Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 338 (2007) 15–20
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Potential application of Metolose® in a thermoresponsive transdermal therapeutic system

G. Csóka [a,*], A. Gelencsér [a], A. Makó [b], S. Marton [a], R. Zelkó [c], I. Klebovich [a], I. Antal [a]

[a] *Department of Pharmaceutics, Semmelweis University, Hőgyes E. Street 7, H-1092 Budapest, Hungary*
[b] *Szent Imre Hospital, ENT Department, Tétényi Street 12-16, H-1115 Budapest, Hungary*
[c] *University Pharmacy Department of Pharmacy Administration, Semmelweis University, Hőgyes E. Street 7-9, H-1092 Budapest, Hungary*

Received 25 April 2006; received in revised form 28 December 2006; accepted 13 January 2007
Available online 19 January 2007

Abstract

The purpose of the present study was to formulate a novel thermoresponsive membrane controlled therapeutic system from Metolose® for possible transdermal application. Metolose® gel shows thermal gelation property, which can be characterized by two (T_1, T_2) temperatures. A sharp decrease of viscosity can be measured at T_1, but gelation can be observed at T_2. Different types of Metolose® polymers were compared considering their thermoresponsive behaviour. Only thermal gelation was observed in the case of Metolose® SM, while Metolose® SH showed a sudden decrease of viscosity at T_1. Since this temperature is above the body temperature, so it should be shifted to the skin temperature in case of possible transdermal application. Modulation of thermoresponsibility was followed by rheological method, and the thermoresponsive drug release from Metolose® gel was studied by static liberation test. Our results demonstrated that the effect of different salts (NaCl, $NaHCO_3$, KCl) of various concentrations in Metolose® SH gel reduced T_1 to the skin temperature, which enabled enhanced drug release.

Keywords: Metolose®; Thermoresponsive behaviour; Thermal gelation; Drug release

1. Introduction

In recent years, controlled drug delivery formulations based on stimuli-responsive polymers have made a new direction for pharmaceutical and medical research, because temporal drug release may be required, e.g. when the severity of disease symptoms fluctuate with time (Nozawa et al., 1991; Lemmer, 1996; Hinrichs et al., 1999; Ramkissoon-Ganorkar et al., 1999). Hydrogels can be applied in the design of responsive drug delivery systems as they may respond sharply to small changes in their physicochemical environment to various external stimuli, such as temperature (Eeckman et al., 2002), pH (Rácz et al., 1996), light intensity (Allen, 2003), ultrasonic effect (Konrad et al., 1998; Lavon and Kost, 2004), electric (Grodzinsky et al., 1990; D'Emanuele and Staniforth, 1992) or magnetic fields (Virooanchatapan et al., 1997), and to specific chemical triggers, such as glucose (Mathiowitz, 1999; Dorski et al., 1997).

When discontinuous changes in drug release rates are required in response to a small change of temperature, thermoresponsive polymers may be used to develop environment-sensitive hydrogels (Dinarvand and D'Emanuele, 1995). Thermosensitive transdermal therapeutics systems consist of thermoresponsive agents (polymer, liquid crystal, liposomes, etc.), which suffer phase transition according to the change of temperature regulating drug delivery (Li and D'Emanuele, 2001; Gelencsér et al., 2005). Since the majority of drugs are unable to cross the skin barrier in sufficient amounts to reach effective concentrations, excipients are commonly applied to optimize the thermoresponsive transdermal systems to enhance the absorption and/or to modulate the thermal sensitivity (Lin et al., 2000; Vavrova et al., 2005).

