International Journal of Pharmaceutics, 92 (1993) 225–231

IJP 03164

Effects of polymer formulation on electrophoretic drug delivery

Antony D'Emanuele [a] and John N. Staniforth [b]

[a] *Department of Pharmacy, University of Manchester, Manchester M13 9PL (UK) and* [b] *School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY (UK)*

(Received 13 October 1992)
(Accepted 30 November 1992)

Key words: Controlled drug delivery system; Electrically modulated drug delivery system; Electrophoresis; Polymer; Crosslinker effect

Summary

A controlled drug delivery device based on the principle of electrophoresis is described in this paper. A model system using propranolol HCl and PHEMA films is used to demonstrate how control over the release of a model drug may be achieved using low constant electric currents. Polymer formulation is shown to be important, highly crosslinked polymer producing a different effect to low crosslinked polymer. The model is used to demonstrate the low power requirements for control over drug transport and indicates the feasibility of using an electrophoretically controlled drug delivery device to provide truly controllable and predictable release rates.

Introduction

Polymers have been used extensively in the development of systems to provide the controlled long-term delivery of drugs and other chemicals (Langer, 1980, 1990). The majority of work in the field of controlled drug delivery has focussed on the development of systems where release rates are a simple function of time eg. zero-order. It has become apparent, however, that this approach may not be the most appropriate and effective manner of delivery for many drugs, and that delivery systems which can provide variable release rates, dependent on the bodies varying requirements, may result in improved therapeutic effects and reduced side-effects (Banga and Chien, 1988; Reinberg, 1988; Pitt, 1990; Staudinger, 1990). This realization has stimulated much recent interest in the development of pulsed and self-regulated drug delivery systems (Kost, 1990; Langer, 1990). One such delivery system that has attracted interest is based on the principles of constant current electrophoresis (D'Emanuele et al., 1988; Lescure et al., 1988). A schematic diagram of the proposed device is shown in Fig. 1. It consists of a polymer reservoir device with the addition of a pair of electrodes placed across the rate limiting membrane. In the absence of an electric field a basal level of drug release will occur which may be modulated in a controlled and predictable manner by altering the magnitude of the electric field between the electrodes (D'Emanuele and Staniforth, 1991). The most innovative and exciting prospect of this type of

Correspondence to: J.N. Staniforth, School of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, U.K.

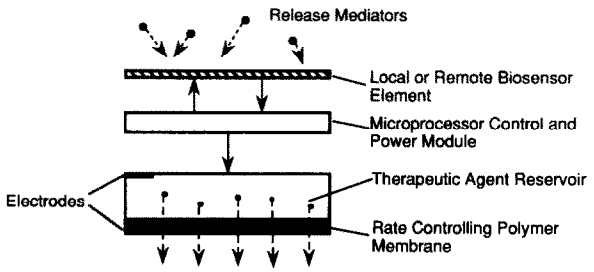

Fig. 1. Schematic representation of an electrophoretic pump.The device consists of a reservoir of therapeutic agent, the release of which is controlled by a rate controlling polymeric membrane. The release may be modulated in either a positive or negative manner by appropriate control of the electric field between a pair of electrodes placed on either side of the polymer membrane. Control over the electric field is by means of a microprocessor which may receive information from a biosensor element.

delivery system is the potential for feedback control where the output from the pump may be varied as a result of information received form a biosensor element (D'Emanuele and Staniforth, 1993).

The polymeric film determines the basal delivery rate and also the behaviour of the device. In the present study a model system based on constant current electrophoresis was examined using crosslinked poly(2-hydroxyethyl methacrylate) (PHEMA) as the rate limiting membrane and propranolol hydrochloride (PHC) as a model drug.

