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Development and Evaluation of a Controlled Release System of TBH Herbicide Using Alginate Microparticles

Daniela Macedo Faria*[a]*, Sidney Macias Dourado Júnior*[a]*, João Pedro Lopes do Nascimento*[a]*, Eloiza da Silva Nunes*[a]*, Renata Pereira Marques*[b]*, Luciana Sgarbi Rossino*[c,d]*, Jéferson Aparecido Moreto*[a,e]**

[a] *Federal Institute Goiano – IF Goiano, Rodovia Sul Goiana Km 01, Zona Rural, Zip code 75.901-970, Rio Verde, GO, Brazil*
[b] *Rede Arco Norte, Federal Institute Goiano – IF Goiano, Rodovia Sul Goiana Km 01, Zona Rural, Zip code 75.901-970, Rio Verde, GO, Brazil*
[c] *Sorocaba Technological College – FATEC, Av. Engenheiro Carlos Reinaldo Mendes, 2015, Alto da Boa Vista, Zip code 18013-280, Sorocaba, SP, Brazil*
[d] *Federal University of São Carlos – UFSCar, Rodovia João Leme dos Santos, Km 110, Bairro do Itinga, Zip code 18.052-780, Sorocaba, SP, Brazil*
[e] *Institute of Exact Sciences, Naturals and Education, Federal University of Triângulo Mineiro – UFTM, Avenida Doutor Randolfo Borges Júnior, Univerdecidade, Zip code 38.064-200, Uberaba, MG, Brazil.*

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The development of controlled delivery system formulations has received increasing interest in the agriculture area. Tebuthiuron (TBH) is the most commonly used herbicide for weed control in sugar cane and cotton crops. The TBH and some of its metabolites are detected in surface water by leaching process, evidencing contamination and the need for an efficient process to decrease pesticide residues. The development of a controlled system release appears as a good solution. The present investigation aimed to study the development and evaluation of alginate microparticles as a delivery system for the TBH. The calcium alginate microparticles were prepared from the crosslinking of sodium alginate by Ca^{++} containing varied amounts of TBH supplied in $CaCl_2$ aqueous solution. The particle size and morphological analysis of microparticles were determined by optical microscopy (OM) and by field emission gun scanning electron microscopy (FEG-SEM). The encapsulation efficiency and release of TBH studies was accessed by UV-vis spectroscopy. The results show that the polymeric microparticles containing TBH can be obtained successfully through a simple method and is suitable as a controlled release carrier system for herbicides and can be effective for controlling weeds.

Keywords: *Biodegradable Polymer, Weed control, Microencapsulation, Controlled release*

1. Introduction

Agrochemicals have become the product class most widely encountered in surface and subterranean hydrological systems worldwide, due to their extensive use in agriculture and in urban areas[1]. Currently, there is a great concern for environmental preservation, where the contamination of water is one of the major problems of the degradation of the environment by human activity in the world[2]. Several technologies have been proposed in order to minimize the spread of agrochemicals in the environment, among them are nanoparticulate[3] and microparticulate[4] systems designed to provide controlled release such class of compounds.

Tebuthiuron (TBH) is one of herbicides most used on sugar cane in the states of São Paulo[5] and Goiás in Brazil for weed control. TBH is a substituted urea herbicide with chemical name N-[5-1,1-dimethylethyl)-1,3,4-thiadizol-2yl]-NN' dimethylurea and molecular structure show in Figure 1. This herbicide is selective recommended for the weed control in the sugar cane crop and applied in pre-emergence. Some of its metabolites were detected in surface water in the city of Ribeirão Preto, São Paulo, evidencing contamination and the need for an efficient process to remove pesticide residues from the environment[6].

Controlled release systems have also been applied extensively in the food and pharmaceutical industries for the release of active substances such as nutrients, drugs and aromas[4,7]. Thus, polymeric microparticles have emerged among the new technologies under study as a potential alternative for the development of release system in agriculture. Silva *et al.*[1] studied the paraquat-loaded alginate/chitosan nanoparticles for soil sorption. The results of this survey showed new perspectives for using biopolymer membranes (particularly alginate and chitosan/alginate) for remediation of areas contaminated with herbicides[2].

According to MIGNON *et al.*[8], alginate is a linear copolymer composed of mannuronic and guluronic acid, covalently linked in varying sequences and blocks and is commercially available as a sodium salt (Na-Alg). Interestingly, when

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* e-mail: jeferson.moreto.uftm@gmail.com

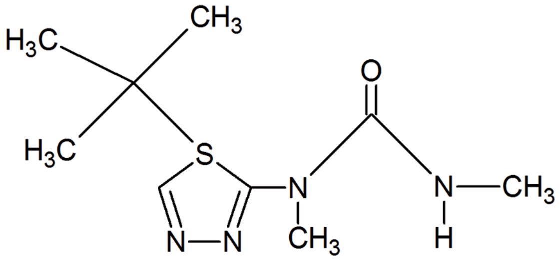


Figure 1: Molecular structure for the THB herbicide.

NaAlg is combined with multivalent cations such as calcium (originating from salts such as calcium chloride, $CaCl_2$), a physically cross-linked network is formed, which becomes insoluble in water. Figure 2 present the chemical structures of Na-Alg and Ca-Alg. Sodium alginate is natural polymer, non-toxic, biodegradable, biocompatible and pH sensitive[9]. Several works used sodium alginate as encapsulant of protein and living cells due to its good biocompatibility, gelation in mild conditions and a relatively inert matrix. The aim of this work is to prepare and characterize a new delivery system for TBH herbicide using polymeric microparticles of alginate.

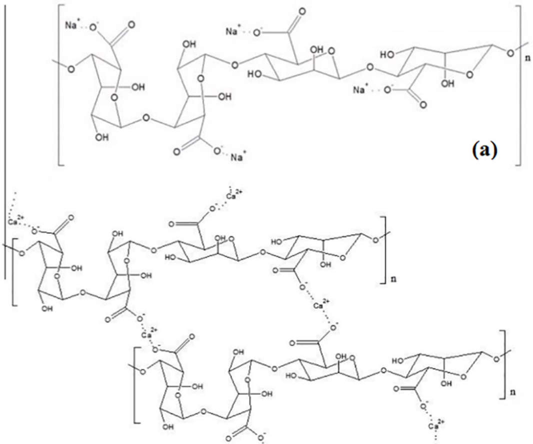


Figure 2: Representation of Na^+ and Ca^{2+} ions interacting with alginate chais (a) Na-Alg and (b) Ca-Alg.

