Drug Release from pH and Ionic Strength Responsive Poly(acrylic acid) Grafted Poly(vinylidenefluoride) Membrane Bags *In Vitro*

Kristiina Järvinen,[1,4] Satu Åkerman,[1] Bror Svarfvar,[2] Tommy Tarvainen,[1] Pasi Viinikka,[3] and Petteri Paronen[1]

Received November 11, 1997; accepted January 30, 1998

KEY WORDS: responsive porous polymer membrane; poly(acrylic acid); pH and ionic strength sensitivity; drug release.

INTRODUCTION

Many drugs, such as insulin, gastric acid inhibitors and nitrates, as well as general hormone replacement and immunization, would require a rhythmic pattern of a drug concentration. Pulsatile or site-specific drug delivery may be achieved by externally regulated and self-regulated delivery systems that are capable of adjusting drug release rates in response to a physiological need, such as changes in the pH in the body. As an example, insulin delivery systems based on the pH-sensitive polymers have been developed by many research groups (1–2). In addition, pulsatile or site-specific delivery systems have been developed for oral drug delivery (3–4), for immunization against tetanus toxoid (5) and for a local delivery of thrombolytic and antithrombotic agents (6).

We have studied the suitability of a pH and ionic strength responsive porous polymer membrane for controlled drug delivery (7). Porous polyvinylidene fluoride (PVDF) membranes have been graft modified with pH and ionic strength sensitive acrylic acid (PAA) by radiation induced grafting utilizing electron beam. Earlier examples Iwata *et al.* (8) and Ito *et al.* (1) have studied insulin delivery systems based on a porous poly(acrylic acid) membrane. Our preliminary study suggested that PVDF-PAA might be capable of controlling release of the drugs in response to the environmental pH (7). Despite their porosity, the PVDF-PAA membranes act reasonably well as cation exchange membranes. Bodmeier *et al.* (9) and Knop (10) have demonstrated that buffer species and strength affect drug release from beads and pellet coated with quaternary acrylic polymers (Eudragit RS, RL 30D). They suggested that this is due to an anion exchange process: the anionic buffer species replace the chloride-counterions of the quaternary ammonium groups of the polymer during the dissolution study.

[1] Department of Pharmaceutics, University of Kuopio, Kuopio, Finland.
[2] Department of Polymer Technology, Åbo Akademi University, Åbo, Finland.
[3] Helsinki University of Technology, Laboratory of Physical Chemistry and Electrochemistry, Espoo, Finland.
[4] To whom correspondence should be addressed. (e-mail: Kristiina.Jarvinen@uku.fi)

In the present paper, the release of some model compounds from PVDF-PAA membrane bags were studied at different pH and ionic strength in order to find out the effects of physicochemical properties of the drug and the conformational stage of the polymer on the drug release from the membrane.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: FITC-dextran (mw 4400) and DL-propranolol-HCl from Sigma (St. Loius, MO); caffeine and salicylic acid, sodium salt from Aldrich-Chemie (Steinheim, Germany); disodiumhydrogen phosphate dihydrate and sodium dihydrogen phosphate dihydrate from Merck (Darmsted, Germany); sodium chloride from FF-Chemicals (Yli-ii, Finland), hydrochloric acid from Riedel de Haen (Seelze, Germany).

Preparation of PVDF-PAA Membrane Bags

Hydrophobic PVDF membranes (Millipore) with pore sizes 0.22 μm, and acrylic acid (AA) (Aldrich, Steinheim Germany) stabilized with 200 ppm hydroquinone, were used as received. Ion-exchange water was used throughout.

Square-shaped (2 cm × 2 cm) membrane bags were prepared by placing two membrane samples on top of each other and hot-sealing three sides to form a membrane bag. One end was left open in order to be able to fill membrane bags with a drug after grafting. The membrane bags were irradiated with 25 kGy under nitrogen atmosphere (< 200 ppm O2) using Electrocurtain electron accelerator (Energy Sciences Inc.) operating at an acceleration voltage of 175 kV. During irradiation the unsealed side of the bag was protected with a cupper plate to enable the bags to be hot-sealed after grafting. Immediately after irradiation the membranes were immersed at ambient temperature in a graft solution containing AA. This solution was continuously purged with nitrogen in order to remove oxygen.

