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HPMC Layered Tablets Modified with Chitosan and Xanthan as Matrices for Controlled-Release Fertilizers

Mariana A. Melaj, Marta E. Daraio

Instituto de Tecnología en Polímeros y Nanotecnología, Grupo de Aplicaciones de Materiales Biocompatibles, Facultad de Ingeniería, Universidad de Buenos Aires, Av. Paseo Colón 850, 1063, Ciudad Autónoma de Buenos Aires, Argentina

Correspondence to: M. A. Melaj (E-mail: mmelaj@fi.uba.ar)

ABSTRACT: Polymeric matrices based on hydroxypropyl methylcellulose (HPMC) with xanthan (X) or chitosan (Q) and using KNO_3 as a model fertilizer were prepared as three-layered tablets and assayed as controlled release fertilizers (CRFs). The dynamic swelling behavior was analyzed in order to interpret the water uptake mechanism, which in general proved to be non-Fickian. The presence of HPMC allows a substantially constant rate of fertilizer release. The release mechanism of KNO_3 was analyzed and can be described as non-Fickian diffusion, with release exponents ranging from 0.85 to 1.01, suggesting polymer relaxation as the major process controlling fertilizer release. Durability in soil indicates the blend Q-HPMC as the more long-lasting matrix of those tested, remaining at least 34 weeks. Both blends improve HPMC properties for agronomical applications, with X-HPMC increasing the swelling rate and Q-HPMC extending the permanence in the soil. Therefore, layered X-HPMC and Q-HPMC matrices can be proposed as suitable materials for the development of CRFs. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40839.

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INTRODUCTION

Plants need to be supplemented because most soils do not offer the essential nutrients required for optimum growth. Fertilizers provide crops with the critical chemical elements needed for growing, particularly nitrogen, phosphorus, and potassium. However, an important percentage of the delivered nutrients are lost to the environment, generally when percolating water leaches them out and by different processes like volatilization, hydrolysis, and the action of microorganisms. When fertilizers are carried by rainwater to rivers and lakes they have various adverse effects on the surroundings.[1,2] Nitrate penetration can cause severe health problems: nitrates are involved in blue baby syndrome (methemoglobinemia) and various tumors. Due to the detrimental biological effects of the direct application of fertilizer substances, controlled release technology has been used in agriculture.[3]

Slow- and controlled-release fertilizers are products that minimize the potential of nutrient losses to the environment, as compared to conventional fertilizers. They delay the accessibility of a nutrient for plant uptake or extend its provision to the plant longer than quickly available nutrient fertilizers such as ammonium nitrate, urea, ammonium phosphate, or potassium chloride. They also increase N use efficiency. Often the rate of N application or the number of applications during the growing season can be reduced, which has the advantage of saving labor. A slow-release fertilizer (SRF) denotes a nitrogen product decomposable by microbes, such as urea-formaldehyde.[4] Nevertheless, the level and extent of the release are not well controlled. Fertilizers in which the factors dominating the release pattern are identified and can be controlled during the preparation are called controlled-release fertilizers (CRFs).[5] Those CRF matrices based on hydrophilic gel-forming polymers are especially effective in regulating the accessibility of the nutrient.[6,7] Furthermore, biocompatible matrices are preferred in order to avoid environmental pollution.[3]

Efentakis and Peponaki[8] prepared Carbopol tablets in the form of matrices and three-layered systems containing isosorbite mononitrate to investigate the effect of the structure of the system on drug release. These authors found that three-layer formulations show lower drug release than the matrices. Also, they inform that the weight and thickness of the barrier layers significantly affect drug delivery and release mechanism. Furthermore, the presence of the barrier layers modifies the hydration/swelling rate of the core and reduces the surface area available for fertilizer release, leading to an extended release.[9] These results highlight the great importance of the morphology on the release property of the tablets. In agreement with these authors, in our previous work[10] the presence of drug-free

Table I. Composition (% w/w) of Matrix Tablets

Components	A	B	C	D	E	B′	C′	D′	E′
KNO_3	31.2	31.2	31.2	31.2	31.2	–	–	–	–
HPMC	–	–	67.4	33.7	33.7	–	98.6	49.3	49.3
Chitosan	67.4	–	–	33.7	–	–	–	49.3	–
Xanthan	–	67.4	–	–	33.7	98.6	–	–	49.3
Magnesium stearate	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4

surface layers proved to be an important factor in modulating the release.

