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Evaluation of carboxymethyl guar films for the formulation of transdermal therapeutic systems

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Abstract

Carboxymethyl guar (CMGS), an anionic semisynthetic guar gum derivative was evaluated for its suitability of use in transdermal drug-delivery systems. Terbutaline sulfate (TS) was used as a model drug. The diffusion of terbutaline sulfate from CMGS solution was relatively slower at pH 5 than at pH 10. It is most likely that the interaction between CMGS and terbutaline sulfate at pH 5 is physical, involving static interaction. The ability of such interactions in modifying the release kinetics of drug from the CMGS transdermal films was studied. The release was exponential from pH 5 formulations whereas the release rate followed zero or Higuchian order from pH 10 formulations. However, the diffusion kinetics of both pH 5 and pH 10 formulations followed zero order across human cadaver epidermis. Such an interaction was also found to alter the pharmacokinetic parameters of the drug. The steady-state concentration of TS was relatively consistent and the bioavailability was ∼50% higher in pH 5 formulations than pH 10. The elimination rate constant/half-life was significantly different between pH 5 and pH 10 formulations.

Keywords: Carboxymethyl guar; Terbutaline sulfate; Transdermal delivery

1. Introduction

Formulation of transdermal therapeutic system (TTS) involves optimization of several factors such as release rate, stability, safety, convenience of use, etc. The key component in a TTS, which monitors the release of an active ingredient, is the rate controlling polymeric membrane. The polymer should possess good film forming properties, should be non-irritating, inert, and stable. Hence, selection of polymer is a challenging task because of the inherent diversity of structures and requires a thorough understanding of the surface and bulk properties of the polymer that can give the desired chemical, interfacial, mechanical and biological functions. Though several polymers are already in use, a constant research is on, to explore new polymers for the TTS utility. Such an approach towards establishing new polymers is necessary, as not all the existing polymers possess all the ideal qualities.

One of the major disadvantages of transdermal drug-delivery system as compared to other controlled release formulations is its high cost. A major percentage of formulation cost is due to the utility of expensive synthetic polymers. Hence, several less expensive natural and semisynthetic polymers have been evaluated for their suitability for TTS (Kotian and Vavia, 2002).

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In this paper, we present our observations about carboxymethyl guar, sodium salt (CMGS), as a polymer candidate for the formulation of transdermal films of terbutaline sulfate. Carboxymethyl guar is a pale yellow colored powder or granules, odorless, tasteless, and slightly hygroscopic. It is prepared from a plant polysaccharide called guar gum, by reacting with sodium monochloroacetate in the presence of sodium hydroxide (Reddy and Tammishetti, 2001). It is soluble in water and forms a transparent solution. The bulk density of the polymer is about 0.75 g/cm^3.

2. Materials and methods

2.1. Chemicals

Terbutaline sulfate was a gift sample from Astra Zeneca LTD, Bangalore. Carboxymethyl guar, sodium (CMGS) was a gift sample from Jagath Pharma LTD, Bangalore, India. Polyethylene glycol-400(PEG 400) and other chemicals were of high-purity grade from Loba Chemicals, Mumbai, India.

2.2. Formulation and evaluation of films

The films subjected for physicochemical evaluation were prepared from casting solution made in distilled water. pH 5 citrate buffer (Series 1) or pH 10 (Series 2) borate buffer (both at 10 mM concentration) was used to prepare two series of formulations containing polymer in the range of 10–50 mg/cm^2 of film. The polymer, plasticizer (PEG 400, in %w/w of polymer concentration) and the drug were dissolved in the solvent and casted on mercury pool present in plastic molds and dried at 50 °C for 6 h in an air circulation dryer. Then the films were taken onto clean polyethylene sheet. The films used for in vitro release studies, in vitro diffusion studies, stability studies and skin reaction test were of 10 cm^2 area. All the films contained 5 mg/10 cm^2 of TS. Accelerated stability studies were carried out at 30, 40, 50, and 60 °C and the films were retested for the reproducibility of the mechanical and vapor transmission properties.