After grafting the membranes were soxhlet extracted with water to remove any remaining monomer and dried overnight.

The degree of grafting (G) for the membrane bags was determined gravimetrically according to,

$$G = ((m_1 - m_0)/ m_0) \times 100\%$$

where m_0 represents the mass of irradiated area of the membrane bags and m_1 the mass of the same area after grafting, extraction and drying. The degree of grafting of the PVDF-PAA membrane bags was about 50wt%.

The PVDF-PAA membrane bags were filled manually with caffeine (50 mg), FITC-dextran (mw 4400) (20 mg), propranolol-HCl (50 mg) or sodium salicylate (50 mg). Finally, the membrane bags were closed by hot-sealing the open side.

Dissolution Studies

The USP 23 rotating basket method (100 rpm, 900 ml of dissolution medium, 37°C) was used to study drug release from the membrane bags (dissolution apparatus from Sotax, Basel, Switzerland). The dissolution medium was 6 mM phosphate buffer at pH 2.0 (pH was adjusted to 2.0 with 4 M hydrochloric

0724-8741/98/0500-0802$15.00/0

acid) and at pH 7.0. The total ionic strength of the buffer solution was adjusted to 0.05, 0.15 or 0.40 with NaCl. At predetermined time intervals, samples (5.0 ml) were withdrawn and replaced with the fresh medium.

The concentrations of caffeine (272 nm), propranolol (288 nm) and sodium salisylate (298 nm) were assayed spectrophotometrically (Hitachi 220, Tokyo, Japan). FITC-dextran concentrations were determined flurometrically (Luminescence Spectrometer LS 50B, Perkin Elmer Ltd., Buckinghamshire, England), excitation at 495 nm and emission at 515 nm. The residual drug content in the membrane bags after the dissolution study was determined spectrophotometrically or flurometrically after releasing the remaining drug by soaking the membrane bags in 0.01 M HCl solution at pH 2.1 (μ = 0.20) overnight. The amount of drug released and the residual drug content in the membrane bags matched the original drug content closely.

The time required to release 50% of drug (t50%) was estimated from percent released vs time data for individual experiments.

Data Analysis

A one-factor analysis of variance was used to test the statistical significance of differences between groups; significance in the differences in the means was tested using Fisher's Protected Least Significant Difference at 95% confidence level.

RESULTS

The effect of pH and ionic strength of the dissolution medium on the drug release from the membrane bags was highly dependent on the charge and molecular weight of a released drug.

Figure I shows the effects of the pH of the dissolution medium on the release of the model compounds from the membrane bags prepared from about 50 wt% grafted PVDF-PAA membrane. At pH = 7.0 (μ = 0.15), the release of the biggest model compound, FITC-dextran (mw 4400), from the membrane bags was considerably slower than the release of small compounds (mw < 300). Release of caffeine, propranolol and FITC-dextran (mw 4400) from the membrane bags into the buffer solution at pH 7.0 was slower than the release into the buffer solution with corresponding ionic strength at pH 2.0. As an example, about 93% of FITC- dextran (mw 4400) was released from the membrane bags at pH 2.0 (μ = 0.15) during 8 hours, while only about 18% was released at pH 7.0 (μ = 0.15). In contrast, salicylate release from the membrane bags was significantly faster at pH 7.0 than at pH 2.0. At pH 7.0, the membrane bags containing salicylate were swollen, looking like a pillow, at the end of the study.

