Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 407–412
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Hydrogel patches containing Triclosan for acne treatment

Tae-Wan Lee[a], Jin-Chul Kim[b,*], Sung-Joo Hwang[a]

[a]*College of Pharmacy, Chung-Nam National University, Daejon, South Korea*
[b]*School of Biotechnology and Bioengineering, Kangwon National University, Kangwon-do, South Korea*

Received 4 November 2002; accepted in revised form 4 August 2003

Abstract

Adhesive hydrogel patches containing Triclosan (TS) were prepared as an anti-acne dosage form. Sodium polyacrylate and carboxymethylcellulose (sodium salt) were used as matrix polymers, and Al^{3+}, produced by the reaction of dihydroxy aluminum aminoacetate and L(+)-tartaric acid, was employed as a crosslinking agent for the negatively charged polymers. The crosslinking reactions were done at 25, 40 and 50°C for predetermined time intervals. The semi-solid gels were obtained only when the reaction period was more than 12 h, but the polymer gels were fluidic with a shorter reaction. The swelling ratios increased as the reaction period was prolonged and the reaction temperature increased, indicating that the degree of the crosslinking is proportional to the reaction period and the temperature. On a scanning electron microphotograph, the crosslinked gel exhibited a honeycomb-like structure having pores of a few micrometers. The adhesive force of a patch, which could be easily attached to and peeled off facial skin, was 45.5 gmf and it increased by adding poly acrylic acid into the patch formulations. *Propionibacterium acnes* (ATCC 6919) growth inhibition area around the patch was not significant on an agar plate when TS content was 0.01 wt.%, but the antibacterial activity was apparent when the content was 0.05 wt.%. In vitro permeation revealed that up to 5 wt.% of Transcutol (TC) content in patch, TC, a permeation enhancer, significantly increased the amount of TS transported into hairless mouse skins but it did not substantially accelerate TS transportation into the receptors of Franz diffusion cells. Since our patches for the treatment of acne was aimed to localize TS into skins, TC content of 5 wt.% seems to be adequate for the dermal delivery of TS. The model patches in this study would be applicable to facial skins for the treatment of acne.

Keywords: Hydrogel; Patch; Triclosan; Transcutol; Anti-acne

1. Introduction

The dermal delivery is to localize a drug within skin to enhance the local effect, and the transdermal delivery is to increase the penetration of a drug through the skin for a systemic effect [1]. Accordingly, the topical dosage forms should be designed depending on what the target sites are. In case of dermato-pharmacotherapy for the treatments of skin inflammation, skin fungal infection, hair growth disorder and acne, the dermal delivery of active ingredients is desirable. The liposomal encapsulations of corticorsteroids, antifungals, minoxidil and retinoids are reported to enhance penetration of the active ingredients into the skin, localizes the drug at the sites of action, and reduces percutaneous absorption [2].

Recently, much attention has been paid to polymer gels as vehicles for drug delivery. One of those studies is adhesive polymer thin film for the use in dermal or transdermal delivery of drugs [3]. In this study, a patch was designed for the treatment of acne. Retinoic acid is a widely used drug in the topical treatments of acnes and other agents such as azelaic acid, benzoyl peroxide, antibiotics may be used in combination with retinoic acid [4,5]. Since one of pathogenic factors responsible for the development of acne is microbial colonization, Triclosan (TS), an antibacterial agent, could be an alternative active ingredient for acne and thus it was used in our study. To enhance the skin accumulation of TS, Transcutol CG (TC, diethylene glycol monoethyl ether), a permeation enhancer, was included in the patch formulation. TC is a potential transdermal permeation enhancer due to its non-toxicity, biocompatibility with skin, and excellent solubilizing properties [6]. It has also been reported to increase the skin accumulation of topically applied compounds without

* Corresponding author. School of Biotechnology and Bioengineering, Kangwon National University, 192-1, Hyoja2-dong, Chunchon, Kangwon-do 200-701, South Korea. Tel.: +82-33-250-6279; fax: +82-33-243-6350.
E-mail address: jinkim@kangwon.ac.kr (J.-C. Kim).

