European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 260–265

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Formulation of thermoresponsive and bioadhesive gel for treatment of oesophageal pain and inflammation

Á. Makó [a,b,*], G. Csóka [b], E. Pásztor [b], S. Marton [b], G. Horvai [a], I. Klebovich [b]

[a] ENT Department, Szent Imre Hospital, Budapest, Hungary
[b] Department of Pharmaceutics, Semmelweis University, Budapest, Hungary

ARTICLE INFO

Article history:
Received 21 May 2008
Accepted in revised form 27 October 2008
Available online 12 November 2008

Keywords:
Thermoresponsive
Bioadhesive
In-situ gelling
Oesophagus
Metolose® 60SH
NSAID

ABSTRACT

The aim of this study was the formulation and examination of a novel thermoresponsive and bioadhesive, in situ gelling drug delivery system, which can be used in the treatment of oesophageal pain and inflammation. A bioadhesive cellulose derivative (Metolose® 60SH) was used as a thermoresponsive material, because Metolose® has thermal gelation properties at certain temperature. The thermal gelation temperature (T_2) of Metolose® 60SH 2 w/w% solution is above body temperature (65–66 °C), but by using different methods (Metolose® 60SH concentration, auxiliary materials), it can be shifted near to body temperature. The pH alteration between pH = 2–10 and the application of different alcohols did not influence the gelation temperature, but using water-soluble salts and changing the concentration of Metolose® 60SH solution between 2 and 3 w/w% the thermal gelation point could be decreased. Different NSAIDs were used as model drugs and which had not influence on thermal gelation temperature, but difference in in vitro liberation and penetration can be observed. In vitro adhesion test pointed out that the condition of investigated membrane can change the adhesion. Morphological test of oesophageal tissue showed that investigated materials had no irritative or tissue-damaging effect on the oesophageal mucosa even after 12 h.

© 2008 Elsevier B.V. All rights reserved.

1. Introduction

Several illnesses related to the oesophagus result in inflammation which causes pain, dysphagia and weight of loss for the patient. It is essential for us to focus on the effective analgetic and anti-inflammatory therapy, as the availability of the conventional oral administered dosage forms is limited. Due to its short transit time and the relative impermeability of the stratified squamous epithelium, drug absorption from the oesophagus is not significant in comparison with the other parts of the gastrointestinal tract. However, it would be desirable that locally acting agents should be used in the treatment of the pain and inflammation in several cases (e.g., oesophageal pain in cancer, inflammation during radiation therapy, fungal infection or reflux disease [1]). In order to reach a considerable drug effect and the absorption from the mucosal surface of the oesophagus (which measures approximately 150–200 cm^2), transit time should be prolonged by using different methods. After the administration of solid dosage forms, unwanted bioadhesive property of the mucosal surface in the oesophagus can be observed in those patients who take their medicine with little or no water at all [2,3]. This phenomenon can be positively used for developing oesophageal dosage forms, e.g., bioadhesive systems formulated by sodium alginate [4,5].

In the past few years, an increasing number of publications have been issued in the subject of the oesophageal drug delivery, but most of them focus only on reflux disease and fungal infection. The development of the responsive dosage forms [6], such as in situ gelling hydrogel systems, is considered a new aspect in the diagnosis and the treatment of illnesses related to the oesophagus [7]. Drug release and physico-chemical properties can be influenced by different external or internal factors (e.g., pH [8], temperature [9,10], electric [11], magnetic field, ultrasound [12,13], or visible wavelength in case of photosensitive systems [14,15]) in responsive systems. Drug release from thermosensitive systems can be affected by changes in the temperature, which result in a phase transition; this can be a sol–gel conversion, soluble–insoluble state variations, liquid crystal phase transitions, or crystalline-amorphous phase-oscillations. Several pharmaceutical dosage forms can be prepared as a thermoresponsive system. Many investigations describe the use of liposomes, microcapsules, microspheres, nanoparticles, films, gels and injectable drug delivery system [16].

Thermoresponsive materials can be liquid crystals, e.g., Monooxyethylene trimethylolpropane tristearate or Polyoxyethylene glyceryl tristearate, used in microspheres and TTS [17], Cholesteryl oleyl carbonate (COC) [18], Glyceryl monooleate [19,20], polymers

* Corresponding author. ENT Department, Szent Imre Hospital, H-1115 Tétényi Street 12–16, Budapest, Hungary. Tel.: +36 1 464 8731.
E-mail address: mc.adam@freemail.hu (Á. Makó).

0939-6411/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2008.10.018

(Polyacrylamide derivatives [21–23]) aliphatic polyesters (Poly-ε-caprolactone (polyCL) [24]) macromolecules (gelatine, alginate [4,5], and different cellulose derivatives [25]).