Phase transition may be sol–gel transition, soluble–insoluble state variation, liquid crystal phase transitions, crystalline–amorphous phase-oscillation, etc. which are called phase transition temperature (T_g). Several factors can affect it, like chemical

* Corresponding author. Tel.: +36 1 2170914; fax: +36 1 2170914.
E-mail addresses: csogab@hogyes.sote.hu, csogab@freemail.hu (G. Csóka).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.01.018

structure (substituents), molecular weight and concentration of the thermoresponsive agent, presence of other components, etc. Some liquid crystals (Engström et al., 1992), polymers (e.g. polyacrylamide derivatives) (Kidchobe et al., 1998), aliphatic polyester (Aoyagi et al., 1994), cellulose derivatives), macromolecules (gelatine), etc. have thermoresponsive properties. The liposomes, microcapsules, microspheres, nanoparticles, films, gels, macromolecular drug systems (Jeong et al., 1999), can be combined with the above mentioned materials resulting in intelligent systems like thermosensitive magnetoliposomes, pH-thermosensitive systems (Virooanchatapan et al., 1997; Negishi et al., 1999).

Metolose® is a nonionic water-soluble cellulose ether, may be applied as gel and film-forming agent in TTSs. Cellulose is not soluble in water due to strong intermolecular hydrogen bonding between OH groups. Substituting the hydrogen atoms of some OH groups to methyl or hydroxypropyl groups, the resulting methoxyl and hydroxyl groups interfere with the inter-molecular hydrogen bonds, so that the polymer chains are less strongly bound to each other, resulting water penetration into the intermolecular spaces, so the polymer becomes water-soluble. Metolose® is available in three forms SM, SH, and SE, according to the kind of the etherification agent. SM type has methyl groups, SH type Metolose® has hydroxypropyl and methyl groups and SE type is cellulose with hydroxyethyl and methyl groups (Rowe et al., 2003).

Metolose® shows thermal gelation properties which can be characterized by two temperatures. Heating the aqueous solution of Metolose®, viscosity evenly decreases, and above a certain temperature (T_1), a sudden fall of viscosity can be observed. Upon heating this system a more intensive gelation can be observed, which causes rise of viscosity at a certain temperature (T_2). Different substitution types have different thermal gelation behaviours (Table 1). The phenomenon is reversible, affect drug liberation, and the temperatures can be shifted using auxiliary materials (Csóka et al., 2005).

Our aim was to formulate a thermoresponsive drug delivery system for possible transdermal application, where drug release can be regulated by body temperature. Membrane controlled drug containing matrices were prepared, and Metolose® was used as thermoresponsive material of the matrix. Heating the Metolose® SH solution at T_1 a sharp fall of viscosity was measured, which can raise the drug release significantly, at T_2 thermal gelation can be observed, characterized by viscosity increase. Metolose® SM has only thermal gelation at T_2, before this temperature sudden viscosity fall cannot be observed. Since T_1 and T_2 are above the body temperature, thus in order to formulate thermoresponsive TTS, they need to be shifted to the temperature of skin by using different auxiliary materials. The effects of different salts of various concentrations were examined on the temperature of thermal gelation of the Metolose®, as well. Raise of body temperature (fever) results in viscosity decrease at T_1 in the matrix of the TTS, and this alteration enhances drug liberation from the matrix.

Table 1
Measured T_1 and T_2 of different types of Metolose (average values, $n = 3$, ±S.D.)

Type of Metolose®	Heating curve		Cooling curve	
	T_1 (°C)	T_2 (°C)	T_1 (°C)	T_2 (°C)
SM	–	52 ± 1.0	–	47 ± 1.5
60 SH	51 ± 1.5	65 ± 2.0	45 ± 1.5	63 ± 2.0

2. Materials and methods

2.1. Materials

Model compound was diclofenac sodium (Boots Chemicals, Nottingham, England). Methylcellulose (Metolose® SM) and hydroxypropyl methylcellulose (Metolose® 60 SH-4000, Shin-Etsu Chemical Co., Tokyo, Japan) were provided as TTS matrix. NaCl, KCl, $NaHCO_3$ salts were used by Reanal Chemicals Ltd. (Budapest, Hungary) and were analytical grade.