0939-6411/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0939-6411(03)00137-1

a concomitant increase in transdermal permeation [7]. This is a rationale to choose TC as a permeation enhancer in the dermal delivery of TS. Sodium polyacrylate (SPA) and carboxymethylcellulose (CMC, sodium salt) was used as matrix polymers of the patch. To obtain a semi-solid thin film the rate of the crosslinking reaction should be moderate and the solidification should not be completed before the fluidic gel of the polymers was cast into a thin film. This concept is a kind of in situ gellation technology, where transition metal ions such as Al^{3+} [8,9], Cr^{3+} [10,11], Zr^{4+} [12] are often used as crosslinkers. Dihydroxy aluminum aminoacetate (DDA) was used in this study as a source of Al^{3+}. It generates Al^{3+} as a result of the reaction with L(+)-tartaric acid. The adhesive patch prepared in this study was investigated in terms of the structure, the degree of swelling, the adhesiveness, the antibacterial activity and the in vitro permeation.

2. Materials and methods

2.1. Materials

TS, an antibacterial agent, was obtained from Ciba Co. (Trade name: Irgasan DP-300). Transcutol CG (TC, diethylene glycol monoethyl ether) was gifted from Gattefose. SPA and dihydroxy aluminum aminoacetate (DDA) were provided by Kyowa Chemical Co. Polyacrylic acid was obtained from Nihon Junyaku Co. L(+)-Tartaric acid was obtained from Yakuri Pure Chemical Co. Glycerin was obtained from LG Chem. Co. Carboxymethylcellulose (CMC, sodium salt) was gifted from Kose Co. *Propionibacterium acnes* (ATCC 6919) was obtained from Korea Genetic Engineering Center (Taejon, Korea) and brain heart infusion (BHI) broth was purchased from Difco (Detroit, MI). All other reagents were in an analytical grade.

2.2. Animals

Female hairless mice (type SKH), 8–10 weeks old, for in vitro permeation test were obtained from LG Chem. (Taejon, Korea). They were housed in suspended wire mesh cages in a room illuminated from 09:00 to 21:00 h and kept 20–25°C with a rodent diet and water ad libitum.

2.3. Preparations of adhesive patches

TS of 0.01–0.3 g was dissolved in TC of 1–10 g contained in a beaker of 200 ml. Glycerin of 25 g, dihydroxy aluminum aminoacetate (DAA) of 0.2 g, CMC of 3 g and SPA of 3 g were put together into the beaker and the mixture was stirred at 400 rpm using a mechanical stirrer (Heidolph RZR 2021). In parallel, tartaric acid of 0.2 g only, or tartaric acid of 0.2 g along with polyacrylic acid of 2 g was dissolved in distilled water. This solution was slowly added to the mixture while stirring at 200 rpm and the stirring was continued until the homogeneous gel phase was obtained. The amount of distilled water was so that the total mass of the formulation is 100 g. The final formulation was over-layered onto the release liner of a polypropylene with a doctor blade so that the thickness of the gel film is 1 mm. And then, a polyester textile (100 g/m^2) was over-layered onto the gel film and they were laminated with a roller (diameter: 10 cm, length: 25 cm, weight: 3.2 kg). Finally, for the gellation of the film through a crosslinking reaction, the laminated sheets were incubate at 25, 40 and 50°C for 6–96 h.

2.4. Scanning electron microscopy

Structural analysis was carried out using a cold-stage scanning electron microscope (Jeol JSM-840A). A patch (containing TS (0.3 wt.%), TC (5 wt.%) and no polyacrylic acid), incubated at 40°C for 48 h, was placed on a metal stub and then immersed in liquid nitrogen. The specimen was transferred to a pre-chamber (Bio-RAD E7450) located outside of the scanning electron microscope, where the frozen specimen was etched at −60°C, 10^{-5} mbar for 2 h. The specimen was then sputtered with gold at −130°C to a thickness of 100–200 Å and viewed in the scanning electron microscope using an accelerating voltage of 10 kV at a stage temperature of −180°C.

2.5. Swelling ratio

After being subjected to various gellation conditions, patches (containing TS (0.3 wt.%), TC (5 wt.%) and no polyacrylic acid) were cut into a square of 30 × 30 mm and they were soaked into distilled water of 25°C for 60 min. And then, the patches were picked out of the water and hung in the air for 10 min to drain out excess free water. The swelling ratio was calculated as follows.

$$\text{Swelling ratio } (\%) = \frac{m_f - m_i}{m_i}$$

Where, m_f is the mass of a patch after soaking it in water and removing excess water, and m_i is the initial mass of the patch before soaking.