The pH of the polymer solutions was measured using Systronics 335 pH meter and the viscosity of the polymer solutions was determined by Brookfiled's DV-II+ digital viscometer.

2.2.1. Thickness uniformity

The thickness of the films was measured by a micrometer at five different places on the film.

2.2.2. Tensile strength

Tensile strength and elongation of the films was determined on Instron 1026 tensile strength testing apparatus (Schimadzu Co., Japan). Rectangular filmstrips of 10 mm × 150 mm were fixed in such a way that the length of film between the jaws was 100 mm. (Okhamafe and York, 1987; Murthy and Hiremath, 2002).

2.2.3. Water vapor transmission rate

The film was fixed over the brim of a glass vial (10-mm diameter), containing 3 g of fused calcium chloride as desiccant, with an adhesive tape. The vial was weighed and kept in desiccator containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 3-h intervals for a period of 72 h. The water vapor transmission rate was calculated from the plots of amount of water vapor transmitted versus time (Munden et al., 1964).

2.3. In vitro release studies

The USP XXIII dissolution apparatus 5 (paddle over disk) was used to study the in vitro release behavior of films. Five circular films of 10 cm^2 films were taken in the disc, the agitation speed was 50 rpm, and distilled water was used as the dissolution medium. The medium from the basket was withdrawn at different time intervals and the amount of drug was determined (Rao et al., 1989). Equal volume of fresh medium was replaced into the jar after each withdrawal.

2.4. In vitro diffusion studies

The in vitro diffusion studies were carried out using a Keshary–Chien diffusion cell. PBS was the receptor medium and epidermis of the fresh human cadaver skin excised from the chest portion (isolated by heat separation method (Berner et al., 1989)) was used as the barrier. The barrier integrity was confirmed by measuring the electrical conductance using two 4-mm Ag/AgCl disk electrodes introduced into the cell, one in the receiver compartment and the other

in the donor compartment of the diffusion apparatus. The skin samples having a resistivity >20 kΩ cm^2 were only used for the transport studies. The active diffusion area was 10 cm^2. The agitation speed of 50 rpm and temperature of 37 ± 1 °C were maintained during the experiment. The samples withdrawn from the receptor compartment (5 ml) at different time intervals were suitably diluted or concentrated and the drug concentration was measured (Rao et al., 1989).

2.5. Skin reaction studies

Three groups each consisting of 10 human volunteers of age between 23 and 33 were recruited for the skin reaction studies. One of the groups was treated with 0.1% w/v sodium lauryl sulfate solution as standard irritant. Control group was applied with the marketed adhesive bandage strip, 'BAND AID' (Johnson and Johnson LTD, Mumbai, India). The transdermal films (without TS) were placed on the forearm of individuals of test group and secured with a non-irritant adhesive tape for 24 h and the skin was observed for any signs of irritation, erythema or edema for a period of 7 days. The grading scale was similar to those in US FDA guidelines.

0	No evidence of irritation.
1	Minimal erythema, barely perceptible.
2	Definite erythema, readily visible, minimal edema, or minimal papular response.
3	Erythema and papules.
4	Definite edema.
5	Erythema, edema, and papules.
6	Vesicular eruptions.
7	Strong reaction spreading beyond test site.

2.6. Pharmacokinetic studies

The study was conducted in six healthy New Zealand rabbits of either sex weighing 2.5 ± 0.5 kg. The skin of 20 cm^2 area was shaved, covering both sides of the vertebral column of each rabbit and care was taken to avoid damage to the skin during shaving. The patches were applied onto the shaved surface. Two milliliters of blood sample was withdrawn from each rabbit at 0, 1, 2, 6, 8, 12, 18, and 24 h from the marginal ear vein and transferred into heparinized test tubes to prevent coagulation of blood. Blood samples were immediately centrifuged at 5000 rpm and plasma was separated, the drug was extracted and estimated by a similar technique as reported by Rajeev et al. (1992).