2. Experimental

2.1. Materials

The biopolymer sodium alginate were purchased from Sigma -Aldrich with molecular weight (M/W) of 100.000 g.mol^{-1}, viscosity of 15-20 cP, 61% of mannuronic acid and 39% of guluronic acid. To obtain the alginate microparticles we also used calcium chloride, $CaCl_2$ (Sigma - Aldrich), sodium chloride, NaCl (Sigma - Aldrich) and deionized water (Milli-Q system (Millipore)).

In the present work the commercial herbicide (Combine®), whose formulation has 500 g.L^{-1} of TBH were used for the encapsulation in the alginate microparticles. One of its main features is its long persistence in soil and its high solubility in water 2.500 mg.L^{-1} to 20 °C. The herbicide analytical grade used was the TBH (PESTANAL® Sigma-Aldrich) with molecular mass 228.31 g.mol^{-1}, whose KOW is 6.17 X 10^{01} at pH 7 to 20ºC, registered under CAS 34014-18-1. All other materials were at least of analytical grade and used without previous purification.

2.2. Preparation of bare- and TBH- loaded alginate microparticles

The apparatus used in this work was built on the basis a scheme presented by Dias *et al.*[10] and Shi *et al.*[11]. Previously, solutions of sodium alginate (1, 2 and 3% m/v) and concentrations of 0.1, 0.3 and 0.5 mol·L^{-1} of $CaCl_2$ were prepared. Subsequently, sodium alginate solution was dropped in $CaCl_2$ solution, resulting in a total of 100 microparticles for each concentration used. After, the microparticles were filtered using a Buchner funnel and cleaned with distilled water. The obtained microparticles were divided in two portions, one was stored in deionized water and the other was dried in oven at 35 °C for 24 h. The number of microparticles was obtained by counting the number of drops of alginate solution deposited into the $CaCl_2$ solution. Each drop acts as a reactor originating one single microparticle.

In order to improve the texture and roundness of the microparticles the alginate solutions was adjusted to 0.1 mol·L^{-1} of sodium chloride and new batches of microparticles were prepared by using the same set of conditions (alginate, $CaCl_2$ concentrations and storage) as described above. The microparticles stored in deionized water passed through a process of water exchange for a period of 3 days. This procedure was adopted in order to withdraw the greatest possible quantity of NaCl at the calcium alginate microparticles.

For TBH encapsulation into alginate microparticles, desired amounts of combine (4 g·L^{-1}, 6 g·L^{-1} and 8 g·L^{-1}) were added to a freshly prepared 3 % (m/v) alginate solution. The TBH-loaded microparticles were obtained by dropping this solution in 0.1 mol·L^{-1} $CaCl_2$ and isolated as described above. The encapsulation efficiency of TBH was measured by the amount of herbicide remaining in the supernatant.

2.3. Characterization of the alginate microparticles

The dried microparticles of calcium alginate were photographed using a scanner (MFP HP Deskjet Ink Advantage 1516). This procedure can be used to decrease the image distortion as cited by Mendoza-Muñoz *et al.*[12].

The dried microparticles of alginate were analyzed by optical microscopy (OM) and scanning electron microscopy

(SEM). The methodology used to prepare the samples to OM and SEM comprises classic methodologies in the material science area. For SEM analysis the microparticles were affixed on the stub and the sputtering was carried out with Au.

The average diameter of the dried calcium alginate microparticles was measured by digital image analysis and the polydispersity distribution curves were obtained using *ImageJ* software. A number of 800 calcium alginate microparticles were used to make the polydispersity distribution.

2.4. TBH release experiments

Prior to encapsulating the TBH herbicide in the alginate microparticles it was verified by ultraviolet–visible spectroscopy (UV-Vis) technique the absorbance of Combine® herbicide when compared to the active ingredient. Following the same procedure was adopted for combined solution of the commercial herbicide and sodium alginate. For this, we used a spectrophotometer PerkinElmer Lambda 750 in the range 200 – 800 nm. The determination of TBH concentration to calculate the encapsulation efficiency and the release experiments was performed by monitoring the absorbance of TBH at 253 nm.

The TBH analytical curve was obtained by preparing aqueous solutions of TBH analytical grade varying the herbicide concentration from 0.0008 g.L^{-1} to 0.02 g.L^{-1} and then measuring the absorbance at 253 nm. The absorbance *versus* concentration data was adjusted using a minimum-square method to obtainment of the best fit as can be seen in Figure 3.

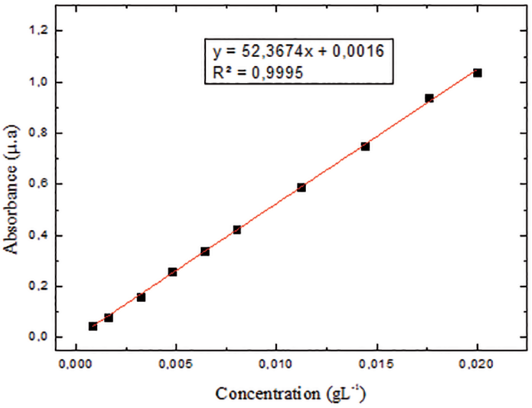


Figure 3: Analytical curve obtained by preparing aqueous solutions of TBH herbicide.

For the controlled release experiment, 40 mg of dried TBH-loaded alginate microparticles were mixed with 20 mL of deionized water in an Erlenmeyer and let stand at room temperature. The initial pH was 5.5 and did not change significantly during the course of the experiment. Aliquots of 2 mL were withdrawn from the solution previously homogenized at different time intervals: 5, 10, 15, 20, 30, 60, 120 min and after the first hour the removal was realized once per hour. After each removal, the same volume was replaced with deionized water.

All release assays was performed in dilution conditions. The encapsulation efficiency (% EE) was evaluated by the difference of the amount of herbicide added in the alginate + TBH solution and the unentrapped amount of TBH remaining in the supernatant after the removal of the formed microparticles, following the equation:

$$\%\text{EE (encapsulation efficiency)} = [(\text{TBH added} - \text{free unentrapped TBH})/\text{THB added}] * 100\% \quad (1)$$

2.5. Mathematical models

To understand the agrochemical release system, mathematical models were used in the present work. To analyze the controlled release behavior of the TBH herbicide from the alginate microparticles the Korsmeyer-Peppas, Higuchi, Baker –Lonsdale, Weibull and Hopfenberg models were performed. Follows a brief description of each mathematical models used in this study:

- Korsmeyer-Peppas model: The Korsmeyer-Peppas model[13] is described by:

$$\frac{M_t}{M_\infty} = Kt^n \quad (2)$$

Where, M_t/M_∞ is the proportion of compound released in the time t, K is the kinetic constant, and *n* is the exponent which reflects the type of release mechanism. The Korsmeyer-Peppas proposed that values of $n \leq 0.43$ are indicative of release mechanisms that follow Fick's law. The Fick's law, which were developed by Adolf Fick in the 19th century relates that the molar flux due to diffusion is proportional to the concentration gradient (First law) and the rate of change of concentration at a point in space is proportional to the second derivate of concentration with space (second law). The first law in a modern mathematical form can be write as:

$$N_i = -D\nabla C_i \quad (3)$$

Where for species i, N_i is the molar flux (mol.m^2.s^{-1}), D_i is the diffusion coefficient (m^2.s^{-1}), and C_i is the concentration (mol.m^{-3}).

