Investigation of Loading and Release in PVA-Based Hydrogels

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ABSTRACT: We used Methylene Blue (MB) and Methyl Orange (MO) as model drugs to investigate the controlled release behavior of hydrogels from poly(vinyl alcohol) crosslinked with ethylenediaminetetraacetic dianhydride. The cationic or anionic character of these compounds and the molecular weight between crosslinks of the hydrogel and the concentration of ionizable groups in the hydrogel greatly affected the loading and release of the drugs. MB loading was favored, therefore, by a higher content of negative charges in the hydrogel, although this implied a greater degree of crosslinking and, therefore, a lower mesh size. On the other hand, the overall loading of negative MO, favored by a higher mesh size, was very low because of unfavorable interactions with the electrolyte charges. Release studies showed that one of the parameters that most affected the drug release behavior of these hydrogels was the pH of the solution. MB and MO were not completely released, even at pH 1. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 85: 1644–1651, 2002

Key words: hydrogels; poly(vinyl alcohol); release; drug delivery systems

INTRODUCTION

Polymeric hydrogels are being studied increasingly for controlled release applications because they are biocompatible and easy to produce. The controlled release kinetics of the entrapped drugs from such hydrogels can be monitored by the regulation of the water uptake of the polymer or by crosslinking it. Hydrogels are attracting more attention as drug delivery systems, especially for the controlled release of pharmaceutically active compounds, whether low in molecular weight[1–7] or like peptides and proteins, high in molecular weight.[8–12] Crosslinked polyelectrolytes are insoluble but swellable polymer networks that carry cations or anions at levels ranging from a few mole percent to 100% of the repeating units. In the last few years, much attention has been paid to polyelectrolyte-type hydrogels that undergo controllable volume changes in response to small variations in the conditions of the solution.[13] The most striking characteristic is that they can absorb up to several hundred times their own weight of water while retaining coherence and elasticity. The mechanical properties of dry hydrogels and their swelling and shrinking behaviors change in response to physical or chemical stimuli, such as temperature, pH, ionic strength, light, solvent composition, or electric fields. These gels are, therefore, expected to act as intelligent

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materials in controlled drug release.[14–18] Crosslinked poly(vinyl alcohol) (PVA) in particular has been extensively studied as a controlled drug delivery device.[19–22]

A drug incorporated into a polymeric system is released when the solute migrates to the medium surrounding the system by molecular diffusion through the polymer. This makes the solubility of the solute in the hydrogel important for controlling its migration, as are the drug's specific interactions with the polymer.

In a previous study,[23] we prepared hydrogels of PVA crosslinked with ethylenediaminetetraacetic dianhydride (EDTAD). This type of crosslinker is not often used with PVA, but via crosslinking, it can introduce ionizable carboxylic acid groups into the network. We investigated how the structural characteristics and ionic content of the polymer and the crosslinking ratio, pH, and temperature affected swelling. These factors also affected the release of drugs from hydrophilic crosslinked polyelectrolytes. In this study, we investigated how these variables affected the loading and release of a cationic model compound [Methylene Blue (MB)] and an anionic model compound [Methyl Orange (MO)] from PVA crosslinked with EDTAD. Previous works[1,2,7] have shown that for low-molecular-weight clinical compounds, the most significant factors that influence the release are the polarity and the presence or absence of charges. Therefore, MB and MO should have predictably shown a similar behavior to these pharmaceutical drugs. Moreover, the loading and release assays could be easily monitored by visible spectroscopy.

EXPERIMENTAL

Materials

PVA (Fluka) had a degree of hydrolysis of 86–89% and a degree of polymerization of 300. EDTAD (Aldrich) and dimethylsulfoxide (DMSO; Panreac) were used as received.

Hydrochloric acid (Prolabo), potassium chloride (Probus), citric acid (Probus), sodium chloride (Panreac), sodium hydroxide (Prolabo), disodium hydrogen phosphate (Probus), potassium dihydrogen phosphate (Probus), and sodium tetraborate (Probus) were used to prepare buffer solutions (pH = 1, 3, 5, 7, or 8).