Potassium nitrate is a model fertilizer with pH-independent solubility. This is a neutral drug, whereas K^+ and NO_3^- do not alter the pH of the receptor medium. Hydroxypropyl methylcellulose (HPMC) is one of the polymers probably considered as a first choice for formulation of hydrophilic matrix systems, due to its different viscosity grades, nonionic nature, reproducible release profiles, and cost effectiveness.[11] HPMC is a nonionic polymer and hence the matrices exhibit pH-independent drug release profiles when drug solubility is pH independent. This polymer has received considerable attention in controlled release of pharmaceutical drugs.[12–15]

Xanthan gum is a natural, biocellulosic edible gum and an extracellular polysaccharide produced by the bacterium *Xanthomonas campestris* and consists of glucose, mannose, and glucuronic acid.[16] Viscosity of xanthan solutions is unaffected by pH changes between pH 1 and 13.[17] For pH > 4 ($pK_a = 3.1$)[18] and going to alkaline medium, negative charges of xanthan develop. The charge repulsion promotes matrix swelling and in these conditions the release would be enhanced. In addition to its wide application in pharmaceutical formulations,[19,20] xanthan is also used in making stable pesticide emulsion for agronomical applications.[21]

Chitosan [(1→4)-2-amino-2-deoxy-β-D-glucan] is obtained by the alkaline deacetylation of chitin, an abundant substance found in the skeletons of insects and shells of crustaceans.[22] When the degree of N-acetylation is lower than 50%, the polymers are called chitosans. They are soluble in aqueous solutions in the presence of acids[23] due to protonation of the amino group. El-Sherbiny et al.[24] reported that the swelling values of chitosan hydrogels were higher at low pH than at neutral pH because of the protonation of the NH_2 groups of chitosan at acidic pH ($pK_a = 6.3$). This leads to dissociation of the hydrogen bonding connecting the amino groups, and resulting enablement of the ingress of solvent into the hydrogels and then the release rate of a drug may be higher at lower pH value. On the other hand, the increase of pH weakens the protonation of NH_2 groups and results in the smaller swelling ratio and a lower release rate near to neutral media.[25] Chitosan has been broadly used as a matrix for the release of pharmaceutical drugs.[26,27] In agronomy, chitosan acts as a carbon source for microorganisms in the soil, assisting the roots of the plants to take additional nutrients from the soil. As an example, chitosan greatly improved the agronomic characteristics of Chinese cabbage, such as whole plant fresh weight, plant height, root length, root fresh weight, and the biggest leaf area.[28] Moreover, the positive charge that chitosan develops in slightly acidic media gives it biocide properties.[29]

It should also be noted that for uses in agriculture, biocompatible matrices are preferred in order to avoid environmental pollution. It is substantial that residual polymers in the soil are nontoxic materials. Hydroxypropyl methyl cellulose (HPMC), xanthan gum, and chitosan may contribute to reduce that kind of pollution. Moreover, our previous work[10] showed that xanthan and chitosan tablets remain virtually unchanged for at least 6 weeks, allowing the delayed release of a fertilizer.

In this work, polymeric matrices based on HPMC with xanthan or chitosan and using KNO_3 as a model fertilizer were prepared as layered tablets to explore their potential as controlled-release fertilizers (CRFs). Dynamic swelling and release behavior are analyzed in detail as an approach to understanding the processes that dominate the fertilizer delivery for different tablet compositions. The durability in soil or dissolution time of these tablets when exposed to a natural environment is also examined. The results show the great suitability of these systems for designing CRFs.