The Fick's second law can be represented as:

$$\frac{\partial c_i}{\partial_t} = D_i \nabla^2 C_i \quad (4)$$

In this case, we can assume that D_i is a constant, which is only true for dilute solution. While, $n > 0.85$ (equation 1) indicates that the mechanism are governed by relaxation processes of the polymeric matrix, defined as case II type transport. Intermediate values $0.43 \leq n \leq 0.85$ suggest anomalous behavior with non-Fickian release (combination of diffusion and relaxation of the polymeric matrix).

- Higuchi Model: The Higuchi Model is based on the quantification of drug release derived from a very simple equation as described below:

$$f_t = (K_h)(t)^{1/2} \quad (5)$$

As can be seen, Higuchi Model describes the release of the TBH herbicide as the square root of time based on the Fickian diffusion. Where K_H is the constant reflecting the design variable of the system [14].

- Baker –Lonsdale Model: This model was developed by Baker and Lonsdale (1974) from the Higuchi model and described the drug release from spherical matrices [15]. Equation 6 has been used to the linearization of release data from several formulations of microcapsules or microspheres.

$$\frac{3}{2}\left[1-\left(1-\frac{M_t}{M_\infty}\right)^{2/3}\right]\frac{M_t}{M_\infty} = K_t \quad (6)$$

Where:

M_t is the drug release amount at time t

M_∞ is the amount of drug released at an infinite time

K is the release constant which corresponds to the slope of the graph when plotted as $[d(M_t / M_\infty)] / dt$ with respect to the root of time inverse.

- Weibull Model: This model has been described for different dissolution processes as described by the equation 7. Weibull model also has two constants, a (time factor) and b (related to the shape of the release curve). The constant b can be correlated to the exponent *n* of Korsmeyer-Peppas model.

$$M = M_0\left[1-e^{-\frac{(t-T)^b}{a}}\right] \quad (7)$$

In this equation, M is the amount of drug dissolved as a function of time t, M_0 is total amount of drug being released and T accounts for the lag time measured as a result of the dissolution process.

- Hopfenberg model: The mathematical model developed by Hopfenberg correlates the release of active compound from surface-eroding devices with several geometries as flat, cylindrical and spherical. The Hopfenberg model can be described by equation 8.

$$\frac{M_t}{M_\infty} = 1-\left[1-k_0 t/C_L a\right]^n \quad (8)$$

According to SUVAKANTA *et al.*[15], k_0 is the zero order rate constant describing the polymer degradation (surface erosion) process, C_L is the initial drug loading throughout the system, a is the systems half thickness and *n* is an exponent that varies with geometry.

3. Results and discussion

Figure 4 shows the OM images of calcium alginate microparticles for 2 and 3% (m/v) concentrations of sodium alginate. It is important to mention that the 1% (m/v) concentration of sodium alginate did not lead to obtaining of microspheres. As can be seen by optical microscopy the best results were obtained at 3% alginate using 0.1 mol.L^{-1} $CaCl_2$ concentration, since, there was no tail formation. The results obtained in this work corroborate with the studies carried out by Strand *et al.*[16] and Burey *et al.*[17]. According to the authors the best microspheres are obtained with higher sodium alginate concentrations [13,17].

Figure 5 presents OM images of calcium alginate microparticles with sodium chloride. According MCCONAUGHY *et al.*[18] and STRAND *et al.*[16] the presence of NaCl promotes a significant increase of the ionic force, leading to lowering values of zeta potential. In order, to verify the influence of NaCl on the alginate microparticles the last procedure was carried out in 3% (m/v) of alginate using 0.1 mol.L^{-1} $CaCl_2$. It was observed that the addition of NaCl promoted the formation of regular microparticles and suitable distribution of sizes. In addition, it was observed that the presence of NaCl promoted an increase in the diameter of the microparticles. Probably the drop sphericity is caused by increased interfacial tension.

Figure 6 presents the polydispersity curve of dried alginate microparticles (3% m/v of alginate) with and without NaCl (0.1 % m/v) using 0.1 mol·L^{-1} $CaCl_2$. As can be seen, the alginate microparticles with NaCl showed a narrow polydispersive curve when compared to alginate microparticles without NaCl. The medium radius of the alginate microparticles with NaCl presented 4.75 % higher than alginate microparticles without NaCl. On the other hand, the medium circumference of alginate microparticles with NaCl showed about 8% better results when compared to microparticles without NaCl. Thus, the addition of NaCl during the alginate microparticles preparation appears as a critical parameter that should be considered to improve the uniformity of the microparticles. SEM micrographs of calcium alginate microparticles for 2 and 3% (m/v) concentrations of sodium alginate in different concentrations of $CaCl_2$ are shown in Figure 7. The SEM micrographs of calcium alginate microparticles for 3% (m/v) + 0.1 mol.L^{-1} $CaCl_2$ + NaCl are present in Figure 8.

Figure 9 show images obtained by optical microscope of the alginate microparticles prepared in the presence of NaCl and different concentrations of herbicide, named as: 4, 6 and 8 g.L^{-1}. Figure 10 presents the polydispersity curves of dried alginate microparticles prepared with NaCl for different concentration of herbicide. The analysis of the polydispersity curves for the different concentrations of herbicide showed the influence of concentration in the quality of the microparticles. The medium circumferences of dried alginate microparticles + herbicide + NaCl were (e.g. 0.8299 mm for 4 g.L^{-1}, 0.8395 mm for 6 g.L^{-1} and 0.8137 mm for 8 g.L^{-1}.