2.2. Apparatuses

Shimadzu UV-16A spectrophotometer (Shimadzu Corporation Spectroscopic Instruments, Kyoto, Japan) was applied for the analytical determination of the active ingredient. RheoStress 100 Rheometer (HAAKE GmbH, Karlsruhe, Germany) was used to determine the viscosity of the Metolose® gel, and the change of temperature was controlled by TC81 Peltier thermocontroller (HAAKE GmbH, Karlsruhe, Germany).

2.3. Methods

2.3.1. Preparation of the Metolose® gel

0.2 g of Metolose® powder was continuously mixed with 5.0 g of water (70 °C) on a heated magnetic stirrer. 5.0 g of cold water was added to the opaque mixture and stirred till it cleared up. The amount of drug (1%, w/w) was dissolved in cold distilled water and it was added to the Metolose gel (Rowe et al., 2003).

The crystalline salts were incorporated under stirring into the obtained transparent gels. Since the applied salts were water-soluble, they were completely dissolved in the gels at the examined concentration ranges. After the *in situ* dissolution of the salts in the gels the resulted systems remained transparent.

2.3.2. Rheological tests of the matrix

The solution of Metolose® prepared according to Section 2.3.1 was poured onto the table of the viscometer. The system was first heated from 20 to 80 °C with 4 °C/min heating rate then cooled down to 20 °C to determine the thermal gelation process. Measurement parameters: $T = 20$–80 °C, $dT/t = 0.0333$ °C/s, $t = 600$ s, $\tau = 1.00$ Pa, $M = 2.094$ Nm, $f = 1.00$ Hz, $\varphi = 6.25$ rad/s, sensor = C20/2°, grap = 0.105 mm.

2.3.3. Study of thermoresponsive drug release (static method)

The drug loaded Metolose® gel was poured into the metal cell of the dissolution tester according to Ph. Eur. (Ph. Eur. 5.0

Vol. 1. 2.9.4.), and it was covered by cellulose membrane. This cell was immersed into the 200 ml acceptor medium (pH 5.5 buffer solution simulating the acidic skin wrap). The buffer was prepared based on the recipe of Ph. Eur. 5.8.

The mixing of the acceptor medium was provided by pads at the rate of 50 rpm, and samples were taken at regular intervals (15–30–45–60–90–120–180 min), the volume being replaced with the buffer solution. The acceptor medium was maintained at different constant temperatures (25, 30, 35 and 40 °C) under the time of examination. Diclofenac sodium concentrations of different samples were determined spectrophotometrically at 276 nm wavelength. Concerning the validation of the analytical procedure, the following could be stated. Repeatability of the spectrophotometric assay at 276 nm was proven on the 10 standard solutions of diclofenac at the concentration of 100 μg/ml.

The results from the intermediate precision test do not differ significantly from those obtained in the method repeatability test. Linear regression analysis demonstrated acceptability of the method for quantitative determinations over the concentration range of 20–120% of the nominal working concentration. The accuracy and recovery of the analytical method was demonstrated in the range of 60–100% of the label amount.

Blind reference solutions were prepared from gel samples prepared without diclofenac sodium. The spectra of these solutions were recorded and no peak overlapping the characteristic absorbance of diclofenac sodium at 276 nm wavelength was found. To avoid the disturbing effect of Metolose®, both the sample and reference solutions were filtered through membrane filter (Sartorius, pore size: 0.2 μm) before the spectrophotometric determination of diclofenac sodium. Analysis of the non-active formulation showed no interference with the quantitative determination of the diclofenac sodium.

Parallel measurements were carried out and the number of parallels and the R.S.D. values were always given in the legends of figures. The evaluation of the results was carried out with Statistica 6.1 software (Statsoft, Inc., Tulsa, USA, 2004).

