formulation 8, demonstrating that the osmotic enhancer can promote the cumulative permeability of drug. The doses of DMSO and 1, 2-propanediol varied for formulation 1 and formulation 8. Compared with formulation 1, formulation 8 increased the dose of DMSO and reduced the dose of 1, 2-propanediol. The cumulative permeability of IMD in formulation 8 was greater than that of formulation 1, indicating that only changing the dosage of DMSO and 1, 2-propylene glycol in the formulation would cause a change in the cumulative permeability of IMD, and the cumulative permeability of IMD was larger when the dosage of DMSO and 1, 2-propylene glycol were 10.12 g and 3.03 g, respectively. In addition, the cumulative permeability of IMD in formulation 54 with lower dose of DMSO and higher dose of 1, 2-propylene glycol turned out to be greater than that of formulation 8 when the time exceeded 25 h. The results showed that when the doses of DMSO and 1, 2-propanediol were 9.68 g and 3.5 g, respectively, after 25 h of use of the formulation drug, the cumulative penetration of the formulation 54 drug IMD was greater. Formulation 55 with higher dose of DMSO presented higher cumulative permeability of IMD, indicating that the DMSO also had the effect of promoting osmosis to a certain extent. At 36 h, the cumulative permeability of IMD in formulation 56 was greater than that of formulation 55 owing to the added 0.2 g HPMC E5 in formulation 56, indicating that HPMC E5 could promote the cumulative permeability of drugs[22].

Fig. 2C illustrated the cumulative permeation of MOX within commercial product (Advocate, Bayer) and formulations 1, 8, 43, 54, 55, and 56 increased through with time. It was observed that the cumulative permeation of MOX in the commercial product (Advocate, Bayer) exhibited significant changes over time, whereas the cumulative

permeation of MOX in the formulations remained relatively stable. This suggested that the changes in the cumulative permeation of the drug over time were associated with the dosage formulation. The temperature-sensitive drop enabled a sustained release of the medication.

Fig. 2D displayed the MOX drug cumulative penetration curve of the temperature sensitive drop composite of IMD and MOX with different dosages of DMSO and 1,2-propylene glycol. The cumulative permeability of MOX in formulation 43 with no osmotic enhancer was less than that of formulation 8 with osmotic enhancer 1, 2-propylene glycol during the experimental period, demonstrating the osmotic enhancer could promote the cumulative permeability of the drug.

The difference between formulation 1 and formulation 8 can be concluded as the doses of DMSO and 1, 2-propanediol. Compared with formulation 1, formulation 8 with higher the dose of DMSO and lower dose of 1, 2-propanediol exhibited greater cumulative permeability of MOX, indicating that the enhancement of DMSO could promote the cumulative permeability of the drug to a certain extent. The reason may be that DMSO can promote the solubility of drug molecules more than 1, 2-propylene glycol, thereby accelerating the penetration of drug into the skin. In addition, when the doses of DMSO and 1, 2-propylene glycol were 9.68 g and 3.5 g, respectively, the cumulative permeability of MOX in formulation 54 was greater than formulation 8, indicating that the cumulative permeability of the drug could be promoted by changing the ratio between the dose of solvent and osmotic promoter to a certain extent. Formulation 55 with higher dose of DMSO than formulation 54 presented higher cumulative permeability of MOX, indicating that the enhancement of DMSO within a certain range can improve MOX permeability([23]; H. X. [24–27]). The cumulative permeability of MOX in formulation 56 with 0.2 g HPMC E5 was greater than that of formulation 55 when the experimental time exceeded 15 h, indicating that HPMC E5 could promote the cumulative permeability of drugs. After calculating Q, the results in Table 1 obviously revealed that temperature-sensitive drop sustained drug penetration compared to drops. In addition, there are significant differences between the drug penetration of formulation 54 and formulation 55 compared to