These intelligent and regulated systems can be combined with each other [26], for example, in thermosensitive magnetoliposomes [27–29], which can be used for chemoembolisation in cancer therapy.

The aim of this study was to formulate a novel thermoresponsive and bioadhesive in situ gelling drug delivery system, which can adhere to the mucosal surface, thus improves the bioavailability, and decreases the side effects as the absorbed drug avoids liver's first pass metabolism effect.

In our study a water-soluble cellulose derivative [30] (Metolose® 60SH) was used as a thermoresponsive and bioadhesive material, because it shows thermal gelation and has excellent bioadhesive features [31].

Cellulose is not soluble in water, however, if the hydrogen atoms of some OH groups are substituted for methyl or hydroxypropyl groups, the polymer becomes water-soluble (Fig. 1). Depending on which etherification agent it contains, Metolose® is available in three forms: SM, SH, and SE.

SM type has methyl groups, SH type Metolose® has hydroxypropyl and methyl groups, and SE type is a cellulose with hydroxyethyl and methyl groups.

Each type of Metolose® aqueous systems is in sol phase at room temperature so it can easily be swallowed, and above body temperature it turns into gel phase which results a prolonged adhesivity. The temperature where the viscosity increases and gelation can be observed is referred to as thermal gelation temperature. The background of thermal gelation is the associations between the highly substituted parts and coverage of hydrophobic molecule parts in the network of polymer chain. This thermal gel is opalescent and reverts to its original solution form when it is cooled down [32]. Different substitution types have different gelation behaviors. The consistence of the Metolose® SM thermal gel is hard, while Metolose® SH thermal gel is soft. In our work, Metolose® 60SH was used as the viscosity of the thermal gel is lower, so it is more tolerable for the patients.

In our previous study [33], Metolose® 60SH was applied as a matrix in thermoresponsive transdermal therapeutic system, diclofenac-sodium was used as a drug, and we demonstrated the thermal gelation of Metolose® 60SH. The process can be characterized by two temperatures (T_1 and T_2). If the temperature is increased, the viscosity of aqueous solution decreases, and at T_1 a breakpoint can be observed where we can experience a dramatic fall in viscosity. Further increasing the temperature, we can observe gelation at T_2. In our previous study, we used the viscosity fall at T_1 as release controlling factor of thermoresponsive TTS.

The T_1 of Metolose® 60SH is above the skin temperature where the TTS is applied but by using 8% KCl this T_1 can be shifted to the desired temperature. The static drug release test confirmed that thermoresponsive drug release at skin temperature was developed from TTS using Metolose® 60SH gel, where the drug release rate constant significantly increases above the skin temperature.

In this present study, the thermal gelation temperature (T_2) of Metolose® 60SH 2 w/w% was used in order to develop a thermoresponsive and bioadhesive gel. At T_2 we can observe an increase in gelation and viscosity. The thermal gelation temperature of Metolose® 60SH 2 w/w% is between 65 and 66 °C, but by using different methods and types of auxiliary materials this T_2 can be shifted to the target temperature. In our study 39 °C was determined as the target temperature, because in the human body the oesophageal temperature corresponds to the core temperature and patients suffering from inflammation or cancer often develop low grade fever. This can be explained by the fact that the released substances change the metabolism, therefore, the body's thermoregulatory set-point temporary elevates and the core temperature rises up to 38–39 °C. Low grade fever can be also a side effect of the chemotherapy in the case of chemotherapy-induced neutropenia [34]. Our aim was developing and evaluating a thermoresponsive and bioadhesive gel for patients suffering from inflammation and fever. In this present study, we have examined the influence of different factors (pH, additives and drugs) on T_2 of Metolose® 60SH gel in order to shift down thermal temperature to target temperature, formulating a novel thermoresponsive and bioadhesive oral hydrogel. In vitro drug release and permeation were investigated by using different NSAIDs as model drugs.

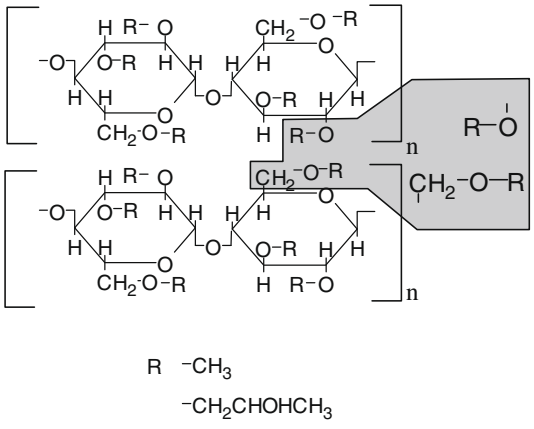

Fig. 1. Chemical structure of Metolose® (R = CH_3 → → Metolose® SM; R = $CH_2CHOHCH_3$ → → Metolose® SH).