EXPERIMENTAL

Materials

HPMC K100M, Methocel (viscosity 10^5 mPa s, 2% solution at 20°C) was provided by Colorcon. Chitosan of medium molecular weight (Batch MKBC3804, Brookfield viscosity 2×10^5 mPa s) was purchased from Sigma-Aldrich. A deacetylation grade of 83%, that is, the proportion of primary amino groups in the polymer backbone, was determined by conductimetric titration with standardized NaOH of the chitosan dissolved in HCl solution. Xanthan was purchased from Biochemika–Fluka (France), potassium nitrate and magnesium stearate from Mallinckrodt were of analytical grade. Water was purified using a Millipore System.

Methods

Preparation of Layered Matrix Tablets. Tablets were prepared with the polymers, using KNO_3 as a model fertilizer for release tests and magnesium stearate as a lubricant. Taking into account the marked importance of the morphology and weight of the barrier layers on the release behavior of the tablets, in all cases, we prepared three-layered tablets with a definite weight and thickness. The corresponding compositions are shown in Table I. The polymers were passed through a sieve with a mesh of 420 μm before processing them. The sieving of the polymers and the compression of the components are important

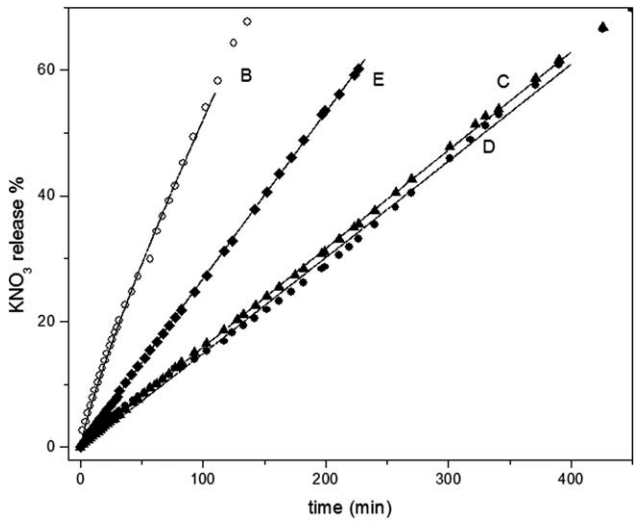

Figure 1. Cumulative KNO_3 release (%) as a function of time for tablets **B**, **C**, **D**, and **E** (see Table I). Lines represent the calculated release values from eq. (2). Best fit parameters were taken from Table II.

procedures that have been kept constant in all formulations as they affect the drug release. The blend of components was mixed. Layered matrix tablets were prepared by adding the preweighed polymer mixture without drug in the die and slightly compressing for uniform spreading. The preweighed mixture with drug was placed over the first layer and again slightly compressed. The other amount of polymer mixture (with or without fertilizer, according to the experiment to be performed) was subsequently placed over the middle layer and the three layers were compressed into tablets using a manual hydraulic press at a fixed compression force of 6 tons for 1 min. The diameter of the tablets was 1.6 cm.

***In Vitro* Release Study.** With the aim to compare the swelling and release behavior for different polymeric matrices, all experiments were conducted in a fixed aqueous medium at constant temperature, taking the polymer composition of the tablets as the variable.

To investigate the release profile of the fertilizer for each CRF, a tablet was located in a stainless steel basket and immersed into a beaker containing 1.00 L of purified water of pH close to 6, at $(25 \pm 2)^{\circ}C$, under constant stirring at 250 rpm. The release of KNO_3 into the water phase was monitored by conductimetry (conductivity meter Hanna Instruments model HI 9033 multi Range) and the cumulative concentrations were determined as a function of time using a calibration curve. Three replicates for each experiment were obtained.