3. Results and discussion

3.1. Rheological study of Metolose® gels

Although sol–gel transition temperature can be measured by several methods, such as differential scanning calorimetry (DSC), test tube inversion method and U-shaped tube method (Takeuchi et al., 2003), the rheometry was chosen because of its sensitivity. The thermal gelation property of Metolose® solution is influenced by the type and concentration of cellulose derivatives and the heating rate. Heating the Metolose® 60 SH solution, viscosity decreased evenly, but it had a clear breakpoint at 55 °C (T_1), after which the viscosity started to decrease fast, but above 65 °C (T_2) thermal gelation could be observed. Metolose® SM did not show the first break point (T_1), in the studied range, viscosity decreased evenly and at 50 °C viscosity started to increase. Metolose® SM has no T_1 but gelation can be observed.

Values of T_1 and T_2 can be specified by measurement of viscoelastic properties applying 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. If G' is greater than G'', it refers to elastic systems. The sol–gel transition can be defined by the temperature at which G' is equal to G'' on the thermogram.

A continuous temperature sweep was carried out, G' and G'' were determined in the cases of Metolose® SM and 60 SH aqueous solutions. Fig. 1a shows temperature sweep experiment of aqueous Metolose® SM solution of 2% concentration. G' first started to decrease, and around 43 °C a sharp rise could be observed. G'' first decreased too, than around 48 °C a slow increase could be seen. At 52 °C G' and G'' were equal, which referred to the sol–gel transition.

Different gelation behaviour of Metolose® 60 SH was confirmed. Fig. 1b shows that upon heating the Metolose® 60 SH solution, two inflexion points could be observed. With increasing the temperature, both values of G' and G'' started to decrease, and demonstrated a sharp fall at 51 °C. With further increasing the temperature, G' started to increase remarkably at 65 °C. As it can

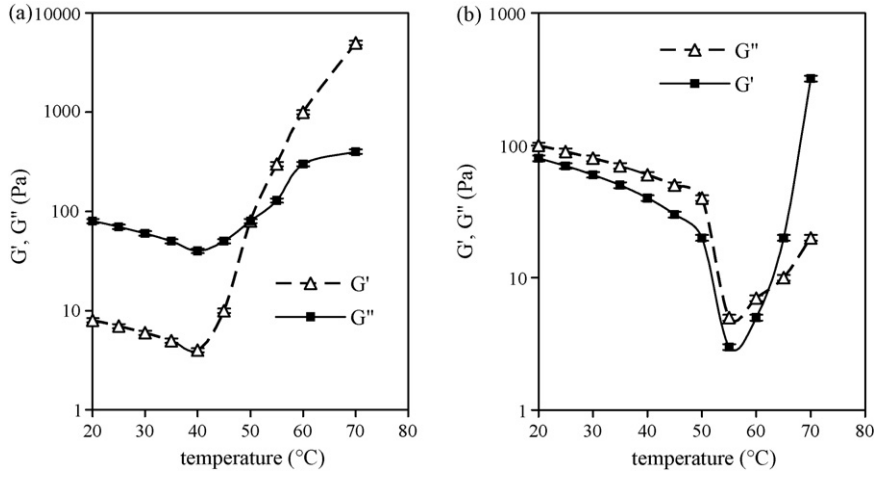

Fig. 1. G' and G'' values of 2% Metolose® SM (a) and 60 SH (b) solution during a temperature sweep (average values, $n = 3$, R.S.D. < 5%).

