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Controlled Release of the Herbicide Norflurazon into Water from Ethylcellulose Formulations

FÁTIMA SOPEÑA, ALEGRÍA CABRERA, CELIA MAQUEDA, AND ESMERALDA MORILLO

Instituto de Recursos Naturales y Agrobiología de Sevilla (CSIC), Apdo. 1052, 41080 Sevilla, Spain

The herbicide norflurazon was encapsulated in ethylcellulose (EC_{40}) microspheres by the solvent evaporation technique to obtain controlled release formulations. The kinetics of release of the active ingredient into the aqueous solution from different preparations was determined. It was found that the percentage release of the incorporated herbicide was a function of the composition and formation conditions of the formulations (amount of emulsifying agent, EC_{40}/herbicide ratio, stirring speed, and percentage of pore-forming agent). The percentage of the herbicide release was related to the properties of the different microspheres obtained, such as particle size distribution, herbicide loading, or surface morphology. The release percentage depended inversely on the particle size of the microspheres and directly on the content of active ingredient and emulsifying and pore-forming agents. An empirical equation was used to fit the herbicide release data, indicating that the release of norflurazon from the various formulations is controlled by a diffusion mechanism. The time taken for 50% of the active ingredient to be released into water (T_{50}) was calculated, showing a wide variation among the different preparations (0.95−16.4 days).

KEYWORDS: Controlled release; norflurazon; ethylcellulose; microspheres; herbicides; release percentage

INTRODUCTION

Controlled release formulations (CRFs) of pesticides have gained importance in the last three decades in the search for safer, more efficient and selective means of dispensing pest control agents, as they can substantially reduce undesired environmental side effects (*1*, *2*). They have important advantages over conventional formulations: extension of duration of activity at an equal level of active ingredient, reduction of phytotoxicity, evaporative losses or leaching through the soil, protection against environmental degradation, etc. It implies a reduction in the contamination of the environment because less active material is needed for maintaining effective biological activity.

Norflurazon [4-chloro-5-methylamino-2 (α,α,α-trifluoro-*m*-tolyl) pyridazin-3 (2*H*)-one] is a fluorinated pyridazinone herbicide that inhibits photosynthesis and is registered for soil-applied use in cotton, soybean, tree fruits and nut crops, citrus, and cranberries (3). Norflurazon, with a molecular weight of 303.67, has a water solubility of 28 mg L^{-1} and a vapor pressure of 2.0×10^{-8} mmHg at 20 °C. Its retention in soil is related to organic matter content; however, norflurazon has been detected in groundwater monitoring studies (*4*). Reddy et al. (*5*) and Morillo et al. (*6*, *7*) observed a large degree of norflurazon desorption in porous soils with low organic matter contents, suggesting an increase in subsequent leaching through the soil profile. Appreciable leaching was observed by Singh et al. (*8*, *9*) in soil columns of a sandy soil. Norflurazon on the soil surface has a half-life of about 41 days with photodegradation contributing significantly to field dissipation. Volatilization is also significant on the surface of the soil. To retard norflurazon leaching in soil, Undabeytia et al. (*10*) and El-Nahhal et al. (*11*) prepared CRFs of norflurazon based on organoclays, which may prevent this herbicide from reaching deep soil layers and injuring perennial crops grown on sandy soils under sprinklers and deep irrigation. Its photodegradation was also reduced by using CRFs (*11*, *12*).

Ethylcellulose is a hydrophobic polymer widely used in the pharmaceutical industry to prepare CRFs of drugs (*13*). Ethylcellulose has also been used to prepare formulations of the herbicides atrazine, metribuzin (*14*), and cianazine (*15*), which have a high herbicidal efficacy due to their controlled release properties. Other cellulose derivatives have also been used to prepare CRFs of pesticides (*16*−*18*). However, little information has been given about the influence of the conditions used in the release of the pesticides from the different formulations obtained.