The SEM micrographs were analyzed to determine and compare the size distribution profiles of the different calcium

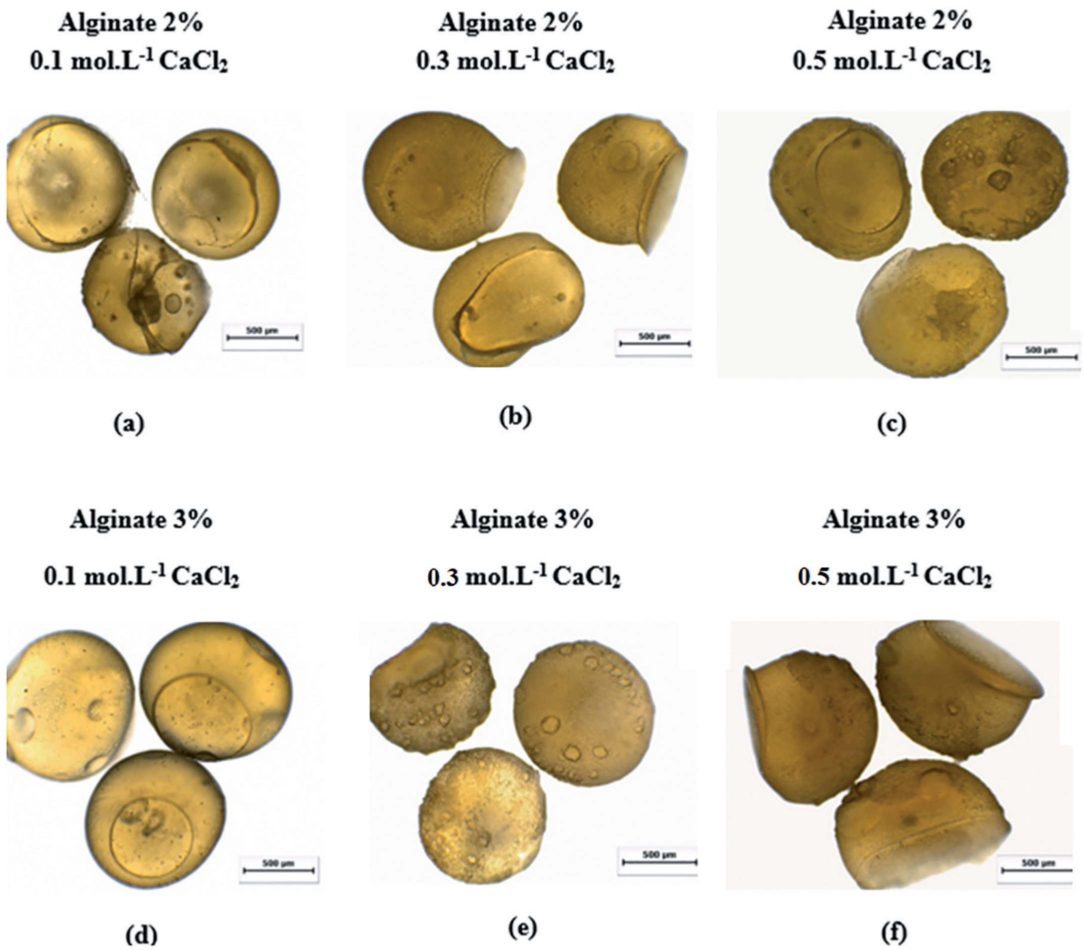


Figure 4: Images obtained by optical microscopy of dried alginate microparticles at different concentrations of $CaCl_2$.

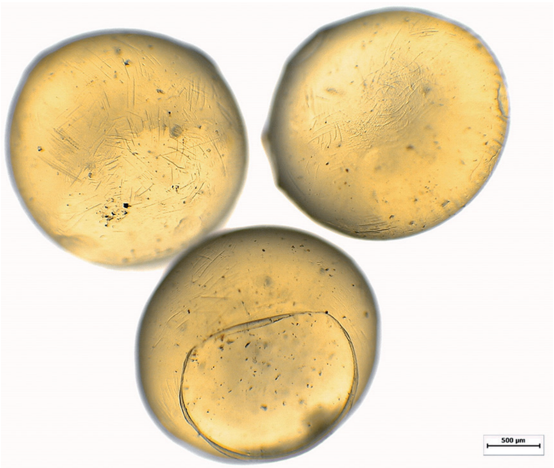
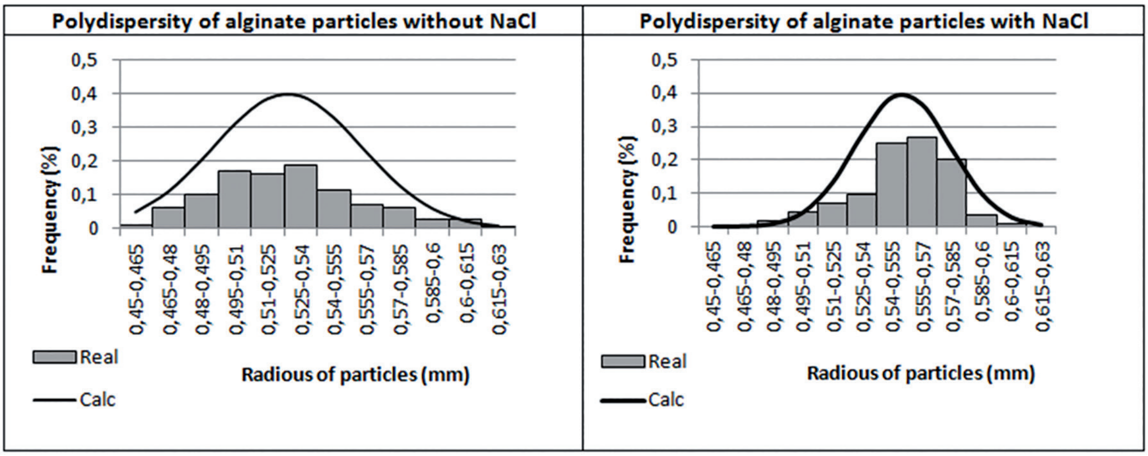


Figure 5: Images obtained by optical microscopy of dried alginate microparticles at 3% alginate + 0.1 mol.L^{-1} $CaCl_2$ + NaCl.

alginate microparticles. Figure 11 shows representative SEM images used for determining the size distribution of the calcium alginate with and without TBH herbicide. It can be noted that the microparticles are spherical with rough surfaces. According to AGRAWAL *et al.*[19] spherical with rough surfaces are typical characteristics of microparticles consisting of sodium alginate. According to LACERDA *et al.*[9] the ionic gelation method produces microparticles with large radius from 550 to 650 µm. In this study, the medium radius of the dried alginate microparticles with NaCl in different concentrations of TBH herbicide were 504 µm for 4 g/L, 561 µm for 6 g/L and 599 µm for 8 g/L. The results of EDX analysis at the point Z1 and Z2 for the alginate microparticles in Figure 10 show the presence of C, O, Na, Cl and Ca.