2.6. Adhesiveness

Patches of 2 × 2 cm^2 (containing TS (0.3 wt.%), TC (5 wt.%) and polyacrylic acid (0 or 2 wt.%)) were attached onto a sample applicator of Dia-Stron (MTT 160) so that the textile faces the applicator. After peeling off the release liner of the patch, the adhesive force was measured ten times subsequently using a holder of 5 mm diameter at 25°C, 55% relative humidity. The contact time of the holder and the sample surface was 1 s, the cyclic delay between the measurements was 1 s, and the separation distance between the holder and the sample surface was 5 mm, the moving

rate of the holder was 300 mm/min. Maximum force and gauge force were 200 and 30 gmf, respectively.

2.7. Antibacterial activity

P. acnes were suspended in BHI broth and pre-cultured in an anaerobic condition. The pre-cultured *P. acnes* were plated on BHI agar plates to the thickness of 3 mm. The patches (containing various amounts of TS (0.01–0.3 wt.%), TC (5 wt.%) and no polyacrylic acid) were put on the plates and they were incubated at 37°C in an anaerobic condition for 2 days. Finally, the area where the growth of *P. acnes* was inhibited was observed.

2.8. In vitro permeation

Female hairless mice (type SKH) aged 8–10 weeks were sacrificed by cervical dislocation. The dorsal skin of each hairless mouse was excised and the adhering fat and other visceral tissue were removed. The patches containing TS (0.3 wt.%) and variable amount of TC (1–10 wt.%) were attached to the skins and they were mounted onto Franz diffusion cells (0.636 cm^2 surface area) equipped with 5 ml receptor compartment. The equi-volumetric solution of ethanol/phosphate-buffered saline (pH 7.0) was used as the receptor content to ensure pseudo-sink conditions, thermostated to 37°C under stirring. At the predetermined time intervals, skins were removed from the diffusion cells and in turn the patches were peeled off the skins. The receptor solutions were assayed for TS using high-performance liquid chromatography (HPLC). In parallel, the skin was soaked in 5 ml of ethanol contained in a 20-ml vial, sealed tightly, sonicated for 30 min using an ultrasonic system (Branson 2210) and stood for 24 h at room temperature. Finally, the amount of TS in the alcohol was analyzed using HPLC. The TS assay was performed in a liquid chromatograph (Waters) equipped with a UV detector. A Microsorb-MV column was eluted with acetonitrile/H_2O (75:25, v/v) at a flow rate of 1.0 μl/min and a sample of 15 μl was injected. The detection wave length was 280 nm.

3. Results and discussion

3.1. Swelling ratio

After being subjected to variable temperatures and periods for the cross-linking reaction, the swelling ratios of the hydrogel patches were measured. As shown in Fig. 1, the swelling ratio increased with increasing the incubation temperature and the period. It was much more dependent on the period. If the degree of crosslinking is lower, more water and uncrosslinked polymer chains would be drained off from the hydrogel patch in the excess water-removing step. The ability of the hydrogel patch to retain water and polymers in the water-removing step would be a measure of

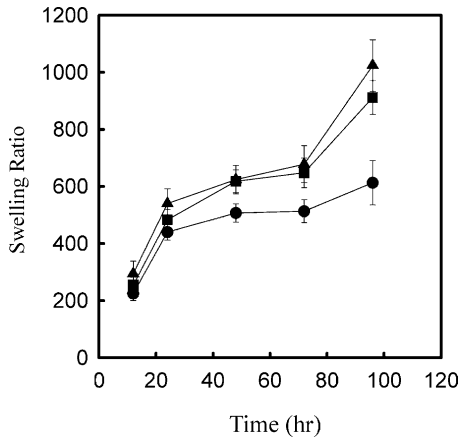

Fig. 1. The swelling ratios of hydrogel patches. The hydrogels were incubated at 25°C (●), 40°C (■) and 50°C (▲) for predetermined time intervals and then the swelling ratios were measured. Each point is the mean of triplicate measurements.

the degree of the crosslinking. Therefore, the increased swelling ratio is because the crosslinking increases with the incubation temperature and period. After 6 h incubation, the polymer gel in a patch was fluidic and thus a portion of the gel was drained off during the step of removing excess water from the gel. The degree of crosslinking formed after 6 h incubation would not be high enough to retain the mass of the hydrogel against gravitational force. The rate-determining step for the crosslinking reaction would be the reaction between DDA and tartaric acid, which produces Al^{3+}, a crosslinker for the hydrogels. In situ gellation, the rate of the crosslinking should be moderate and the crosslinking should not be completed before the fluidic gel of the polymers was cast into a thin film. Thus, the slow reaction producing Al^{3+} seems to be adequate for the fabrication of the hydrogel patches. In fact, the rate of crosslinking caused by an inorganic electrolyte such as aluminum chloride is too fast to fabricate the thin films of hydrogels.