2. Materials and methods

2.1. Materials

Piroxicam (PX), acetyl salicylic acid (ASA), ibuprofen (IB), indometacin (IM) (Boots Chemicals, Nottingham, England), aminophenasone (AM) (Reanal Chemicals Ltd., Budapest, Hungary) were used as drugs. Hydroxypropyl methylcellulose (Metolose® 60SH, Metolose® 90SH Shin-Etsu Chemical Co., Tokyo, Japan) was used to formulate a thermoresponsive gel system. Auxiliary materials: sodium chloride, sodium hydrogen carbonate, citric acid, glycerine, propylene glycol, polyethylene glycol 400 were supplied by Reanal Chemicals Ltd. (Budapest, Hungary) and were of analytical grade.

2.2. Apparatuses

The analytical determination of the active ingredient was carried out with Shimadzu UV-16A spectrophotometer (Shimadzu Corporation Spectroscopic Instruments, Kyoto, Japan). HAAKE VT550 Rheometer (HAAKE GmbH, Karlsruhe, Germany) was used to determine the viscosity of gel, and the change in the temperature was controlled by TC81 Peltier thermocontroller (HAAKE GmbH, Karlsruhe, Germany), in vitro drug release and permeation tests were carried out with a Franz-cell.

2.3. Methods

2.3.1. Preparation of the Metolose® gel

Metolose® powder of 0.2 g was continuously mixed with 5.0 g of water (70 °C) on a heated magnetic stirrer. Cold water (4.8 g) was added to the opaque mixture and was stirred until it became transparent. Drug of 0.05 g was dissolved in cold distilled water

and was added to the system. Drugs and auxiliary materials were added after the preparation of gel.

2.3.2. Determination of temperature of thermal gelation

The prepared solution of Metolose® was poured into the cup (20 °C) of the rotation viscometer, and rotation was started at $G = 100$ 1/s with sensor SV2. Time interval was 900 s. The system was first heated from 20 °C to 80 °C then cooled down to 20 °C to determine the thermal gelation process. Heating rate was 4 °C/min.

2.3.3. Examination of drug release with Franz-cell

A magnetic stirrer rod was placed into the container of the Franz-cell and 14 ml of buffer solution of pH = 7 was poured in it, then it was covered with the cellulose membrane. The upper part of the cell was placed on the membrane, and drug containing Metolose® gel was added to it. The contact surface was continuous without air bubbles, and the samples were withdrawn through the orifice in appropriate time intervals. Samples of 1 ml were taken out and were replaced with the buffer. The absorbance was determined at the following wavelengths:

Indometacin	325 nm
Aminophenasone	257 nm
ASA	276 nm
Ibuprofen	265 nm
Piroxicam	350 nm

2.3.4. Study of drug permeation with Franz-cell

A magnetic stirrer rod was placed at the bottom of the Franz-cell and 14 ml of buffer solution with pH = 7.4 (pH of plasma) was poured in it. The liquid surface was covered with a special impregnated membrane (Sartorius membranfilter, typ. RS, Sartorius GmbH, 3400 Göttingen, Germany), which simulates the mucosal surface. The contact surface was continuous without air bubbles and no vortex was formed during stirring. The freshly prepared gel which contained drug was fixed directly to the surface of the impregnated membrane. Stirring started and at appropriate time intervals, samples of 1 ml were taken out through the orifice and were replaced with the buffer. The absorbance was determined at the same wavelengths as in the release test (see Section 2.3.3.).

2.3.5. In vitro adhesion test

In our in vitro adhesion test a special impregnated membrane (Sartorius membrane typ. RS, 10 cm diameter, Sartorius GmbH, 3400 Göttingen, Germany) was used which simulates the mucosa surface. Freshly prepared 2 ml 2 w/w% Metolose® 60SH gel with 5% $NaHCO_3$ was poured on the membrane which lay on a 10×10 cm glass surface, then it was placed in a temperated (39 °C) chamber in the vertical position. We determined the flow time as the gel was flowing down from the top until the bottom of the membrane.

2.3.6. Thermal gelation time

1 g freshly prepared 2 w/w% Metolose® 60SH gel with 5 w/w% $NaHCO_3$ was poured on 10×10 cm glass surface in a temperated (39 °C) chamber, and the gelation time was determined when the system turned to opalescent.

2.3.7. Morphological test of oesophageal 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.

Male Wistar rats weighting 407 ± 15 g were fed by a 22G feeding needle with 0.4 ml Metolose® 60SH solution (2 w/w%) containing 5 w/w% sodium hydrogen carbonate, and saline solution was administered for control into the oesophagus. Immediately after the feeding, anaesthesia was carried out by using urethane 1.3 g/kg intraperitoneal. Twelve hours after the administration, the oesophagus was isolated and rinsed with saline solution. Then it was fixed in 10% neutral carbonate-buffered formaldehyde and embedded in paraffin, in an embedding center, and finally it was cut into slices. The slices were stained with hematoxylin-eosin and observed under a light microscope (Carl Zeiss Axio, Germany). Representative pictures were taken with an AxioCam MRc 5 camera and an AxioVision Rel. 4.5 software (Carl Zeiss, Germany).

