Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Sundell, Annika M. and Luttikhedde, Hendrik J. G.(1999) 'DRUG RELEASE FROM IONOMER CEMENTS BASED ON HYDROLYZED POLY(VINYLACETATE-MALEIC ANHYDRIDE)', Journal of Macromolecular Science, Part A, 36: 7, 1045 — 1059
To link to this Article: DOI: 10.1080/10601329908951199
URL: http://dx.doi.org/10.1080/10601329908951199

J.M.S.—PURE APPL. CHEM., A36(7&8), pp. 1045–1059 (1999)

DRUG RELEASE FROM IONOMER CEMENTS BASED ON HYDROLYZED POLY(VINYLACETATE-MALEIC ANHYDRIDE)

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Key Words: Ionomer Cements, Poly(vinyl alcohol-co-maleic acid), Poly(vinyl acetate-co-maleic acid), Drug Release, Drug Loading, Setting Time, Zero Order Release

ABSTRACT

Ionomer cements based on hydrolyzed copolymers of maleic anhydride and vinyl acetate were investigated as carrier materials in the release of model drugs, toremifene and Acid Red 88. Poly(vinyl acetate-co-maleic acid) and poly(vinyl alcohol-co-maleic acid) with viscosity average molecular weight of 40,000 g/mol were prepared. Cement matrices were formed by reacting the dissolved polymers with calcium hydroxide. At physiological pH, drug release was found to be dependent on the rate and ability of the surrounding media to penetrate the matrix. Setting time influences the degree of crosslinking, and a longer setting time resulted in a more compact matrix with decreased release rate. Cements based on p(VAc-MA) and p(VOH-MA) with high toremifene loading were found to release drug with kinetics close to zero order. The prepared cements were not stable in acidic

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environments. At pH 2, complete disintegration of the sample disks occurred in less than 100 hours.

INTRODUCTION

The most investigated ionomer cements are glass-ionomer cements. These were first introduced into clinical dentistry in the 1970s by McLean and Wilson [1]. These materials, generally classified as acid-base cements, were originally designed for preventive restoration in low stress areas of anterior teeth, but development of the cements have since diversified the application areas. They are no longer used only in the world of clinical dentistry, but have also found use as biomaterial in other medical applications [2], like bone cements [3], alveolar bone substitute [4], splint bandages [5], and more recently in drug delivery formulations [6].

Acid-base cements are formed through a acid-base reaction when a basic powder is brought together with a polyacid to form a salt hydrogel. The cement sets and hardens by transfer of metal ions from the powder to the polyacid, which causes gelation in the aqueous phase. The reactions involved in the setting has been reported extensively elsewhere [1, 7, 8, 9].

Because of the cements good biocompatibility [10] they form an interesting material as implants. In biological evaluations Jonck *et al.* [11] found no inflammation or irritation with any of the glass polyalkenaoate cement implants after several months.

Toremifene is a triphenylethylene antiestrogen used in treatment of breast cancer [12]. In the present work, water-soluble polyacids were synthesized as hydrolyzed copolymers of vinylacetate and maleic anhydride. The cements formed after reacting the polyacid with calcium hydroxide were investigated as possible carrier materials for the delivery of toremifene. Release of anionic molecules was also studied.

EXPERIMENTAL

Materials

Maleic anhydride was obtained from Merck and recrystallized from ethanol prior to use. α-α′-azoisobutyronitrile (AIBN) from Fluka was recrystallized from methanol. Vinylacetate (Merck) was vacuum distilled. Ion exchanged

water was obtained with a Millipore Corporation System; Milli-Q. The solvents and other reagents used were all of analytical grade and used as received.

Instrumentation

^{1}H-NMR spectra were recorded with a Jeol 400 spectrometer. Acid-base titration was conducted with a Metrohm 665 Dosimat titrator. Viscosity average molecular weight was measured using a Cannon-Ubbelohde Semi-Micro Dilution Viscometer, Cannon Instrument Corporation. Energy dispersive X-ray analysis was performed using an Princeton Gamma Tech IMIX analyser. Drug release was monitored at (λ= 280 nm (toremifene) and (λ= 505 nm (Acid Red 88) using a Spectroflow 757 Absorbance detector from Kratos Analytical Intruments. Toremifene was separated prior to spectrophotometrical detection using a HPLC system consisting of 400 Solvent delivery systems, Applied biosystems, 7725 Rheodyne injector with a 20 μL injector loop and a ISRP-HPLC column (GFF-S5-80, 15 cm · 4.6 mm) from Regis Chemical.