3.2. Scanning electron microscopy

Fig. 2 shows the structure of a dry hydrogel, which had been subjected to the crosslinking reaction at 40°C for 48 h. The matrix has macro-pores of a few micrometers and a honeycomb-like structure was observed. As water was evaporated from the hydrogel during the preparation of the SEM sample, the polymer chains is likely to bundle into the strands of the chains, leaving behind the macro-pores. The strands would have a high crosslinking density since the polymer chains having a higher crosslinking density would get close to each other more favorably during the dry process. The structure of the wet hydrogel could not observed due to a technical problems but it is believed that the wet hydrogel, on the contrary to the dry hydrogel, would not have macro-pores, and it may have a homogeneous matrix of corsslinked polymers.

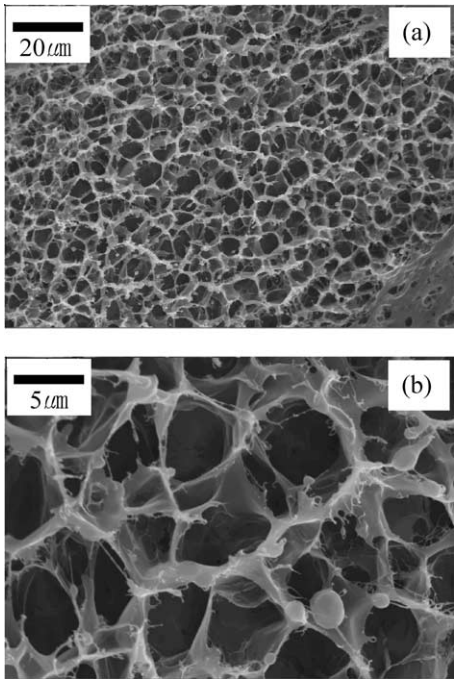

Fig. 2. Scanning electron microphotographs of a hydrogel patch. The contents of Triclosan, Transcutol and polyacrylic acid in the hydrogel were 0.3 wt.%, 5 wt.% and 0 wt.%, respectively. For the crosslinking of the hydrogel, it was incubated at 40°C for 48 h. The magnifications of panel (a); and panel (b) were × 1000 and × 4000, respectively.

3.3. Adhesiveness

Fig. 3 shows the adhesiveness of the patches with or without poly(acrylic acid). The adhesiveness was higher when poly(acrylic acid) was contained in the patch. The polymer is known to be bioadhesive due to the hydrogen bonding between carboxyl group of the polymer and a substrate and it is often included in the mucoadhesive formulations [3,13,14]. While the maximum adhesive forces of the patch free of poly(acrylic acid) were almost constant with the number of the measurements but those of the patch containing poly(acrylic acid) decreases. This is probably because the surface of the patch containing poly(acrylic acid) is deteriorated and roughed more easily during the measurements due to the higher adhesiveness between the surface and the holder. The roughed surface would prevent the close contact of the patch and the holder. In fact, after the first measurement the disintegrated surface was observed. Although a significant difference in the adhesive force was observed, the two kinds of the patches both were well-adhesive to facial skins and they could be detached from the skins without any pain.

3.4. In vitro antibacterial activity

Fig. 4 shows the anti-bacterial activities of hydrogel patches containing various amounts of TS. The areas of the growth inhibition were shown as dark ones around the patches and they were proportional to the content of