Figure 2 shows the effects of the ionic strength of the dissolution medium on the release of the model compounds from the membrane bags. The ionic strength of the dissolution medium did not affect the release rate of sodium salicylate. The release rate of propranolol was significantly decreased with increasing ionic strength of the dissolution medium. At pH 7.0, the release rate of caffeine tended to decrease by increasing ionic strength of the dissolution medium from 0.05 to 0.40. Due to the limited number of membrane bags, caffeine release was not tested in the dissolution medium with an ionic strength of 0.15. At pH 2.0, no relationship was found between the release of caffeine and the ionic strength of the dissolution medium. Figure 2 shows that the relative standard deviation (81%) was exceptionally high when caffeine was released from the membrane bags into the pH 2.0 buffer solution with μ = 0.15.

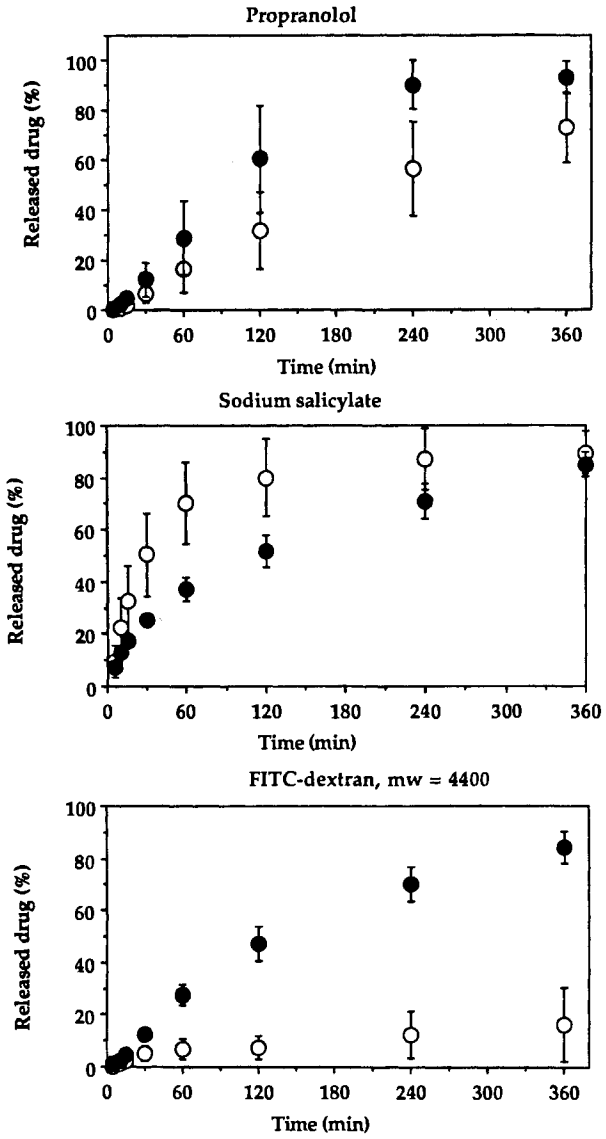

Fig. 1. Release of model compounds (sodium salicylate, propranolol, FITC-dextran, mw = 4400) from membrane bags prepared from 50 wt% PAA grafted PVDF membranes into the dissolution medium (μ = 0.15) at pH 2.0 (●) and pH 7.0 (○). Means ± SEM are shown (n = 3).

Drug release from the membrane bags followed neither zero-order nor square-root of time kinetics in buffer solutions with μ = 0.05 or 0.15 (Table I, Figure 1). At μ = 0.40, drug release was best described by the diffusional square-root of time release at pH 2.0 while caffeine and propranolol release from membrane bags tended to follow zero-order kinetics at pH 7.0 (Table I).