The encapsulation efficiency (%) was evaluated by the difference of the amount of herbicide initially present in the alginate + TBH solution and the remaining amount of TBH in the supernatant after the removal of the formed microparticles. The concentration of TBH was determined by UV-Vis spectroscopy. The encapsulation percentages were: 92% for the 4 gL^{-1}, 89% for 6 gL^{-1} and 86% for 8 gL^{-1} microparticles.



(a) (b)

Figure 6: Polydispersity curve of dried alginate microparticles (a) without and (b) with NaCl.

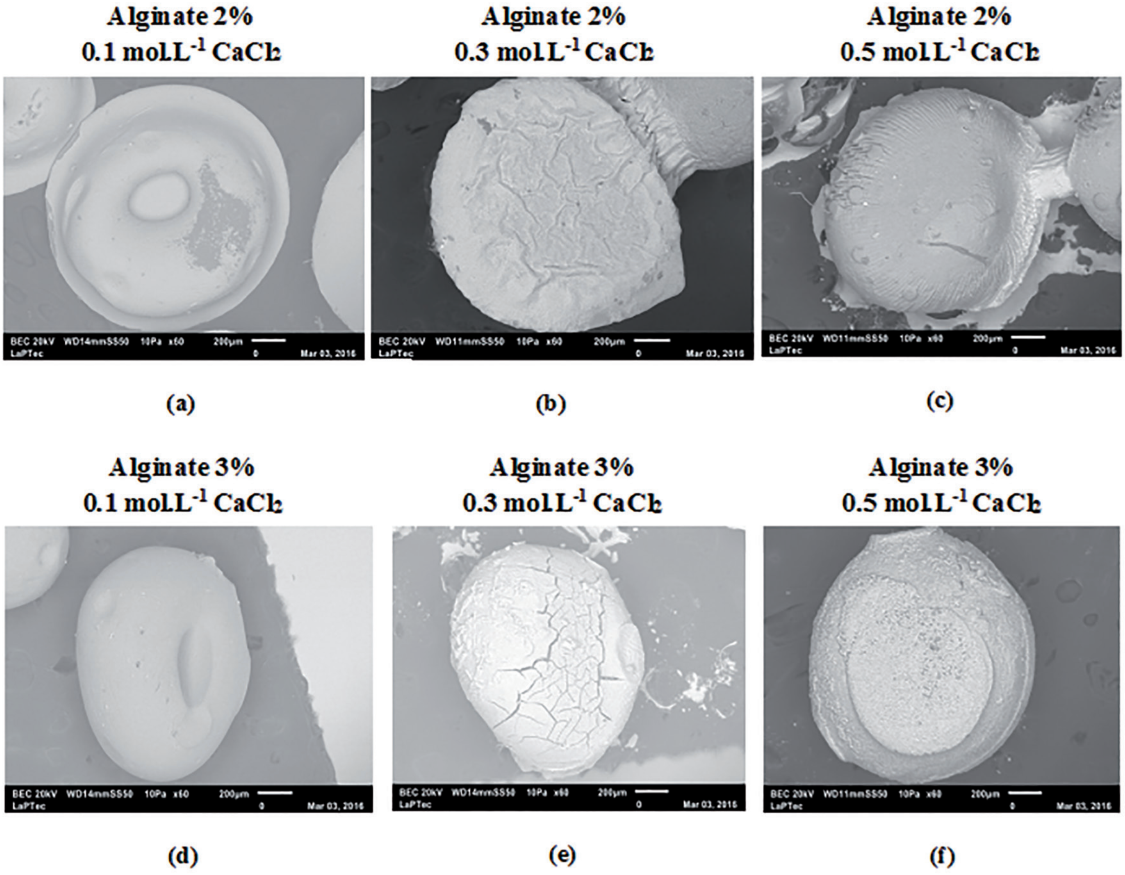


Figure 7: SEM micrographs of calcium alginate microparticles for different concentrations of $CaCl_2$ and alginate.

The electronic spectra of TBH analytical standard with Combine® solution at the same concentration of TBH were compared. As result, the two spectra superimposed in the whole range analyzed and exhibit a single band with maximum absorbance at 253 nm as can be seen in (Figure 12 (a)). This band can be attributed to a $\pi \rightarrow \pi^*$ transition in organic compounds with conjugated doubled bonds [20] and was used to monitor the TBH concentration in Combine® solutions. The obtained analytical curve presents 12 points, in the concentration range from 0.0008 gL^{-1} to 0.02 gL^{-1} of TBH with correlation coefficient (R^2) 0.995.

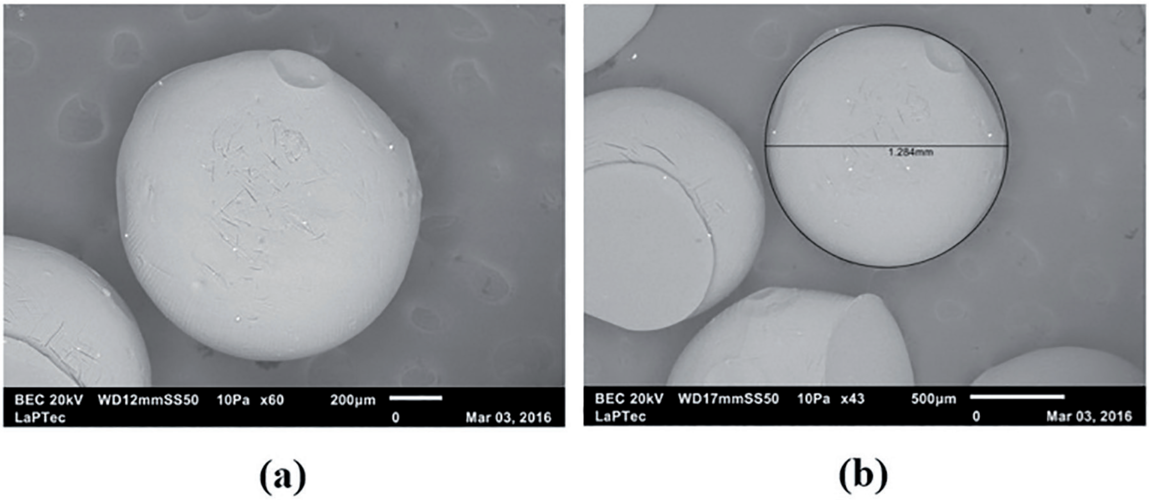


Figure 8: SEM micrographs of calcium alginate microparticles for 3% (m/v) of alginate +0.1 mol.L^{-1} $CaCl_2$+ NaCl. (a) Overview and (b) measurement of the diameter.