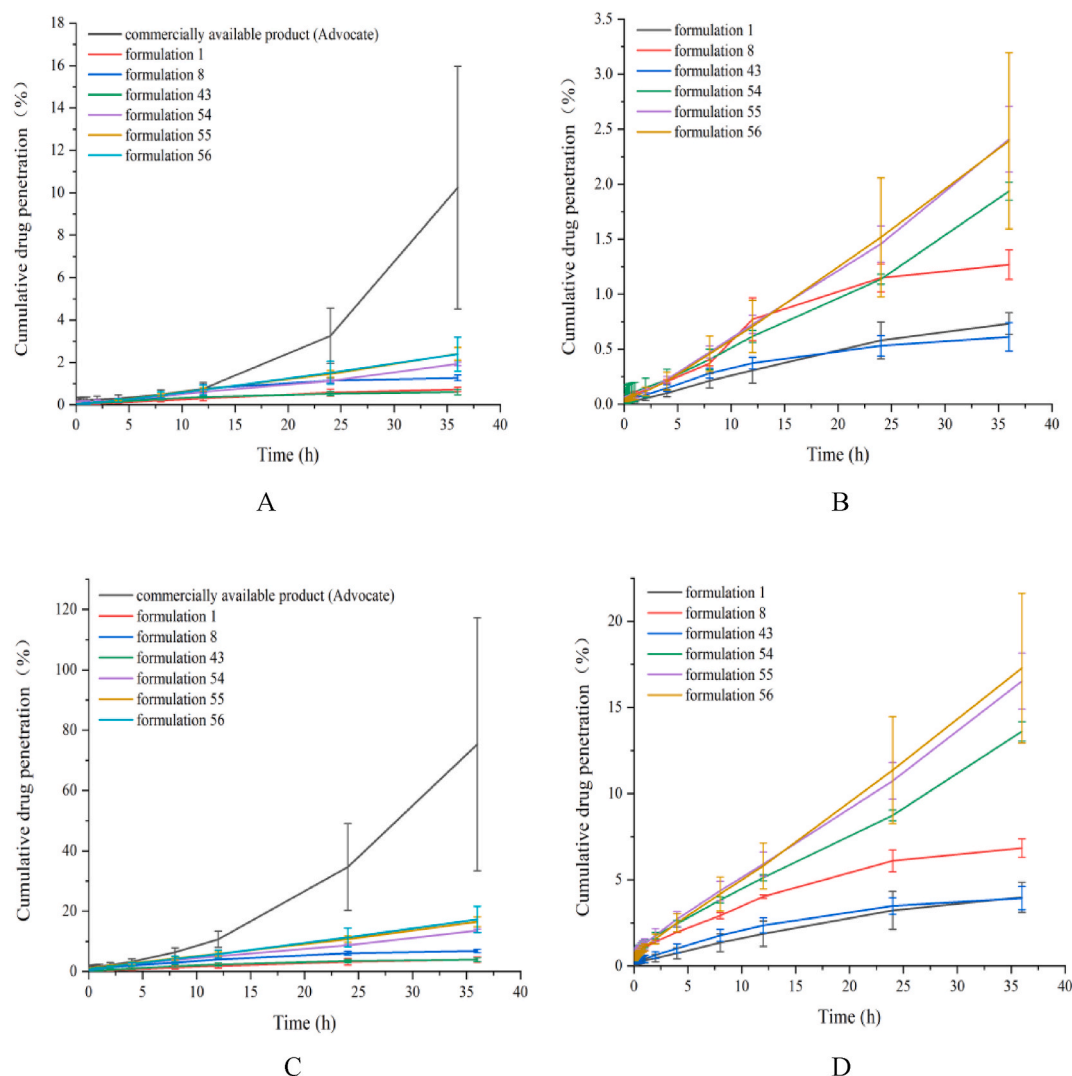


Fig. 2. Cumulative drug penetration curves of IMD (A and B) and MOX (C and D) from commercial available product and various formulation of IMD and MOX temperature-sensitive drop.

Table 1

Drug penetration of IMD and MOX temperature-sensitive drop.

Formulation	Q (mg·cm ⁻²)	
	IMD	MOX
Commercially product (Advocate, Bayer)	2.66	1.96
1	0.19	0.10
8	0.18	0.08
43	0.17	0.11
54	0.50**	0.35**
55	0.63	0.43*
56	0.62**	0.45**

*P < 0.05, compared with formulation 43; **P < 0.01, compared with formulation 43.

formulation 43, sufficiently demonstrated that 1,2-propylene glycol was crucial for achieving high drug penetration while the addition of HPMC E5 can control its function, showing the drug penetration enhancement effect of HPMC E5 for formulation 56 was superior because the dosage of 1,2-propylene glycol can not be so high to remain safe application. The relatively large error in transdermal results was mainly due to the fact that the thickness of each piece of skin varied, and the skin conditions of different mice also differed, which was reasonable.

3.2. Design expert

According to the central composite stochastic response surface design, the equation was drop temperature (°C) = 27.33-1.48A + 0.1354B + 1.81C (A is P407, B is P188, C is DMSO), indicating that adding A can reduce the drop temperature, and adding B and C can increase the drop temperature.

According to Fig. 3A and B, when P407 was 4.4 g and 5.2~8.8 g, and P188 with dosage of 1.2 g and 1.6~3.2 g, the drop temperature of the preparation was 25°C, showing that preparation has been gelled at room temperature (25°C) and there is no fluidity. However, when 4.8 g P407 and 1.4 g P188 were applied, the gelation temperature could be varied by changing the dosage of DMSO. Fig. 3C showed that when DMSO was 4.4 g, 8.8 g and 10.12 g, the gelation temperature turned out to be 25°C. However, when DMSO was in the range of 8.8 to 10.12 g or 10.56 to 14.08 g, the gelation temperature was higher than 25°C with a certain fluidity. 9.68 g or 14.08 g DMSO can obtain the gelation temperature of 32°C, which was qualified for application. Fig. 3D~F showed the dosage of P407, P188 and DMSO in different formulations, which can provide a reference for the preparation of the optimal formulation.

Fig. 4 displayed the gelation temperature after adding different doses of P407 and P188. Here, the axes A, B, and C represent the dose (g) of P407, the dose (g) of P188, and the gelling temperature (°C),