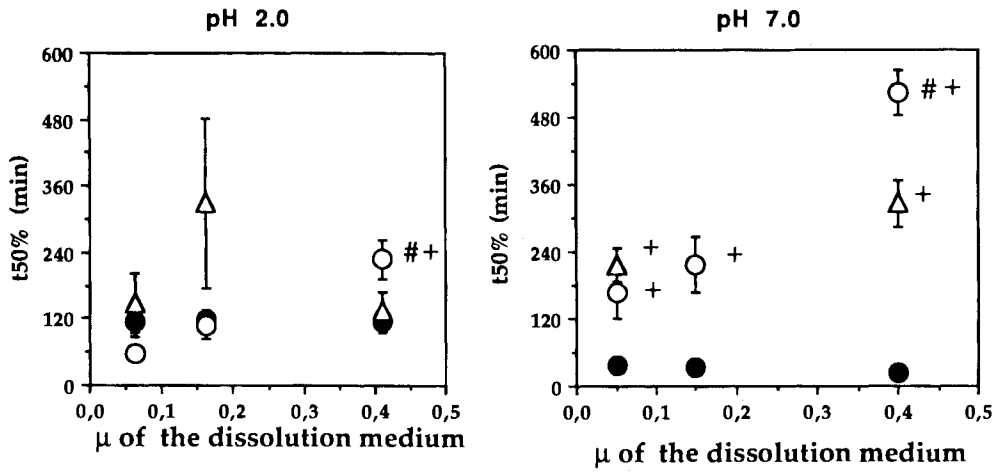

Fig. 2. Time to release 50% of caffeine (Δ), propranolol (○) and sodium salicylate (●) from membrane bags prepared from 50 wt% PAA grafted PVDF membranes into dissolution mediums with different ionic strengths (μ) at pH 2.0 and at pH 7. Means ± SEM are shown (n = 3). # Significantly different from the value for propranolol release at μ = 0.05 or 0.15. + Significantly different from the value for sodium salicylate at corresponding μ.

DISCUSSION

Effect of pH on Drug Release

Releases of caffeine, FITC-dextran (mw = 4400) and propranolol from the membrane bags were decreased with an increasing pH. This was due to changes in the conformation of the grafted PAA chains as a function of pH. The pKa value of PAA is about 4 (11). At pH 2.0, the polymer chains are undissociated which results in a compact conformation. The compact conformation leaves pores in the PVDF-PAA membrane open and the drugs can diffuse through the membrane quite easily (7). However, at pH 7.0, the diffusional flux of drug is reduced due to swollen dissociated PAA chains which partially block the pores in membrane. The slower release of FITC-dextran than small molecules from membrane bags is in a good accordance with the earlier study, where a diffusional flux of FITC-dextran (mw 4400) across the 58 wt% grafted PVDF-PAA membrane was substantially less than the diffusional flux of small molecules (7). The release rate of FITC-dextran from the membrane bags was affected significantly more than the release rates of small molecules by pH of the dissolution medium, suggesting that PVDF-PAA membranes might be suitable for a stomach specific delivery of macromolecules. Iwata *et al.* (8) and Ito *et al.* (1) have demonstrated that a porous poly(acrylic acid) grafted membrane containing glucose oxidase may be useful as glucose-responsive insulin delivery systems.

In contrast to the small neutral (caffeine, pKa 0.6 and 14) and positively charged (propranolol, pKa 9.4, base) model compounds, salicylate (pKa 3, acid) release from the membrane bags increased by increasing pH from 2.0 to 7.0. Despite their porosity the PVDF-PAA membranes act reasonably well as cation exchange membranes (7,12). Thus, PVDF-PAA membranes facilitate the transport of cationic drugs and repel anionic ones. At pH 7.0, both the membrane and sodium salicylate are negatively charged. Thus, the electrostatic repellation between the drug and the charged carboxylic groups within the polymer chain hinders the free diffusional flux of salicylate through the membrane. The swollen salicylate containing membrane bags indicated that the buffer solution penetrated into the membrane