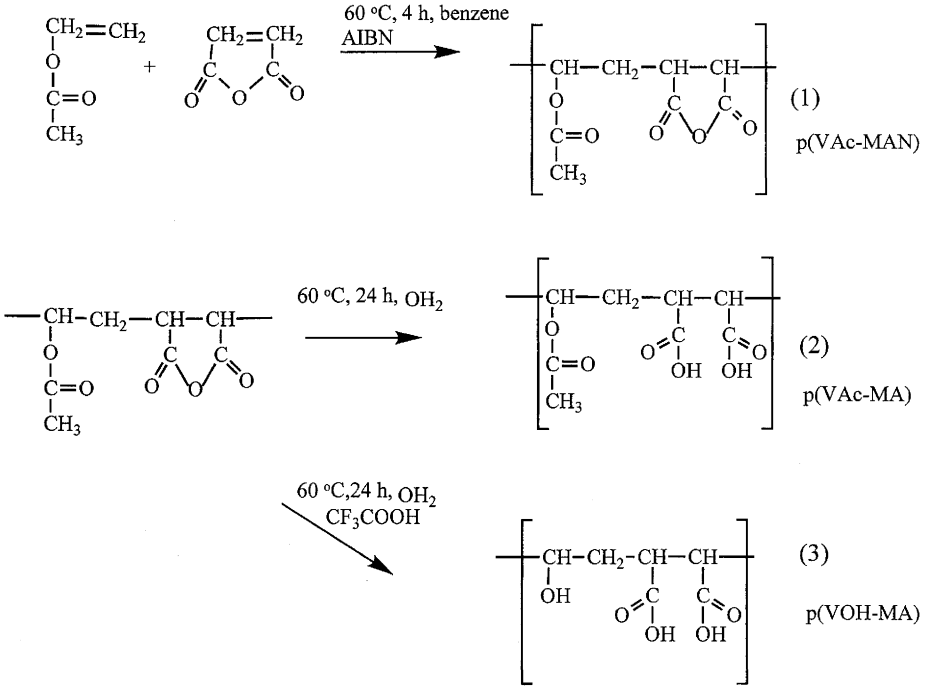
Polymer Synthesis

Maleic anhydride copolymer was synthesized by the method shown in Scheme 1. Maleic anhydride (8.86 g, 20 mol%) was dissolved in 150 ml benzene and 0.05 g AIBN was added. The solution was purged with nitrogen. Vinylacetate (31.12 g, 80 mol-%) was added dropwise with stirring at 70°C. The solution was refluxed for 4 hours with stirring at 70°C. The obtained polymer, poly(vinylacetate-co-maleic anhydride) (**1**) henceforth designated as p(VAc-MAN) was washed with warm benzene, precipitated in diethyl ether, filtered and dried in vacuum.

Hydrolysis of the anhydride was achieved by dispersing the polymer in 100 mL distilled water. The reaction was carried out with continuous stirring at 60°C for 12 hours. To achieve hydrolysis of the acetate group 0.06 g (1.5 wt%) trifluoroacetic acid was added to the solution. The formed polymers, poly(vinyl-acetate-co-maleic acid), p(VAc-MA), (**2**), and poly(vinylalcohol-co-maleic acid), p(VOH-MA), (**3**), were collected by filtration and freeze-dried.

Cement Formation

Polymer samples, p(VAc-MA) or p(VOH-MA) were dissolved in ion exchanged water. Model drugs, toremifene citrate (M_w=588.09 g/mol) or Acid Red 88 (M_w= 400.39 g/mol) were added to the polymer solutions (20 and 40 wt% of the total cement weight, respectively). Calcium hydroxide was brought



Scheme 1. Polymerization and hydrolysis routes.

together with the solution and the formed paste was processed until an even distribution was achieved. Samples were prepared in a plastic mold (radius 10 mm, height 2 mm). The samples were left to set for predetermined times. After setting, the cements were weighed and immediately immersed in buffer solutions.