The transport mechanism of PHC through PHEMA hydrogel films is dependant on the proportions of bound and free water within the polymer, and can be controlled by appropriate manipulation of the polymer formulation (Ratner and Miller, 1973; Lee et al., 1978). In particular, crosslinker content may be altered to provide different mechanisms of transport for PHC through crosslinked PHEMA films (D'Emanuele and Staniforth, 1987, 1988; D'Emanuele, 1989). It is thought that at low crosslinker content (approx. 3% or less) the transport of PHC through PHEMA is via a pore mechanism, but as the crosslinker content is increased, transport becomes predominantly partition mechanism dominated. The present study investigates the effect of polymer formulation on the electrophoretic transport of PHC.

The proposed system requires a power source to produce an electric field. The power requirements of the model system are examined in order to demonstrate that low power requirements obtainable from small batteries, for example, may be used to provide effective control over drug transport.

Materials and Methods

Materials

Propranolol hydrochloride was received as a gift from Forum Chemicals Ltd (Redhill, U.K.). 2-Hydroxyethyl methacrylate (stated purity > 97%) and ethylene glycol dimethacrylate (stated purity > 96%) were obtained from Fluorochem Ltd (Glossop, U.K.). Ammonium persulphate (electrophoresis grade) was obtained from FSA Laboratory Supplies (Loughborough, U.K.). Platinum foil (0.025 mm thickness) and wire (0.5 mm diameter) were obtained from FSA Laboratory Supplies (Loughborough, U.K.). All water used in these studies was freshly distilled. All other chemicals used were of analytical reagent purity.

Preparation of PHEMA Films

Films of homogeneous PHEMA films were prepared by chemical initiation. Films were polymerized in a mould which consisted of two thin glass plates separated by a spacer. The films were crosslinked by the addition of either 0.1, 1 or 7% EGDMA in the presence of 0.5% ammonium persulphate with a total water content of 37.5% in the polymerizing solution. The solution was degassed thoroughly with helium prior to the addition of the ammonium persulphate. The polymerization was allowed to proceed for 18 h at 60°C, after which the glass plates were separated and the polymer films peeled away. The films were stored in distilled water at 4°C, the distilled water being changed daily for three weeks. The purpose of this being to leach out any ammonium persulphate or unreacted monomers, and to allow the polymer to swell to its equilibrium volume. The polymer was then cut into disc form using a

cylindrical bladed metal cutter and immersed in pH 4.48 Walpole acetate buffer and stored at 4°C until ready for use. The hydrogel film thickness was measured by placing it between two glass plates of known thickness and measuring the total thickness with a precision digital micrometer (Mitutoyo, supplied by RS Components Ltd, Corby, U.K.), using the torque control so as not to over-compress the hydrogel. The discs used in the present study were approx. 0.09 cm in thickness and 4 cm in diameter.

Electrophoresis studies

The methodology and its validation have been fully described previously (D'Emanuele and Staniforth, 1991). A schematic diagram of the equipment used in electrophoresis studies is shown in Fig. 2. Briefly, each compartment of the glass electrophoresis cell contained 210 ml of buffer (pH 4.48 Walpole's acetate) with the reservoir containing PHC at a concentration of 4.3 mg/ml. Both compartments were stirred and maintained at 25°C. The receptor compartment buffer was pumped through an ultraviolet spectrophotometer at a rate of 0.5 ml/min and the concentration of PHC continuously monitored at 288 nm. The computer was used to collect and analyze data, as well as to control the power supply in response to inputted data if desired. The power supply, which produced currents in the range of 0–2.5 mA, was connected to the electrodes which were composed of 1 cm^2 platinum foil.

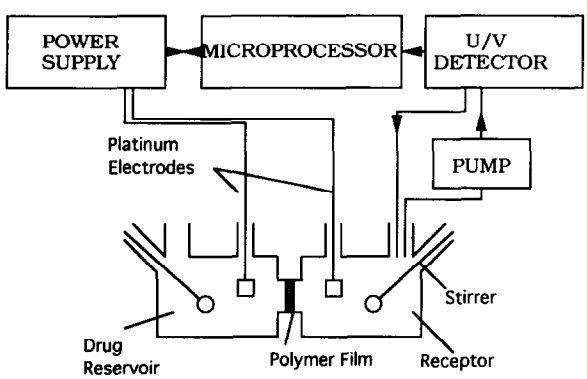

Fig. 2. Schematic diagram of the apparatus used in electrophoresis studies.