Data Treatment for the Release Experiments. The release data (up to 60% of the fractional release curve) were fitted according to a power law–type relationship[30,31]:

$$C_t/C_\infty = kt^n \quad (1)$$

where C_t/C_∞ (C, molar concentration of KNO_3 in the aqueous phase) is the fraction of drug released at time t, k is a constant depending on kinetic features and structural and geometrical properties, and n is a diffusional exponent that depends on the drug release mechanism and the geometry of the tested system. Three different release mechanisms can be suggested from the value of n. For a cylindrical device, such as the CRFs studied in this work, when n takes the value 0.45, it indicates a Fickian mechanism (diffusion-controlled drug release), while the value 0.89 points to Case II transport (polymer relaxation- or swelling-controlled process). In the last case, the relaxation process of the macromolecules occurring upon water absorption by the system is the rate-determining mechanism. Values of n between 0.45 and 0.89 are described as anomalous or non-Fickian kinetics and can be regarded as coupled diffusion/polymer relaxation, a superposition of the two mechanisms described earlier.[32]

The cumulative percentages of released fertilizer were calculated and plotted as a function of time. Equation (2) was used to fit the data:

$$KNO_3 \text{ release } (\%) = k' t^n \quad (2)$$

where the constant k' includes k, C_∞, the volume of the water receptor phase, the molar mass of KNO_3 and the initial mass of this drug in the tablet.

Swelling Study

Swelling is associated with polymer chain relaxation with volume expansion. Hydrogels have the ability to maintain their original cylindrical shape during swelling due to isotropic swelling[33]; in fact, swelling changes only the size of the device while maintaining the original shape.

The fertilizer-free tablets (see Table I) were swollen in purified water at $(25 \pm 2)^{\circ}C$, inside glass beakers. The morphological changes occurring during the swelling process were registered photographically. The volume of the tablets at time t, V_t, was estimated from the measurement of the diameter and the thickness. The percentage of volumetric swelling (ratio between the incorporated solvent and polymer volumes) was calculated as[10]:

$$\text{Swelling } (\%) = ((V_t/V_0) - 1) \times 100 \quad (3)$$

where V_0 is the initial volume of the tablet.

Data Treatment for the Swelling Experiments. To gain understanding into the transport of water, the dynamic swelling curves were fitted to an exponential equation describing the behavior of penetrants in polymers[34]:

$$\text{Swelling } (\%) = k_S t^m \quad (4)$$

where Swelling $(\%)_t$ is the percentage of volumetric swelling at time t, k_S is a constant characteristic of the system, and m is an exponent representative of the mode of transport of the water penetrating the polymer tablet.

Taking into account eqs. (2) and (4), the following relationship is obtained:

$$KNO_3 \text{release } (\%) = K(\text{Swelling } (\%))^{(n/m)} \quad (5)$$

where $K = (k'/k_S^{(n/m)})$ and n and m are the exponents described above.

Statistical Approach

A nonlinear least-squares procedure was used for fitting the data to eqs. (2), (4), and (5). A 95% confidence interval of the

Table II. Fertilizer Release Kinetic Parameters[a]

Tablet (see Table I)	n	k' (min^{-n})	R^2
B	0.85 ± 0.02	1.05 ± 0.08	0.9985
C	0.99 ± 0.01	0.17 ± 0.01	0.9998
D	1.01 ± 0.03	0.14 ± 0.02	0.9968
E	0.99 ± 0.01	0.28 ± 0.01	0.9999

[a] Kinetic parameters were obtained by fitting the data through eq. (2). Mean and confidence intervals are informed. Statistical treatment of data is described in **Methods** section.

nonlinear least-squares estimation was reported for all parameters (MATLAB R2012b, TheMathWorks, Inc., Natick, MA, 2012).

Durability of the Tablets in Soil

With the aim of evaluating the dissolution time of these polymers when exposed to a natural environment, the durability of the compressed polymers was tested in soil, using a Mollisol from Buenos Aires, Argentina.

Five types of tablets prepared with chitosan, xanthan, HPMC, and the blends (1 : 1) of xanthan-HPMC and chitosan-HPMC, with the addition of magnesium stearate, were used to contrast their durability. Samples of 900 g of moist soil were weighed in glass beakers covered with plastic films with small holes. Tablets were placed between the soil and the lateral wall of the beaker. The beakers were weighed three times a week and the evaporated water was replenished. For each tablet, the area in contact with the glass was calculated as a function of time.