Polymer Characterization

Determination of Carboxylic Group Ratio

The concentration of carboxylic groups was determined by acid-base titration. A known amount of polymer was dissolved in ion exchanged water. Titration was conducted with 0.1 M NaOH and the concentration of the carboxylic group was calculated from the formula:

$$\frac{V_{NaOH} \bullet c_{NaOH}}{m} = mmol\ \text{COOH}/\ mg\ polymer\ sample \qquad (1)$$

Determination of Degree of Hydrolysis

The degree of hydrolysis was determined by 1H-NMR. The sample concentration was approximately 20% (w/v) in DMSO-d_6. By calculating the

decrease of the integral of the acetate methy-lene peak at 1.9 ppm in reference to the carbon backbone the degree of hydrolysis could be estimated.

Determination of the Viscosity Average Molecular Weight

The viscosity of the polymer was measured in tetrahydrofuran at 30°C. The viscosity average molecular weight M_v, was determined using the relation:

$$[\eta_{iv}] = KM_v^a \tag{2}$$

where η_{iv} is the intrinsic viscosity. The constants K= $13.4 \cdot 10^3$ ml/g and a = 0.69 were used [13].

Cement Characterization

Drug Distribution

The distribution of model drug was studied by Energy Dispersive X-ray analysis. The distributions of calcium and chloride ions in the cross section of the cement samples were recorded.

The Degree of Swelling

The cement disks were immersed in buffer solution (based on 0.02 M KH_2PO_4 and 0.02 M Na_2HPO_4) at pH 7.4 at room temperature and 37°C. The water uptake was determined gravimetrically by weighing the sample disks at appropriate intervals after removing excess water by blotting. The degree of swelling was calculated from the formula:

$$\frac{m_{wet} - m_{fresh}}{m_{fresh}} \bullet 100\% = swelling\ index \tag{3}$$

In Vitro Drug Release Behavior

Drug release studies were carried out in buffer solutions at pH 2.0 and pH 7.4 at physiological temperature, 37°C. The cement disks were immersed in beakers containing 30 ml buffer solutions. The beakers were continuously shaken at 30 rpm. At predetermined time intervals samples, (15 ml) were withdrawn and replaced with fresh medium. To enhance the solubility of toremifene 11 mg/ml non-ionic surfactant (Berol OX 91-8) was added to the buffersolution. A calibration curve in toremifene and Acid Red 88 concentration range 0-0.5 mg/ml was used to determine the amount of drug released as a function of time.

For the HPLC separations of toremifene a solution of 40% methanol (w/v), 40% buffersolution (w/v) and 20% acetonitrile (w/v) was used as eluent.

The amount of model drug released was determined using the relation:

$$\frac{M_t}{M_\infty} \bullet 100\% = \text{Fractional release \%} \tag{4}$$

where M_t is the fractional release at time t, and M_∞ is the total amount of drug incorporated in the cement disk. To examine the nature of the release profiles the expression used was:

$$\frac{M_t}{M_a} = k_a t^n \tag{5}$$

where M_t is the amount of drug released by time t, M_∞ is the total amount of drug and k_α and *n* are system parameters who depends on the nature of polymer/penetrant/active agent interaction [14].

RESULTS AND DISCUSSION

Polymer Characterization

Titration of the obtained polymers gave a carboxylic acid content of 8.5 mmol/g. The theoretical value for a completely alternating and hydrolyzed poly(vinylacetate-alt-maleic acid) copolymer is 9.9 mmol/g. While the NMR spectra indicated that the anhydride was fully hydrolyzed it is assumed that the polymer was not completely alternating but consisted of shorter blocks of vinylacetate. The hydrolysis of the acetategroup only succeeded partly. It is estimated that the degree of hydrolysis is between 20-50%. The molecular weight of the polymers used in cement formation was 40,000 g/mol.

Cement Formulation

It has been suggested that calcium ions either forms a complex of ionic crosslinks between the polymer chains or a complex with two adjacent carboxylic groups in the same chain [15]. The amount of calcium hydroxide added to the polymer solutions was calculated from the concentration of carboxylic acid groups of the polymer used. The different formulations are listed in Table 1. However, the theoretical stoichiometric ratio 1:2 of Ca^{2+}:COOH (C1) resulted in a cement showing poor setting behavior. Earlier studies have shown that higher

TABLE 1. Changes in Ca^{2+}:COOH Ratio, Setting Time, and Setting Temperature in Cement Formulation

Sample ID	Ca^{2+}/COOH	drug	time (minutes)	temp. (°C)
C1	1:2	-	-	23
C2	1:2	-	-	37
C3	1:1	-	5	23
C4	1:1	toremifene citrate 20 wt-%	15	23
C5	1:1	toremifene citrate 40 wt-%	60	23

setting temperatures results in shorter setting times [16] but even after the setting temperature was raised to 37°C, (C2) no relevant setting was observed after 24 hours.