Interactions between dissolution media, polymer, and herbicide are the primary factors in release control. However, other variables also influence herbicide release percentage to a greater or lesser extent (*19*). The effect of some preparation conditions, such as pesticide/polymer ratio, the percentage of emulsifying

* To whom correspondence should be addressed. Fax: 34-954624002. E-mail: morillo@irnase.csic.es.

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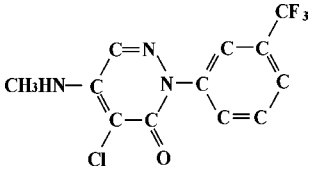

Figure 1. Structural formula of noflurazon.

agent, and the solvent on microencapsulation of this herbicide with ethylcellulose was presented in a previous paper (*20*). The aim of the present work is to examine the influence of those conditions and other variables (influence of stirring speed, particle size distribution, or the addition of plasticizers and pore-forming agents) on the controlled release of norflurazon into water, to know the best conditions for preparing CRFs of this herbicide.

MATERIALS AND METHODS

Materials. Technical grade norflurazon (97.8% purity) was kindly supplied by Syngenta Agro S. A. (Barcelona, Spain). Its structural formula is shown in **Figure 1**. Ethylcellulose (EC_{40}) (30−50 mPa, Ethocel 40) was purchased from Fluka (Buchs, Switzerland). Poly(vinyl alcohol) (PVA) with a molecular weight of 30000−70000 was obtained from Sigma (St. Louis, MO). High-performance liquid chromatography (HPLC) acetronitrile, methanol, and chloroform were purchased from Merck (Darmstadt, Germany).

Methods. *Microsphere Preparation.* Microspheres were prepared by the oil-in-water emulsion solvent evaporation technique. The principal norflurazon property that enables use of this encapsulation method is the low aqueous solubility of norflurazon related to its high solubility in the organic phase used. Ethyl cellulose (1 g) was dissolved in 15 mL of chloroform. Different amounts of norflurazon (0.1, 0.2, and 0.3 g) were dissolved in this polymer solution at room temperature. The herbicide−polymer solution was then emulsified into the aqueous phase, by adding it dropwise to 150 mL of aqueous solution containing 60 (0.040%), 112.5 (0.075%), or 225 (0.15%) mg of PVA and dispersed under continuous stirring at 300, 600, or 900 rpm. The ratio of organic to aqueous phase was the same in all of the experiments (1/10). One or two drops of octanol were added to the stirred emulsion to reduce foaming. Poly(ethylene glycol) 4000 (PEG) was used as a channel forming agent in three of the formulations, adding 100 (10%), 200 (20%), or 400 (40%) mg of PEG to the organic polymeric solution prior to the formation of the emulsion with the aqueous phase. After 24 h of stirring to allow the total evaporation of the inner organic phase, the microspheres obtained were filtered (PB microfiber glass filters, with retention above 1.2 μm) and washed with 250 mL of distilled water to remove any undesired residuals. The product was air-dried at room temperature for 24 h and then in an oven at 40 °C to constant weight. Three replicate batches of each formulation were prepared in order to confirm the reproducibility of the results.

The solvent evaporation technique has been previously used to prepare microencapsulated pesticides yielding positive and interesting results. Tefft and Friend (*21*) used this technique to obtain dicamba microspheres with an effective release control by combination of two polymers. As mentioned above, other authors have found that microcapsules of alachlor, atrazine, metribuzin, metholaclor, and cyanazine, obtained by the solvent evaporation method, consistently exhibited controlled release properties, volatilization reduction, and herbicidal activity over time equal to, or greater than, the commercial formulation (*14*, *15*, *22*, *23*).

Microsphere Characterization. To determine the efficiency of the microencapsulation process, the microspheres were characterized using three parameters: herbicide loading (HL), solids recovery (SR), and encapsulation efficiency (EE).