2.7. Statistical analysis

The curve fitting and statistical analysis were carried out using GraphPad Prism 3.03 software. The *t*-test was selected as the test for significance and *P* value less than 0.05 was considered statistically significant.

3. Results and discussion

The film formed is slightly opaque and uniform with a maximum variation in the thickness of ±2.5%. The film with 10 mg polymer/cm^2 was about 85 μm and the increase in thickness was linear with an increase in the polymer concentration (Fig. 1). However from the slope of Fig. 1, it is seen that the increase in thickness was as low as 1 μm/mg/cm^2 of polymer content. This is a desirable property in the polymers used in TTS. When the polymer–drug ratio is increased to achieve retarded release kinetics, drastic increase in the thickness of the film might alter the physical and mechanical properties of the film. The rate of water vapor transmission, tensile strength, and the percent elongation of the films formulated with different concentration of the polymer are shown in Fig. 2. The tensile strength and water vapor transmission rate of cellulose acetate films prepared from 2% w/v casting solution

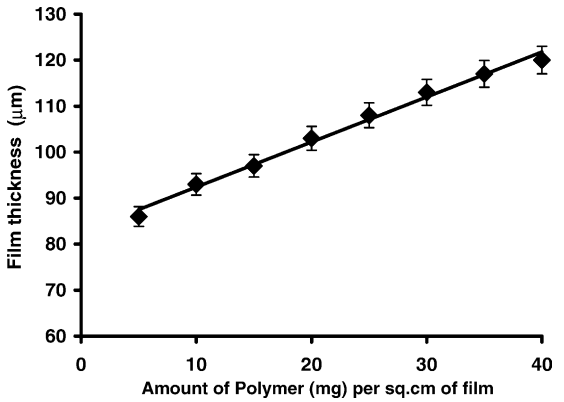

Fig. 1. Relationship between the polymer content (mg/cm^2) and the film thickness ($n = 6 \pm$ S.D.).

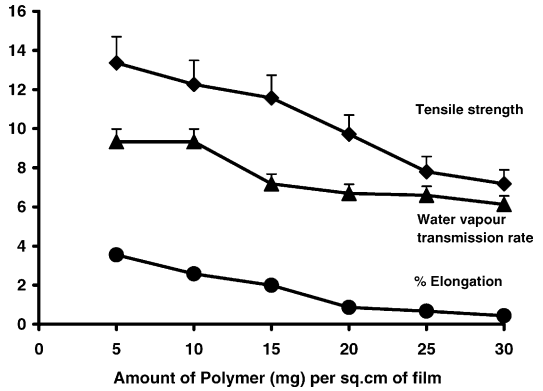

Fig. 2. Properties of CMGS films with different amount of polymer (mg) per cm^2. Tensile strength (dyn/cm^2 $\times$ 10^7; ◆), percent elongation (●), water vapor permeability (g/cm^2 24 h $\times$ 10^{-4}; ▲) ($n = 5 \pm$ S.D.).

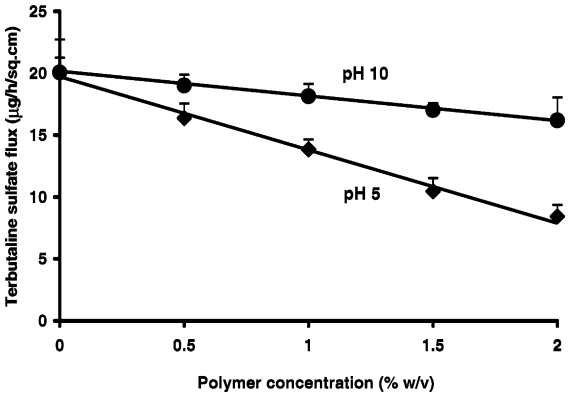

Fig. 3. Influence of polymer concentration at donor solution pH 5 (◆) and pH 10 (●) on the passive diffusion flux of TS across human cadaver epidermis ($n = 3 \pm$ S.D.).

