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ORIGINAL ARTICLE

New formulation of in situ gelling Metolose-based liquid suppository

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Abstract

Context: An in situ gelling liquid suppository is liquid at room temperature but forms a gel at body temperature. In our work, Metolose® SM-4000 (methylcellulose) is studied that basically shows thermal gelation at 68°C (2%, w/w). *Objective*: The objective was to study the potency of different factors (concentration, pH, additives) to change the value of thermal gelation temperature (T_t) for Metolose® to form an in situ gelling liquid suppository. *Materials and methods*: We studied the effect of Metolose® concentration, pH, and salts (sodium chloride, potassium chloride, sodium hydrogen carbonate, and sodium monohydrogen phosphate) on T_t by viscosimetry. To choose the appropriate compound, in vitro drug release was examined. Rectal safety test was performed on rats in vivo after 12-hour application. *Results*: Increasing the Metolose® concentrations (0.5–4%, w/w), T_t can be decreased, but it also altered the consistency of gel. pH does not affect the T_t. The water-soluble salts allowed reducing the gelation temperature to 37°C. Sodium monohydrogen phosphate in 4.5% concentration was found to be the most appropriate. The impact of examined factors on in vitro drug release of piroxicam from the in situ-formed gel was characterized according to Fickian diffusion. Metolose® and the chosen salt did not cause any morphological damage on the rectal tissues. *Discussion*: According to our study, Metolose® has the physical and chemical potential to be used as base for liquid suppositories.

Key words: In situ gelling suppository, Metolose®, piroxicam

Introduction

Thermosensitive in situ forming gels respond to temperature change as stimuli to show sol–gel transition[1]. These systems are liquids before minimally invasive administration into the body (applicators are commercially available, e.g., for liquid glycerin suppositories), and then the increase of temperature from the ambient to the physiological value gelation or solidification occurs. Several polymers may function as thermoresponsive hydrogel systems for potential biomedical and pharmaceutical applications, including controlled drug delivery[2,3].

The conventional suppository is a traditional favorable rectal dosage form for children and non-cooperating patients. Ideal suppository should be applied without any pain and remain at the administered sites to avoid the first-pass effect in the liver, so the bioavailability can be increased. Usually semisolid suppositories can cause a feeling of discomfort and refusal of the patients, lowering patient's compliance[4,5]. These problems can be solved using in situ gelling, bioadhesive, and liquid suppositories. The liquid suppository exists as solution at room temperature, so it can be administered easily with suitable applicator[6], but at body temperature it instantly gels in the rectum[7–9] and adheres to the mucous membrane. Therefore, an important eligibility criterion of the system is the suitable bioadhesivity so as not to be leaked out from the anus after administration. There were several attempts to develop a temperature-sensitive and mucoadhesive liquid suppository using poloxamer[10,11], but in this cases

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mucoadhesive additives (cellulose derivatives) had to be applied[7].

Many polymers, also having proper attribute like carbopol and sodium alginate, were not suitable vehicles as they were precipitated in the presence of other agents[8].

In our work, water-soluble cellulose ether (Metolose®) was used as a thermoresponsive base of the liquid suppository. These derivatives are often used in poloxamer-based liquid suppositories as bioadhesive additives[12]. Metolose® is nonionic water-soluble cellulose ether, which can be used as gel and film-forming agent. Metolose® is available in three forms: SM type has methyl groups, SH type Metolose® has hydroxypropyl and methyl groups, and SE type has cellulose with hydroxyethyl and methyl groups[13]. On heating the aqueous solution of Metolose® to a certain temperature (T_t), reversible thermal gelation can be observed. The gelation temperature depends on the type of substituents, the concentration of Metolose®, and the rate of heating. The background of thermal gelation is the association between the high substituted parts and the coverage of hydrophobic molecule parts in the network of polymer chain. In a previous article, we studied the effect of different salts on the T_t for hydroxypropyl methyl cellulose (Metolose® SH) to formulate a transdermal therapeutic system[14]; as methyl cellulose has a different gel construction the influence of salts needed to be observed.

The aim of our work was to investigate the applicability of Metolose® as an in situ gelling suppository base. To select the suitable Metolose® type, the consistency of the thermal gel and the thermal gelation behavior were evaluated. As the gelation temperature is above the body temperature, different approaches were studied to shift the temperature with change in the concentration of Metolose®, pH, and using different additives such as sodium chloride, potassium chloride, sodium hydrogen carbonate, and sodium monohydrogen phosphate.