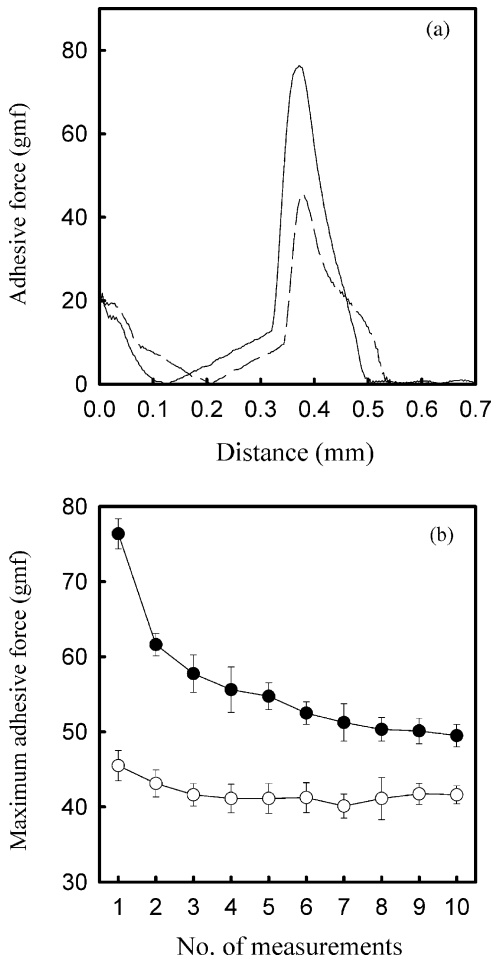

Fig. 3. Adhesive forces of the hydrogel patches. Panel (a) is adhesive forces versus the distance between a holder and the patch surfaces in the first measurement. Panel (b) is the maximum adhesive forces in the subsequent ten-time measurements. The contents of poly(acrylic acid) in the patches were 0 wt.% (dashed line in panel (a), blank circle in panel (b)) and 2 wt.% (solid line in panel (a), filled circle in panel (b)). Each point in Panel (b) is the mean of triplicate measurements.

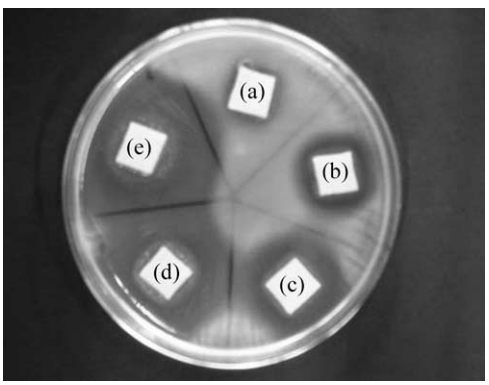

Fig. 4. Anti-bacterial activities of hydrogel patches on an agar plate. The contents of Triclosan in the patch were 0.01 wt.% (a); 0.05 wt.% (b); 0.1 wt.% (c); 0.2 wt.% (d); and 0.3 wt.% (e). No Transcutol and no polyacylic acid were included in the patches.

the anti-bacterial agent. The inhibition area was not significant when the TS content was 0.01 wt.%, but in case of 0.3 wt.% the area was six to seven times that of the patch. The inhibition area is due to the lateral diffusion of TS through solid agar medium. Thus, it can be assumed that the patch would be effective not only in the skin beneath it but also in the skin around it. TS, a hydrophobic anti-bacterial agent, is likely to diffuse readily through the lipidic skin layers. On the other hand, the contents of the TS in the agar at the edge of the inhibition area were not determined but they were probably in the order of the minimum inhibitory concentration (MIC) of TS. The MIC was 7.8 ppm [15].

3.5. In vitro permeation

Fig. 5 shows the amount of TS transported into and across hairless mouse skins in 8 h when the content of TC in patches increase from 1 to 10 wt.%. Up to 5 wt.% of TC content, TC significantly increased the amount of TC transported into the skins but it did not substantially accelerate TS transportation into the receptors of the diffusion cells. At the relatively low content of TC, the permeation-enhancing action of TC would be effective only in the upper layers of the skin but not in deeper layers of the skin. This may account for the enhanced dermal transportation without a substantial increase in the transdermal delivery. In fact, TC was reported to increase the skin accumulation of topically applied compounds without a concomitant increase in transdermal permeation [11]. Above 5 wt.% of TC content, the transdermal permeation of TS increased but the dermal accumulation was almost constant. At the higher content of TC, the permeation-enhancing action of TC would be extended into deeper layers of the skin. Therefore, the transportation into the receptor would increase due to the increased permeability of

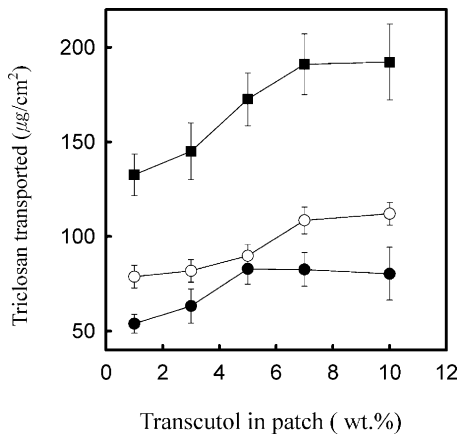

Fig. 5. Amount of Triclosan transported into (●) and across (○) hairless mouse skin in 8 h as function of Transcutol contents in patches. The total amount of Triclosan transported was also represented (■). The contents of Triclosan were 0.5 wt.% in all the patches. Each point is the mean of triplicate measurements.