was reported to be $\sim 20 \times 10^7$ dyn/cm^2 and 11.9×10^{-3} g/cm^2 24 h, respectively (Rao and Diwan, 1997). These films were found to be suitable for formulation of transdermal drug-delivery systems. The properties of CMGS films with 10 mg/cm^2 were comparable with the cellulose acetate films. The tensile strength of these CMGS films was 12.26×10^7 dyn/cm^2 and the vapor transmission rate of 9.33×10^{-3} g/cm^2 24 h. However, the percent elongation of CMGS films were less at least by a factor $\sim$10. A detailed report of influence of different plasticizers on various mechanical properties of CMGS has been published elsewhere (Murthy and Hiremath, 2001). In brief, the polymeric films with concentrations less than 40% w/w plasticizer were somewhat brittle and lacked the folding endurance. The films with plasticizer concentration over 50% w/w did not further improve the film properties or diffusion of drug significantly (compared to those with 40% w/w). Hence 40% w/w was fixed as optimum concentration for plasticizer.

The films were subjected to accelerated stability studies. A model film with 10 mg/cm^2 of the polymer was chosen for these studies. The films exhibited temperature–time-dependent changes in their properties. However, the thickness, percent elongation, water vapor permeability, and the tensile strength did not vary significantly up to 40 °C. Above 40 °C, the films lost its moisture content and became brittle.

The pH of 1% w/v solution of CMGS is about 6, which is the same as that of the skin surface ($\sim$5). The human volunteers subjected to skin reaction studies scored 0–1 for series 1 and 0–2 for series 2 films. Mild erythema with the series 2 formulations may be due to their alkalinity. The score of SDS treated group was 5 ± 1 whereas the control group score was zero.

This paper was part of a project of formulation of transdermal drug-delivery systems for controlled release of antiasthmatic drugs. Hence, TS was used as a model drug for the formulation of transdermal films.

The steady-state flux of TS across human cadaver epidermis from saturated solution prepared in deionized water was 20.91 ± 2.61 µg/h/cm^2. We studied the influence of ionized and unionized state of TS (pK_a 9.2) on its diffusion. The flux did not differ significantly on varying the pH of the donor solution (pH 5–10) as both the ionized and unionized forms of the drug are equally hydrophilic and their partitioning into the lipid pathways would be negligible (Poctanol $\sim$0.5). In parallel, we carried out the diffusion studies of the drug from CMGS solutions of pH 5 and pH 10, across human cadaver epidermis. Obviously, the flux of TS decreased when the polymer concentration was increased due to increased viscosity. It is notable from Fig. 3 that the slope of the trend line is higher for pH 5 than pH 10. At the concentration range considered for this study, the viscosity at pH 5 and pH 10 did not differ significantly. To determine the influence of viscosity alone on the diffusion of TS, we prepared polyethylene glycol mixtures (PEG 400 and 4000 in pH 5 and pH 10 buffers) of the same viscosity as that of CMGS solutions (the viscosity of CMGS solution

was about ~500 cps at pH 5 and pH 10). The flux of TS from the PEG base remained same from both pH 5 and pH 10 formulations. The flux of TS from PEG vehicles was comparable with the flux from CMGS solution at pH 10. Hence, we may assume that, at pH 10, viscosity is the predominant controlling factor for diffusion of TS from CMGS solution. Whereas, at pH 5, the reduced diffusion rate may be due to the drug–polymer interaction also.

The polymeric solution was dried and the mixture as well as the extracted drug were subjected to chromatographic and FTIR studies. Neither the chromatograms nor the IR spectra revealed any kind of interaction or degradation of the drug or polymer. The interaction between the polymer and ionized TS at pH 5 may be physical and could involve vanderwall's or static interactions.