The HL is the amount of herbicide encapsulated by the microspheres, determined as follows:

$$\mathrm{HL} = \left(\frac{\text{herbicide encapsulated}}{\text{final weight of microspheres}}\right) \times 100$$

This parameter was obtained by dissolving the microspheres (25 mg) in methanol (100 mL). Norflurazon analysis was performed by HPLC. The presence of the polymer did not interfere in the analytical determinations. HPLC conditions for norflurazon analysis were as follows: mobile phase, acetonitrile:water (50:50); flow, 0.6 mL/min; chromatographic column kromasil 100 C18-5 μm reverse phase, 15 × 0.40 i.d. (Teknokroma, Spain); diode array detector (Shimadzu SPD-M10AVP), at a wavelength of 415 nm. HL determination was carried out in triplicate for each experiment.

The SR was defined as the percentage of weight of microspheres obtained with respect to the total weight of ethyl cellulose + herbicide employed as follows:

$$\mathrm{SR} = \left[\frac{\text{weight of microspheres}}{\text{weight of (herbicide + polymer) employed}}\right] \times 100$$

The EE was defined as the percentage of the herbicide encapsulated by the microspheres with respect to the herbicide used and was calculated from the expression:

$$\mathrm{EE} = \left(\frac{\text{herbicide encapsulated}}{\text{herbicide used}}\right) \times 100$$

The particle size and surface morphology of the microspheres were measured by scanning electron microscopy (SEM) in a Philips apparatus (model XL30). The dried microspheres were coated with a thin layer of gold to make the surfaces conductive. During the SEM examination, an electron beam (2.6-5 keV), incident on the sample, caused the emission of X-rays (secondary fluorescence), which are characteristic of the elements present in the particle and allow a qualitative analysis of its chemical composition. The electron beam was very precise, so analysis could be performed on well-defined areas of the sample.

The size distribution of microspheres was determined by sieving them into several categories: >1 mm, 1 mm to 800 μm and 800 to 500, 500 to 400, 400 to 200, 200 to 100, and <100 μm, by the use of ISO standard sieves.

Release Studies. To compare the release behavior of the different microspheres obtained, dissolution tests of commercial norflurazon and of all the microspheres prepared were performed in triplicate with a rotating paddle apparatus (Sotax). The operating conditions were as follows: A quantity of microspheres containing 5 mg of norflurazon was added to 1000 mL of deionized water as dissolution medium at 25 °C and with stirring at 50 rpm. At appropriate time intervals (0.5, 1, 2, 3, 5, 22, 24, 27, 30, 45, 48, 54, 72, 75, 78, 94, 96, and 100 h), 1 mL samples were taken and replaced by distilled water, to maintain a constant volume. Samples were analyzed by HPLC. The dissolution profiles of commercial norflurazon and microsphere formulations were compared graphically. The release kinetics of norflurazon from microspheres obtained in the different experiments was evaluated, fitting the data to the generalized model of Korsmeyer et al. (*24*), which is the most generic equation used to describe Fickian diffusion release mechanisms (the dynamic dispersion of a concentrated material in a larger medium in which a concentration gradient is the primary driving force):

$$M_t/M_z = k\,t^n + c \qquad (1)$$

where M_t is the amount of herbicide released from the controlled release device at any time t, M_z is the total amount of herbicide encapsulated, k is a constant that incorporates characteristics of the macromolecular network system and the active ingredient, c is another constant, and n is the diffussional exponent that indicates the mechanism of release. Fickian diffusion is defined by n close to 0.5 and non-Fickian by n greater than 0.5 (*25*). From these constants, the time needed for 50% release of norflurazon (T_{50}) was calculated.