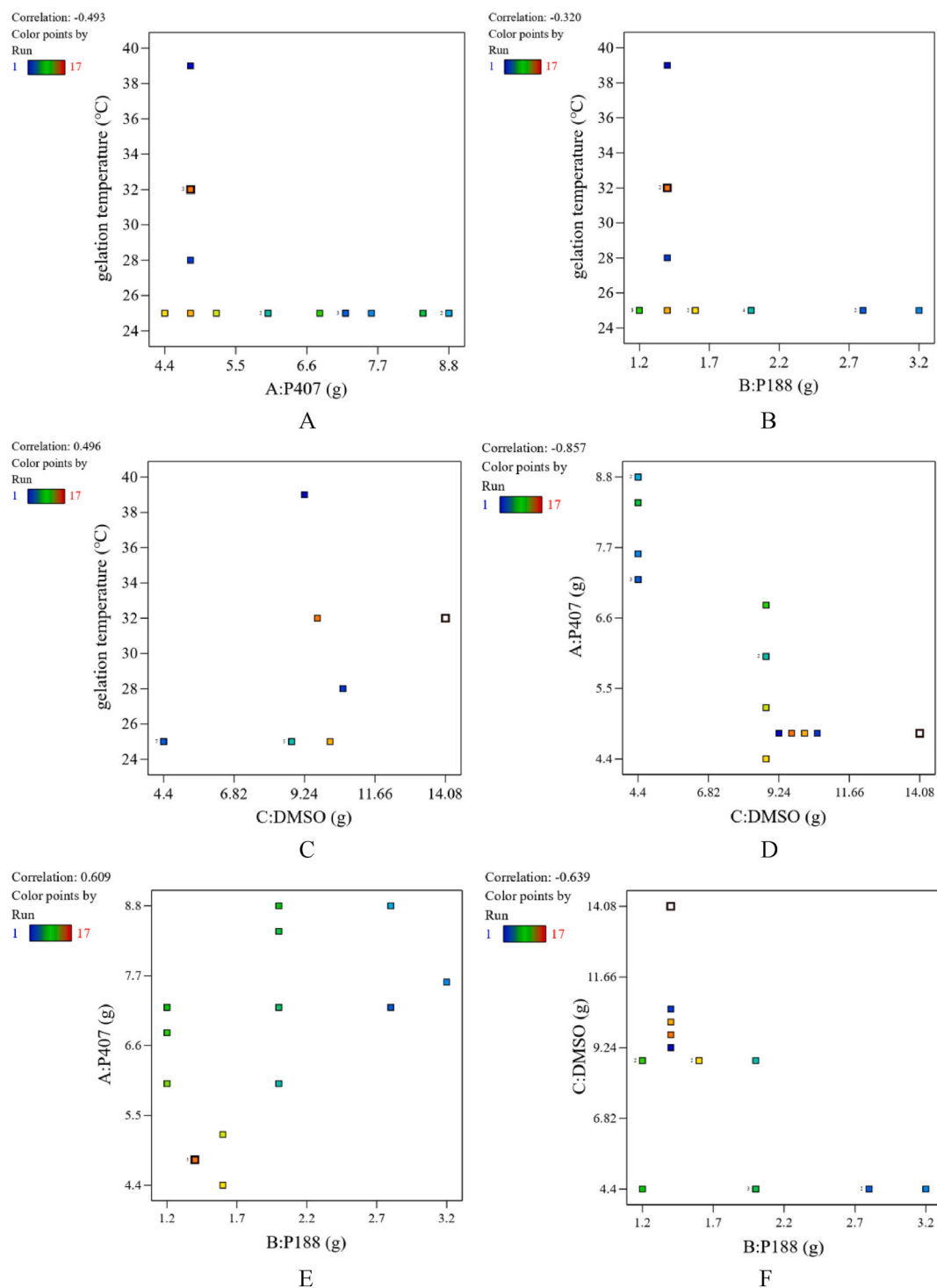


Fig. 3. Central composite design of interaction relationship between factors.

respectively. Fig. 4A showed that when P407 was in the range of 6.6 to 8.8g and P188 was within 1.2-3.2 g, the preparation formed gel at about 25°C, which did not meet the ideal preparation gelation conditions. According to Fig. 5, 4.8 g P407 and 1.4 g P188, the gelling temperature of the preparation was higher than 30°C. In this case, the fluidity of the preparation can be adjusted by changing the type or dose of the osmosis agent to make it meet the condition of gelling temperature. Overall, DMSO and P407 had stronger impacts on gelation temperature than P188 according to two dimensional and three dimensional effect surface maps, demonstrating that drug solvent and assistant drop matrix

performed vital roles in IMD and MOX temperature-sensitive drop.

3.3. Infrared spectroscopy analysis

According to Fig. 6, IMD spectrum mainly showed the following absorption peaks: the strong O-H stretching vibration at 3200-3600 cm^{-1} , C-H stretching vibration at 2900-3000 cm^{-1} , -C=N stretching vibration at 1600-1700 cm^{-1} , C-C stretching vibration at 1400 to 1600 cm^{-1} . MOX presented peaks in the spectra were derived from the O-H, -C=O and other functional groups. Stretching vibrations

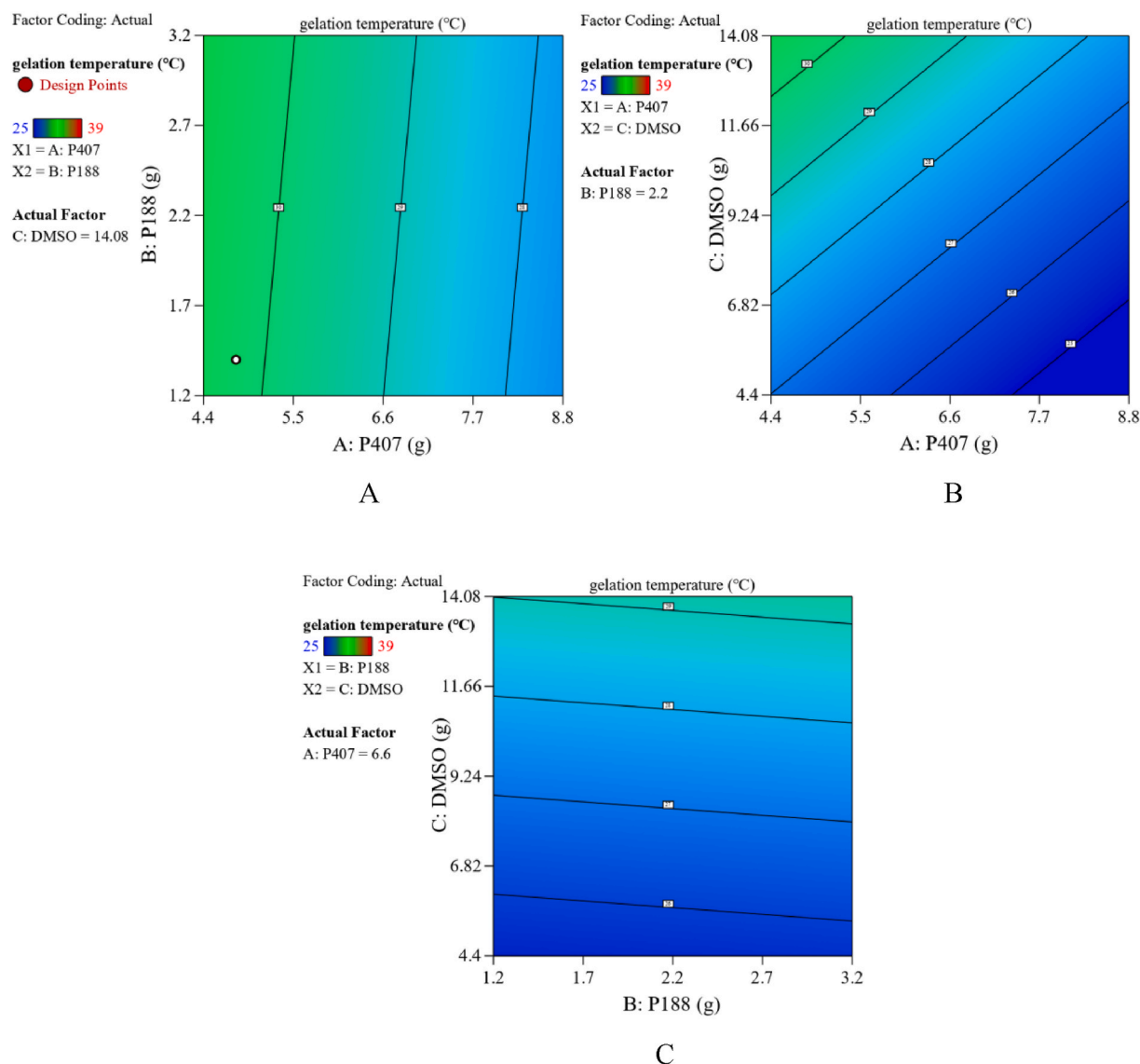


Fig. 4. Central composite design of two dimensional effect surface map.