MB (J. T. Baker) and MO (Panreac) were used as drug models in the loading and release essays.

Preparation of Gel Films: Crosslinking with EDTAD

PVA (1 g, 18 mmol of OH group) was dissolved in 5 mL of DMSO at room temperature (RT). The dianhydride compound was dissolved in 2 mL of DMSO at RT and added in OH/anhydride group ratios of 1/0.250, 1/0.100, 1/0.050, 1/0.033, and 1/0.025. The reaction mixture was then stirred for 2 min and introduced between two 170 × 120 × 3 mm glasses separated by microscope slides to adjust the thickness (~1 mm). Gels were formed in a few minutes, although the total time of reaction was 24 h. To remove DMSO, we washed the gels by immersion in a great volume of deionized water to swelling equilibrium. This washing process was repeated four times.

Loading and Release of Drug Models

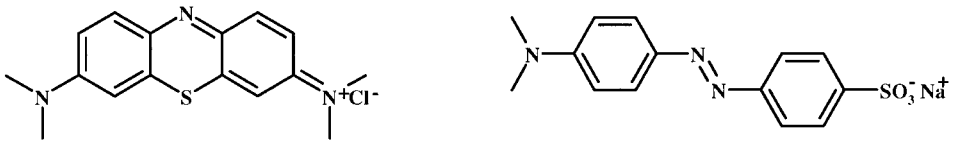
Gels in relaxed state (after crosslinking and before swelling equilibrium) were cut into disks with approximate dimensions of 15 mm (diameter) × 1 mm (thickness). DMSO was removed as shown previously. Hydrogels in swollen state were placed in a desiccator over P_2O_5 under vacuum to establish a constant weight. We loaded MB and MO by transferring dry gels into 10 mL of buffer solution of KH_2PO_4/NaOH (pH = 7; [MB] = 0.22 mg/mL or [MO] = 0.18 mg/mL). The solutions were shaken at 20 rpm to keep the concentrations constant. At different times, small aliquots (0.2 mL) were withdrawn, and the same amount of fresh buffer solution was added. The loaded amounts of MB and MO were analyzed at 656 and 466 nm, respectively, with an ultraviolet–visible spectrophotometer.

We released MB and MO by transferring previously dried loaded gels (placed on a Teflon slab into a desiccator over P_2O_5 at RT, first at atmospheric pressure and then under vacuum) into 10 mL of buffer solution and measuring the concentration of the solution in the same way as shown previously.

Instrumentation

Equilibrium absorption was measured for all samples with an electronic microbalance (Mettler AB204), which had an accuracy of $\pm 10^{-4}$ g.

Ultraviolet–visible spectra were recorded with a HP8452A diode array spectrophotometer with Hellma 10-mm quartz cuvettes.



Methylene Blue Methyl Orange

Scheme 1 Drug models used in loading and release assays.

An oil bath with a mechanical shaker (Selecta Unitronic 320 OR) was used in loading and release assays to keep the concentration constant.

RESULTS AND DISCUSSION

The swelling behavior of hydrogels depends on the nature of the polymer and on the environmental conditions. The nature of the polymer involves the charge and ionic and crosslinking-agent contents. Environmental conditions include pH, ionic strength, and temperature. These variables can also influence drug absorption and delivery. To investigate the drug release behavior of PVA–ethylenediaminetetraacetic acid (EDTA) hydrogels, we studied two model compounds: MB and MO, which were positively and negatively charged, respectively (Scheme 1). Most drugs have relatively low molecular weights, about 150–500. So, MB and MO, whose molecular weights are low and whose shapes are comparable to those drugs, may be suitable model compounds for the study of how these hydrogels release active compounds.