TS through the skin. Since our patches for the treatment of acne is aimed to localize the anti-bacterial agent into the skin, the content of a permeation enhancer should be optimized to enhance the dermal accumulation rather than the transdermal permeation. As long as our in vitro system is concerned, TC content of 5 wt.% seems to be adequate for the dermal delivery of TS.

In summary, hydrogel patches were prepared using SPA and CMC as matrix polymers, and Al^{3+}, produced by the reaction of DAA and tartaric acid, as a cross linker. The patches were well-adhesive to facial skins and they could be detached from the skins without any pain. In vitro anti-bacterial activities of the patches containing TS of 0.01–0.3 wt.% was explicit on an agar plate. TC of 5 wt.% in the patches enhanced the skin accumulation of TS without a concomitant increase in the transdermal permeation. The model patch in this study would be applicable to face skins for the treatment of acne

Acknowledgements

We thank Mr Hyoung-Man Kim for the technical support in the preparation of the hydrogel patches.

References

[1] M. Carafa, E. Santucci, G. Lucania, Lidocaine-loaded non-ionic surfactant vesicles: characterization and in vitro permeation studies, Int. J. Pharm. 231 (2002) 21–32.
[2] M. Mezei, Biodisposition of liposome-encapsulated active ingredients applied on the skin, in: O. Braun-Falco, H.C. Korting, H.I. Maibach (Eds.), Liposome dermatics, Springer-Verlag, Berlin, 1992, pp. 206–214.
[3] H.S. Tan, W.R. Pfister, Pressure-sensitive adhesives for transdermal drug delivery systems, PSTT 2 (1999) 60–69.
[4] E.J. van Hoogdalem, Transdermal absorption of topical anti-acne agents in man: review of clinical pharmacokinetic data, J. Eur. Acad. Dermatol. Venereol. 11 (1998) S13–S19.
[5] H. Gollnick, M. Schramm, Topical therapy in acne, J. Eur. Acad. Dermatol. Venereol. 11 (1998) S8–S12.
[6] D.A. Godwin, N.-H. Kim, L.A. Felton, Influence of Transcutol CG on the skin accumulation and transdermal permeation of ultraviolet absorbers, Eur. J. Pharm. Biopharm. 53 (2002) 23–27.
[7] W.A. Ritschel, R. Panchagnula, K. Stemmer, M. Ashraf, Development of an intracutaneous depot for drugs. Binding, drug accumulation and retention studies, and the mechanism of depot, Skin Pharmacol. 4 (1991) 235–245.
[8] R.B. Needham, C.B. Threlkeld, J.W. Gall, Control of mobility using polymers and multivalent cations. SPE 4747 presented at the SPE Improved Oil Recovery Symposium, Tulsa, OK, April 22–24, 1974.
[9] H.T. Dovan, R.D. Hutchins, Development of a new aluminum/polymer gel system for permeability adjustment, SPE Reservoir Eng. May (1987) 177–183.
[10] T.P. Lockhart, P. Albonico, G. Burrafato, Slow-Gelling Cr^{+3}/polyacrylamide solutions for reservoir profile modification: Dependence of the gelation time on pH, J. Appl. Polym. Sci. 43 (1991) 1527–1532.
[11] P. Albonico, G. Burrafato, T.P. Lockhart, Polyacrylamide gels formed with Cr^{+3} ion and $Cr(acetate)_3$: thermodynamically and kinetically

controlled crosslinking reactions, J. Polym. Sci.: Part A: Polym. Chem. 30 (1992) 1071–1075.
[12] A. Omari, Rheological study of the gelation kinetics of the scleroglucan-zirconium system, Polymer 36 (1995) 815–819.
[13] N.A. Peppas, J.J. Sahlin, Hydorgels as mucoadhesive and bioadhesive materials: a review, Biomaterials 17 (1996) 1553–1561.
[14] N.A. Peppas, P. Bures, W. Leobandung, H. Ichikawa, Hydrogels in pharmaceutical formulations, Eur. J. Pharm. Biopharm. 50 (2000) 27–46.
[15] J.-C. Kim, M.-E. Song, M.-J. Kim, E.-J. Lee, S.-K. Park, M.-J. Rang, H.-J. Ahn, Preparation and characterization of Triclosan-containing vesicles, Colloids Surf. B: Biointerfaces 26 (2002) 235–241.