for O-H typically occurred in the range of 3300 to 3500 cm^{-1} , for -C=O in the range of 1700 to 1750 cm^{-1} , for C-C stretching vibrations in the range of 1500 to 1800 cm^{-1} , and for -CH_3 in the wavenumber range of 2870 to 2960 cm^{-1} . Formulation 1, 8, 55, 56 showed the same peak as IMD at the wavenumber of 1567.8 cm^{-1} , while the blank control group with formulation 1, 8, 55 and 56 did not display the same peak as the drug at the wavenumber of 1567.8 cm^{-1} , indicating that the C-C bond of IMD only had C-C stretching vibration in the preparation. The control groups of formulation 1, 8, 55 and 56 did not show the same peak as IMD at the wavenumber of 3355.5 cm^{-1} , indicating that the O-H of the IMD drug structure in the preparation was not stretching vibration at the wavenumber of 3200 – 3600 cm^{-1} , which may be caused by the low concentration of IMD. On the contrary, these groups all showed the same peak at the wavenumber of 2983.3 cm^{-1} as that of IMD and MOX. MOX presented a stretching vibration peak of -C=O at wavenumber of 1722.1 cm^{-1} , while the formulations 1, 8, 55, 56 and their blank controls did not show the same peak as MOX, but the formulations 1, 8, 55, 56 and their blank controls all showed the same absorption peak at the same wavenumber. In addition, DSC result that shown in supporting data Fig. S1 demonstrating that the two drugs were amorphous in the matrix since no drug melting peaks (IMD: 140°C , MOX: 132°C) were presented.

3.4. Rheometry

Fig. 7 A to D showed the shear rate-viscosity curves of compound temperature-sensitive drop of IMD and MOX with different formulations at 25°C , 30°C , 32°C , and 37°C , respectively. Figure A illustrated the shear rate-viscosity curve of compound temperature-sensitive drop of IMD and MOX with different formulations at 25°C . The difference between formulation 8 and formulations 45, 47, and 48 is that HPMC was not added to formulation 8, whereas HPMC E5 was added to formulations 45, 47, and 48. In addition, formulation 56 contained 0.2 g more HPMC compared with formulation 55. The viscosity of formulations 8 and 55 increased with the shear rate, while the viscosity of formulations 45, 47, 48 and 56 decreased with the shear rate, indicating that HPMC E5 played a thickening role in the preparation. The difference between formulation 1 and 8 was that the ratio of DMSO and 1, 2-propylene glycol used in formulation 8 was greater than that in formulation 1, indicating that the degree of change in viscosity with increasing shear rate can be greater when the ratio of DMSO and 1, 2-propylene glycol increased. The models of HPMC used for formulation 47 and 48 were different, with HPMC E5 and HPMC E50 used for formulation 47 and 48 respectively. At temperatures including 25°C , 30°C , and 32°C , the viscosity of formulation 48 was higher than that of formulation 47 during

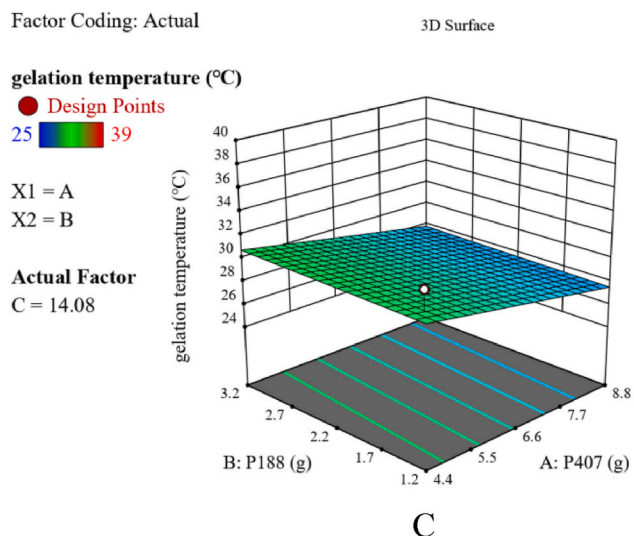
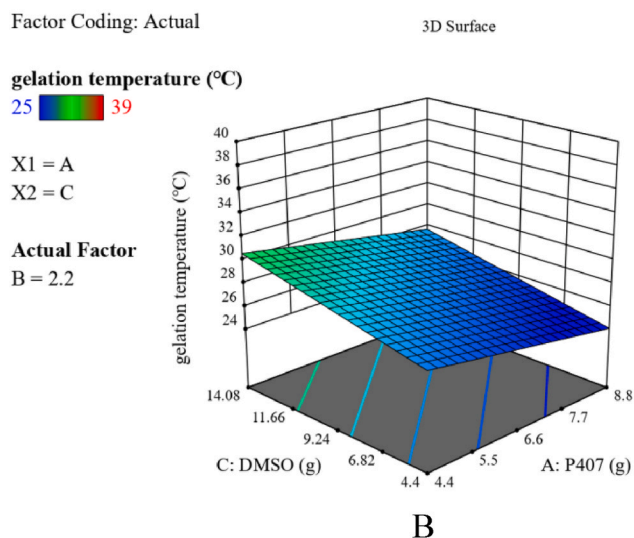
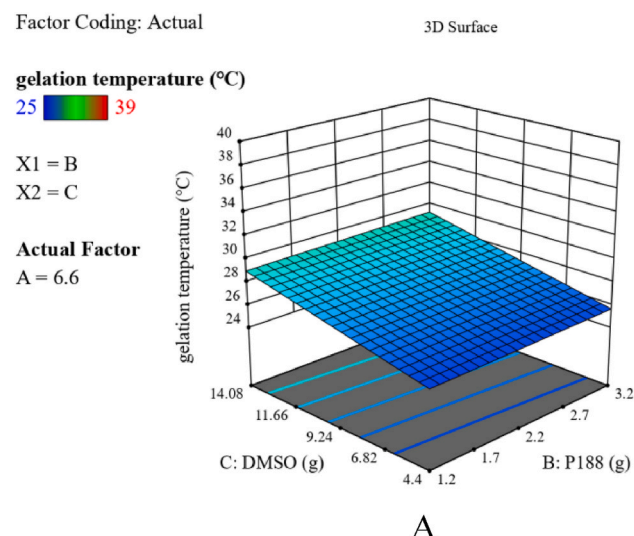


Fig. 5. Central composite design of three dimensional effect surface map.