Cement formation at a molar ratio of 1:1 (C3), giving an excess of Ca^{2+}-ions, resulted in a remarkable decrease in setting and working time.

When the crosslinking proceeds, the calcium ions will be increasingly hindered in their movements toward carboxylic sites. From the energy dispersive X-ray analysis of the cross-section of the cement in Figure 1, it can be seen that calcium ions are partly present in the matrix as particles. Only a limited number

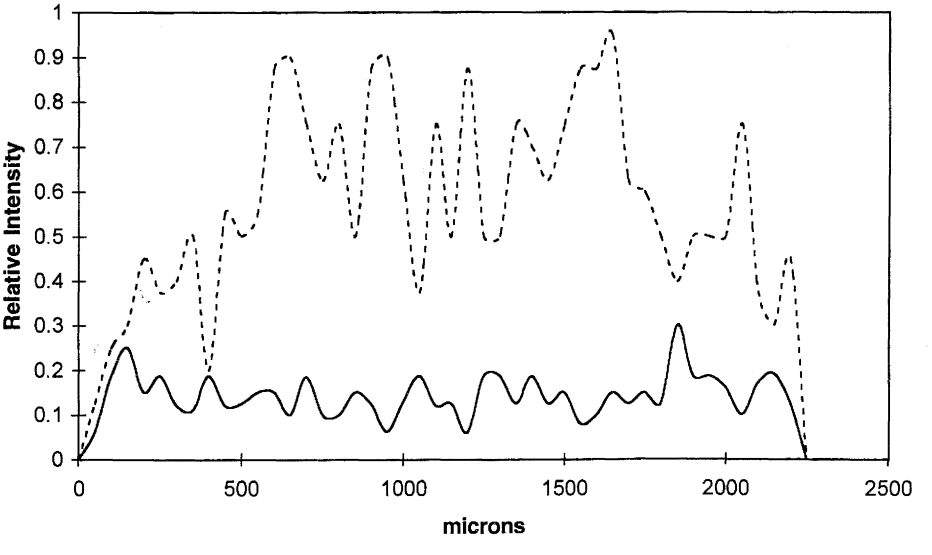


Figure 1. Energy dispersive X-ray analysis of chlorine (—) and calcium (- - -) distribution in the cross section of p(VAc-MA) cement.

of calcium ions are available for crosslinking. This requires an excess of calcium hydroxide in order to get a proper setting of the cement.

As the model drug, toremifene, was incorporated into the cement matrix (C4) the working and setting time again increased. While the model drug is manufactured and distributed as toremifene citrate, calcium hydroxide is also required to neutralize the citrate, the citrate is assumed to control the initial setting of the cement in a similar manner to tartaric acid [17]. Cement C4 set to a leather like matrix in 15 minutes, while the cement with 40 wt-% toremifene citrate (C5) required a setting time of 60 minutes.

Swelling Behavior

Figures 2 and 3 represents the swelling of p(VOH-MA) cements at pH 7.4. Swelling indices of cements containing toremifene is slightly higher than the corresponding cements containing Acid Red 88. The absence of citrate in the latter cements results in a faster crosslinking in the beginning of cement formation and a more compact matrix.

The initial swelling in all cases is rapid enough to compensate for weight loss due to loss of unset polymer from the surface and more importantly in the case of toremifene, the loss of formed calcium citrate. Since calcium citrate dis-