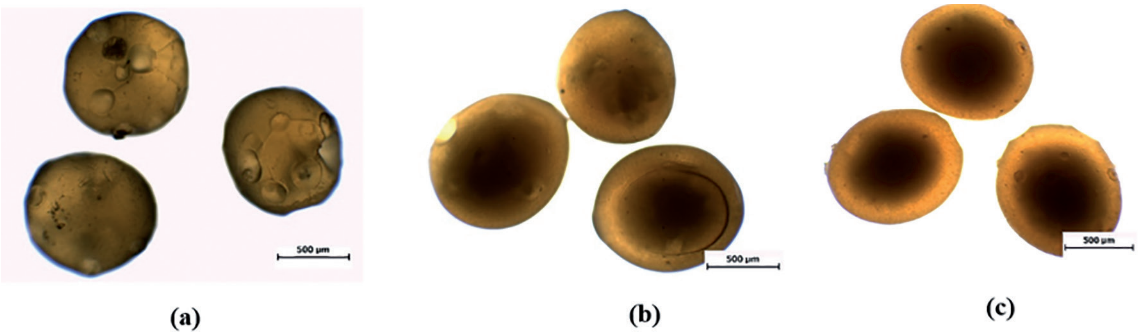


Figure 9: Images obtained by optical microscopy of dried alginate microparticles at different concentrations of herbicide (a) Alginate 3% + NaCl + Herbicide 4 g.L^{-1} (b) Alginate 3% + NaCl + Herbicide 6 g.L^{-1} (c) Alginate 3% + NaCl + Herbicide 8 g.L^{-1}.

As can be seen in Figure 12 (b) the remaining concentration of alginate in solution in contact with the microparticles do not influenced in the electronic spectra in the range considered for TBH and Combine® analysis. Figure 13 (a) presents the results of release assays, comparing the kinetic profiles of encapsulated TBH in calcium alginate microparticles at ambient temperature for different concentrations of herbicide. Analysis of the release kinetics curves indicated that Combine® was released much more rapidly for 4 gL^{-1} herbicide concentration (50% of release during the first 140 min). Thus, the difference observed between the release profiles of encapsulated herbicide could be explained by the structural characteristics of the microparticles [7].

As reported by GRILLO *et al.*[7] the herbicide release profile curves were analyzed to obtain information on the possible mechanisms governing the release process. In this work we found that the alginate microparticles showed a slow and sustained release profile. The results of the analyses of calcium alginate microparticles containing Combine® were compared by different mathematical models. The criteria used to determine the best model was based on the correlation coefficient (R^2). To define the best model it was necessary to analyze each sample dissolution results using various mathematical equations and linear regression. The mathematical model to present higher value of "R^2" is the most suitable for each sample.

The results showed that only 4 g.L^{-1} herbicide concentration was adjusted by Korsmeyer-Peppas model. The rate as a function of time (t^{n-1}), the release constant K = 0.41 min^{-1}, correlation coefficient R^2 = 0.97 and diffusion exponent n = 0.49 were found for the 4 g.L^{-1} herbicide concentration, see Figure 13 (b). According to CARBINATTO *et al.*[21], the correlation between release exponent (*n*) values for the Korsmeyer–Peppas equation and drug release mechanisms depending on the geometry shape and for the sphere particle form $0.43 < n < 0.85$.

The release of TBH from alginate microparticles followed anomalous behavior with non-Fickian release, where the release is controlled by combination of diffusion and relaxation of the polymeric matrix. As reported by

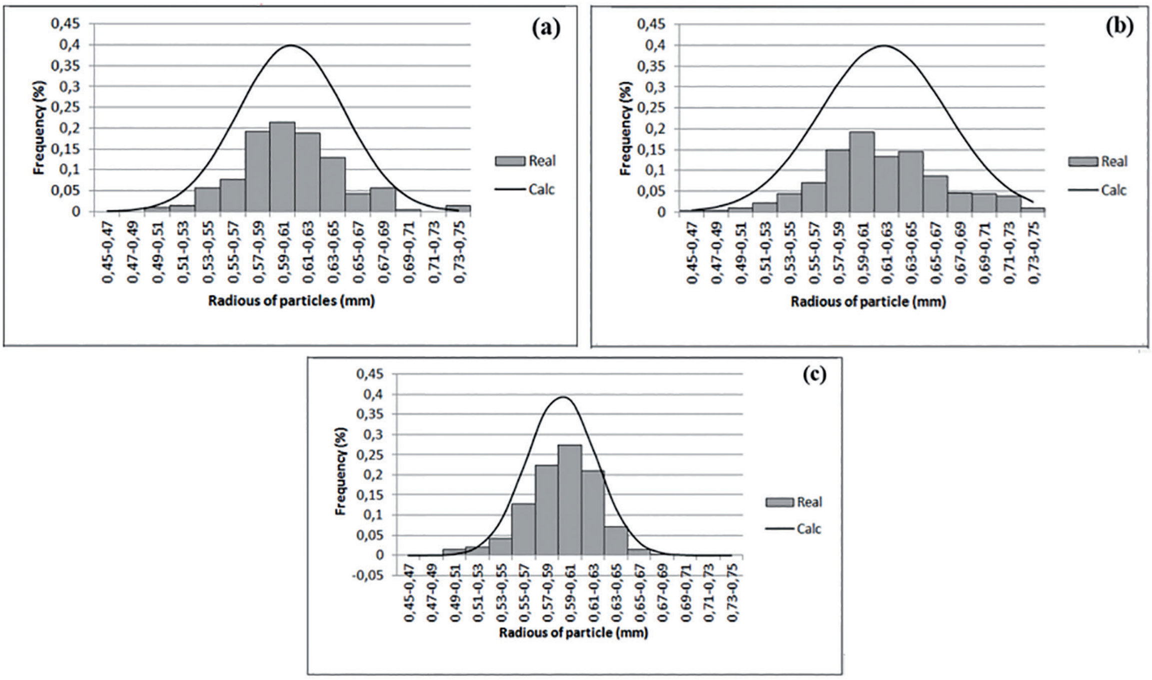


Figure 10: Polydispersity curves of dried alginate microparticles with NaCl for different concentration of herbicide. (a) 4 g.L^{-1} herbicide concentration (b) 6 g.L^{-1} herbicide concentration and (c) 8 g.L^{-1} herbicide concentration.