Effect of crosslinker content

The effect of using 0.1, 1 and 7% w/w EGDMA crosslinker on electrophoresis was examined. Previous studies showed that crosslinker content has a significant effect on the transport of PHC through PHEMA films (D'Emanuele and Staniforth, 1987, 1988; D'Emanuele, 1989). A pore mechanism of transport of PHC through PHEMA is believed to predominate with the 0.1 and 1% crosslinked polymers whereas a partition mechanism of transport is thought to occur using the 7% crosslinked polymer. Transport via a pore mechanism is associated with free, or bulk water within the polymer where as a partition mechanism of transport is associated with bound water within the polymer.

The electrophoresis cell was assembled with PHEMA of the appropriate crosslinker content. After the delivery rate due to diffusion had become constant, a current was produced by the power supply for a period of 4 h, then turned off again. Electrophoresis studies were performed after steady state conditions had been established, since electrophoresis studies prior during the lag period of diffusion produces different effects (D'Emanuele and Staniforth, 1991). For any given crosslinker content the effect of different currents on electrophoresis was examined over the range 0–2.5 mA.

Power requirements

The power requirements of the model electrophoretic system was examined. The voltage across the platinum electrodes was measured using a voltmeter (Weston 6100, supplied by RS Components Ltd, Corby, U.K.). In all electrophoresis experiments, the voltage was measured 10 min after the start of electrophoresis. This was used as an estimate of the voltage during an experiment since it has been shown that the voltage remains constant during experiments (i.e., constant power conditions) (D'Emanuele and Staniforth, 1991). The power requirements and resistance of the model system could then be calculated to give an approximation of

the power requirements of an electrophoretic device.

Results and Discussion

Effect of Electric Current

Fig. 3 shows the relationship between PHC receptor compartment concentration and time using 1% crosslinked PHEMA film, showing the effect that an electric current of 2.4 mA has on the delivery rate of PHC into the receptor compartment when applied for 4 h. The profile shown is representative of those obtained with all the currents examined in the range of 0–2.5 mA; the magnitude of the change in drug delivery rate was found to vary with current. The drug delivery rate increases almost immediately on application of an electric current, the delivery rate decreasing significantly on removal of the current, though between 6 and 10 h is usually required for the rate to decrease to pre-electrophoresis levels (D'Emanuele and Staniforth, 1991). Delivery rates during application of an electric current were found to be constant and reproducible. The relationship between PHC delivery rate and current was found to be linear as shown in Fig. 4, each point representing the mean of three experiments (error bars were too small to be shown). Previous studies on

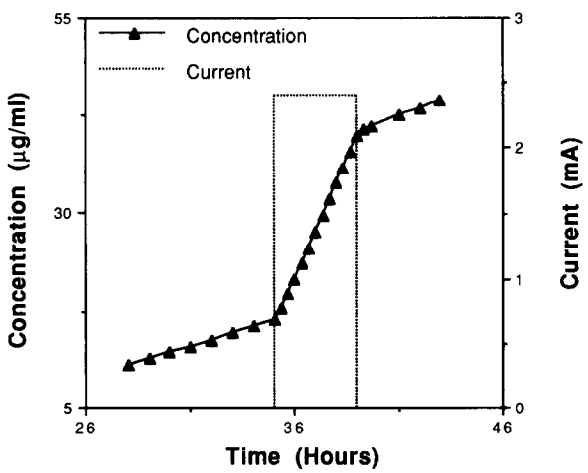

Fig. 3. Effect of current on the transport of PHC into the receptor compartment of the electrophoresis cell with 1% crosslinked PHEMA films.