RESULTS AND DISCUSSION

Release of Potassium Nitrate

Although the release patterns obtained under stirring do not reproduce the release behavior in soil, these experiments provide the required data to contrast the profiles for different CRF tablets in order to choose the polymer matrices with the most suitable release profiles.[35,36]

As shown in our previous work,[10] it can be expected that the release time will be much higher in soil due to the reduced availability of a water phase and because there is no agitation of the adjacent medium.

Mechanism of Fertilizer Release

Tablet **A**, containing chitosan as a single polymer, could not be satisfactorily studied as a delivery system because it was rapidly disintegrated in water (pH near to 6). For tablets **B**, **C**, **D,** and **E**, the release data were treated as described in Methods section and the results are shown in Figure 1. Table II shows the release kinetic parameters obtained by fitting the data through eq. (2), where high correlation coefficients were achieved with the model used. The values of n, related to the release mechanism, range from 0.85 to 1.01. For the xanthan-based tablet **B**, the n value of 0.85 indicates anomalous (non-Fickian) diffusion with a significant relaxation contribution to the release kinetics. For tablets **C**, **D**, and **E**, the results are indicative of Case II drug release, where the relaxation process of the polymeric chains taking place in the course of water absorption by the system appears to be the rate-determining step of the release process. The exponent n with a value of 1 corresponds to a drug release rate independent of time or zero-order release kinetics.

The comparison between the release patterns of tablets **B** and **E** shows the interesting effect of blending xanthan with HPMC. The incorporation of HPMC to xanthan decreased the rate of fertilizer release because when the tablet absorbs water, HPMC forms a strong gelatinous barrier layer at the surface, resulting in decreased penetration of the solvent molecules in to the matrix and outward diffusion of drug molecules into the dissolution medium. Otherwise, by contrasting the behavior of tablets **C** and **E**, we can observe the effect of xanthan on HPMC. A steeper drug release pattern is obtained by incorporating xanthan (with rapid gel formation ability) to HPMC (with strong gelling capacity). The faster hydration rate of the more hydrophilic xanthan increases the fertilizer release from the X-HPMC matrix compared with the single HPMC tablet.

The release patterns observed for tablets **C** and **D** are quite similar. While tablet **A**, with only chitosan, was rapidly disintegrated in water, the presence of HPMC leads to the formation of a robust gelatinous layer that surrounds chitosan and the release behavior is controlled by HPMC. However, as will be shown below, the chitosan in the blend with HPMC is effective in considerably extending the permanence of the tablet in soil, by a factor greater than four.

For tablets **C**, **D**, and **E**, the presence of HPMC enables the system to reach a nearly zero-order release kinetic (n is close to 1). This fact allows the delivery of the fertilizer at a substantially constant rate, while prolonging the drug release process. This is a promising effect for practical applications.

Swelling Study

Figure 2 shows the volumetric changes of the tablets during swelling and Figure 3 illustrates the swelling curves for HPMC-containing tablets together with the xanthan initial profile, as a comparison. The swelling behavior of the X-HPMC tablet **E′** can be seen as a result of the prevalence of the rapid hydration ability of xanthan on the strong gelling capacity of HPMC. On the other hand, the rates of water ingress into the tablets **C′** (HPMC) and **D′** (Q-HPMC) are slower than that of **E′**. This can be interpreted as a predominant effect of the strong gel layer around the matrix produced by HPMC, resulting in decreased penetration of the solvent molecules.

The inset of Figure 3 details the swelling behavior of the HPMC tablet **C′**. This matrix appears resistant to erosion until about 100 h after the start of the experiment. This fact is consistent with the statement that the resistance of the gel layer to erosion is generally controlled by the viscosity grade of the HPMC used. Therefore, for HPMC-containing matrices, it could be considered that the matrix integrity was maintained during testing. In any case, it should be noted that the dipping of the tablet in water is an extreme condition when compared to soil.