RESULTS AND DISCUSSION

Table 1 shows the conditions used to prepare EC_{40} norflurazon microspheres and different parameters of the formulations obtained: HL, EE, SR, and the amount of norflurazon

Table 1. Different Conditions Used in Microspheres Formulations and Mean Values ± SD[a] of HL, EE, SR, and Amount of Norflurazon Released (R) for Each One

sample	EC_{40}/N ratio	PVA (%)	PEG (%)	stirring speed (rpm)	HL (%)	EE (%)	SR (%)	R[b] (%)
N17	3.33	0.075		600	22.3 ± 0.54	63.4 ± 1.55	65.6 ± 1.60	58.7 ± 3.11
N4	5	0.075		300	16.4 ± 0.02	70.1 ± 0.10	71.3 ± 0.10	41.3 ± 0.75
N2	5	0.075		600	15.9 ± 0.59	78.0 ± 2.91	81.6 ± 3.04	49.0 ± 2.62
N3	5	0.075		900	15.9 ± 0.05	69.4 ± 1.49	72.9 ± 1.57	81.6 ± 1.26
N18	10	0.040		600	7.92 ± 0.54	65.1 ± 4.45	74.6 ± 4.79	24.3 ± 1.52
N1	10	0.075		600	8.37 ± 0.57	65.6 ± 4.48	71.2 ± 3.05	30.0 ± 1.79
N6	10	0.150		600	7.69 ± 0.16	42.8 ± 0.89	50.6 ± 1.06	76.4 ± 3.64
N23	10	0.075	10	600	6.55 ± 0.30	68.1 ± 2.76	94.5 ± 3.83	31.1 ± 1.67
N5	10	0.075	20	600	5.60 ± 0.35	53.5 ± 2.46	85.1 ± 3.74	37.8 ± 2.17
N16	10	0.075	40	600	6.55 ± 0.45	62.7 ± 1.99	86.8 ± 2.76	56.0 ± 1.99

[a] SD, standard deviation of three replicates. [b] After 100 h of liberation.

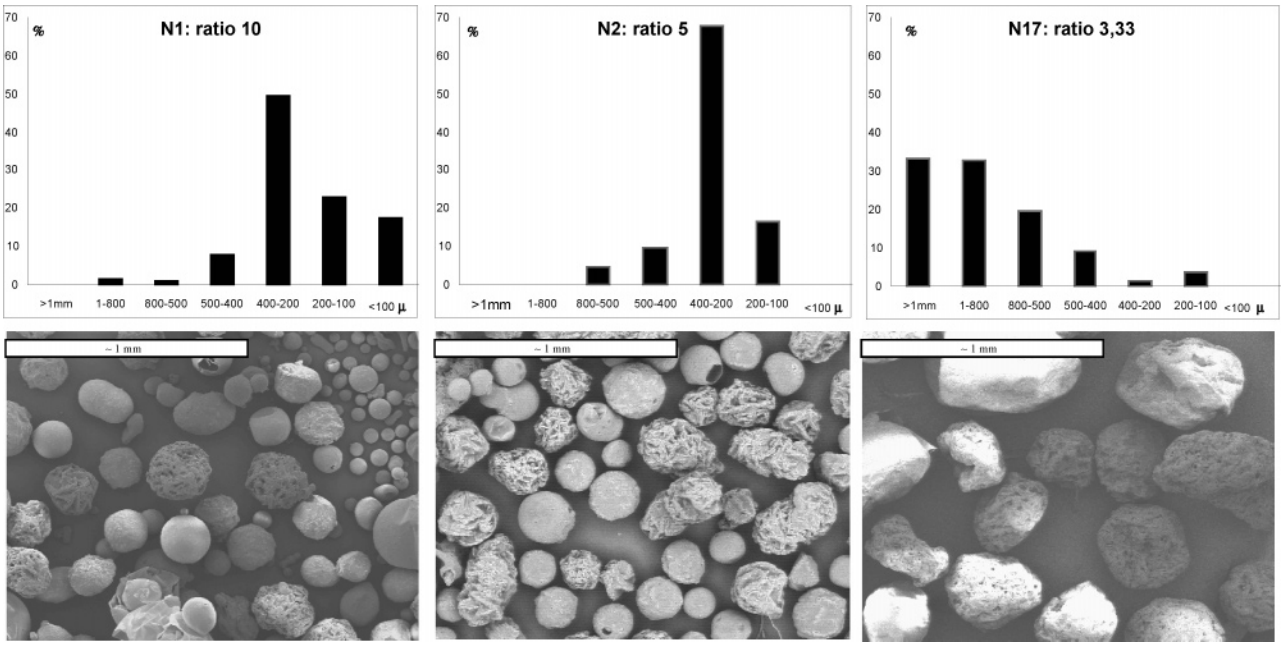

Figure 2. Particle size distribution (% vs size μm) and SEM observation (×50) of microspheres N1, N2, and N17 prepared with different EC_{40}/norflurazon ratios.