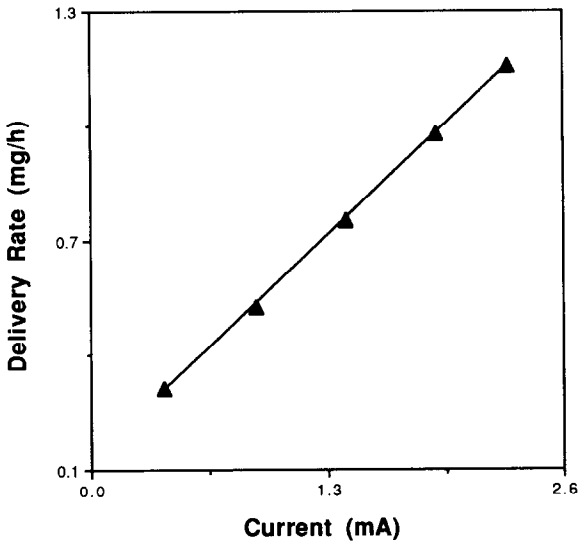

Fig. 4. Effect of applied current on the delivery rate of PHC into the receptor compartment of the electrophoresis cell with 1% crosslinked PHEMA films.

electrophoretic drug delivery devices have shown a similar linear relationship when insulin was investigated using constant voltages (Kumar, 1986) and bovine serum albumin using constant currents (Lescure et al., 1988), both these studies used polyacrylamide as the membrane material. The results show that drug delivery rates may be predictably increased by a significant amount using low electric currents.

Effect of crosslinker content

The effect of PHEMA crosslinker content on the delivery rate of PHC produced by constant current electrophoresis is shown in Fig. 5. Linear regression analysis of the three curves indicated that for 0.1 and 1.0% crosslinked PHEMA the relationship between delivery rate and current is linear, however, for 7.0% crosslinked PHEMA the relationship appears curvilinear. The results are surprising and do not follow the pattern of delivery which might be expected; in the current range examined the delivery rate produced for a given current was greatest for 1% followed by 0.1% and was lowest for 7% crosslinked PHEMA. This was not expected because the diffusion coefficients, calculated from the steady state diffusion period prior to electrophoresis, showed the fol-

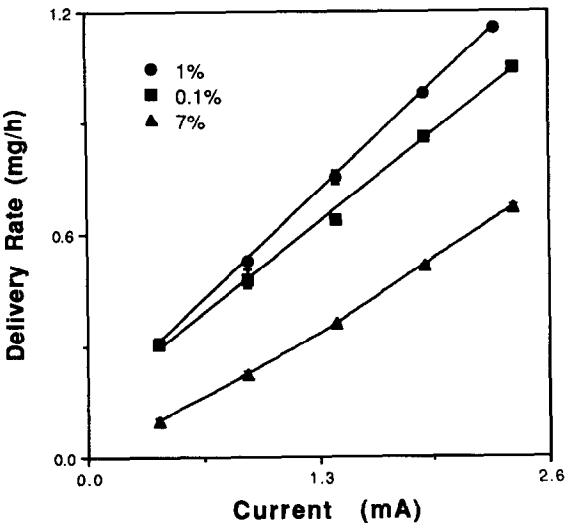

Fig. 5. Effect of crosslinker content on the electrophoretic transport of propranolol HCl through PHEMA films.

lowing expected order of drug transport rates: 0.1% > 1.0% > 7%. The lines of best fit for the 0.1 and 1.0% crosslinked PHEMA, if extrapolated to zero current, cross over and give approximate intercepts of drug delivery produced by diffusion alone, with the intercept being greatest for the 0.1% crosslinked PHEMA film, as would be expected. Thus the change produced in drug delivery rate by changes in current are greater for the 1.0% than the 0.1% crosslinked PHEMA. The order of drug delivery produced by the various crosslinked polymers is also surprising when the electrical resistance across these films is measured (Table 1); the pattern of resistance follows the expected order with 0.1% crosslinked PHEMA producing the lowest resistance.