The model drug used in our formulation was piroxicam. Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) and is widely used in therapy in different dosage forms (capsule, tablet, and of course suppository). NSAIDs are often used as rectal delivery system because of the faster effect compared with oral forms. Piroxicam has a long biological half-life, and by rectal administration of this drug it can further be increased, so the time interval of administration can be extended. The anti-inflammatory effect of piroxicam expressed as a long half-life. Added to this advantage, NSAIDs have been shown to reduce risk of colorectal cancer[15]. Because of the well-known side effects of NSAIDS (e.g., NSAID colitis), they are usually used in shorter terms as rectal delivery systems.

Materials and methods

Materials

The model drug was piroxicam (Boots Chemicals, Nottingham, England). Methyl cellulose (Metolose® SM-4000, Shin-Etsu Chemical Co., Tokyo, Japan) and hydroxypropyl methyl cellulose (Metolose® SH-4000 Shin-Etsu Chemical Co.) were applied as suppository base. Sodium chloride, potassium chloride, sodium hydrogen carbonate, sodium monohydrogen phosphate, and citric acid were purchased from Reanal Chemicals Ltd. (Budapest, Hungary) and all were of analytical grade.

Preparation of the Metolose® gel

The required amount (0.5–4%, w/w) of Metolose® powder was continuously mixed with 5.0 g of water (70°C) on a heated magnetic stirrer. Calculated amount of cold water was added to the opaque mixture and stirred until it cleared up. This gel was used as vehicle of the liquid suppository. The required amounts of auxiliary material, such as 9% (w/w) potassium chloride, 8% (w/w) sodium hydrogen carbonate, 7% (w/w) sodium chloride or 5% (w/w) sodium monohydrogen phosphate, and 1% (w/w) piroxicam were added to this system.

Determination of thermal gelation temperature

Two grams of Metolose® solution prepared according to the previously given prescription (Point 2.2.) was poured onto the container (Cup MV) of the HAAKE VT550 rotation viscotester (Haake GmbH, Karlsruhe, Germany) at 20°C, and after setting the measuring parameters the viscosity–temperature curve was determined. The system was first heated from 20°C to 80°C, then cooled back to 20°C to determine the thermal gelation temperature. The following were the measuring parameters: rotor: SV2; heating range: 20–80°C; t = 900 seconds; G = 89 per second; rate of heating, 4°C/min; and thermostat: HAAKE K15 (Haake GmbH).

In vitro drug release test

Rotating basket method was used according to Ph. Eur. 5 at 50 rpm (Pharmatest PTW2 Dissolution Tester, Pharma Test Apparatenbau GmbH, Hamburg, Germany). The dissolution medium was 500 mL of pH 6.8 phosphate buffer solution at 37 ± 0.5°C. The liquid suppositories were thermostated to 37°C in a suppository molding unit to solidify before placing into the basket.

The drug release was continuously monitored for 6 hours with three parallels. The absorbance of the piroxicam of samples was determined by Shimadzu UV-160A Spectrophotometer (Tokyo, Japan) at 350 nm.

Mathematical models for the drug release

Different mathematical models were used to study the liberation profiles of the drug from liquid suppository[16–19]. The comparison was based on the relative standard deviation (RSD) values of liberation rate constants and the regression values (R^2) of linearization.

1. *First-order model:*

$$\frac{M_t}{M_{\max}} = 1 - \exp(-kt), \tag{1}$$

where k is the liberation rate constant, M_t the amount of drug released at time t, and M_{max} the maximal amount of drug released at infinity time.

2. *Higuchi square-root time model:* This model describes diffusion-controlled drug release from matrices, derived from Higuchi's for a planar matrix; however, it is also applicable for systems of different shapes:

$$\frac{M_t}{M_{max}} = kt^{\frac{1}{2}}. \quad (2)$$

3. *Fick's equation:*

$$\frac{M_t}{M_{max}} = kt^n, \quad (3)$$

where n is the release exponent.

Safety test of rectal tissue

All investigations conform to the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1985) and were approved by the ethics committee at Semmelweis University.

Three male Wistar rats weighing 407 ± 15 g were anesthetized with 1.3 g/kg urethane intraperitoneally. Liquid suppository containing 1.5% (w/w) Metolose® SM-4000 with 5% (w/w) sodium monohydrogen phosphate or saline solution for controls were administered at 1.5 g/kg into the rectum 4 cm above the anus through a 22 G feeding needle. The animals were deprived of food and water during the test. The rectum of animals was glued during anesthesia to prevent the leakage of suppository.