CAHYANINGRUM; HERDYASTUTI and QOMARIAH[22] this indicate that the release mechanism of drug is through mechanism combination of erosion and diffusion.

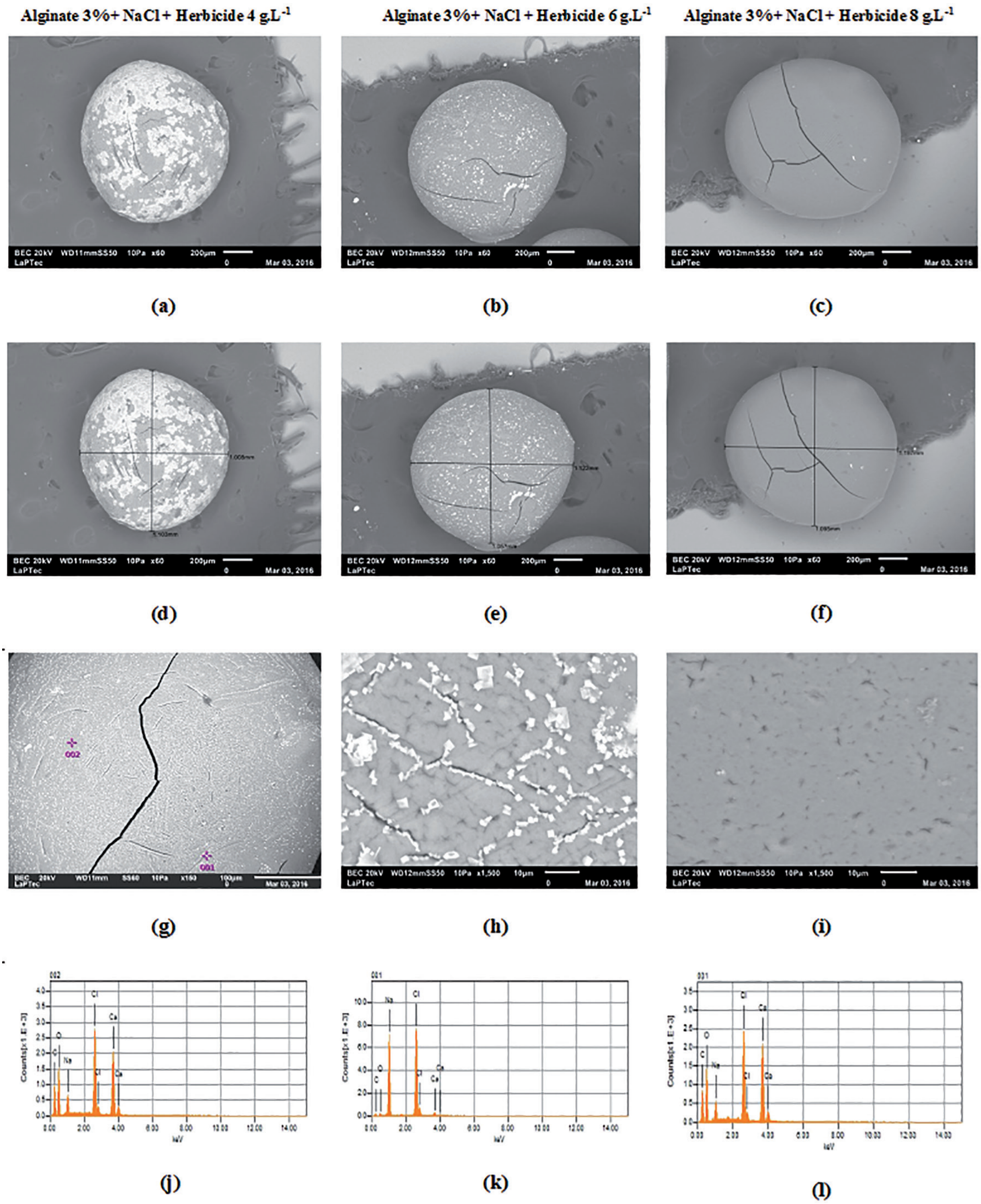
For the 6 g.L^{-1} herbicide concentration the best result was obtained using Higuchi model. The Higuchi model suggests that the agrochemical release by diffusion. A graph is plotted between the square root of time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line. Correlation coefficient ($R^2 > 0.99$) indicates that the herbicide release followed the Higuchi equation. The data obtained were plotted as cumulative percentage herbicide release *versus* square root of time as can be seen in Figure 13 (c).

All the models used before were not sufficient to describe the behavior of the 8 g.L^{-1} herbicide concentration. However, the release mechanism can be described by $M_t/M_{infinite} = (2/3) \times t^{0.2}$ equation for the first 20 % of herbicide released as can be seen in Figure 13 (d). The correlation coefficient is $R^2 = 0.96$. It is very important to note the results obtained in this survey show the new carrier system has the potential to reduce detrimental effects of the herbicide and can be used for weed control. Table 1 presents all the parameters obtained from each model for the different concentrations of herbicide.

4. Conclusions

In this work we studied the controlled system release of TBH herbicide using microparticles of alginate. The conclusions of this study are:

- Polymeric microparticles containing TBH were obtained successfully through a simple method. Based on the performed tests, it was found that the drip is suitable for the formation of alginate microparticles;
- The OM and SEM techniques demonstrated the strong influence of sodium chloride on the alginate microparticles morphology;
- The addition of NaCl promoted an increase in the diameter of the microparticles confirming the formation of regular microparticles and suitable distribution of sizes;
- The Korsmeyer-Peppas mathematical modeling revealed anomalous behavior with non-Fickian release (combination of diffusion and relaxation of the polymeric matrix) for the 4 g.L^{-1} TBH concentration;
- The Higuchi equation was used to describe the release mechanism for the 6 g.L^{-1} herbicide concentration;
- The alginate microparticles presented high encapsulation efficiency of TBH herbicide and are potential candidates for controlled release platforms in agricultural applications;
- These results demonstrate that the structure of kinetic properties of alginate microparticles is suitable as a controlled release carrier system for herbicides and can be effective for controlling weeds.
- The release of the Combine® herbicide occurred faster in the concentration of 4 g.L^{-1}.



(a) (b) (c)

(d) (e) (f)

(g) (h) (i)

(j) (k) (l)

Figure 11: SEM micrographs and EDX spectra of calcium alginate microparticles for 4 g.L^{-1} herbicide concentration, 6 g.L^{-1} herbicide concentration and 8 g.L^{-1} herbicide concentration.