3. Results and discussion

3.1. Rheological study of Metolose® 60SH gels

We have examined the different factors which have an influence on T_2 and the thermal gelation such as type of Metolose®, the Metolose® 60SH concentration, pH, auxiliary materials, and different drugs. Three types of Metolose® SH (60SH, 65SH, 90SH) can be distinguished, each of them has a different viscosity behavior depending on the methoxyl and hydroxypropoxyl content. In our study, 60SH and 90SH were examined. Fig. 2 shows that the thermal gelation of both Metolose® SH types are above body temperature ($T_{2\ 60SH} = 65$–66 °C, $T_{2\ 90SH} = 75$–76 °C). For further investigations Metolose® 60SH was used because it has a lower T_2 value, thus a smaller amount of auxiliary materials was needed to reduce the thermal gelation temperature to the target temperature (39 °C).

By increasing Metolose® 60SH concentration, the T_2 can be reduced, but as gel structure above 3 w/w% is relatively hard at room temperature, the oral application may be difficult and the reduction of T_2 may not be sufficient. The results demonstrated that Metolose® 60SH 2 w/w% solution ensures the most optimal gel structure, however, increasing the Metolose® 60SH concentration is not an appropriate method to reach the optimal temperature.

Results of the investigation proved that the viscosity of thermal gel and the thermal gelation temperature are independent of the pH value between 2 and 10. The fact that the viscosity of thermal gel was not affected by pH is very important as it means that the

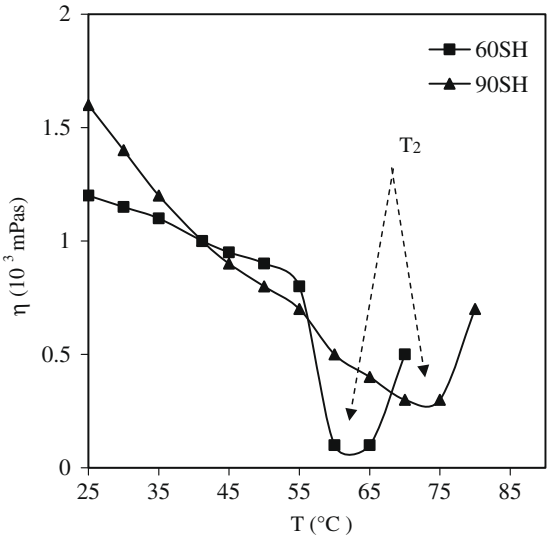

Fig. 2. Thermal gelation of 2 w/w% Metolose® 60SH and 90SH solution during a temperature sweep (average values, $n = 3$, RSD < 5%).

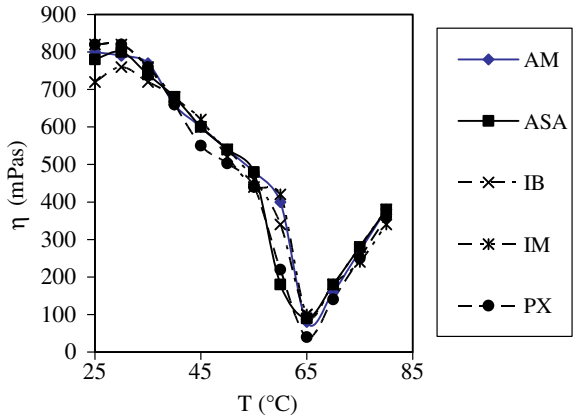

Fig. 3. Effect of different NSAIDs on thermal gelation temperature (T_2) of 2 w/w% aqueous solutions of Metolose® 60SH (n = 3, RSD < 5%).

gel structure is stable. Our results showed that by using different alcohols (propylene glycol, glycerin, PEG 400) instead of water for preparing Metolose® gel, the gel structure could not be reached, and that by adding only 5–20 w/w% of alcohols, the gel structure was formed, but the temperature of thermal gelation did not change significantly at any concentration.

In our previous study, we presented that by using 5 w/w% $NaHCO_3$, the T_2 (where the thermal gelation happens) can be reduced near to the target temperature (39 °C). It is preferable applying $NaHCO_3$ as it ensures a basic medium which is more beneficial in the oesophagus, and irritates less the mucosa. Further investigations were carried out by using 5 w/w% $NaHCO_3$.