Table III shows the swelling kinetic parameters obtained by fitting the data through eq. (4). The m values obtained for the tablets **C′** and **D′**, 0.66 and 0.60, respectively, indicate an

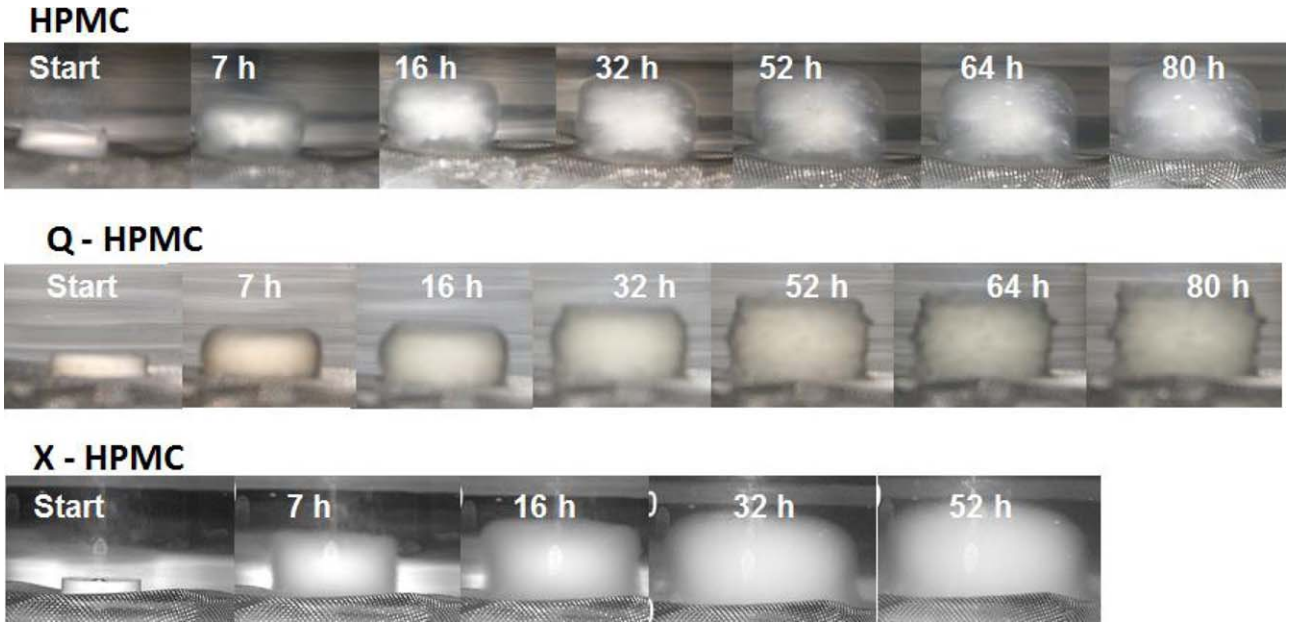

Figure 2. Morphological changes of the tablets during swelling. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

anomalous non-Fickian mechanism for the water uptake. In the case of tablets **B′** and **E′** ($m = 0.83$ and 0.80, respectively) the anomalous mechanism encloses a main contribution from the relaxation of the chains, probably due to the rapid swelling of xanthan.

Relationship Between Swelling and Drug Release

Figure 4 shows the percentage of released fertilizer as a function of the percentage of swelling. We found a well-defined relationship between these two variables. This is similar to what was reported by Huanbutta et al.,[37] who inform a linear relationship between the swelling and the fractions of drug released from chitosan matrix tablets. Otherwise, our data are adequately fitted by the nonlinear eq. (5) (see Table IV, second column), with correlation coefficients over 0.97 for the four polymeric matrices. The fourth column in Table IV shows the values of (n/m) calculated from Tables II and III. A good agreement (within 5%) between the fitted and calculated values of (n/m) is observed excepting for the Q-HPMC polymeric blend which shows a discrepancy of 19%. Equation (5) considers simultaneously both processes: drug release and swelling of the matrix. It has to be mentioned that for drug release eq. (2) applies up to 60% of the fractional release curve[30,31] (about 400 min for Q-HPMC). On the other hand, eq. (4) of which is obtained m of Table III holds up to 80% of the swelling curve[34] (around 2000 min for Q-HPMC). In order to consider both processes, the fitting to eq. (5) takes into account the short time data, reflecting the m value at the initial stage. Rotta et al.[38] provide information about the important increase in rigidity of a polymeric matrix by addition of chitosan to HPMC. This effect may affect the rate of relaxation of polymer chains slowing down the water uptake in the initial stage of swelling. Later, when the swelling develops, the looseness of polymer chains is facilitated. This could lead to a lower value of m when applying eq. (4) than when applying eq. (5). Therefore, the lesser agreement with eq. (5) for Q-HPMC could be ascribed to a variation of the rate of relaxation of the polymeric matrix through the swelling process.