released (R). Taking into account that for EC/herbicide ratios 10, 5, and 3.33, the theoretical values of HL (in case all of the herbicide used was encapsulated) are 9.1, 16.7, and 23.1%, respectively, and the HL values experimentally obtained are very close to the theoretical ones in the cases of EC/herbicide ratios 5 and 3.33 but not for the formulations with ratio = 10 prepared using PEG (N23, N5, and N16). The reason for this behavior will be discussed later.

EE values obtained from the different preparations of microspheres (**Table 1**) indicate that in all cases the herbicide content in the microspheres is lower than the theoretical content, suggesting that the remainder of the herbicide is dissolved in the aqueous solution. Although the range of values obtained for this parameter is wide (42.8−78.0%), the majority of values are around 70%.

SR values obtained indicate also that in all cases not all of the polymer forms microspheres, since the total percentage of solids unrecovered is higher than the percentage corresponding to the herbicide lost.

The influence of EC_{40}/herbicide ratio on the parameters EE and SR can be observed when formulations N17, N2, and N1 are compared (**Table 1**). The results indicate that an increase in EC_{40}/herbicide ratio from 3.33 to 5 gave as a result higher EE, but a further increase of the ratio to 10 caused the herbicide EE to decrease once again. This last result was unexpected, since the higher the EC/norflurazon ratio, the higher the probability of the herbicide being surrounded by the polymer. A possible explanation of this fact could be that the amount of herbicide used in this case was the lowest (0.1 g), and then, a greater percentage of this herbicide, in relation to that initially used, can remain dissolved in the aqueous solution when the organic phase is evaporated.

The best chance of SR also corresponded to the formulation N2 (ratio = 5). In addition, the different EC_{40}/herbicide ratio used gave as a result a different particle size distribution and surface morphology for the microspheres obtained (**Figure 2**). Microsphere size distribution shifted to a smaller size spectrum as the EC_{40}/norflurazon ratio increased. This behavior has also been observed by other authors using ethylcellulose microspheres (*26*, *27*). The reduction of the microsphere size may be due to a decrease in the viscosity of the internal phase as a result of a decrease in the concentration of solids in the polymer solution.

The study of the surface morphology of the microspheres obtained when the EC_{40}/norflurazon ratio was 10 (**Figure 2**) revealed that there were particles with plain surfaces near to