The thermal gelation time of 5 w/w% $NaHCO_3$ containing Metolose® 60SH gel, determined by in vitro method, is very short (15–20 s). The in vitro adhesion test showed that the flow time depends on the preparation of the membrane. When using wet unimpregnated membrane, flow time took about 30 min, while by using lipophil impregnated membrane this time could be reduced to a few minutes. In case of an unimpregnated membrane, a thin opalescent gel layer remained on the surface which adhered to the membrane.

In the following part of this study the effect of some non-steroid anti-inflammatory drugs (ASA, AM, IB, IN, PX) on gel structure and T_2 were investigated. As it can be seen in Fig. 3, none of the examined drugs at the given concentration had a significant influence on the thermal gelation temperature and on the viscosity of gel at room temperature and at target temperature. When Metolose® 60SH gel contains $NaHCO_3$ besides the drug, the consistency changes significantly at room temperature and the value of T_2 falls down. Fig. 4 shows that the drug containing Metolose® 60SH gels needs different amounts of auxiliary materials to be able to reduce the thermal gelation temperature. Metolose® 60SH gel containing aminophenasone and 5 w/w% $NaHCO_3$ could not reduce thermal gelation temperature below 40 °C, however, by improving the amount of $NaHCO_3$ to 6 w/w% a precipitation could be observed. Metolose® 60SH gel containing piroxicam and 5 w/w% $NaHCO_3$ reduced thermal gelation temperature to 38 °C. Metolose® 60SH gel containing indometacin and 4.5 w/w% $NaHCO_3$ also reduced the thermal gelation temperature, although not to a sufficient level. Further on improving the amount of the auxiliary material in the gel up to 5 w/w%, the indometacin precipitated during the preparation. Neither Metolose® 60SH gel containing ibuprofen and 5 w/w% $NaHCO_3$, nor acetyl salicylic acid containing Metolose® 60SH gel with 5 w/w% $NaHCO_3$ could reduce the gelation temperature. In the case of improving the amount of the $NaHCO_3$ up to 6 w/w%, the gel containing ibuprofen precipitated during the preparation.

3.2. In vitro release and permeation tests

During the in vivo adhesion test (3.3) a considerable amount of gel could be observed in the rat oesophagus 12 h after the administration. Although the abovementioned results show a long lasting adhesive time, we can presume that in human body this adhesive time is shorter because of the washing out effect of saliva and the oesophageal peristalsis. Patients suffering from dysphagia swallow less frequently and we suppose that abovementioned functions are less dominant in the case of these patients. To sum up the abovementioned experiences, we can assume that the adhesion of thermal gel lasts 1 h, for this reason in vitro release and permeation test were carried out in a time period of 60 min. By comparing the in vitro release of different examined drugs from Metolose® 60SH gel with that of 5 w/w% $NaHCO_3$, piroxicam, acetyl salicylic acid, aminophenasone it was found that these showed good result after 1 h (Fig. 5), and that the amount of the released piroxicam was prominently high (60%). An additional advantage of the piroxicam is the long plasma half-life (from approximately 30–60 h) which ensures good bioavailability. After examining the permeation ability of drugs from preparation under the studied circumstances, piroxicam and acetyl salicylic acid (ASA) proved to be the most advantageous drugs.

As both ASA and AM are degradable in this system, we chose piroxicam for carrying out further tests.

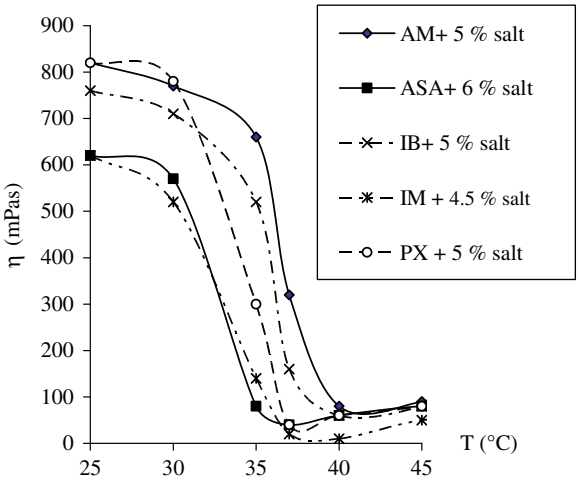

Fig. 4. Effect of NSAIDs on thermal gelation temperature (T_2) of 2 w/w% aqueous solutions of Metolose® 60SH with 5 w/w% $NaHCO_3$ (n = 3, RSD < 5%).