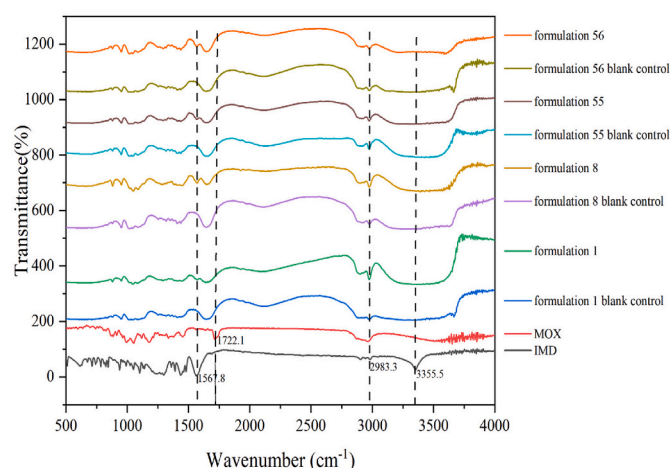


Fig. 6. Infrared spectroscopic analysis of IMD, MOX, and IMD and MOX temperature-sensitive drop.

the shear rate was 0-40 1/s, while the viscosity of formulation 47 was similar to that of formulation 48 during the shear rate was 40-110 1/s, indicating that at low shear rates, HPMC E50 had little effect on the viscosity of the preparation, and at high shear rates, HPMC E50 had a great effect on the viscosity of the preparation. HPMC E5 and HPMC E50 had similar effects on the viscosity of the temperature-sensitive drop. At 37°C, when the shear rate was 0-60 1/s, the viscosity of formulation 48 was higher than that of formulation 47, while when the shear rate was 60-110 1/s, the viscosity of formulation 47 was similar to that of formulation 48, indicating that HPMC E50 had a great influence on the viscosity at low shear rate, and HPMC E50 had little influence on the viscosity at high shear rate. HPMC E5 and HPMC E50 had similar effects on the viscosity of the preparation. The doses of HPMC used in formulation 45 and 47 were different, and the HPMC E5 used in formulation 45 and 47 were 0.2 g and 0.08 g, respectively. At 25°C, the viscosity of formulation 45 was higher than that of formulation 47 with the shear rate of 0-5 1/s, while the viscosity of formulation 47 was higher than that of formulation 45 when the shear rate was 5-110 1/s, indicating that higher doses of HPMC E5 had little effect on the viscosity at low shear rate. Conversely, at high shear rates, the viscosity of the preparation was higher than that of formulation 45. Lower doses of HPMC E5 had a greater effect on the viscosity of the preparation. At 30°C, 32°C and 37°C, the viscosity of formulation 45 and 47 decreased with the increase of shear rate, and the viscosity of formulation 47 was always higher than that of formulation 45, indicating that the thickening effect of HPMC E5 was related to the dose used. The proportions of DMSO and 1,2-propylene glycol used in formulation 45 and 56 were different, and formulation 56 was greater than formulation 45. At 25°C, 30°C, 32°C and 37°C, the viscosity of formulation 56 was always greater than that of formulation 45 with the increase of shear rate, indicating that higher dosage ratio of DMSO/1, 2-propylene glycol had little effect on the viscosity of the preparation with the increase of shear rate.

Fig. 8 showed the rheological curves of temperature-sensitive drops of IMD and MOX compounds of formulations 1, 8 and 55 at different temperatures, respectively. When the shearing rate was less than 20 1/s, the viscosity of the compound temperature-sensitive drop of IMD and MOX turned out to be the highest at 32°C and the lowest at 37°C, indicating that the drop had better fluidity as the temperature increased. However, the viscosity at 25°C was less than that at 32°C and greater than that at 30°C, suggesting that the viscosity of the temperature-sensitive drop decreased with the increase in temperature less than or equal to 30°C. When the shearing rate was between 20 and 110 1/s, the viscosity of the formulation at 25°C remained almost unchanged. When the formulation temperature was 30°C, 32°C, and 37°C, the viscosity decreased with the increase in shearing rate, and the viscosity decreased