The rectum was isolated 12 hours after administration, rinsed with a saline solution, fixed in 10% neutral carbonate-buffered formaldehyde, embedded in paraffin using an embedding center, and cut into slices. The slices were stained with hematoxylin–eosin and observed under a light microscope (Carl Zeiss Axio, Jena, Germany). Representative pictures were photographed using AxioCam MRc 5 camera and AxioVision Rel. 4.5 software (Carl Zeiss).

Results

Study on gel consistence

In the first step of our study, the consistency of different Metolose® types (SH and SM) was compared at same concentration (2%, w/w). There was no significant difference between the consistency at 25°C, but the thermal gelation behavior differed. Different Metolose® types have different thermal gelation temperature. On heating the Metolose® solution above T_t value, different thermal gel consistencies can be observed; SH type forms a pseudoplastic gel whereas the SM type solidifies to a hard, elastic thermogel at 68°C (2%). Based on the comparison of thermal gel consistency of different types of Metolose® systems, Metolose® SM was found suitable because the Metolose® SH type is very soft and can leak out easily from the anus, whereas the thermogel formed from SM type is plastic so it is more appropriate to adhere to the mucosa and avoid leakage. The thermal gel was very soft using Metolose® SH, so it was neglected in further investigations.

The influence of Metolose® concentration on thermal gelation temperature

The thermal gelation temperature of 2% Metolose SM-4000 was determined by measurement of viscosity. The thermal gelation can be observed at 68°C where the viscosity starts to increase indicating the sol–gel transition. T_t of Metolose SM-4000 is above body temperature. The different factors (such as Metolose® concentration, pH and additives) affecting this gelation happening at body temperature by shifting the value of Tt to 37°C were studied.

The change of Metolose® SM-4000 concentration between 0.5% and 4% (w/w) caused a slight decrease in gelation temperature. Figure 1 shows a linear relationship between Metolose® SM-4000 concentration and T_t. The gelation temperature of 4% (w/w) Metolose® SM-4000 solution was at 64°C. It can be concluded that increasing the concentration of Metolose® SM-4000 decreased the T_t values, but the higher concentration solution (4%) is not applicable because of its relative high viscosity (8 Pa·s) at room temperature, which results in a difficult applicable system.

The influence of pH on the value of T_t

Usually, the properties of rheological fluids can be influenced by pH of the dispersion medium, because it can change the gelation process and the gel structure. In our study, the pH of the distilled water applied as dispersion medium was adjusted in the range 2–10 with sodium hydroxide and hydrochloric acid. The gelation temperature of Metolose® SM-4000 gels was not significantly influenced by the pH. Metolose® SM-4000 solution and thermogel were stable at various pH values, and T_t of

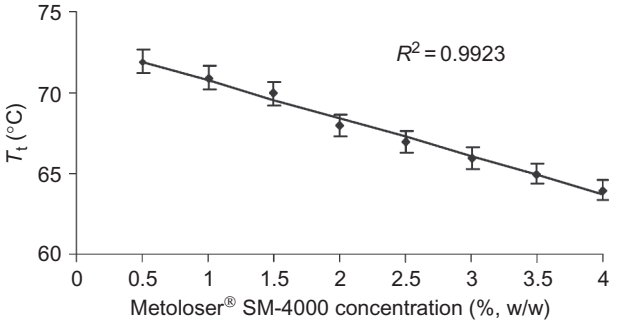

Figure 1. Effect of Metolose® SM-4000 concentration in solution on T_t values (n = 4; RSD ± 3%).

Metolose® SM-4000 could not be decreased with the change of pH.

The influence of salts on the value of T_t

In the next step, the effect of salts (sodium chloride, potassium chloride, sodium hydrogen carbonate, and sodium monohydrogen phosphate) was studied. Different water-soluble salts in different concentration were added to the previously prepared gel. If the salts were added during the preparation of the system, the gel was not formed. Results show that T_t value can be reduced by applying the studied salts in different concentrations: 9% KCl, 8% $NaHCO_3$, 7% NaCl, or 4.5% Na_2HPO_4 is necessary to shift the value of T_t to the body temperature. Plotting the T_t as a function of the concentration of salts linear correlation was observed (Figure 2). The slopes of the straight lines in the case of sodium chloride, potassium chloride, and sodium hydrogen carbonate were similar, and high concentration was required to decrease the T_t to body temperature compared to sodium monohydrogen phosphate. Based on the results, 4.5% (w/w) concentration of sodium monohydrogen phosphate was selected for further work, because it was enough to achieve the body temperature, so it is possible to use a least amount of excipient (Figure 3).