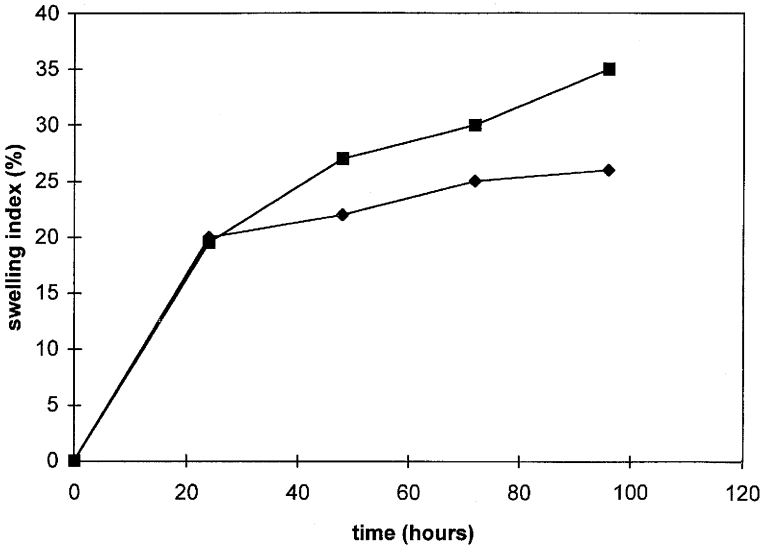


Figure 2. Swelling index for p(VOH-MA) cements, with 15 minutes (■) and 30 minutes (◆) setting time, containing 20 wt-% toremifene.

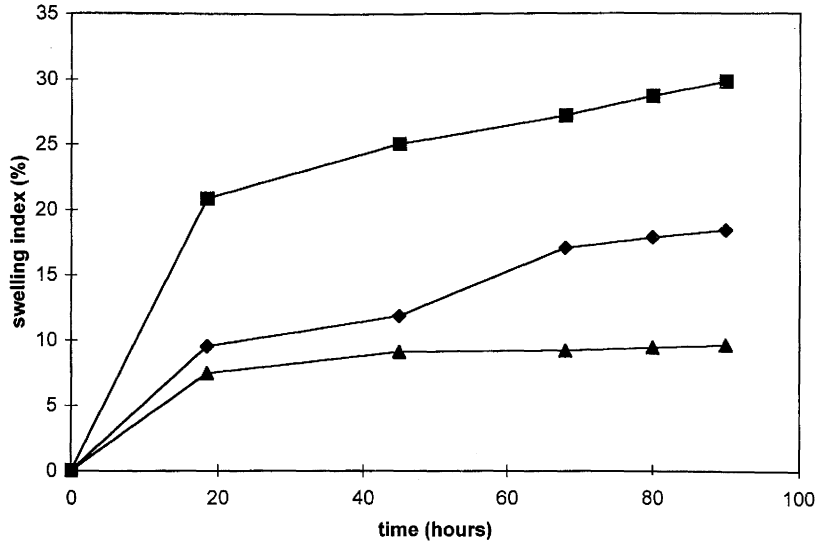


Figure 3. Swelling index for p(VOH-MA) cements, with 15 minutes (■), 30 minutes (◆), and 60 minutes (▲) setting time, containing 20 wt-% Acid Red 88.

integrates completely when placed in water [18], it is also assumed that the more porous structure formed due to solubilization of calcium citrate has an increasing effect on the degree of swelling.

The erosion process of the cements described in earlier studies [19] can be discovered in the form of material loss in an earlier stage for the cements with shorter setting time. The figures clearly show that the swelling behavior of the cements is affected by setting time. At predetermined setting times, a limited amount of carboxylic groups is allowed to set. Longer setting times are accompanied by larger fraction of carboxylic groups participating in the crosslinking process. As the degree of crosslinking is increased, a more compact network is established and consequently the swelling index is decreased. The higher percent of uncrosslinked ionized carboxylic acid groups in cements with a shorter setting time provides more sites for water to coordinate, resulting in a increased swelling index.

As can be seen from Figure 4, none of the matrices shows any swelling at pH 2. The rapid decrease in weight is due to protonization of the polyacid. A complete solubilization of the cement was achieved after about 4 days.