Loading Behavior of Hydrogels

The hydrogels were loaded by immersion into aqueous solutions of MB or MO at ambient temperature and pH 7 for 2 days. Figures 1 and 2 show the loading assays of MB and MO, respectively, for PVA–EDTA hydrogels with different degrees of crosslinking. The concentration of the remaining model compound in the solution is plotted against time. We can see that in the load-

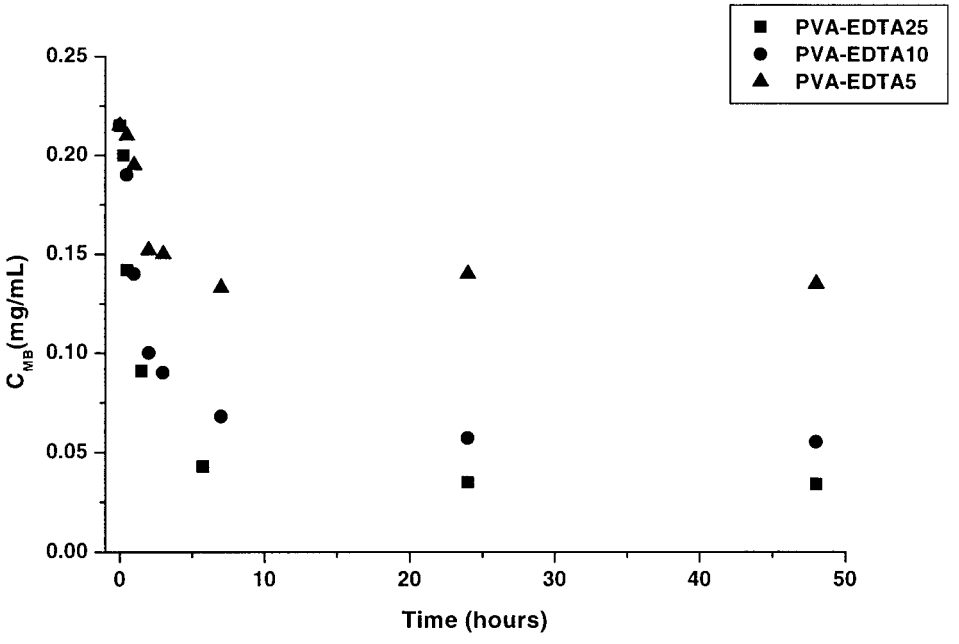


Figure 1 MB loading assays. [MB] versus time for the PVA–EDTA25 (OH/anhydride 1/0.250), PVA–EDTA10 (OH/anhydride 1/0.100), and PVA–EDTA5 (OH/anhydride 1/0.050) dried gels.