Values of thermal gelation temperature can be determined by the measurement of viscoelastic properties by dynamic (oscillation) methods. G' is the storage modulus and characterizes the elastic property of the material. G'' is the so-called loss modulus and it measures the viscous component of the material. Sol–gel transition can be defined by the temperature at which G' is equal to G'' on the thermogram. A continuous temperature sweep (from 20°C to 70°C at a rate of 1°C/min) was carried out in the case of 2% Metolose® SM-4000 aqueous solutions with 4.5% Na_2HPO_4, and G' and G'' were determined. Figure 3 shows temperature sweep of this experiment, and at 37°C G' and G'' were equal, which referred to the sol–gel transition. The pH value of this system is 8, which later proved to be beneficial in terms of solubility and release of the active substance.

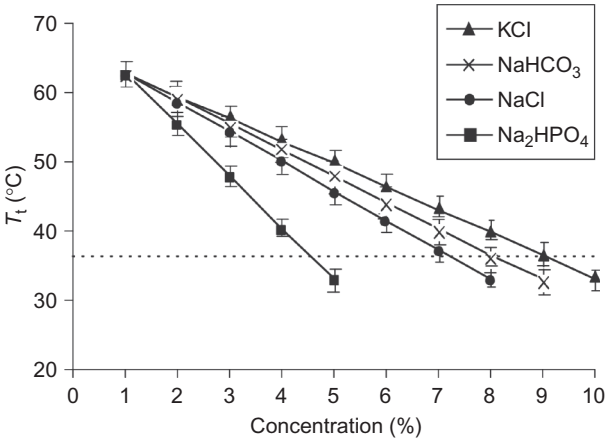

Figure 2. Effect of salts concentration on T_t of 2% (w/w) Metolose® SM-4000 solution ($n = 3$; RSD ± 2%).

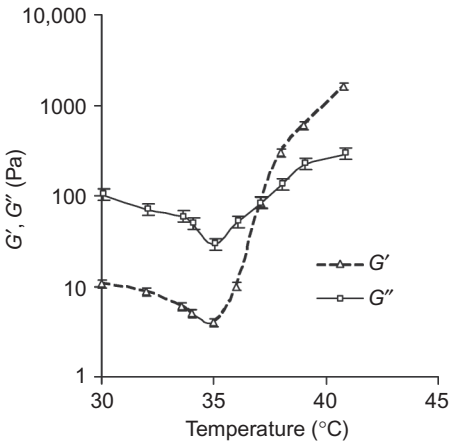

Figure 3. Effect of temperature on the viscosity of 2% (w/w) of Metolose® SM-4000 with 4.5% Na_2HPO_4 ($n = 3$; RSD ± 3%).

In vitro release test

According to the previous results, 4.5% (w/w) of sodium monohydrogen phosphate was chosen to formulate liquid suppository. Anti-inflammatory and analgesics suppositories are widely applied, therefore piroxicam, as model drug, was used in our liquid suppository. Drug content of suppository was 1%. Piroxicam scarcely dissolves in water, but in this basic system, which was provided by 4.5% Na_2HPO_4, this drug (1%) dissolved completely.

Because the concentration of Metolose® SM-4000 as gel-forming agent influences the viscosity and gel strength, it can be expected that the drug release from the gel is also influenced. Examining the effect of Metolose® concentration on the in vitro drug release, the results showed that by decreasing the Metolose® concentration the drug release could be increased significantly. Using 2% (w/w) Metolose® SM-4000 solution 60% drug release can be observed during 6 hours, whereas by decreasing the Metolose® SM-4000 concentration to 1.5% (w/w) this value could be increased to 100% piroxicam during 6 hours. Figure 4 shows that even a little alteration of the gel concentration results in a significant change on drug release: a half percent reduction results in doubly released substance. Our results also show that the Metolose®-based liquid suppository provides sustained drug release, which is an advantageous aspect, and so it allows prolonged action and rarer drug administration.