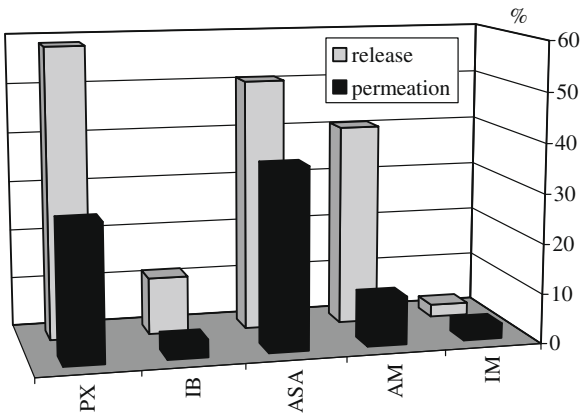

Fig. 5. In vitro release and permeation tests of NSAIDs from 2 w/w% aqueous solutions of Metolose® 60SH with 5 w/w% $NaHCO_3$ at 39 °C (time interval = 1 h) (n = 3, RSD < 5%).

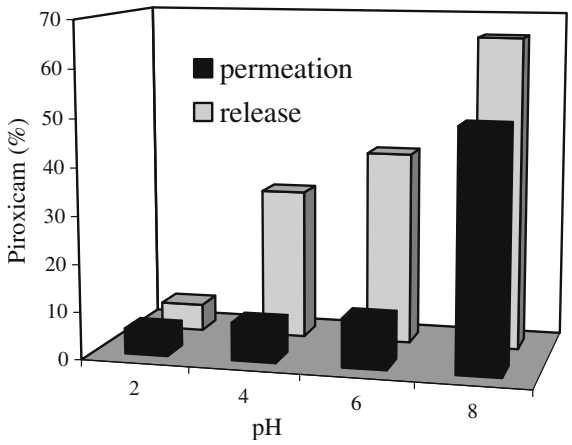

Fig. 6. pH dependence of in vitro release and permeation tests of piroxicam (time interval = 1 h) (n = 3, RSD < 5%).

In our next investigations we aimed to find out if the alteration of the pH of the system could have an influence on the piroxicam release. Although the temperature of the thermal gelation is independent from the pH, piroxicam release and permeation from Metolose® 60SH gel depends on the pH (Fig. 6) because the solubility of the piroxicam can be influenced by the pH of the hydrogel

$$\mathrm{pH} = \mathrm{pK_a} + \lg\frac{c-s}{s} \quad (1)$$

c is the solubility of drug in gel, s is the solubility of drug in water

Fig. 6 demonstrates that in acidic medium the release and permeation level was lower than in a basic medium, this can be optimised by the preparation of the gel.

3.3. Morphological test of oesophageal tissue

A morphological test was carried out by using 5 w/w% $NaHCO_3$ containing Metolose® 60SH. In our in vivo test the possibility of oesophageal mucosa damage was investigated. In the in vivo adhesion test a considerable amount of gel could be observed in the rat oesophagus 12 h after the administration. In the histological investigation mucosal injuries (irritation) could not be observed with light microscope neither in the treated, nor in the control rat oesophagus slices (Fig. 7) which proves that the abovementioned Metolose® solution did not damage the mucosa after 12 h.

4. Conclusion

In our recent study, we investigated the thermal gelation property of Metolose® 60SH in order to formulate a novel thermoresponsive and bioadhesive in situ gel system which can be used in the treatment of several diseases related to the oesophageal part of the gastrointestinal tract. Based on our in vitro results, we can conclude that Metolose® 60SH sol is able to form a thermal gel and can adhere easily to the surface at certain temperature within few seconds, so it can be used as a thermoresponsive and bioadhesive drug delivery system. By increasing the temperature, the thermal gelation can be realised. In normal conditions the gelation temperature (T_2) of Metolose® 60SH is above body temperature (65–66 °C), while by using 5 w/w% $NaHCO_3$ this temperature can be shifted to 39 °C. The application of alcohols and the alteration of the pH had no influence on T_2. As this system is in sol phase at room temperature, it can be used easier than the conventional oral administered pharmaceutical dosage forms. Near body temperature it turns into a gel phase which results a better adhesivity to the mucosal surface. Based on our experiments, piroxicam and