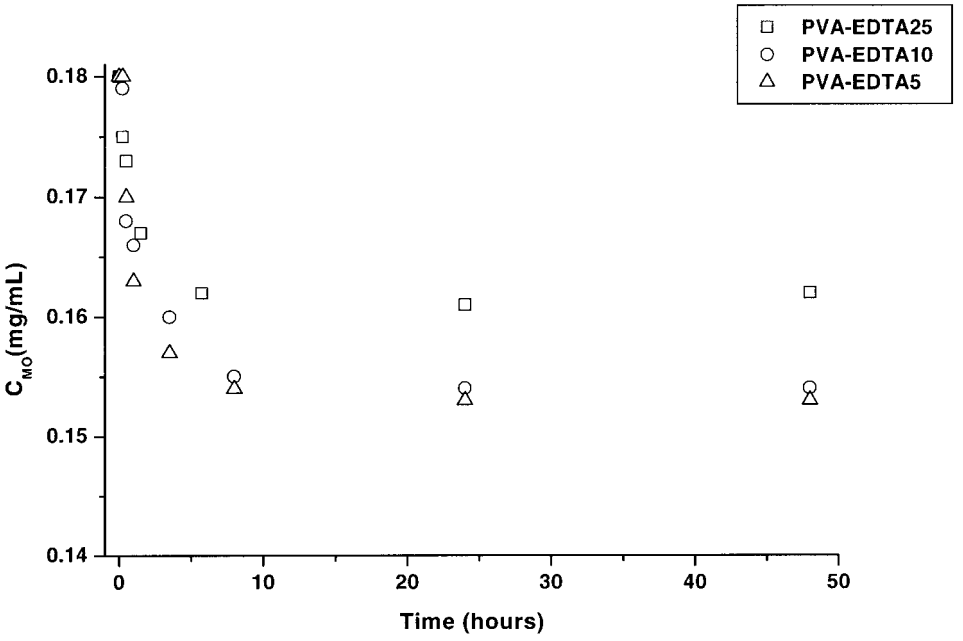


Figure 2 MO loading assays. [MO] versus time for the PVA–EDTA25 (OH/anhydride 1/0.250), PVA–EDTA10 (OH/anhydride 1/0.100), and PVA–EDTA5 (OH/anhydride 1/0.050) dried gels.

ing of MB, the concentration depended greatly on the degree of crosslinking and that the MB loading increased as the crosslinking increased. This was because more carboxylic groups were present and because these moieties were introduced when the crosslinking took place, which favored the specific bonding of the positively charged compound to ionized hydrogel. Normally, when the degree of crosslinking increases, the mesh size decreases, which makes the loading more difficult. The effect of a smaller mesh size can be seen if we compare PVA–EDTA25 and PVA–EDTA10. With about two and a half times as much crosslinking, tested by spectroscopic, differential scanning calorimetry, and elemental analysis data,[23] PVA–EDTA25 loaded only 35% more than PVA–EDTA10 when it had two and a half times as many negative charges. PVA–EDTA10 and PVA–EDTA5 behaved in a similar way. Table I shows the values in milligrams of the loaded drug per milligram of dry polymer.

Figure 2 shows that the overall loading of MO was much lower than that of MB, so the degree of crosslinking had only a slight influence. In the case of MO, the negatively charged compound, the presence of carboxylate groups in the polymeric matrix made it difficult to access. Therefore, the more crosslinked the PVA–EDTA was, the less MO loading was observed. This means that if a small amount of crosslinker was used, that is, if there were few charged groups and the mesh size was large, more of the model drug was loaded. Table I shows that more MB was absorbed than was MO. It also shows the differences in function of the degree of crosslinking. MO was only slightly absorbed, and the slight differences between the degrees of crosslinking were in opposite directions; that is, the less crosslinked polymer there was, the more absorption there was.

Release Behavior of Hydrogels

Figure 3 plots the release of MB in a pH 7 buffer solution against time. This solution was removed,

Table I Loadings of Model Drugs for PVA–EDTA Hydrogels

	Swelling Ratio[a]	MB/Polymer (mg/mg)	MO/Polymer (mg/mg)
PVA–EDTA25	7.0	0.046	0.007
PVA–EDTA10	9.1	0.034	0.008
PVA–EDTA5	12	0.026	0.011

[a] Swelling ratio (hydrogel/dried polymer, w/w), ionic strength = 0.1*M*.