Table I. Correlation Coefficients (R^2; Mean ± S.D.; n = 3) for Plots of the Released Drug (%) Versus Time or Versus Square Root of Time[a]

	pH = 2.0						pH = 7.0					
	μ = 0.05		μ = 0.15		μ = 0.40		μ = 0.05		μ = 0.15		μ = 0.40	
	Time	$Time^{1/2}$	Time	$Time^{1/2}$	Time	$Time^{1/2}$	Time	$Time^{1/2}$	Time	$Time^{1/2}$	Time	$Time^{1/2}$
Caffeine	0.915 ± 0.042	0.975 ± 0.023	0.876 ± 0.089	0.950 ± 0.042	0.946 ± 0.014	0.996 ± 0.001	0.970 ± 0.011	0.988 ± 0.006	ND	ND	0.993 ± 0.001	0.959 ± 0.008
Propranolol	0.942 ± 0.048	0.966 ± 0.013	0.942 ± 0.026	0.971 ± 0.005	0.964 ± 0.009	0.995 ± 0.002	0.933 ± 0.038	0.983 ± 0.009	0.976 ± 0.017	0.977 ± 0.011	0.998 ± 0.001	0.970 ± 0.006
Salicylate	0.912 ± 0.034	0.980 ± 0.012	0.921 ± 0.016	0.992 ± 0.004	0.929 ± 0.013	0.994 ± 0.003	0.719 ± 0.031	0.873 ± 0.024	0.775 ± 0.038	0.907 ± 0.026	0.802 ± 0.025	0.923 ± 0.017
FITC-dextran, mw = 4400	ND	ND	0.928 ± 0.015	0.991 ± 0.004	ND	ND	ND	ND	0.746 ± 0.119	0.845 ± 0.058	ND	ND

[a] ND = Not Determined.

bags at pH 7.0. Due to the water penetration, the osmotic pressure inside membrane bags was increased, which resulted in a fast salicylate release from the membrane bags. At pH 2.0, both the membrane and the salicylate are mainly in an unionized form. Thus, the electrostatic repellation between the drug and the polymer does not affect the drug diffusion across the membrane.

Effect of Ionic Strength on Drug Release

Salicylate and caffeine release was not considerably affected by the ionic strength of dissolution medium while propranolol was released faster into a $\mu = 0.05$ buffer solution than into a $\mu = 0.40$ buffer solution. Hautojärvi *et al.* (12) demonstrated that the convective permeability of PAA grafted PVDF membrane is increased considerably when ionic strength of a solution is increased from 10 mM to 1 M. They explained that the expanded conformation of the grafted PAA chains block the pores in dilute solutions while the compact conformation of chains in concentrated solutions leaves the pores open. This study indicates that the release of small molecules, such as salicylate and caffeine, from the membrane bags is not considerably affected by the ionic strength induced conformational changes in the grafted PAA chains. Also our earlier study suggested that small molecules are able to diffuse across the studied membrane also when the expanded PAA chains partly block the pores (7).

Chang and Bodmeier (13) reported that the ionic strength of the dissolution medium ($\mu = 0.25 - 1.0$) does not considerably affect the release rate of propranolol HCl (100–300 mg) from monoglyceride matrices into a 0.1 M pH 7.4 buffer solution (300 ml) because monoglycerides are non-ionic amphiphilic molecules. Diltiazem HCl release from beads coated with cationic copolymers stabilized with quaternary ammonium groups (Eudragit®) decreased when the ionic strength of the different buffer solutions was increased with NaCl (9). Bodmeier *et al.* (9) explained that the buffer species and concentration affected diltiazem release due to a lower solubility of the drug and a decreased water uptake of the polymer in the dissolution medium with a high osmotic pressure. In the present study, propranolol HCl release from the membrane bags decreased with an increasing ionic strength of the dissolution medium. This might be due to a slower dissolution rate of propranolol in a dissolution medium with a high osmotic pressure. A high osmotic pressure of the dissolution medium could also decrease water penetration into the membrane bags which results in a decreased dissolution of propranolol inside the bag. The decreased release rate of propranolol with the increased ionic strength of the dissolution medium may also be due to the cation exchange properties of the membrane. Transport of propranolol across the membrane can be expected to decrease with the increased amount of the cations present in the dissolution medium if the cations are able to bind to the membrane. In the present study, interactions between the PVDF- PAA membrane and cations present in the dissolution medium were not evaluated. Earlier studies (14–15), however, indicate that polyacrylic acid polymers bind monovalent (e.g. Na^+) and divalent cations.