It was reported that pH influences the water permeability of skin due to the changes brought about in the nature of the stratum corneum (Mauro et al., 1998). Hence, to ascertain whether the difference in flux of TS was due to the pH influence on the barrier properties of skin, we determined the diffusion flux of TS from the polymer solution of pH 5 and pH 10 across a dialysis membrane (10 μm thickness and 0.1 μm pore size). The diffusion flux of TS across the membrane did differ significantly between pH 5 and pH 10 polymer solutions similar to that observed in case of human epidermis (Fig. 4). This further confirmed our assumption of interaction between polymer and TS at pH 5.

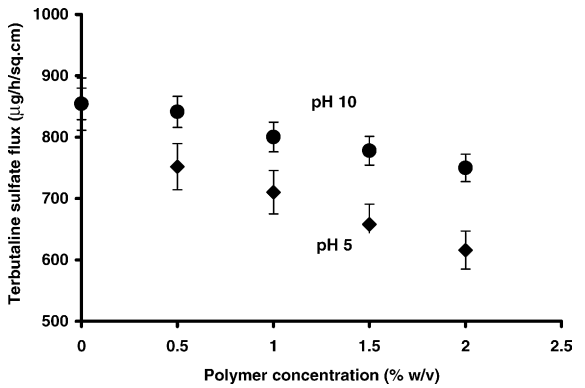

Fig. 4. Influence of polymer concentration at donor solution pH 5 (◆) and pH 10 (●) on the passive diffusion flux of TS across dialysis membrane ($n = 3 \pm$ S.D.).

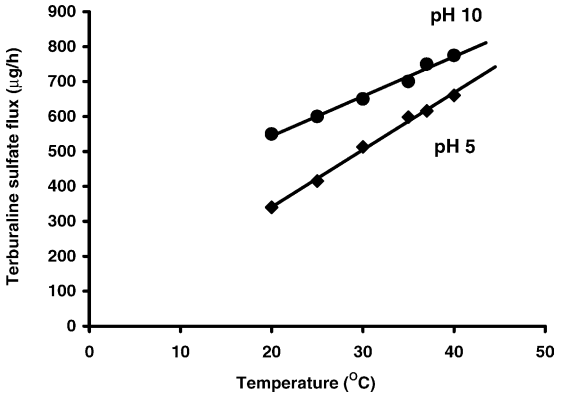

Fig. 5. Influence of temperature on the diffusion of TS from CMGS solution (2% w/v) at pH 5 (◆) and pH 10 (●) across dialysis membrane (0.1 μm) ($n = 3 \pm$ S.D.).

A similar experiment across the dialysis membrane was carried out to study the influence of temperature on the diffusion flux of TS from the polymeric solution of 2% w/v concentration. Increase in temperature increased the rate of passive diffusion of TS both at pH 5 and pH 10. In case of pH 5 solution, the increase in the flux was more with rise in temperature. The two lines meet at a temperature over 60 °C. An increased flux may be due to two reasons such as decrease in the viscosity of the medium and due to an increased kinetic energy of the molecules (Fig. 5). pH does not seem to have any bearing on the temperature-dependent viscosity changes of the polymer solution at 2% w/v concentration. The linear relationship between reciprocal of absolute temperature to viscosity (centipoises) at 2% w/v polymer concentration in pH 5 and pH 10 could be fit to equation $\eta = 2.2164(1/T) \times 10^4 - 271.54$ (the regression coefficient was 0.97 and 0.91 at pH 5 and pH 10, respectively).