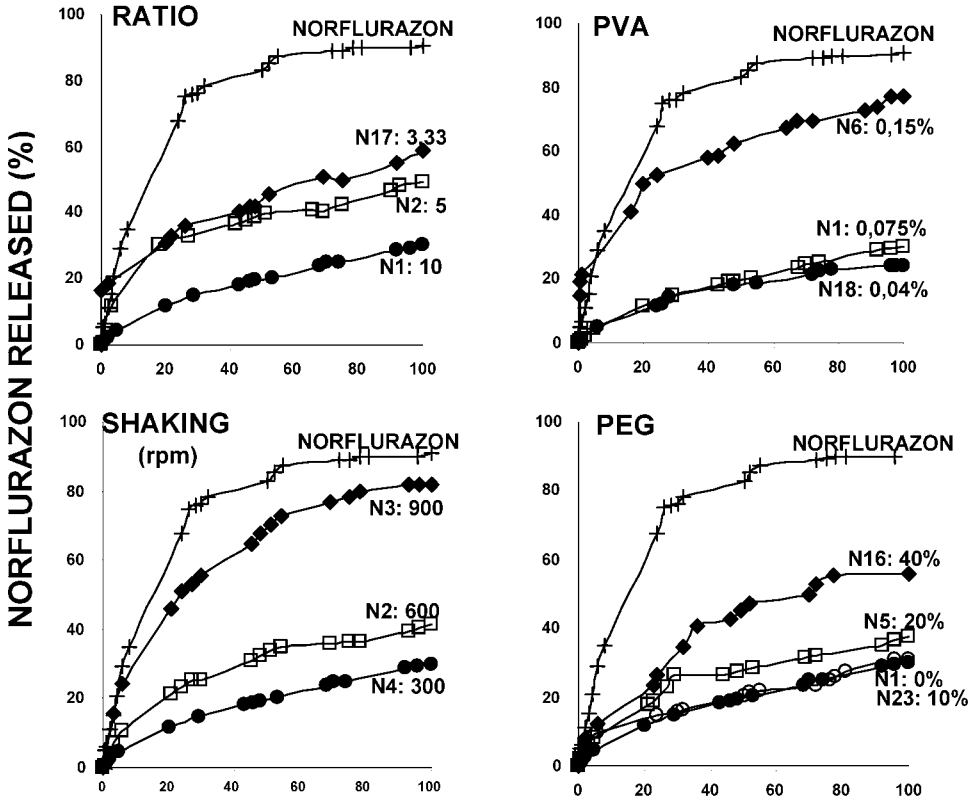

Figure 3. Amount of norflurazon released into water from the different formulations obtained. Influence of EC_{40}/norflurazon ratio, PVA (%), PEG (%), and shaking speed used.

others with highly irregular and rough surfaces, although all showed more or less spherical shapes. At lower ratios, the rough particles were more abundant and presented highly irregular shapes.

The influence of microencapsulation variables on the release percentage of norflurazon into aqueous solution is shown in **Figure 3**. In all cases, the release of norflurazon from microspheres was retarded when compared with that of the commercial herbicide, because the herbicide entrapped in the polymer has to diffuse out of the microspheres into the sink solution. The release of norflurazon from all formulations was nonlinear, characterized by an initial fast release in the first few hours. This initial fast release might be due to release from the surface of the particles (*28*). However, it is desirable that a high concentration of herbicide is to be released during the first few days, in which most of the weeds are in the germination process, followed by a constant release of lower concentrations over a longer period of time. The cumulative percentage of herbicide released after 100 h (R) was selected to compare the effect of the different formulations on the release kinetics (**Table 1**).

The dissolution profiles obtained from the different formulations fitted first-order kinetics, and **Table 2** shows the constants *K*, *c*, and *n* obtained, according to eq 1.

The values of *n* between 0.41 and 0.61 indicate that the release is mainly diffusion controlled (*29*, *30*). The majority of our formulations present *n* values within this range, but in some cases, lower values are obtained, indicating that in such cases other mechanisms are operating. The differences in size among particles of the same formulations could be a possible cause for obtaining *n* values outside the range, especially in the cases of formulations N6 and N17, in which more than 30% of the particles presented a size >1 mm. T_{50} values obtained for the different microspheres were calculated from the constants in **Table 2**. T_{50} for norflurazon was 0.61 days, but for all of the formulations obtained with EC_{40}, T_{50} was higher, varying in a wide range of values (0.95−16.4 days) depending on the formulation.

Table 2. Parameters of First-Order Kinetic Equations Corresponding to the Release Data in Water of Norflurazon from Microspheres and T_{50} Values (Days) ± SD[a]

sample	*K*	*n*	*c*	R^2	T_{50}
norflurazon	0.0883	0.657	–0.0143	0.9984	0.61 ± 0.05
N6	0.2000	0.289	0.0058	0.9976	0.95 ± 0.30
N3	0.1100	0.475	–0.0084	0.9986	1.04 ± 0.20
N16	0.0505	0.557	–0.0089	0.9935	2.63 ± 0.12
N17	0.1308	0.290	0.0318	0.9876	3.34 ± 0.52
N2	0.0810	0.388	0.0023	0.9901	4.47 ± 0.91
N4	0.0668	0.404	–0.0117	0.9938	6.41 ± 0.21
N5	0.0582	0.412	–0.0154	0.9917	8.29 ± 0.57
N1	0.0208	0.585	–0.0072	0.9996	9.74 ± 0.59
N23	0.0240	0.536	0.0146	0.9916	11.40 ± 0.93
N18	0.0275	0.488	–0.0107	0.9997	16.43 ± 1.04

[a] R^2, coefficients of determination; SD, standard deviation of three replicates.