Previous electrophoretic studies using polyacrylamide have shown that as crosslinker content increases, electrophoretic mobility decreases (Hedrick and Smith, 1968; Brackenbridge and Bachelard, 1969). Studies into electrophoretic drug delivery devices using polyacrylamide have, however, shown a biphasic relationship between mobility and crosslinker content; as crosslinker content is increased initially, a decrease in mobility is found, which reaches a minimum and then increases again as crosslinker content is increased further (Kumar, 1986; Lescure et al., 1988). This effect was attributed to a re-arrangement of the polyacrylamide network with changes in crosslinker content. At low crosslinker contents, as crosslinker concentration is increased, a decrease in gel mesh size is thought to occur, and thus a decrease in mobility is found. At higher crosslinker contents a re-arrangement of the network is thought to occur resulting in an increase in mesh size and thus increase in mobility. A similar pattern of delivery rate and crosslinker content may be followed with PHEMA, however there is no evidence to suggest that such a re-arrangement of PHEMA structure occurs as crosslinker content is altered.

TABLE 1

Effect of PHEMA crosslinker content on the measured resistance between platinum electrodes at 25°C

Crosslinker content (%)	Resistance (Ω)
0.1	778
1.0	835
7.0	1685

An alternative explanation for the effect found in the present study is that the structure of PHEMA may somehow be affected by the application of an electrophoretic field, indeed polyacrylamide has been shown to swell slightly during electrophoresis (Kumar, 1986). If there is a change in structure occurring as a result of electrophoresis, then this change may be related to the electric field strength, which is directly related to the applied electrophoretic current. In the case of both 0.1 and 1% crosslinked PHEMA, transport within PHEMA is believed to be via a pore mechanism (D'Emanuele and Staniforth, 1987, 1988), the diffusion coefficients of these two crosslinked films being similar. One would expect a more rigid structure in the higher crosslinked 1.0% crosslinked PHEMA than the 0.1% crosslinked PHEMA film, thus the 1.0% crosslinked PHEMA may be more resistant to changes in structure produced by an electric field. This effect may explain the results obtained if the changes in the structure of PHEMA caused by an electric field results in the transport of propranolol HCl through PHEMA being hindered. This

explanation however may be an oversimplification since changes in the crosslinker content in PHEMA has effects on both the effective pore size and the structure of water within the polymer (Roorda et al., 1986).

The crosslinker content can also dictate the type of effect produced by a constant current. Fig. 6 shows the relationship between receptor propranolol HCl concentration and time using a 7% crosslinked PHEMA film, and the effect of application of a current of 2.4 mA. The effect is in contrast to that produced with 1% crosslinked PHEMA as shown in Fig. 3. The increase produced by a current is highly dependent on the PHEMA crosslinker content. As an example, the ratio between delivery rate during electrophoresis and delivery rate due to diffusion prior to an electrophoretic current of 1.9 mA is 32 for 7% crosslinked PHEMA. The same ratios calculated for 0.1 and 1.0% crosslinked PHEMA are 6 and 7.5, respectively. Thus with the lower crosslinked PHEMA (0.1 and 1.0%), even though a much higher delivery rate is produced by a given current, the change in delivery rate caused by electrophoresis over that due to diffusion prior to electrophoresis is much greater with the higher crosslinked PHEMA (7%). This difference may be a result of the difference in transport mechanisms between the high crosslinked polymer film and the lower crosslinked films. A difference in the properties of the films is also indicated by the resistance data (Table 1); the resistance across the 7% crosslinked PHEMA was found to be much greater than that of the 0.1 and 1.0% crosslinked PHEMA.