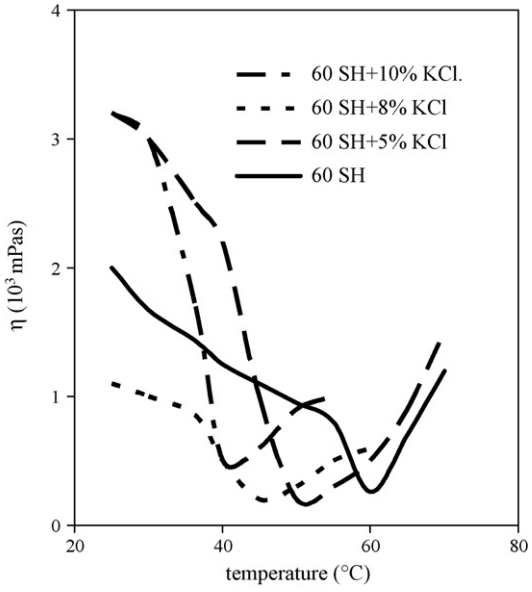

Fig. 2. Effect of KCl concentration on thermosensitive breakpoint of 2% Metolose® 60 SH aqueous solutions (average values, $n = 3$, R.S.D. < 5%).

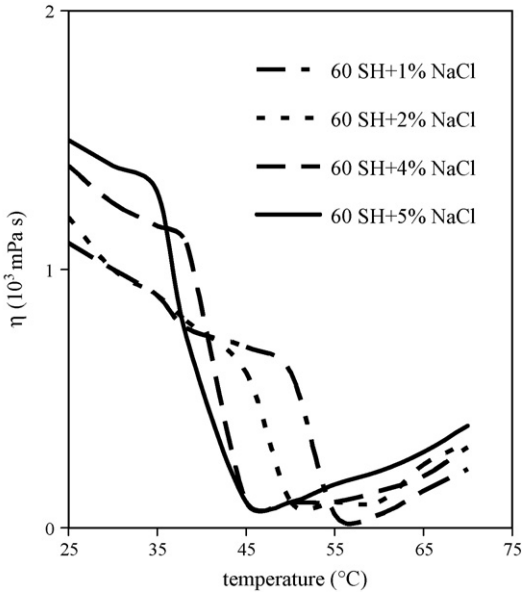

Fig. 4. Effect of NaCl concentration on T_1 of Metolose® 60 SH aqueous solution of 2% (w/w) concentration (average values, $n = 3$, R.S.D. < 5%).

be seen, G' had minimum values, and it crossed the G'' value at T_2, where gelation took place. These phenomena are reversible, with cooling the systems in the case of SM type. In the case of Metolose® SH, two break points can be distinguished on the viscosity–temperature curves. These temperatures are summarized in Table 1. It is clear from Table 1 that T_1 and T_2 are above the body temperature. T_1 can be reduced by addition of different salts in different concentrations. Figs. 2–4 show the thermal gelation temperatures as a function of the salt concentration. There was a tendency for T_1 and T_2 to decrease with the increase of salt concentration. Applying 8% KCl in the Metolose® 60 SH gel, T_1 could be shifted to the body temperature. Similar results can be observed using of 5% $NaHCO_3$ and 5% NaCl (Figs. 3 and 4). One of the possible explanations could be that the salts dehydrate the Metolose® gel, thus resulting in gel–sol transition. The higher the concentration of the salt in the gel system, the lower the temperature needed to the transition (Mitchell et al., 1993). Use of $NaHCO_3$ can change the pH value of gel, but the Metolose® solution maintains a constant viscosity over the pH range of 3–11 (Rowe et al., 2003). Fig. 5 summarizes the effect of different salts of different concentrations on T_1. A linear relationship could be observed between the salt concentration and T_1 in the studied range. This relationship can be used to determine the necessary amount of salts to shift T_1 to body temperature. Our results show that 8% KCl, 5% NaCl, 5%