Figure 3 and the values of *R* in **Table 1** show that the pesticide release increased with increasing pesticide loading, that is, when decreasing EC/N ratio, as can be observed by comparing the formulations N17, N2, and N1 (the only different parameter among them is EC/N ratio). This behavior has also been observed in other CRFs (*26*, *31*) and has previously been attributed to the lengthening of the diffusional pathway through the polymer as the EC/herbicide ratio increases. This latter increase is due to the tendency of the tortuosity to increase with decreasing solute load, which is very strong in the case of hydrophobic polymer matrices, such as ethylcellulose (*31*). However, not all of the formulations with similar herbicide contents show the same effect, as can be observed when the release percentage of formulations N2, N3, and N4 are compared

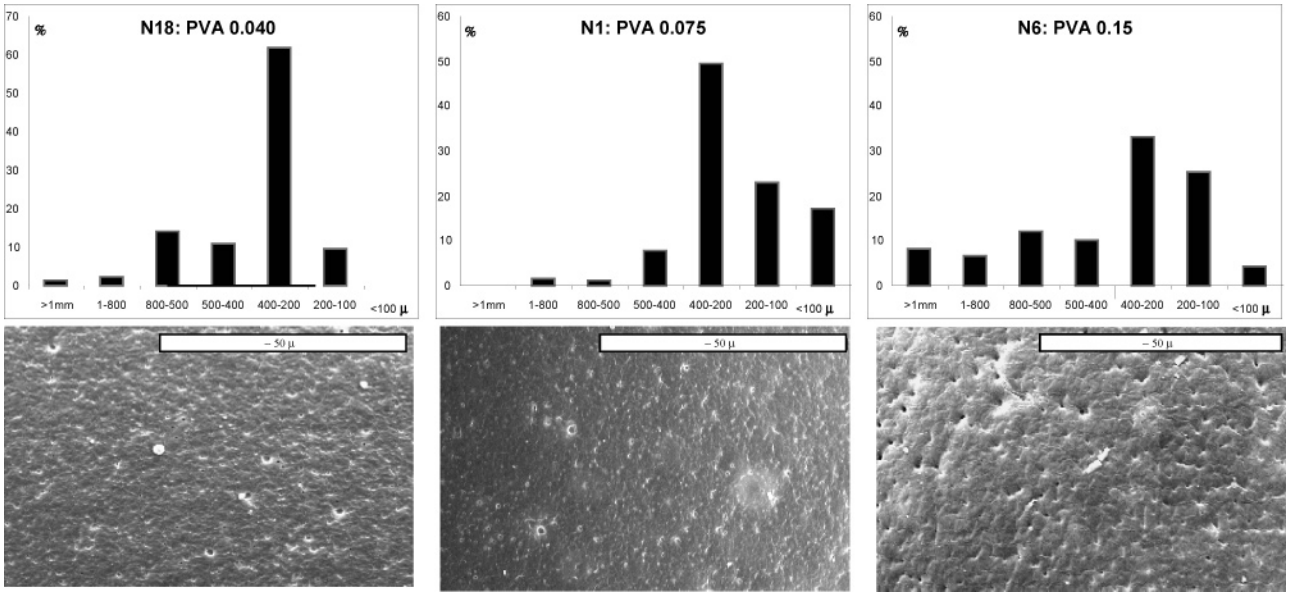

Figure 4. Particle size distribution (% vs size μm) and SEM observation (×1000) of microspheres N18, N1, and N6 prepared with different percentages of PVA.