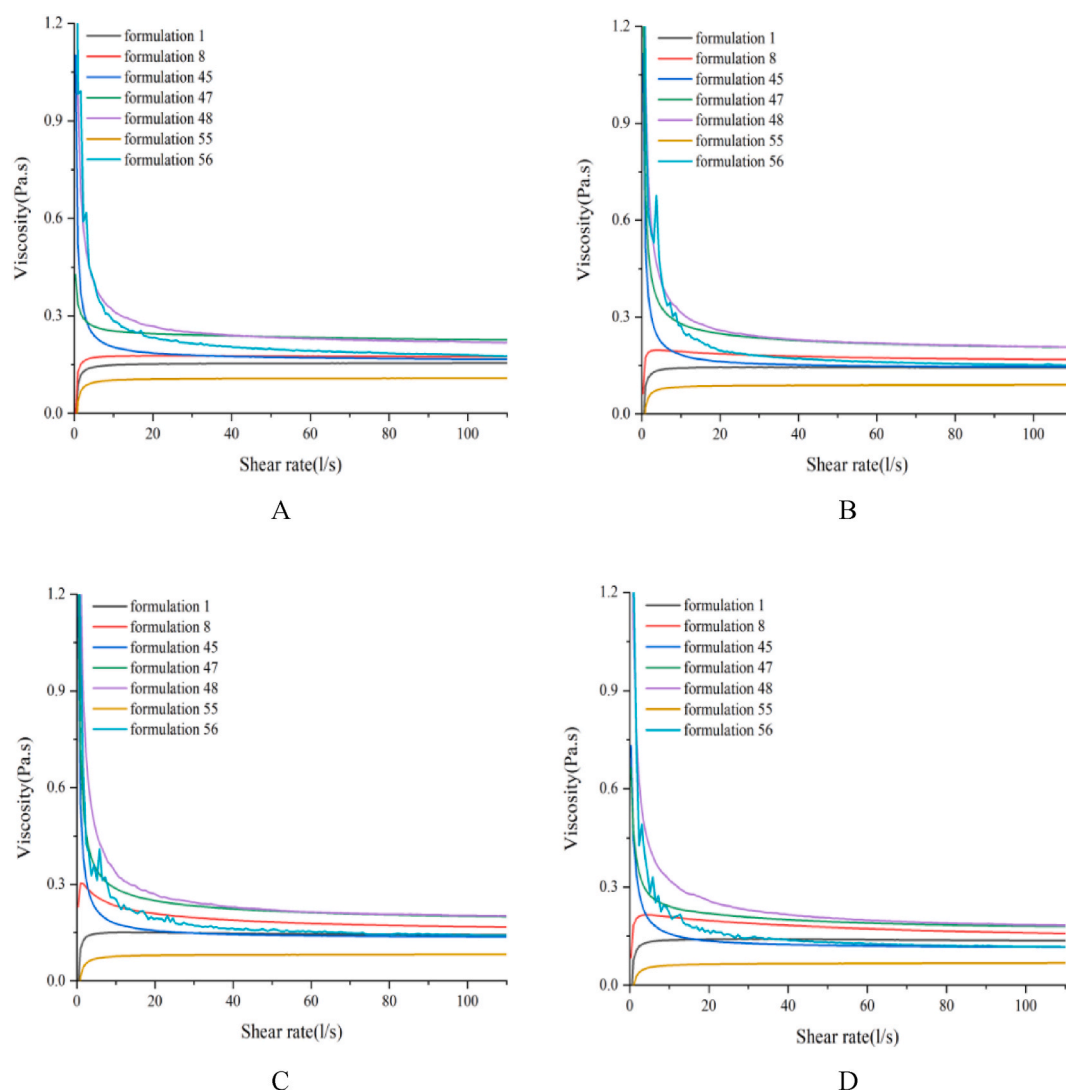


Fig. 7. A, the shear rate-viscosity curves of compound temperature-sensitive drop of IMD and MOX with different formulations at 25°C; B, the shear rate-viscosity curves of compound temperature-sensitive drop of IMD and MOX with different formulations at 30°C; C, the shear rate-viscosity curves of compound temperature-sensitive drop of IMD and MOX with different formulations at 32°C; D, the shear rate-viscosity curves of compound temperature-sensitive drop of IMD and MOX with different formulations at 37°C.

the most at 32°C, which suggested that the gelation time was shorter at 32°C, which can avoid the loss of drugs and improve the utilization rate of drugs. In formulation 8, the dose of DMSO was higher and the dose of 1, 2-propylene glycol was lower compared with formulation 1. The result demonstrated that when the shear rate was less than 5 l/s, the viscosity of the compound temperature-sensitive drop of IMD and MOX increased with the increase of the shear rate. It was possible that more solvent DMSO was subject to change in shear rate to alter viscosity with the temperature less than or equal to 32°C and the degree of viscosity change enhanced with the increase of temperature. When the shear rate was 5~110 l/s, the viscosity of the preparation at 25°C almost did not change with the shear rate. At 30°C, 32°C and 37°C, the viscosity of temperature-sensitive drops decreased with the increase of shear rate, and the viscosity decreased the most when the preparation temperature was 32°C. It can be inferred that the preparation has a shorter gelling time at 32°C, which can avoid large drug loss and improve the utilization rate of drugs. Fig. 3 showed the rheological curves of formulation 55 at different temperatures. According to the information available, formulation 55 has a larger dose of DMSO compared to formulation 1, and a smaller dose of permeation enhancer 1,2-propylene glycol. Compared to Formulation 8, Formulation 55 has a larger dose of both

DMSO and permeation enhancer. When the shear rate ranged from 0 to 110 l/s, formulation 55 exhibited increased viscosity across various temperatures, indicating it behaved as a shear-thickening fluid. At the same shear rate, the viscosity decreased with increasing temperature, suggesting that the higher concentration of DMSO may be affected by the shear rate, resulting in changes in viscosity.

Fig. 4H to K showed the rheological curves of temperature-sensitive drops of IMD and MOX compounds of formulations 45, 47, 48 and 56 at different temperatures, respectively. According to the attached Table 1, formulation 45, which contains 0.2 g more HPMC E5 compared to formulation 8, exhibited reduced viscosity across various temperatures when the shear rate ranged from 0 to 110 l/s, demonstrating that it behaved as a pseudoplastic fluid. Additionally, as the temperature increased, the viscosity decreased, indicating that HPMC E5 improved the rheological properties of the formulation, allowing it to better adhere to skin at body temperature, thereby preventing drug loss, extending the drug action duration and enhancing stability. It can be obtained from the attached table, formulation 47, which contains 0.08 g less HPMC E5 compared to Formulation 45, showed reduced viscosity in various temperatures when the shear rates ranged from 0 to 110 l/s, indicating that it belonged to a pseudoplastic fluid. Specifically, at shear