Comparing the effect of different salts [9% (w/w) KCl, 8% (w/w) $NaHCO_3$, 7% (w/w) NaCl, or 4.5% (w/w) Na_2HPO_4] on drug release from suppositories, significant differences can be observed. A concentration of 1.5% Metolose® SM-4000 was used in this test. Because piroxicam is insoluble in water, in the presence of NaCl and KCl, which proves neutral medium, suspension-type

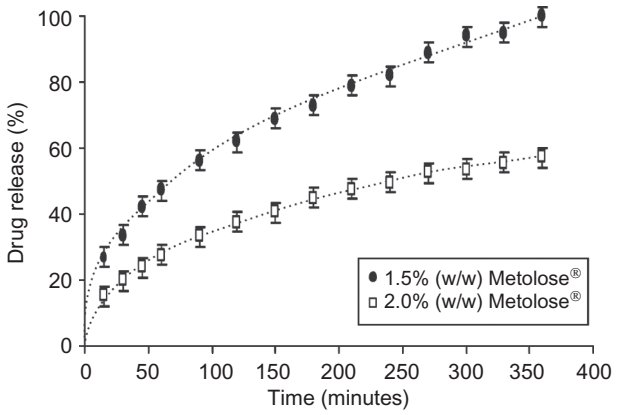

Figure 4. Effect of Metolose® SM-4000 concentration on drug release from 1.5% and 2% (w/w) aqueous thermal gel of Metolose® SM-4000 using 4.5% (w/w) sodium monohydrogen phosphate at 37°C (n = 3; RSD ± 3%).

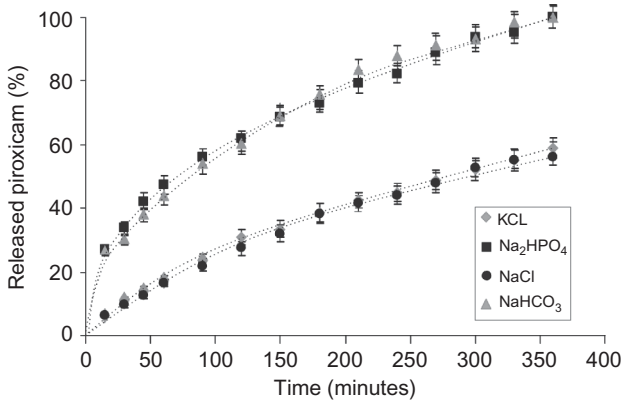

Figure 5. Effect of different salts on drug release from 1.5% (w/w) aqueous thermal gel of Metolose® SM-4000 at 37°C (9% KCl, 4.5% Na_2HPO_4, 7% NaCl, 8% $NaHCO_3$) (n = 3; RSD ± 3%).

suppositories were formed. In the presence of $NaHCO_3$ and Na_2HPO_4, as their alkaline hydrolysis results in basic medium, solution-type system formed, which showed a higher drug release[20].

The dissolved hydrate form of piroxicam released completely during the time of the drug release, but the released amount from suspension-type suppository was under 60% (Figure 5).

The suppositories kept their shape and consistency during the whole examination in all cases. The Metolose® SM-4000-based system dissolves very slowly for several hours in dissolution medium.

Examining the effect of pH on piroxicam release, our results showed that acidic medium did not help the drug liberation, whereas above pH 7 the amount of released piroxicam significantly increased. It can be explained by the pH dependence of the solubility of piroxicam: the solubility of this drug is higher in the basic than in the acidic medium.

Because of sustained drug release, the liberation kinetics was studied. Different kinetic models (first-order model, Fick's model, and Higuchi square-root time model) were compared and Table 1 details the kinetic parameters of drug release. RSD and linear regression coefficient (R^2) were used for comparison. Because the RSD is less in the case of Fick's model, it can be established that the piroxicam release from this in situ-formed suppositories followed Fickian diffusion regardless of the type of applied salts.

Safety test of rectal tissue

Because the selected formulation [1.5% (w/w) Metolose® SM-4000 with 4.5% (w/w) sodium monohydrogen

Table 1. Release rates, regression values (R^2), standard deviations (SDs), and relative standard deviations (RSDs) of drug release of piroxicam from 1.5% Metolose thermal gel containing different salts calculated by different kinetic models.