5. Acknowledgements

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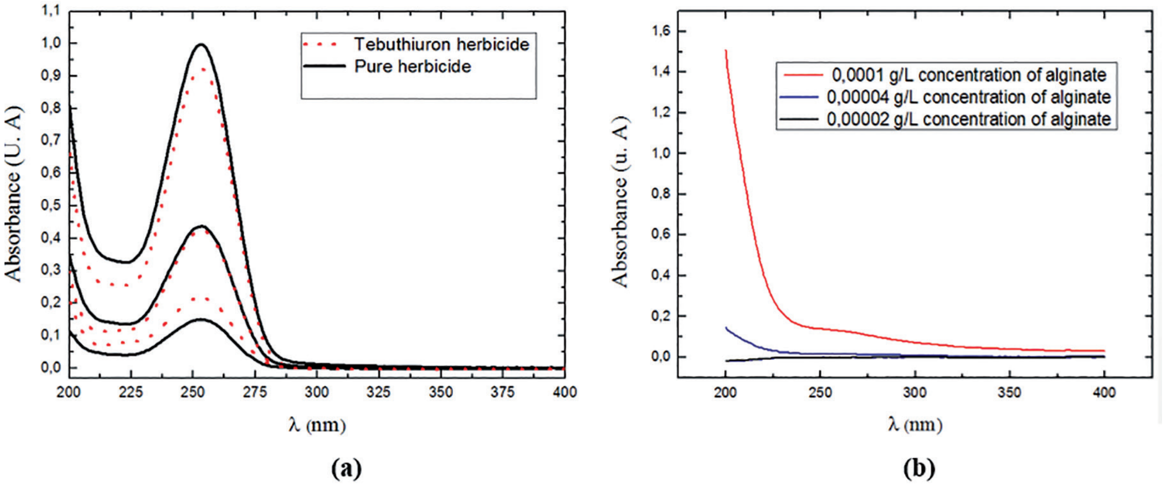

Figure 12: (a) Spectra of tebuthiuron (TBH) analytical standard and a Combine® (500 g.L^{-1} of TBH) solutions and (b) spectra of alginate in different concentrations.

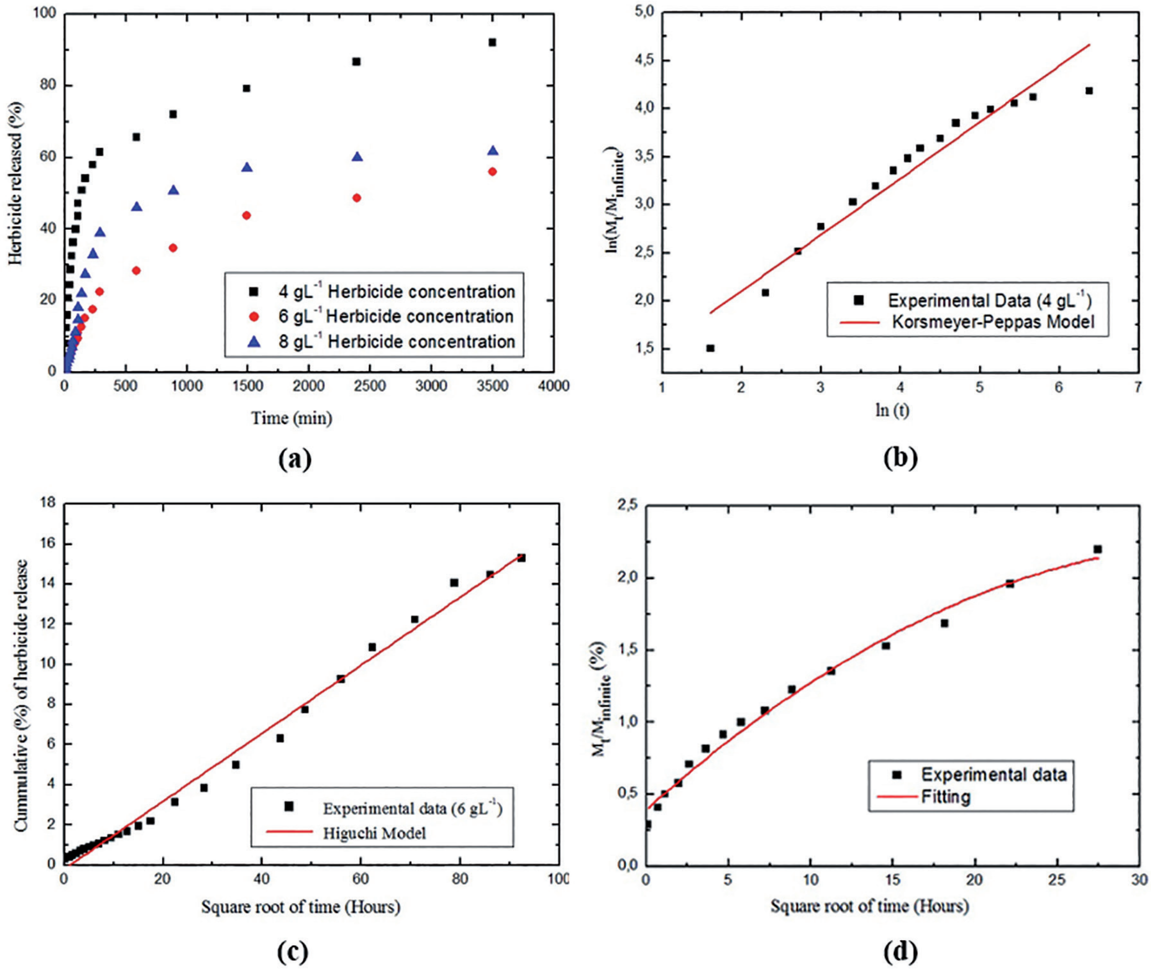

Figure 13: (a). Release assays, comparing the kinetic profiles of encapsulated Combine® in calcium alginate microparticles at ambient temperature for different concentrations of herbicide. (b). Mechanism of herbicide release by Korsmeyer-Peppas model for the 4 g.L^{-1} herbicide concentration. (c). Mechanism of herbicide release by Higuchi model for the 6 g.L^{-1} herbicide concentration. (d). Mechanism of herbicide release by proposed model for the 8 g.L^{-1} herbicide concentration.

Table 1: Parameters obtained from each model for the different concentrations of herbicide.

Concentration of Herbicide	Korsmayers-Peppas Model	Higuchi Model	Baker-Londsdale Model	Weibull Model
4 g.L^{-1}	R^2=0.97	R^2=0.87	R^2=0.94	R^2=0.96
6 g.L^{-1}	R^2=0.90	R^2>0.99	R^2=0.95	R^2=0.87
8 g.L^{-1}	-	-	-	-

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