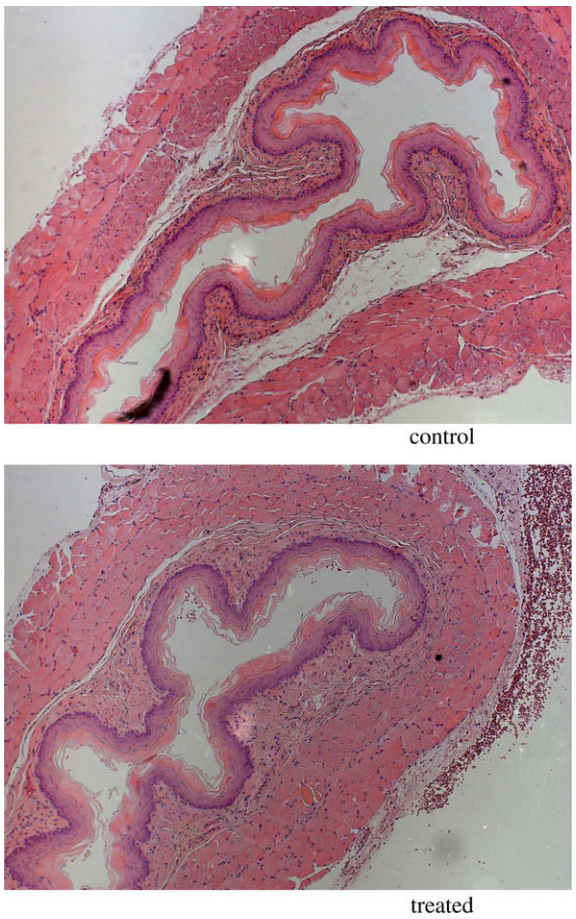

Fig. 7. Morphology of control and Metolose® 60SH 2 w/w% with 5 w/w% $NaHCO_3$ gel treated (after 12 h) oesophageal tissue.

ASA proved to have the best permeation and release abilities from the thermal gel. Based on the investigations that were carried out to examine the dependence of these processes on pH, we can conclude that the basic medium is preferable for the release and permeation. Our investigation gives the opportunity to develop a special behavior carrier system by using Metolose® 60SH. As this system is independent from the pH value and the materials it contains, it can be used in other thermoresponsive dosage forms as well.

The results of the morphological test showed that the thermoresponsive gel had no tissue-damaging effect on the oesophageal mucosa even after 12 h.

Acknowledgement

The authors are grateful to Shin-Etsu Chemical Co. (Japan) for providing Metolose®.

References

[1] H.K. Batchelor, Bioadhesive dosage forms for esophageal drug delivery, Pharm. Res. 22 (2005) 175–176.
[2] M. Marvola, K. Vahervuo, A. Sothmann, E. Martilla, Development of a method for study of the tendency of drug products to adhere to the oesophagus, J. Pharm. Sci. 71 (1982) 975–977.
[3] H. Al-Dujaili, A.T. Florence, E.G. Salole, The adhesiveness of proprietary tablets and capsules to porcine oesophageal tissue, Int. J. Pharm. 34 (1986) 75–79.
[4] H.K. Batchelor, M. Tang, P.W. Dettmar, F.C. Hampson, I.G. Jolliffe, D.Q.M. Craig, Feasibility of a bioadhesive drug delivery system targeted to oesophageal tissue, Eur. J. Pharm. Biopharm. 57 (2004) 295–298.
[5] H.K. Batchelor, D. Banning, P.W. Dettmar, F.C. Hampson, I.G. Jolliffe, D.Q.M. Craig, An in-vitro mucosal model for prediction of the bioadhesion of alginate solution to the oesophagus, Int. J. Pharm. 238 (2002) 123–132.