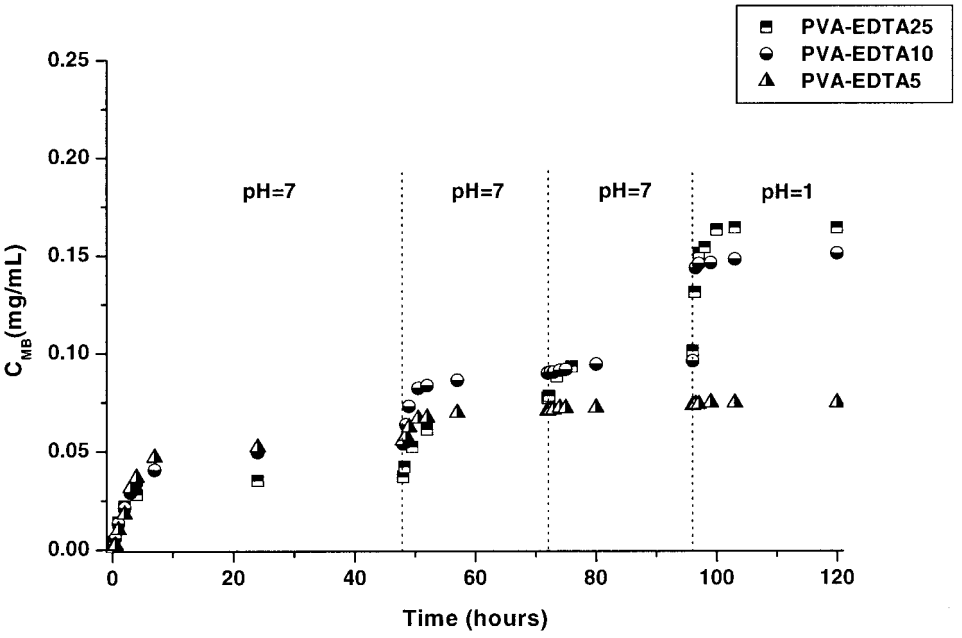


Figure 3 MB release assays. [MB] versus time for the PVA–EDTA25 (OH/anhydride 1/0.250), PVA–EDTA10 (OH/anhydride 1/0.100), and PVA–EDTA5 (OH/anhydride 1/0.050) dried loaded gels.

and a new fresh one was replaced twice during the process. In each step, the release was fast at the beginning and then reached a plateau, although the MB concentration in the external solution was lower in each step. The plateau was reached because of the equilibrium between the amount of released MB and the remaining MB in the hydrogel. However, with the least crosslinked polymer, replacement of the buffer solution did not increase the release in the third step, which shows that the model compound was completely released at the previous stages. Finally, another replacement solution with pH = 1 increased the released MB for two more crosslinked hydrogels, whereas the least crosslinked hydrogel (and, therefore, the one with the least loading) did not change. This indicates that at pH 7, the maximum release of MB had already been reached.

Figure 4 shows the release of MO. As expected, the release was also lower than the MB release. This was due to the small loading of MO. After replacing the buffer solution, we found no significant differences for PVA–EDTA25 and only small differences in the other two cases; release was higher for the least crosslinked hydrogel, which contained more MO.

As a drug acts in a physiological medium with different pH's, from the highly acidic conditions of the stomach (pH = 1.2) to the slightly basic conditions of the small intestine (pH = 7.4), it must be studied how pH affects the release. This study was especially significant for polyelectrolytes because ionization affected the properties of the polymer, for example, swelling, and this must be reflected in the specific interactions of the drug with the polymer, that is, in the mechanism of binding of the low molar mass substances to the polymer.

Therefore, we also studied the release behavior of the most crosslinked hydrogel, that is, the one with the highest drug loading at different pH's. Figure 5 shows the release kinetics of MB from this polymer in a pH range of 1–8. As shown, the lower the pH was, the higher the MB release was. This was because the polymeric hydrogels containing carboxylic acid groups were ionized as the pH of the external medium increased.[24] The lower ionization of carboxylic groups at lower pH's, therefore, reduced interaction with the cationic compound and decreased the repulsive effect of the negative charges of carboxylate groups on the gels. This made the swelling difficult and, therefore, favored the release of MB.

MB and MO release were maximum at the initial stages of swelling after the gels were immersed in the solution. A release even took place