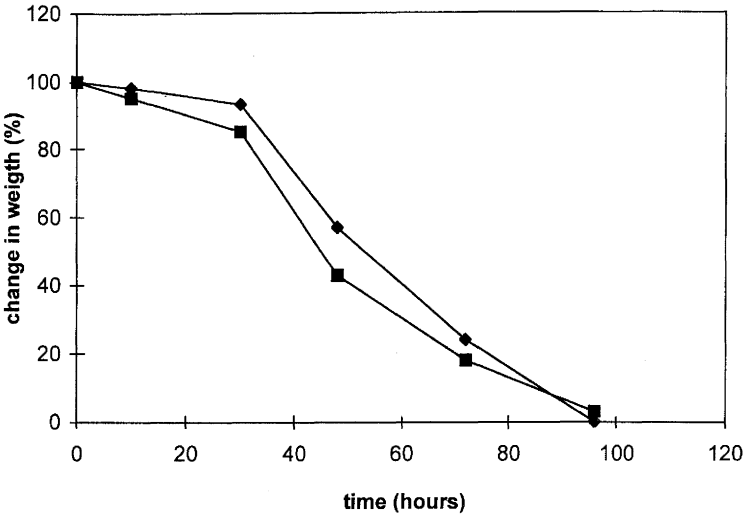


Figure 4. Weight loss of p(VOH-MA) (■) and p(VAc-MA) (◆) cements in pH 2 buffer solution.

In Vitro Drug Release

The cumulative release of toremifene from p(VAc-MA) and p(VOH-MA) cements with 20 wt% drug loading are presented in Figure 5.

The drug release can be divided into three phases. Initially, the drug is released in a sustained fashion. After immediate drug release from the surface,

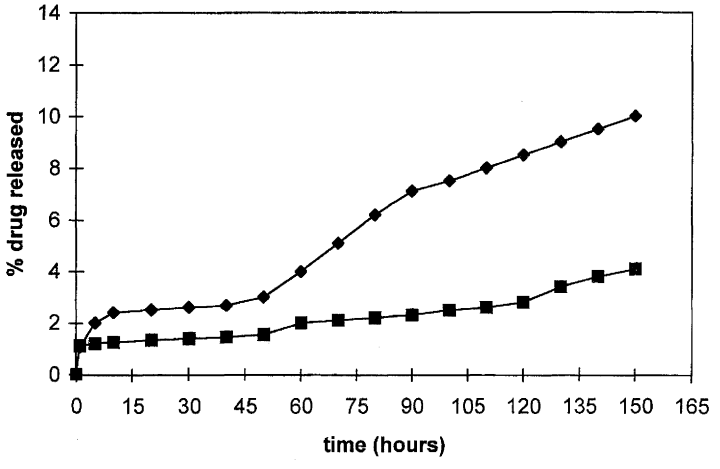


Figure 5. Drug release from p(VAc-MA) (◆) and p(VOH-MA) (■) cements with 20 wt% toremifene loading.

practically no release occurs for 40 hours. As the penetration of water advances from the surface towards the center of device, a sharp interface separates an inner glassy core from an outer gel-like region. Release occurs by diffusion from the gel-region, the diffusivity is in turn influenced by the time dependent macromolecular relaxation phenomena in this region [20]. A second release phase is observed as the rate of relaxation increased, between 50-90 hours. When fitting the experimental data of this time period into Equation 5, the value of the kinetic exponent was $n=1$, which indicates a linear release. As the matrix is fully swollen, a decrease in release rate is observed.

The release profiles for p(VAc-MA) and p(VOH-MA) cement with 40 wt% toremifene loading are illustrated in Figure 6. No significant initial lag time is observed for the matrices. Again, calculating the kinetic exponent the value can be determined to $n=1$, indicating that release from the systems with higher drug loading is very close to zero ordered. Longer setting times for these matrices (60 minutes) result , as earlier discussed, in a more compact matrix. The rate of solvent penetration is slower compared to matrices with shorter setting times. This in combination with a high drug loading establishes an equilibrium where drug molecules are released at the rate the interface proceeds. When the drug is distributed evenly throughout the matrix and when drug loading is high enough a linear release profile is maintained.