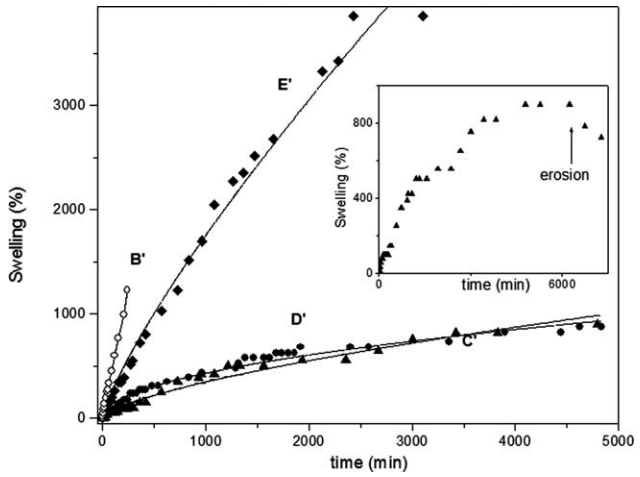

Figure 3. Swelling (%) as a function of time for tablets **B′**, **C′**, **D′**, and **E′** (see Table I). Lines characterize the calculated release values from eq. (4). For best fit parameters, see Table III.

Table III. Swelling Kinetic Parameters[a]

Tablet (see Table I)	m	k_S (min^{-m})	R^2
B′	0.83 ± 0.04	11.3 ± 2.1	0.9975
C′	0.66 ± 0.04	3.6 ± 1.1	0.9762
D′	0.60 ± 0.03	6.9 ± 1.4	0.9923
E′	0.80 ± 0.05	7.0 ± 2.6	0.9899

[a] Kinetic parameters were obtained by fitting the data through eq. (4). Mean and confidence intervals are informed. Statistical treatment of data is described in **Methods** section.

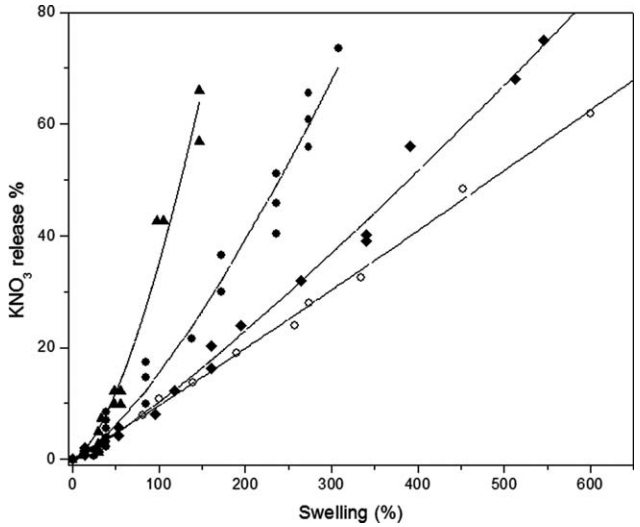

Figure 4. Relationship between KNO_3 release (%) and Swelling (%) for HPMC (▲), Q-HPMC (●), X-HPMC (◆), and X (○). Lines indicate the calculated release values from eq. (5). Best fit parameters were taken from Table IV.

This variation results more pronounced in Q-HPMC than in the other matrices assayed probably due to the initial increase in rigidity of the matrix by the presence of chitosan in HPMC.