From all the above experimental results, it is most likely that the difference in the TS flux between pH 5 and pH 10 donor solutions of CMGS is neither due to the changes in the permeability characteristics of the barrier, nor due to the pH-dependent structural changes in the formulation. It may be due to the difference in the concentration of the free drug (ionized or unionized) present in the polymer solution. The amount of free drug at pH 5 would be less due to the interaction between the polymer and the TS, which dissociate on increase in temperature. Thus, an increased chemical potential leads to increased flux at

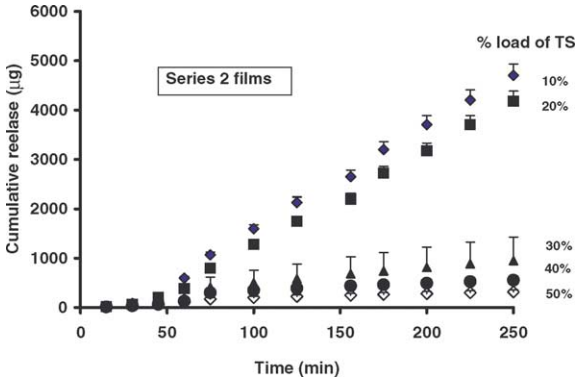

Fig. 6. In vitro release profile of TS from CMGS films of series 2, containing 10% (◆), 20% (■), 30% (▲), 40% (●), 50% (◇) load of TS ($n = 3 \pm$ S.D.).

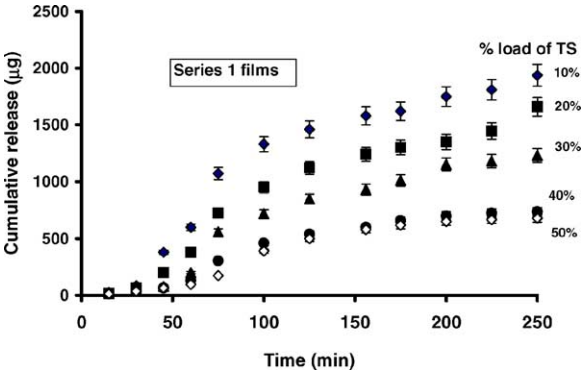

Fig. 7. In vitro release profile of TS from CMGS films of series 1, containing 10% (◆), 20% (■), 30% (▲), 40% (●), 50% (◇) load of TS ($n = 3 \pm$ S.D.).

elevated temperatures. Assuming no interaction exists at pH 10, the activation energy associated with the interaction at pH 5 was calculated by the Arrhenius equation (the difference between E_a of diffusion at pH 5 and at pH 10). The activation energy of 4 kCa indicates that the interaction between CMGS and TS at pH 10 could be physical involving vanderwall's and static interactions.

Though such interactions are considered very week, they play a major role in determining the kinetics of drug release from controlled release formulations. Hence, the CMGS films containing TS prepared by casting solutions of pH 5 and pH 10 were subjected to in vitro release studies. The release rate decreased with an increase in the polymer content in the film. In case of films of series 2, the drug release was proportional to the time after a lag period following a $Q = Kt^n$ profile. 'n' was ~0.95–1 (Fig. 6).

The release pattern of TS (Fig. 7) from the films of series 1, remained exponential with a curve fit equation [$y = b(1 - e^{Kt})$], where K is the release rate constant, which decreased with an increase in the polymer content (mg/cm^2) in the film. According to the law of consecutive processes (Celis et al., 2001), the rate of release of TS from series 1 polymeric matrix film is limited by the dissociation of free drug from the polymer bound form. This rate process is much slower than the rate of diffusion of free drug from the polymeric matrix. Hence, according to the law of consecutive processes this step acts as a predominating rate determining step over the other.

The diffusion profile of transdermal films from series 1 and series 2 are shown in Fig. 8. The lag period increased with an increase in the polymer concentration. The diffusion of TS from both the series followed zero order kinetics. However, the rate of release was slower in series 1 than 2.