[6] A.J. Grodzinsky, P.E. Grimshaw, J. Kost (Eds.), Pulsed and Self-Regulated Drug Delivery, CRC Press, Boca Raton, FL, 1990. pp. 47–64.
[7] S. Collaud, T. Warloe, O. Jordan, R. Gurny, N. Lange, Clinical evaluation of bioadhesive hydrogels for topical delivery of hexylaminolevulinate to Barret's esophagus, J. Control. Rel. 123 (2007) 203–210.
[8] I. Rácz, I. Antal, J. Plachy, Formulation of controlled release drug preparations with antacid effect, Pharmazie 51 (1996) 323–327.
[9] J. Fujimori, E. Yonemochi, K. Terada, Application of Eudragit RS to the thermoresponsive drug delivery systems: II. Effect of temperature on drug permeability through membrane consisting of Eudragit RS/PEG 400 blend polymers, J. Control. Rel. 102 (2005) 49–57.
[10] W.L.J. Hinrichs, N.M.E. Schuurmans-Nieuwenbroek, P. van de Wetering, W.E. Hennink, Thermoresponsive polymers as carriers for DNA delivery, J. Control. Rel. 60 (1999) 249–259.
[11] A. D'Emanuele, J.N. Staniforth, Electrically modulated drug delivery device. Part 3. Factors affecting drug stability during electrophoresis, Pharm. Res. 9 (1992) 312–315.
[12] R. Konrad, A. Christ, G. Zessin, U. Cobert, The use of ultrasound and penetrometer to characterise the advancement of swelling and eroding fronts in HPMC matrices, Int. J. Pharm. 163 (1998) 123–131.
[13] A. Lavon, J. Kost, Ultrasound and transdermal drug delivery, Drug Disc. Tod. 9 (2004) 670–676.
[14] N.S. Allen, Photoresponsive polymer materials, J. Photochem. Photobiol. 155 (2003) 1.
[15] L. Bourre, S. Thibaut, A. Briffaud, Y. Layat, T. Patrice, Potential efficacy of a delta 5-aminolevulinic acid thermosetting gel formulation for use in photodynamic therapy of lesions of the gastrointestinal tract, Pharm. Res. 45 (2002) 159–165.
[16] B. Jeong, Y.K. Choi, Y.H. Bae, G. Zebtner, S.W. Kim, New biodegradable polymers for injectable drug delivery systems, J. Control. Rel. 62 (1999) 109–114.
[17] I. Nozawa, Y. Suzuki, S. Sato, Application of a thermoresponsive membrane to the transdermal delivery of non-steroidal anti-inflammatory drugs and antipyretic drugs, J. Control. Rel. 15 (1991) 29–37.
[18] Y.Y. Lin, K.S. Chen, S.Y. Lin, Development and investigation of a thermoresponsive cholesteryl oleyl carbonate-embedded membrane, J. Control. Rel. 41 (1996) 163–170.
[19] S. Engström, L. Lindhal, R. Wallin, J. Engblom, A study of polar lipid drug carrier systems undergoing a thermoresponsive lamellar-to-cubic phase transition, Int. J. Pharm. 86 (1992) 137–145.
[20] S.Y. Lin, K.S. Chen, Y.Y. Lin, pH of preparations affecting the on-off drug permeation behavior through the thermoresponsive liquid-embedded membrane, J. Control. Rel. 55 (1998) 13–20.
[21] R. Dinarvand, A. D'Emanuele, The use of thermoresponsive hydrogels for on-off release of molecules, J. Control. Rel. 36 (1995) 221–227.
[22] A. D'Emanuele, R. Dinarvand, Preparation, characterisation and drug release from thermoresponsive microspheres, Int. J. Pharm. 118 (1995) 237–242.
[23] T. Kidchobe, S. Kimura, Y. Imanishi, Thermoresponsive release from poly(glu(ome))-block-poly (sar) microcapsules with surface-grafting of poly(*N*-isopropylacrylamide), J. Control. Rel. 50 (1998) 205–214.
[24] T. Aoyagi, F. Miyata, Y. Nagase, Preparation of cross-linked aliphatic polyester and application to thermo-responsive material, J. Control. Rel. 32 (1994) 87–96.
[25] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N.C. Elliott, J.E. Hogan, C. Roston, The influence of drug on the properties of gels and swelling characteristics of matrices containing methylcellulose or hydroxypropylmethylcellulose, Int. J. Pharm. 100 (1993) 165–173.
[26] C. Ramkissoon-Ganorkar, F. Liu, M. Baudyš, S. Wan Kim, Modulating insulin-release profile from pH/thermoresponsive polymeric beads through polymer molecular weight, J. Control. Rel. 59 (1999) 287–298.
[27] A. D'Emanuele, R. Dinarvand, Preparation, characterisation, and drug release from thermoresponsive microspheres, Int. J. Pharm. 118 (1995) 237–242.
[28] E. Virooanchatapan, H. Sato, M. Ueno, I. Adachi, K. Tazawa, I. Horikoshi, Release of 5-fluorouracil from thermoresponsive magnetoliposomes induced by an electromagnetic field, J. Control. Rel. 46 (1997) 263–271.
[29] M. Negishi, A. Hiroki, Y. Horikoshi, M. Miyajima, M. Asano, R. Katakai, M. Yoshida, Swelling and ketoprofen release characteristics of thermo- and pH-responsive copolymer gels, Drug Dev. Ind. Pharm. 25 (1999) 437–444.
[30] R. Rowe, P. Sheskey, S. Owen (Eds.), Handbook of Pharmaceutical Excipients, 4th ed., Pharmaceutical Press, London, UK, 2003. pp. 386–389.
[31] H.G. Choi, J.H. Jung, J.M. Ryu, S.J. Yoon, Y.K. Oh, C.K. Kim, Development of in situ-gelling and mucoadhesive acetaminophen liquid suppository, Int. J. Pharm. 165 (1998) 33–44.
[32] M. Takeuchi, S. Kageyama, H. Suzuki, T. Wada, Y. Notsu, F. Ishii, Rheological properties of reversible thermo-setting in situ gelling solutions with the methylcellulose–polyethyleneglycol–citric acid ternary systems, Coll. Polymer Sci. 28 (2003) 1178–1183.
[33] G. Csóka, A. Gelencsér, Á. Makó, S. Marton, R. Zelkó, I. Antal, I. Klebovich, Novel termoresponsive application of Metolose in transdermal therapeutic system, Int J. Pharm. 338 (2007) 15–20.
[34] Y.P. Ruan, W.Y. Zhang, Correlation of fever to infection in patients with chemotherapy-induced neutropenia, Ai Zheng. 27 (8) (2008) 879–881.