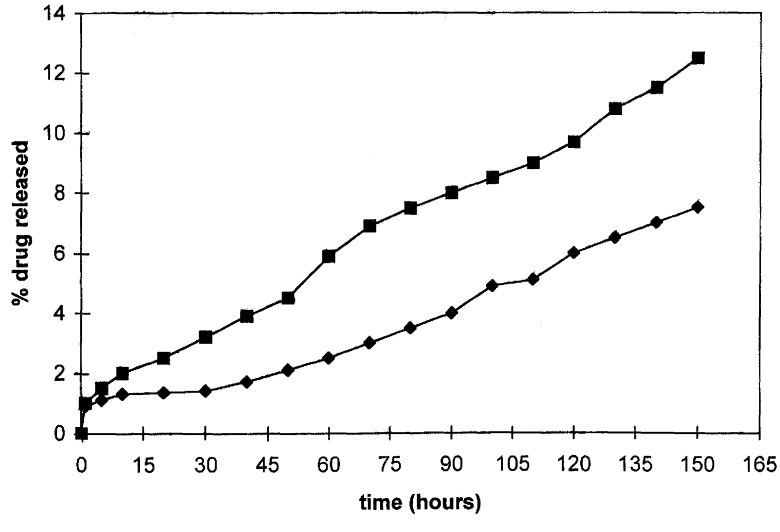


Figure 6. Drug release from p(VOH-MA) (■) and p(VAc-MA) (◆) cements with 40 wt% toremifene loading.

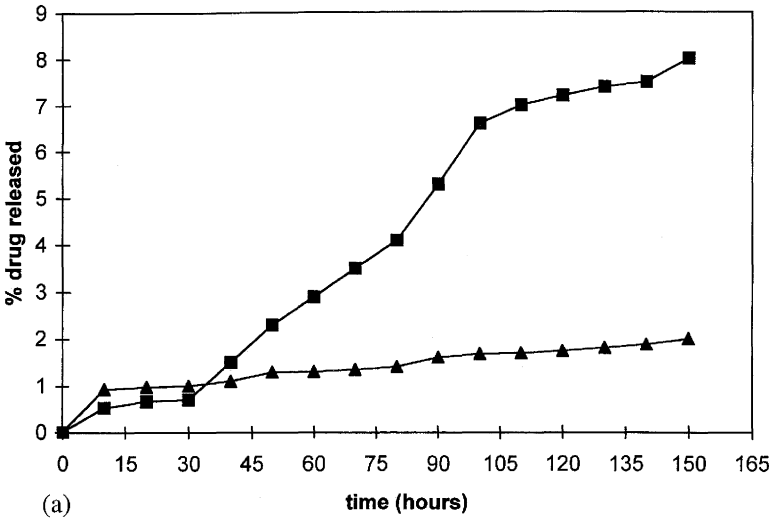


Figure 7a. Drug release from p(VAc-MA) cements with 20 wt% Acid Red 88 content setted 15 minutes (■) and 60 minutes (▲).

The absence of lag time is assumed to be due to the significant amount of surface calcium citrate released initially providing a porous surface structure and thus increasing the amount of drug molecules solubilized and released.

The influence of setting time on release is illustrated in Figures 7 a-d showing the release profiles of Acid Red 88. Longer setting times results in

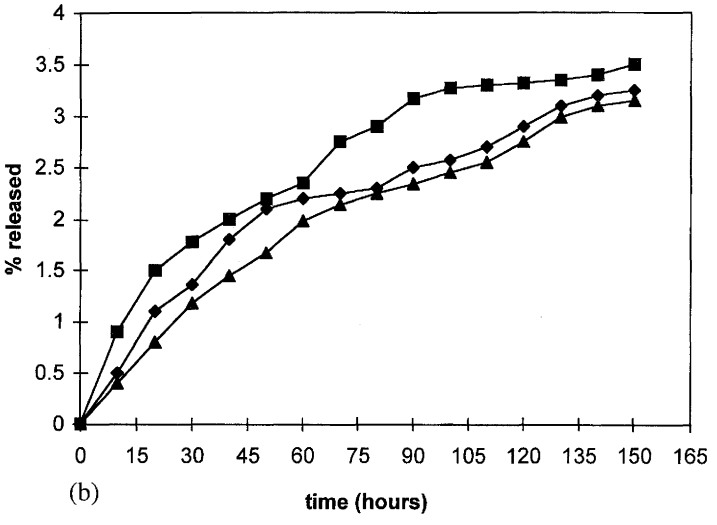


Figure 7b. Drug release from p(VOH-MA) cements with 20 wt% Acid Red 88 content setted 15 minutes (■), 30 minutes (◆), and 60 minutes (▲).