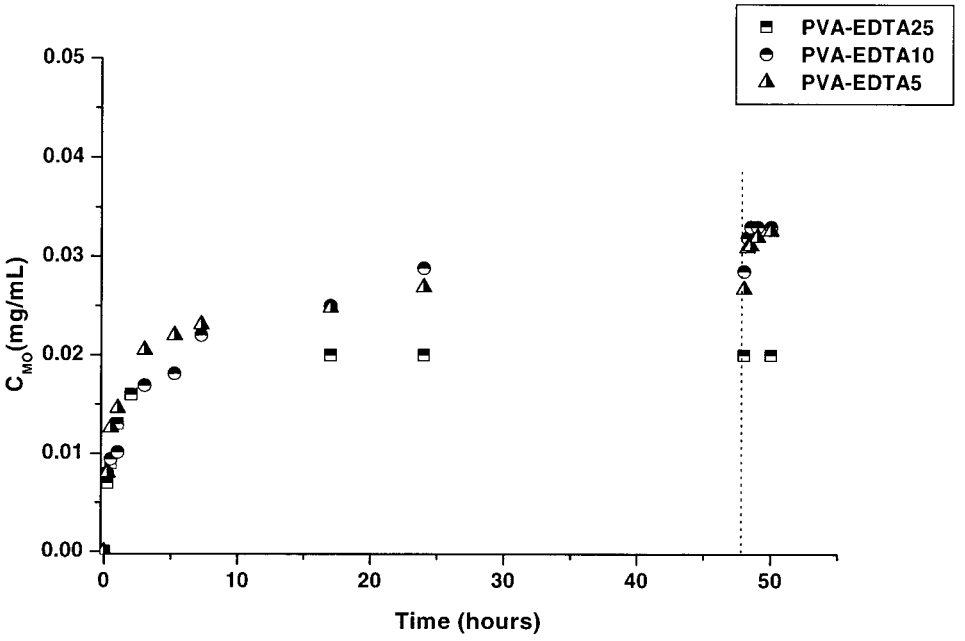


Figure 4 MO release assays. [MO] versus time for the PVA–EDTA25 (OH/anhydride 1/0.250), PVA–EDTA10 (OH/anhydride 1/0.100), and PVA–EDTA5 (OH/anhydride 1/0.050) dried loaded gels.

at time zero, which showed that when the dry gels were immersed in the buffer solution, a certain amount of model compound from the surface layer of the samples was quickly solubilized. However, as reported for more loaded hydrogels,[1] a drug reuptake at the initial stages was not observed.

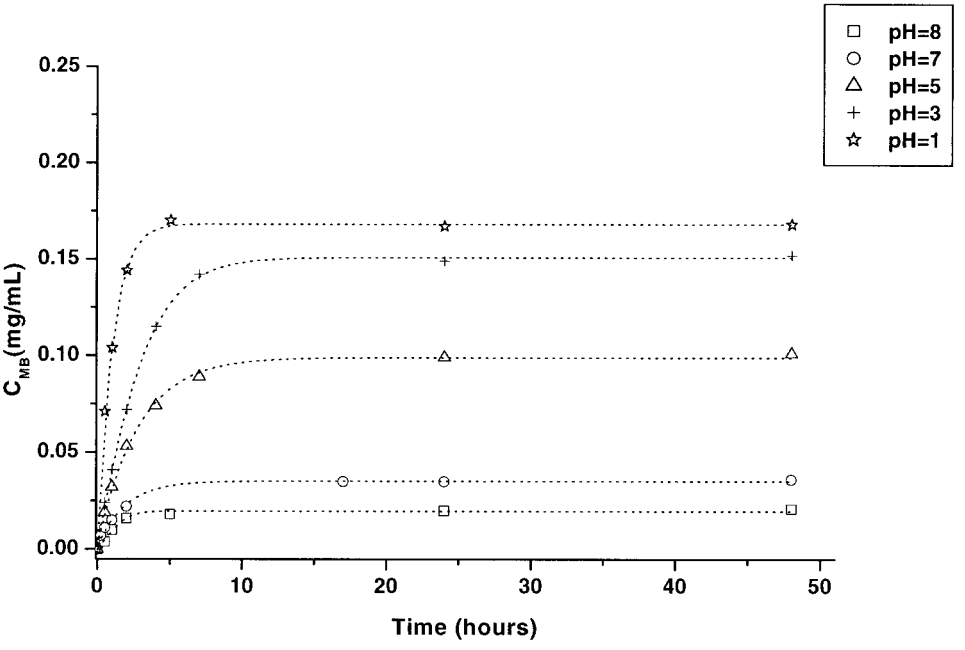


Figure 5 MB release assays in buffer solutions of pH 1, 3, 5, 7, and 8. [MB] versus time for the PVA–EDTA25 (OH/anhydride 1/0.250) dried loaded gel.