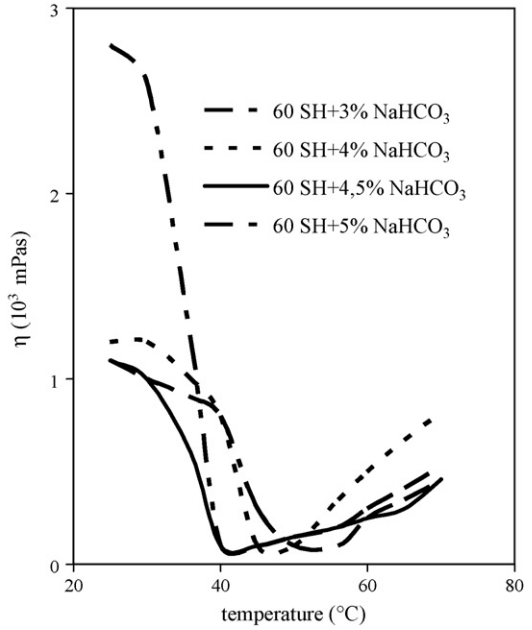

Fig. 3. Effect of $NaHCO_3$ concentration on T_1 of 2% aqueous solutions of Metolose® 60 SH (average values, $n = 3$, R.S.D. < 5%).

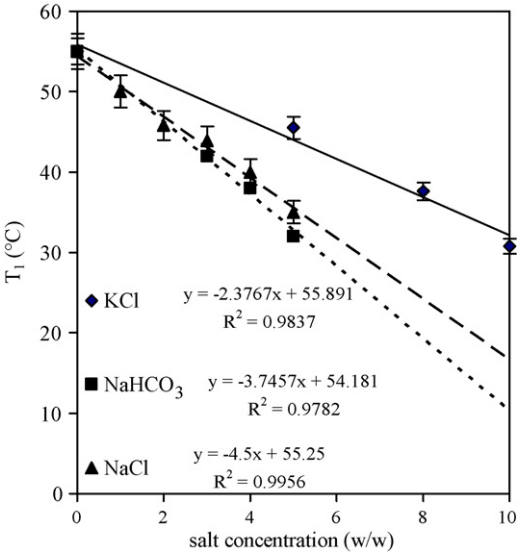

Fig. 5. Effect of salt concentration on T_1 of Metolose® 60 SH aqueous solution of 2% (w/w) concentration (average values, $n = 3$, R.S.D. < 5%).

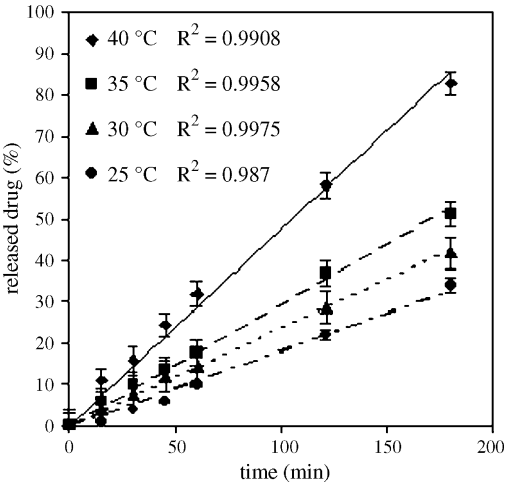

Fig. 6. Thermoresponsive drug release (1%, w/w diclofenac-Na) from Metolose® 60 SH gel with 8% KCl (average values, $n = 3$, R.S.D. = 3%).

$NaHCO_3$ concentrations are sufficient to shift T_1. In the case of drug loaded Metolose® 60 SH gel containing 8% KCl, the increase of temperature caused viscosity fall of the gel. The process is reversible, and generates a jump of drug release, which can be followed by static drug release test.

3.2. Thermoresponsive static drug release test

Fig. 6 demonstrates the drug release profile of diclofenac-Na at different temperatures (25–30–35–40 °C). Although it is common that the higher the temperature the higher the release, but the amount of released drug was not proportionally increased with the increase of the temperature, as it can be seen in Fig. 7. The calculated release rate constants proportionally increased between 25 and 35 °C, but after 35 °C a jump was observed, in compliance with the change of the gel structure above 35 °C. It can be explained by the sharp decrease of viscosity of Metolose® 60 SH gel above 35 °C, which affects the drug release (Fujimori et al., 2005).