Kinetic model	Release rate constant (1/min)	R^2	SD	RSD (%)
	4.5% Na_2HPO_4			
First-order model	0.01	0.9639	0.0043	40.70
Fick's model (n = 0.419)	0.077	**0.9981**	0.0015	**1.93**
Higuchi square-root time model	0.044	0.9928	0.0016	3.59
8% $NaHCO_3$				
First-order model	0.02	0.9567	0.0073	35.53
Fick's model (n = 0.435)	0.092	**0.9923**	0.0022	**2.37**
Higuchi square-root time model	0.038	0.9867	0.0032	8.31
7% NaCl				
First-order model	0.012	0.9598	0.0034	28.33
Fick's model (n = 0.401)	0.0067	**0.9912**	0.00051	**7.61**
Higuchi square-root time model	0.0044	0.9875	0.00061	13.86
9% KCl				
First-order model	0.0095	0.9639	0.0053	55.79
Fick's model (n = 0.445)	0.0072	**0.9981**	0.00022	**3.05**
Higuchi square-root time model	0.0038	0.9928	0.00092	24.2

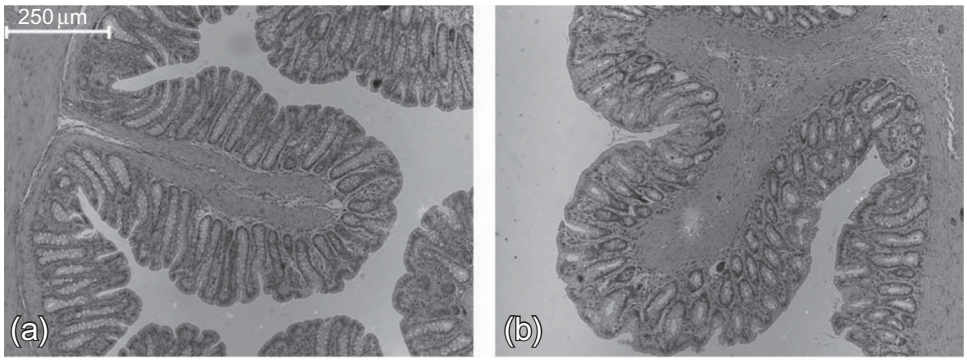

Figure 6. Morphology of rectal mucosa of rats after rectal administration of liquid suppository containing 1.5% (w/w) Metolose® SM-4000 and 5% (w/w) sodium monohydrogen phosphate: (a) control and (b) 12 hours after administration ($n = 2$).

phosphate] was hypertonic, the possibility of rectal mucosa damage was studied. Safety test was performed by observing any irritation on the rectal tissues[21]. The morphology of rectal tissues indicates that this compound did not irritate the rectal tissues (Figure 6) during the test. Previously hypertonic enema was reported to cause disruption on the surface epithelium on rectal mucosa[22,23]. The lack of irritation of the suppository containing Metolose® and sodium monohydrogen phosphate might be explained by the content of sodium phosphate (4.5%, w/w), which was lower than the tissue-damaging threshold level. No leakage was observed during the whole examination in all cases. The ulcer-causing effect of NSAIDs decreases in basic medium, so this developed suppository with pH 8 value reduces this side effect.

Discussion

The thermal gelation behavior of Metolose® SM-4000 was used to develop an in situ gelling liquid suppository. The thermal gelation temperature (T_t) of Metolose® SM-4000 is above the body temperature and so requires the reduction of T_t using different additives. Studying the effect of pH, Metolose® SM-4000 concentration, and some water-soluble salts (sodium chloride, potassium chloride, sodium hydrogen carbonate, and sodium monohydrogen phosphate) on thermal gelation temperature, the Metolose® SM-4000 solution containing 4.5% (w/w) sodium monohydrogen phosphate was found to be the most suitable. By in vitro examination, 60% drug release can be observed during 6 hours using 2% (w/w) Metolose® SM-4000. Decreasing the Metolose® SM-4000 concentration, this value can be increased; in case of 1.5% (w/w) Metolose® SM-4000, the drug release was 100% during 6 hours, but under 1.5% (w/w) Metolose® the consistence of thermal gel was very soft. In the presence of those salts, which generate basic medium, piroxicam was able to dissolve in the gel and released completely from the suppository during the time of the test. The kinetics of drug release in all cases followed Fickian diffusion, so the drug release demonstrated to be matrix-controlled. Metolose® SM-based liquid suppository results in sustained drug release. After 12 hours, no histological damage was observed, which might mean that the used amount of sodium phosphate is under the tissue-damaging value.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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