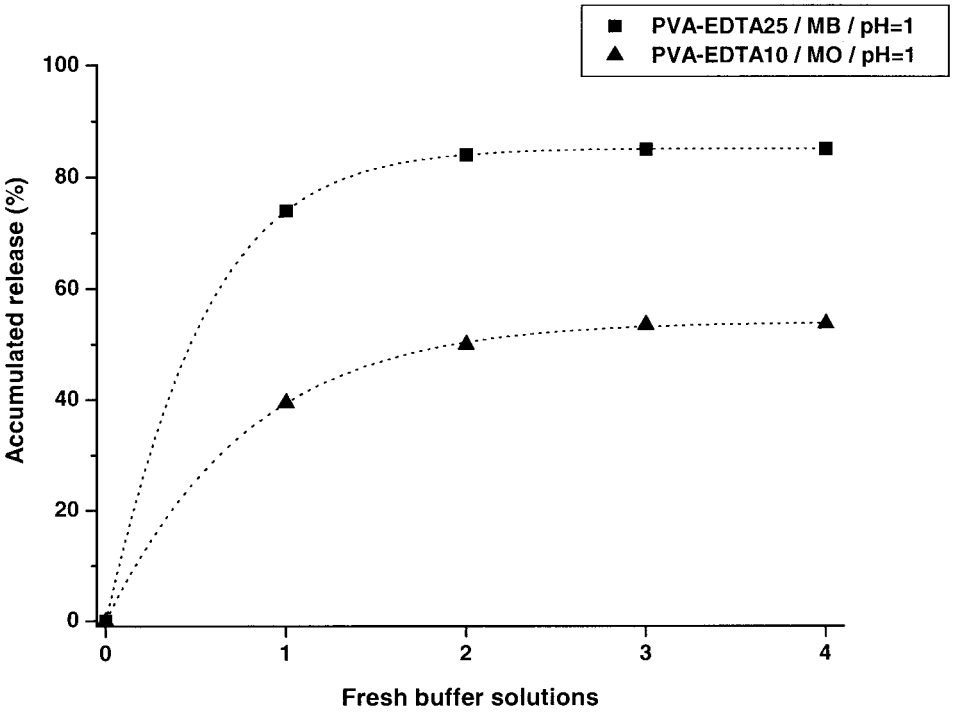


Figure 6 MB and MO release assays in buffer solution of pH 1. Accumulated release (%) versus number of fresh buffer solutions.

MB and MO were not completely released in any case because there was still a light blue or orange color, respectively, in the hydrogel. We performed a new assay to calculate the amount of MB and MO remaining at the most favorable release conditions [pH = 1, with replacement of the buffer solution every day until there was no release (4 days); see Fig. 6]. We calculated the amounts of released drugs in the solutions for each step. The accumulated weights of the drug were 1.52 mg (85 %) and 0.21 mg (54 %) for MB and MO, respectively. Although these percentages were different, the absolute amounts of unreleased MB (0.30 mg) and MO (0.18 mg) were similar. Similar results were reported for thermoreversible hydrogels of *N*-isopropylacrylamide derivatives,[3] where release was not directly proportional to the initial loading and incomplete release was attributed to the formation of water pockets at temperatures above the lower critical swelling temperature. However, in our case, the hydrogels were not thermosensitive,[23] and there was no collapse in the temperature range studied. Here, the most likely explanation seems to be that at high loading the drug formed insoluble clusters in the polymer, which prevented the complete release of the model drugs.[1]

This work allowed us to obtain information on the loading and release of low-molecular-weight compounds with positive or negative charges. The charge was the most important factor that influenced the both loading and release processes. Data obtained with this methodology are a starting point for a better knowledge of release patterns in physiological conditions.

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