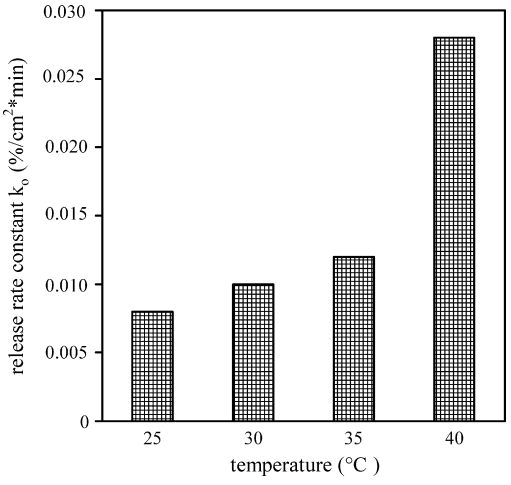

Fig. 7. Effect of temperature on release rate constants (k_o) of diclofenac-Na from Metolose® 60 SH gel with 8% KCl (average values, $n = 3$, R.S.D. = 3%).

Fig. 7 illustrates well that at 40 °C temperature a significant increase was observed compared to the lower temperature values.

4. Conclusion

With the application of Metolose® 60 SH gel, as a thermoresponsive matrix in TTSs, a sharp decrease of viscosity was observed, and this alteration in the gel was reversible. The temperature sensitivity of the Metolose® gel could be modulated with different salts (NaCl, KCl, $NaHCO_3$) of various concentrations to approach the physiological temperature stimulus. Using Metolose® 60 SH gel containing 8% KCl, the drug release was highly dependent on the temperature change.

Acknowledgements

Authors are grateful to Shin-Etsu Chemical Co. (Tokyo, Japan) for providing Metolose. Gabriella Csóka is grateful to the Hungarian Academy of Sciences for providing Bolyai Grant for her.

References

Allen, N.S., 2003. Photoresponsive polymer materials. J. Photochem. Photobiol. 155, 1.
Aoyagi, T., Miyata, F., Nagase, Y., 1994. Preparation of cross-linked aliphatic polyester and application to thermo-responsive material. J. Control. Release 32, 87–96.
Csóka, G., Marton, S., Gelencsér, A., Klebovich, I., 2005. Thermoresponsive properties of different cellulose derivatives. Eur. Pharm. Sci. 25, S74–S75.
D'Emanuele, A.D., Staniforth, J.N., 1992. Electrically modulated drug delivery device. Part 3. Factors affecting drug stability during electrophoresis. Pharm. Res. 9, 312–315.
Dinarvand, R., D'Emanuele, A., 1995. The use of thermoresponsive hydrogels for on–off release of molecules. J. Control. Release 36, 221–227.
Dorski, C.M., Doyle, F.J., Peppas, N.A., 1997. Preparation and characterization of glucose-sensitive P(MAA-g-EG) hydrogels. Polym. Mater. Sci. Eng. Proc. 76, 281–282.
Eeckman, F., Moes, A.J., Amighi, K., 2002. Evaluation of a new controlled-drug delivery concept based on the use of thermoresponsive polymers. Int. J. Pharm. 241, 113–125.
Engström, S., Lindhal, L., Wallin, R., Engblom, J., 1992. A study of polar lipid drug carrier systems undergoing a thermoresponsive lamellar-to-cubic phase transition. Int. J. Pharm. 86, 137–145.
Fujimori, J., Yonemochi, E., Terada, K., 2005. 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. Release 102, 49–57.
Gelencsér, A., Csóka, G., Rácz, I., Marton, S., Antal, I., 2005. Pharmaceutical application of thermoresponsive materials. J. Control. Release 101, 293–295.
Grodzinsky, A.J., Grimshaw, P.E., Kost, J. (Eds.), 1990. Pulsed and Self-regulated Drug Delivery. CRC Press, Boca Raton, FL, pp. 47–64.
Hinrichs, W.L.J., Schuurmans-Nieuwenbroek, N.M.E., van de Wetering, P., Hennink, W.E., 1999. Thermoresponsive polymers as carriers for DNA delivery. J. Control. Release 60, 249–259.
Jeong, B., Choi, Y.K., Bae, Y.H., Zebtner, G., Kim, S.W., 1999. New biodegradable polymers for injectable drug delivery systems. J. Control. Release 62, 109–114.
Kidchobe, T., Kimura, S., Imanishi, Y., 1998. Thermoresponsive release from poly(glu(ome))-block-poly (sar) microcapsules with surface-grafting of poly(*N*-isopropylacrylamide). J. Control. Release 50, 205–214.