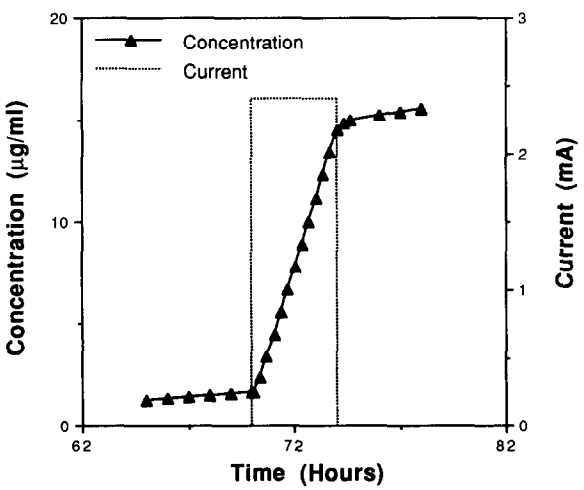

Fig. 6. Effect of current on the transport of PHC into the receptor compartment of the electrophoresis cell with 7% crosslinked PHEMA films.

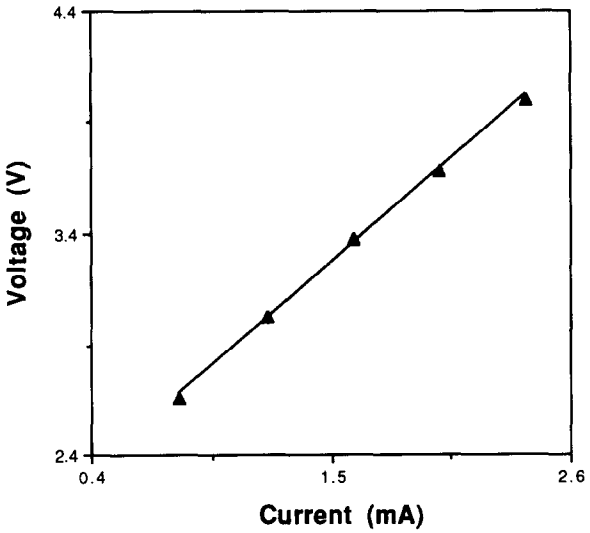

Fig. 7. Relationship between voltage and current across 1% crosslinked PHEMA films in the electrophoretic cell.

The effects produced by altering polymer formulation could be utilized in the design of a drug delivery system, so that the formulation of the polymer would be optimized for individual applications.

Power requirements

Fig. 7 shows the relationship between voltage and current across 1% crosslinked PHEMA at 25°C. The linear relationship between voltage and current in Fig. 7 was typical of that found in all experiments in this study, which allowed the resistance across the system to be calculated from the gradients of these plots (Table 1).

The measured voltage across the electrodes during electrophoresis enables the calculation of the power requirements of the model system. It should be noted that the resistance calculated is that across the whole cell and that the actual power requirements of a prototype device is likely to be lower. As an example, for a 1% crosslinked

polymer film, at 37°C, the calculated power requirements at a constant current of 2.0 mA is 2.5 mW. This value has significant implications with respect to the use of a low-power electrophoresis drug delivery device for clinical use. Such a device could be powered by batteries, for example a typical button-type lithium cell is capable of supplying 200 mA h at a constant 3 V (RS Components Ltd, Corby, U.K.), which is approximately equivalent to 200 operating hours at the power consumption calculated above. The model systems thus demonstrates that power requirements are relatively low, thus demonstrating the feasibility of an electrophoretic device.

Conclusions

Low constant current electrophoresis was shown to allow control of the transport rates of PHC through PHEMA films. Currents in the range of 0–2.5 mA had a significant effect on transport rates of PHC, the effects being rapid and reversible. The results also indicated that the delivery rate of PHC during electrophoresis can be predicted using currents in the range examined. The crosslinker content of the polymer strongly affects the changes in transport produced by an electric current permitting the optimization of the polymer formulation for individual applications. The low power requirements and control over drug transport demonstrate the feasibility of an electrophoretically modulated drug delivery system.