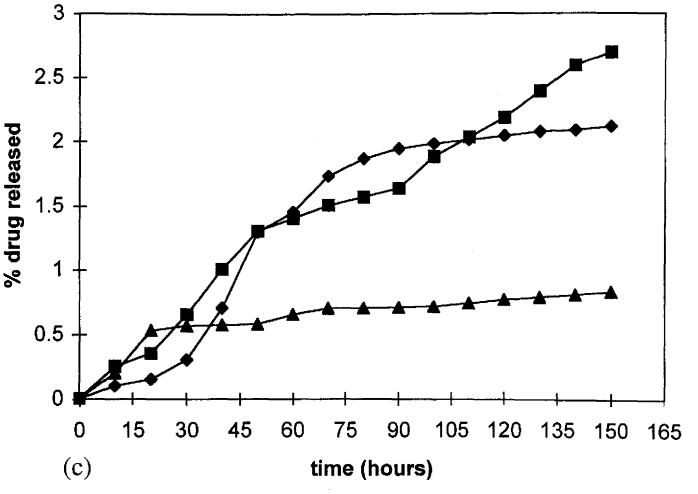


Figure 7c. Drug release from p(VOH-MA) cements with 40 wt-% Acid Red 88 content setted 15 minutes (■), 30 minutes (◆), and 60 minutes (▲).

decreased release, due to the formation of a more compact structure as earlier stated. Release profiles differ substantially from the release profiles of toremifene. For cements with 20 wt% Acid Red 88 an initial lag was observed only for the cement based on p(VAc-MA) setted 15 minutes, no initial lag time is observed in any of the other cements. The release rate is fast in the beginning due to surface release but is then decreasing rapidly. For the cements with

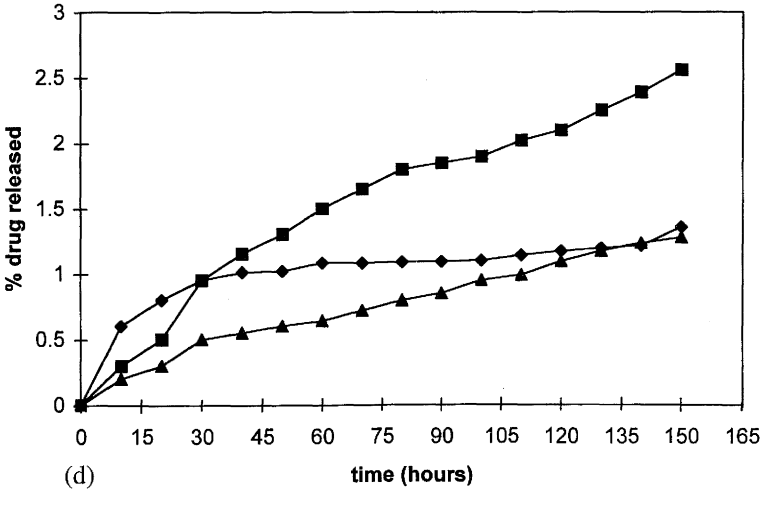


Figure 7d. Drug release from p(VAc-MA) cements with 40 wt-% Acid Red 88 content setted 15 minutes (■), 30 minutes (◆), and 60 minutes (▲).

40 wt% Acid Red 88 a lag time is observed only for the cements with shorter setting times.

The rate of water penetration in Acid Red 88 containing cements is much slower than for corresponding toremifene cements and the cements swells to a lower extent, resulting in limited release. Additionally, the anionic nature of the model compound possibly causes formation of a non water soluble complex where the model compound is bonded to the polymer chain via a calcium ions.

CONCLUSION

At pH 7.4, drug release from the investigated ionomer cements is dependent on the rate and ability of surrounding media to penetrate and swell the matrices. p(VAc-MA) and p(VOH-MA) cements with high drug loading, 40 wt%, have been found to release toremifene with a release kinetics close to zero order. Release profiles of toremifene from corresponding cements with lower drug loading, 20 wt-%, can be divided into three phases: an initial lag-time followed by a phase with linear release rate and finally a decline in release rate. Cements containing Acid Red 88 show a limited release rate compared to toremifene containing cements. The presence of complex forming citric acid in toremifene containing cements leads to formation of a matrix with a faster water penetration rate and thus more favorable release profiles. Release rate was found to be influenced by setting time. Longer setting times result in a more complete crosslinking, forming compact matrices with slower release rates.

The investigated cements are not stable at pH 2. All cements were found to disintegrate completely after less than 100 hours.

ACKNOWLEDGEMENTS

Financial support of the Technology Development Center of Finland (TEKES) is greatly appreciated. We also wish to thank Orion-Farmos Oy for a gift of toremifene citrate.

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