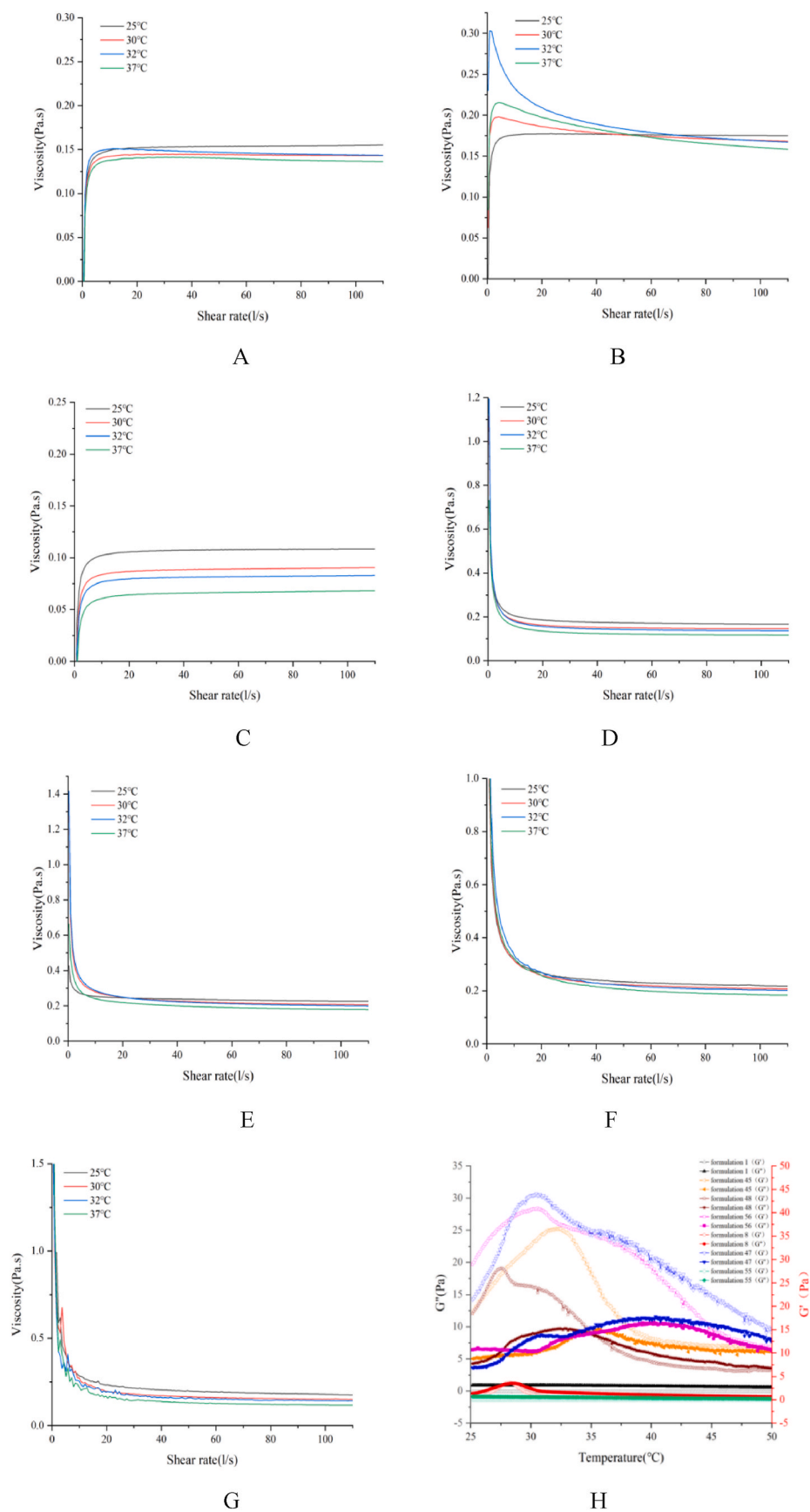


Fig. 8. A to C showed the rheological curves of temperature-sensitive drops of IMD and MOX compounds of formulations 1, 8 and 55 at different temperatures, respectively. D to G showed the rheological curves of temperature-sensitive drops of IMD and MOX compounds of formulations 45, 47, 48 and 56 at different temperatures, respectively.

rates between 30 and 110 l/s, the viscosity decreased more significantly with increasing temperature for formulation 47. When the shear rate ranged from 0 to 10 l/s, the decrease in viscosity was greater at 25°C, 37°C, and 30°C, suggesting that HPMC E5 improved the rheological properties of the formulation and enhanced its stability. A smaller dosage of HPMC E5 can alter the rheological performance of the formulation. It can be seen from the schedule, formulation 48 differed from Formulation 47 only in the HPMC type, formulation 48 applied HPMC E50 instead of HPMC E5. When the shear rate ranged from 0 to 110 l/s, formulation 48 exhibited decreased viscosity in various temperatures, indicating it behaved as a pseudoplastic fluid. At shear rates between 20 and 110 l/s, the viscosity decreased significantly with increasing temperature, while at shear rates between 0 and 20 l/s, the decrease in viscosity was greater at 25°C, 30°C and 37°C. This suggested that HPMC E50 can improve the rheological properties of the formulation, allowing it to better adhere to skin at body temperature, preventing drug loss and extending the drug's action duration, thereby enhancing stability[22]. However, the decrease in viscosity was not directly related to temperature changes at low shear rates. Available from the attached table, formulation 56 contained 0.2 g more HPMC E5 than formulation 55. When the shear rate ranged from 0 to 110 l/s, formulation 56 exhibited reduced viscosity at various temperatures, indicating it behaved as a pseudoplastic fluid, and the viscosity decreasesd with increasing shear rate, suggesting improved rheological properties that allowed better adherence to skin at body temperature, preventing drug loss and extending the action time, thus enhancing stability. Compared to formulation 45, formulation 56 had increased doses of DMSO and 1,2-propylene glycol, potentially influenced by the shear rate, leading to lower viscosity under similar conditions.

Fig. 8H showed the variation curves of storage modulus and loss modulus of formulation 1, 8, 45, 47, 48, 55 and 56, where G' and G'' represented for storage modulus and loss modulus respectively. According to the provided information, the G' and G'' did not change with temperature for formulations 1 and 55, indicating the system mainly existed in a sol state. For formulation 8, both G' and G'' increased with increasing temperature within the initial temperature range, with G' lower than G'' , suggesting the system was primarily in a sol state. At one certain temperature value, both G' and G'' increased, and G' increased faster than G'' , implying the transition from sol to drop state. The phase transition temperature interval for formulation 8 was around 27–28°C. When the temperature exceeded 30°C, G' and G'' remained almost constant, and G'' was higher than the G' , showing the system was in a drop state. Formulation 45 had an increased amount of HPMC E5 compared to formulation 8, leading to higher G' and G'' . Within the initial temperature region, G' and G'' rose with temperature, with G' increasing faster than G'' , suggesting a phase transition at 25–33°C. When the temperature ranged from 33 to 40°C for formulation 45, both the G' and G'' decreased with temperature rise with a more significant drop in the G' compared to the G'' , while the G' remained higher than the G'' . When the temperature exceeded 40°C, the G' and G'' remained relatively stable without significant changes, indicating the system still existed in a drop state. Compared to formulation 45, formulation 47 had a reduced dose of HPMC E5 (0.08 g). In the initial temperature region, both G' and G'' increased with temperature rise with the former being higher than the latter, indicating the system mainly existed in a sol state. At temperatures between 27 and 31°C, the G' increased faster than the G'' , suggesting a phase transition from sol to drop state occurred within this temperature range. Above 31°C, the G' decreased with temperature rise, while the G'' increased between 31 and 40°C and decreased beyond 40°C. The reduction in HPMC E5 likely affected the size of these modulus with temperature change. Formulation 48 differed from formulation 47 only in HPMC type; formulation 48 used HPMC E50. Below 32°C, the G'' enhanced with temperature increase, remaining below the G' . Between 25 and 27°C, the G' increased with temperature, but fell above 27°C with higher than the initial modulus. Above 32°C, the G' was lower than the initial value and decreased with further