Acknowledgement

This work was supported with the aid of a grant from the Science and Engineering Research Council.

References

Banga, A.K. and Chien, Y.W., Systemic delivery of therapeutic peptides and proteins. *Int.J. Pharm.*, 48 (1988) 15–50.

Brackenbridge, C.J. and Bachelard, H.S., The effect of some variables on protein separation by polyacrylamide gel electrophoresis. *J. Chromatogr.*, 41 (1969) 242–249.

D'Emanuele, A., A study of controlled drug delivery using low constant current electrophoresis, Ph.D thesis, University of Bath (1989).

D'Emanuele, A. and Staniforth, J.N., The anomalous diffusion of propranolol HCl through crosslinked pHEMA films. *J. Pharm. Pharmacol.*, 39 (1987) 28P.

D'Emanuele, A. and Staniforth, J.N., Effect of pHEMA carboxyl content on the diffusion of propranolol HCl through crosslinked pHEMA films. *J. Pharm. Pharmacol.*, 40 (1988) 6P.

D'Emanuele, A. and Staniforth, J.N., An electrically modulated drug delivery device. I: *Pharm. Res.*, 8 (1991) 913–918.

D'Emanuele, A. and Staniforth, J.N., Feedback controlled drug delivery using an electro-diffusion pump. *J. Controlled Rel.*, 23 (1993) 97–104.

D'Emanuele, A., Staniforth, J.N. and Marsden, R., Controlled release of propranolol HCl using constant current electrophoresis. *Proc. Int. Symp. Controlled Release Bioact. Mater.*, 15 (1988) 76–77.

Hedrick, J.L. and Smith, A.J., Size and charge isomer separation and estimation of molecular weights of proteins by disc gel elecrophoresis. *Arch. Biochem. Biophys.*, 126 (1968) 155–164.

Kost, J., *Pulsed and Self-Regulated Drug Delivery*, CRC Press, Boca Raton, 1990.

Kumar, R., A study of low voltage polyacrylamide gel electrophoresis as a means of providing controlled drug release, Ph.D Thesis, University of Bath, Bath (1986).

Langer, R., Polymeric delivery systems for controlled drug release. *Chem. Eng. Commun.*, 6 (1980) 1–48.

Langer, R., New methods of drug delivery. *Science*, 249 (1990) 1527–1533.

Lee, K.H., Jee, J.G., Jhon, M.S. and Ree, T., Solute transport through crosslinked poly(2-hydroxyethyl methacrylate) membrane. *J. Bioeng.*, 2 (1978) 269–278.

Lescure, F., Gurny, R., Doelker, E. and Augustynski, J., In vitro evaluation of a new electrophoretically controlled drug delivery system based on a crosslinked gel. *Proc. Int. Symp. Controlled Release Bioact. Mater.*, 15 (1988) 362–363.

Pitt, C.G., The controlled parenteral delivery of polypeptides and proteins. *Int.J. Pharm.*, 59 (1990) 173–196.

Ratner, B.D. and Miller, I.F., Transport through crosslinked poly(2-hydroxylethyl methacrylate) hydrogel membranes. *J. Biomed. Mater. Res.*, 7 (1973) 353–367.

Reinberg, A., New concepts in chronopharmacology. *News Physiol. Sci.*, 3 (1988) 84–88.

Roorda, W.E., Bodde, H.E., De Boer, A.G. and Junginger, H. E., Synthetic hydrogels as drug delivery systems. *Pharm. Weekbl. Sci. Ed.*, 8 (1986) 165–189.

Staudinger, K.H., V. Chronopharmacology as a rationale for the development of controlled release products. *Paperback APV*, 22 (1990) 83–97.