Konrad, R., Christ, A., Zessin, G., Cobert, U., 1998. The use of ultrasound and penetrometer to characterise the advancement of swelling and eroding fronts in HPMC matrices. Int. J. Pharm. 163, 123–131.

Lavon, A., Kost, J., 2004. Ultrasound and transdermal drug delivery. Drug Discov. Today 9, 670–676.

Lemmer, B., 1996. The clinical relevance of chronopharmacology polymers for thermosensitive drug release. Pharmacol. Res. 33, 107–115.

Li, S.K., D'Emanuele, A., 2001. On–off transport through a thermoresponsive hydrogel composite membrane. J. Control. Release 75, 55–67.

Lin, S.Y., Chen, K.S., Lin, Y.Y., 2000. Artificial thermo-responsive membrane able to control on–off switching drug release through nude mice skin without interference from skin-penetrating enhancers. J. Bioact. Comp. Polym. 15, 170–181.

Mathiowitz, E. (Ed.), 1999. Encyclopedia of Controlled Drug Delivery, vol. 1. John Wiley and Sons Inc., New York, USA, pp. 225–248.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E., Roston, C., 1993. The influence of drug on the properties of gels and swelling characteristics of matrices containing methylcellulose or hydroxypropyl methylcellulose. Int. J. Pharm. 100, 165–173.

Negishi, M., Hiroki, A., et al., 1999. Swelling and ketoprofen release characteristics of thermo- and pH-responsive copolymer gels. Drug Dev. Ind. Pharm. 25, 437–444.

Nozawa, I., Suzuki, Y., Sato, S., 1991. Application of a thermoresponsive membrane to the transdermal delivery of non-steroidal anti-inflammatory drugs and antipyretic drugs. J. Control. Release 15, 29–37.

Rácz, I., Antal, I., Plachy, J., 1996. Formulation of controlled release drug preparations with antacid effect. Pharmazie 51, 323–327.

Ramkissoon-Ganorkar, C., Liu, F., Baudyš, M., Wan Kim, S., 1999. Modulating insulin-release profile from pH/thermoresponsive polymeric beads through polymer molecular weight. J. Control. Release 59, 287–298.

Rowe, R., Sheskey, P., Owen, S. (Eds.), 2003. Handbook of Pharmaceutical Excipients, 4th ed. Pharmaceutical Press, London, UK, pp. 386–389.

Takeuchi, M., Kageyama, S., Suzuki, H., Wada, T., Notsu, Y., Ishii, F., 2003. Rheological properties of reversible thermo-setting in situ gelling solutions with the methylcellulose–polyethylene glycol–citric acid ternary systems. Colloid Polym. Sci. 28, 1178–1183.

Vavrova, K., Zbytovska, J., Hrabalek, A., 2005. Amphiphilic transdermal permeation enhancers: structure–activity relationships. Curr. Med. Chem. 12, 2273–2291.

Virooanchatapan, E., Sato, H., Ueno, M., Adachi, I., Tazawa, K., Horikoshi, I., 1997. Release of 5-fluorouracil from thermoresponsive magnetoliposomes induced by an electromagnetic field. J. Control. Release 46, 263–271.