To determine the influence of such physical interactions on the pharmacokinetic parameters of the drug, the representative formulations (with 10 mg of polymer/cm^2) were subjected to pharmacokinetic studies in rabbits. The pharmacokinetic parameters of the formulations are given in Table 1. The C_{max} in case of pH 5 formulation was attained after 6 h, as compared to 4 h of pH 10 formulation. The

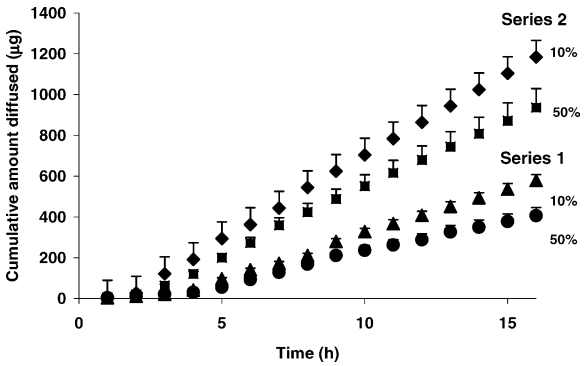

Fig. 8. In vitro diffusion profile of TS from CMGS films of series 1 (10% (▲), 50% (●) mg/cm^2 of film) and series 2 (10% (◆), 50% (■) mg/cm^2 of film). ($n = 6 \pm$ S.D.).

Table 1
Pharmacokinetic parameters of TS in rabbits on application of the 10 cm^2 transdermal films of CMGS (10 mg polymer/cm^2) containing 5 mg of TS

Pharmacokinetic parameters	Series 1	Series 2
C_{max} (μg/ml)	3.53 ± 2.40	3.85 ± 1.38
T_{max} (h)	6.0 ± 1.2	4.0 ± 0.9
AUC_{0-24} (μg/ml h)	58.50 ± 18.12	39.99 ± 10.22
AUC_{total} (μg/ml h)	82.41 ± 12.67	45.91 ± 20.96
$AUMC_{0-24}$ (μg/ml h^2)	697.57 ± 91.96	381.81 ± 66.74
$AUMC_{total}$ (μg/ml h^2)	1724.77 ± 338.88	585.74 ± 143.58
MRT (h)	20.93 ± 7.14	12.82 ± 2.74
K_{el} (h^{-1})	0.053 ± 0.010	0.096 ± 0.02
$T_{1/2}$ (h)	13.15 ± 3.61	7.21 ± 1.46

Series 1 and 2 represent the pH 5 and pH 10 of the casting solution, respectively. The values are mean of $n = 6$ ± S.D.

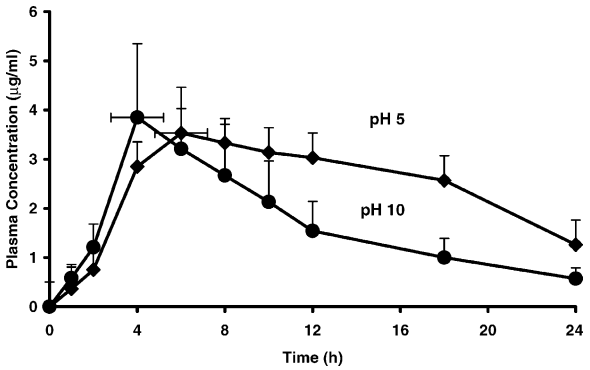

Fig. 9. Plasma TS concentration-time profile of 10 mg/cm^2 films of series 1 (◆) and series 2 (●). The values are means of $n = 6$ ± S.D.

steady-state concentration was more consistent and the AUC was at least 50% higher in case of pH 5 formulation compared to pH 10 (Fig. 9). The elimination rate constant and thus the elimination half-life were significantly ($P < 0.014$) different between the two formulations.

4. Conclusions

The experiments on CMGS have shown that the polymer is a candidate of consideration for the formulation of transdermal drug-delivery systems. The polymer exhibits good film forming ability and could be formulated into films possessing desired properties by varying the composition of the casting solution. The polymer is non-sensitizing and safe. CMGS films are to be stored at a temperature below 40 °C. The ionized/unionized state of drug is an important factor to be considered while preparing the casting solution to induce or minimize the interaction between the polymer and the drug. Though the interaction is physical, it is capable of bringing about significant changes in the release rate, which in turn alters the pharmacokinetic parameters of the drug.

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