In conclusion, this study clearly demonstrates that a drug release from the pH and ionic strength responsive drug delivery systems based on polymer swelling is strongly affected both by the environmental factors and the physicochemical properties of the drug.

ACKNOWLEDGMENTS

Financial support from TEKES (the Technology Development Centre in Finland) is gratefully acknowledged.

REFERENCES

1. Y. Ito, M. Casolaro, K. Kono, and Y. Imanishi. An insulin-releasing system that is responsive to glucose. *J. Control. Release* **10**:195–203 (1989).
2. I. Hisamitsu, K. Kataoka, T. Okano, and Y. Sakurai. Glucose-responsive gel from phenylborate polymer and poly(vinyl alcohol): Prompt response at physiological pH through the interaction of borate with amino group in the gel. *Pharm. Res.* **14**:289–293 (1997).
3. P.-Y. Yeh, M. M. Berenson, W. S. Samowitz, P. Kopeckova, and J. Kopecek. Site-specific drug delivery and penetration enhancement in the gastrointestinal tract. *J. Control. Release* **36**:109–124 (1995).
4. H. Chen, and R. Langer. Magnetically-responsive polymerized liposomes as potential oral delivery vehicles. *Pharm. Res.* **14**:537–540 (1997).
5. M. Cardamone, S. A. Lofthouse, J. C. Lucas, R. P. Lee, M. O'Donoghue, and M. R. Brandon. *In vitro* testing of a pulsatile delivery system and its *in vivo* application for immunization against tetanus toxoid. *J. Control. Release* **47**:205–219 (1997).
6. C. S. Brazel, and N. Peppas. Pulsatile local delivery of thrombolytic and antithrombotic agents using poly(N-isopropylacrylamide-co-methacrylic acid) hydrogels. *J. Control. Release* **39**:57–64 (1996).
7. S. Åkerman, P. Viinikka, B. Svarfvar, K. Järvinen, K. Kontturi, J. Näsman, A. Urtti, and P. Paronen. Transport of drugs across porous ion exchange membranes. *J. Control. Release* **50**:153–166 (1998).
8. H. Iwata, H. Amemiya, T. Hata, T. Matsuda, H. Takano, and T. Akutsu. Development of novel semipermeable membranes for self-regulated insulin delivery systems. *Proceed. Intern. Symp. Controlled Rel. Bioact. Mater.* **15**:170–171 (1988).
9. R. Bodmeier, X. Guo, R. E. Sarabia, and P. F. Skuelty. The influence of buffer species and strength on diltiazem HCl release from beads coated with the aqueous cationic polymer dispersions, Eudragit RS, RL 30D. *Pharm. Res.* **13**:52–56, (1996).
10. K. Knop. Influence of buffer solution composition on drug release from pellets coated with neutral and quaternary acrylic polymers and on swelling of free polymer films. *Eur. J. Pharm. Sci.* **4**:293–300 (1996).
11. J. Harada, R. T. Chern, and V. T. Stannet. Polyelectrolyte gels. In R. S. Harland and R. K. Prundhomme (eds.) *ACS Symp.Ser. 480,480,* ACS, Washington DC, 1992, Ch. 5.
12. J. Hautojärvi, K. Kontturi, J. H. Näsman, B. L. Svarfvar, P. Viinikka, and M. Vuoristo. Characterization of graft modified porous membranes. *Ind. Eng. Chem. Res.* **35**:450–457 (1996).
13. C.-M. Chang and R. Bodmeier. Binding of drugs to monoglyceride-based drug delivery systems. *Int. J. Pharm.* **147**:135–142 (1997).
14. B. Kriwet and T. Kissel. Interactions between bioadhesive poly(acrylic acid) and calcium ions. *Int. J. Pharm.* **127**:135–145 (1996).
15. W. N. Charman, D. P. Christy, E. P. Geunin, and D. C. Monkhouse. Interactions between calcium, a model divalent cation, and a range of poly(acrylic acid) resins as a function of solution pH. *Drug Dev. Ind. Pharm.* **17**:271–280 (1991).