The relationship found between the swelling and the fractions of drug released confirms that the swelling behavior plays an important role in controlling the drug release mechanism. Water absorption results in swelling of the polymer matrices, which acts as the central factor in governing the fertilizer release from these systems. Accordingly, due to the direct influence of swelling on the release found for these polymer matrices, the modification of the swelling behavior by preparing blends with other polymers proves to be an interesting approach to modulate the release of the fertilizer.

Durability of Tablets in Soil

The permanence time of a compressed polymer matrix in the soil is a characteristic that should be taken into account for the application of these devices. The polymer degradation in soil due to enzymatic hydrolysis may be delayed by the addition of minor quantities of a microbicide, or by the use of polymers with antimicrobial behavior, such as chitosan.[29]

For the five matrices assayed (see Methods section) the area of the tablet was measured as a function of time. The durability of a tablet was ordered on a scale of 0 to 9, taking into account the percentage of initial area existing after a given time.[39] A durability Level 0 was assigned to a tablet maintaining 0–9% of its initial area whilst durability level 9 corresponds to a tablet holding 90–100% of its original area.

Table IV. Relationship Between Swelling and Fertilizer Release

Polymer matrix	$(n/m)^a$	$(R^2)^a$	$(n/m)^b$
X	1.05 ± 0.06	0.9967	1.02
HPMC	1.56 ± 0.24	0.9711	1.50
Q-HPMC	1.36 ± 0.17	0.9798	1.68
X-HPMC	1.17 ± 0.11	0.9895	1.24

[a] Parameter obtained by fitting the data through eq. (5). Mean and confidence intervals are informed. Statistical treatment of data is described in **Methods** section.
[b] Values calculated from Tables II and III.

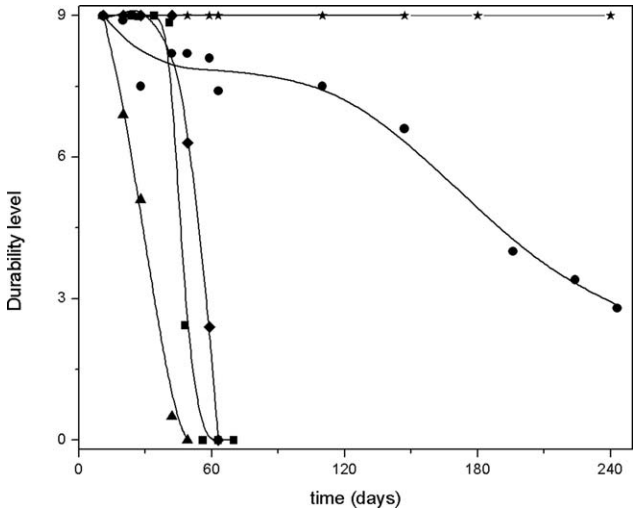

Figure 5. Durability level in soil for HPMC (▲), Q (*), X (■), X-HPMC (◆), and Q-HPMC (•).

Figure 5 shows the results for the durability tests in soil. Chitosan remains fairly constant until at least 34 weeks. Both xanthan and HPMC show durability shorter than 8 weeks. It is observed that the presence of xanthan increases the permanence of HPMC. However, the addition of chitosan to HPMC has a more pronounced effect on the durability of the polymer matrix, increasing the permanence in soil from 2 months to more than 8 months.

CONCLUSIONS

HPMC containing matrices with a three-layer design were successfully prepared by direct compression, using KNO_3 as a model fertilizer. The incorporation of X or Q in a blend with HPMC makes it possible to obtain different release rates for the delivery of the fertilizer. Extended release patterns at a substantially constant rate were obtained with X-HPMC and Q-HPMC blends. While HPMC- and Q-HPMC-based tablets show similar release patterns, the presence of chitosan considerably extends the durability of HPMC in soil, which represents an important result for agronomical applications. The dynamic swelling studies and the relationship obtained between swelling and fertilizer release kinetics both point to the important role of polymer swelling in drug release mechanisms. Thus, the adjustment of the swelling behavior by formulating mixtures with other polymers proves to be an interesting tactic to modify the release of the fertilizer.

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