temperature rise, possibly due to weakened intermolecular forces. At 35 to 36°C, there was an intersection point where both modulus decreased with rising temperature with a faster decrease in G' than G'' , indicating HPMC E50 responded to temperature change. For formulation 56, the G' rose with temperature up to 31°C and then decreased above 31°C. This indicates that the higher temperature (more than 31°C), the lower viscosity, and the better systemic fluidity.

To sum up, the results of cumulative drug penetration was formulation 56 > formulation 55 > formulation 8 > formulation 1. In addition, it can be seen from rheological properties that the viscosity of formulations 1, 8, 55 at low shear rates (0–5 l/s) increased with the shear rate at 32°C, and the viscosity at 5–60 l/s no longer increased with the shear rate. However, the viscosity of formulation 56 at low shear rate (0–60 l/s) decreased with the increase of shear rate, and the viscosity greater than 60 l/s no longer enhanced with the increase of shear rate. When the shear rate was greater than 60 l/s, the viscosity order turned out to be formulation 8 > formulation 56 > formulation 1 > formulation 55, where the viscosity of formulation 56 and formulation 1 was similar. According to the paper [28–31], the increase of drop viscosity will reduce the drug release rate and drop dissolution time, and the drug release rate of poloxamer varies according to the composition ratio of the drop matrix and the physicochemical drug properties. In summary, the cumulative drug penetration of formulation 55, 56 was greater than that of formulations 1 and 8, and the viscosity of formulation 8, 56 turned out to be greater than that of formulations 1 and 55 when the shear rate was greater than 60 l/s, which may be affected by factors such as the addition of HPMC E5 and a larger dose of DMSO. The rheology lacked of cooling process to obtain cooling ramp, which was its limitation.

3.5. Skin irritation

The rabbit skin irritation test is a commonly used experimental method for assessing the irritancy of drugs, cosmetics, or other chemicals on the skin of rabbits. After observing the skin conditions of rabbits for 1 h and 24 h, it demonstrated that there was no obvious edema or erythema on the skin of rabbits (see Fig. 9, Table 2, Table 3). The skin irritation test result demonstrated imidacloprid and moxidectin sustained temperature-sensitive drop was safe for external use on skin.

4. Conclusion

In several studies, HPMC has been used to develop controlled release systems due to its unique drop-forming ability and temperature sensitive properties. HPMC as a nonionic polymer offers a range of advantages for drug delivery systems [22], including minimal sensitivity to drug interactions, consistent drug release curves, and pH-independent behavior. This suggests that HPMC E5 may also play a similar role in controlled release in thermodrops of IMD and MOX.

Temperature-sensitive drops were designed to change physical properties in response to ambient temperature changes, thereby controlling drug release. This design was particularly suitable for drugs that require continuous release to maintain a therapeutic effect over a long period of time. Although no studies specific to IMD and MOX were identified, these drops have been shown to be effective in other areas, such as ophthalmic medications and transdermal drug delivery systems. Long-term stability of this formulation should be studied in the future and several important points that consist of systemic compatibility and storage conditions should be seriously explored to remain long stability.

Two drugs, IMD and MOX, are commonly used in the veterinary field, particularly as antiparasitic agents. By incorporating them into a continuous release system, the frequency of administration can be reduced and treatment compliance and effectiveness improved. Thus, if the study was realized, it may provide a more efficient mode of drug administration, especially in animals that are difficult to handle frequently. It is reasonable to speculate that the study may show how



Fig. 9. The skin irritation test at 24 h of commercial available product, the optimal formulation; the optimal formulation without drug; normal saline.

Table 2

Skin irritation evaluation of IMD and MOX temperature-sensitive drop.

Conditions	Grading Criteria	
Skin Redness		Nonirritant
None	0	0-0.4
Mild	1	
Moderate	2	Mild irritation
Severe	3	0.5-2.9
Purple-red erythema to mild eschar	4	
Skin Swelling		Moderate irritation
None	0	3.0-5.9
Mild	1	
Moderate	2	Severe irritation
Severe(1 mm)	3	6.0-8.0
Severe(>1 mm)	4	

Table 3

Skin irritation score of IMD and MOX temperature-sensitive drop.

Time	Commercial available product	Optimal formation	Optimal formulation without drug	Normal saline
0 h	0	0	0	0
1 h	0	0	0	0
24 h	0	0	0	0

HPMC E5 can be used to create an effective, temperature sensitive controlled release drop to improve the traditional delivery.

CRediT authorship contribution statement

Ye Sun: Writing – review & editing, Writing – original draft. **Xuemei Xiao:** Investigation. **Sisi Huang:** Methodology. **Qian Liu:** Validation. **Yu Wang:** Formal analysis. **Jing Li:** Writing – review & editing.

Ethics approval and consent to participate

The animal experiment was performed in accordance with the Ethical Guidelines that approved by the Ethics Review Committee for Animal Experimentation of Shenyang Medical College (Shenyang, China).

Consent for publication

All authors agree to public this submission.

Funding

No funding.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.matadv.2026.100973>.

[org/10.1016/j.mtadv.2026.100973](https://doi.org/10.1016/j.mtadv.2026.100973).

Data availability

Data will be made available on request.

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