(different stirring speed), or formulations N18, N1, and N6 (different % PVA used), or formulations N23, N16, and N5 (different % PEG used). It can be concluded that all of these parameters play an important role during the microencapsulation process and, therefore, on the release percentage from the microspheres.

PVA was used as an emulsifying agent in order to facilitate the formation of a stable emulsion during the microencapsulation process. The role of the emulsifying agent is both to facilitate the emulsification process and to prevent agglomeration of the microspheres. The amount of herbicide in the microsphere depends on its solubility in the processing medium, i.e., unless the herbicide is relatively insoluble in the processing medium, a proportion of the herbicide will be lost from the microspheres during preparation. The type and concentration of emulsifying agent used during microencapsulation can alter the solubility of the herbicide in the continuous phase and thereby influence drug loading of the microspheres (*32*). The effect of PVA use during microsphere formation can be observed by comparing the formulations N18, N1, and N6, where 0.040, 0.075, and 0.150% concentrations of PVA were used, respectively (**Table 1**). The HL ability of the microsphere formations was unaffected, but the EE and the SR were (**Table 1**) diminished drastically where the highest concentration of PVA was used, due to the higher solubilization of the herbicide into the aqueous phase, thereby increasing the loss of norflurazon from the microspheres. This behavior was also observed by Soppimath et al. (*33*) using the same microencapsulation method with cellulose acetate microspheres. An increase in PVA from 0.040 to 0.075% yielded a slightly larger proportion of small particles (**Figure 4**), although the majority was between 200 and 400 μm for both concentrations. The increase of PVA to 0.15% showed a more heterogeneous particle size distribution.

It is apparent from this work that the amount of PVA used affects not only the size distribution but also the surface of the microspheres. The study by SEM of the microspheres N18, N1, and N6 (**Figure 4**) shows rougher and more porous surfaces in microspheres N6 [obtained using the highest percentage of PVA (0.150%)], in comparison to microspheres prepared with 0.040 and 0.075%. This accounts for the higher release percentage of the herbicide from this formulation (**Figure 3**), whereas formulations N18 and N1 presented very similar surfaces (**Figure 4**) and release behaviors.

The stirring speed used during the encapsulation process also influenced some properties of the formulations obtained. While parameters such as HL, SR, and EE were not particularly affected, the particle size distribution and the surface morphology of the microspheres were dramatically changed. **Figure 5** shows higher irregularities in the shape and a much rougher surface of the microspheres obtained using 300 and 900 rpm, with an increase in particle size in the former and a decrease in the latter case.

All of these different physical properties gave as a result an increased herbicide release with increasing stirring speed (**Figure 3**), since, the smaller the particle size, the more rapid the release as a consequence of the greater effective surface area of the smaller particles.

The macromolecular polymer PEG was used as a pore-forming agent. This polymer can increase the water permeability of the ethylcellulose matrix of the microspheres due to its hydrophilic properties. Water can easily dissolve the PEG present into the microspheres, which is leached, creating pores on the microspheres. Through the forming pores, aqueous medium can occupy regions into the polymeric matrix to allow herbicide release. As previously mentioned for the formulations prepared using PEG (N23, N5, and N16), the theoretical value of HL was 9.1% (**Table 1**), but the HL values experimentally obtained were much lower (6.55, 5.54, and 6.55%, respectively), indicating that a large fraction of the herbicide used was not in the microspheres obtained but in the solution. This is the reason the EE values were also very low. On the contrary, the values corresponding to SR are relatively high (higher the lower the percentage of PEG used), especially when the lower percentage of PEG was used. It seems to indicate that PEG is not completely leached from microspheres when it comes into contact with the aqueous medium and, therefore, is not recovered in the solution, remaining trapped in the microspheres. As a result, the total weight of microspheres obtained is greater. However, the calculation of SR values does not include the amount of PEG added in the process; therefore, SR values are higher. The possible explanation to this behavior can be deduced from **Figure 6**. When using 40% PEG (N16), the surface of

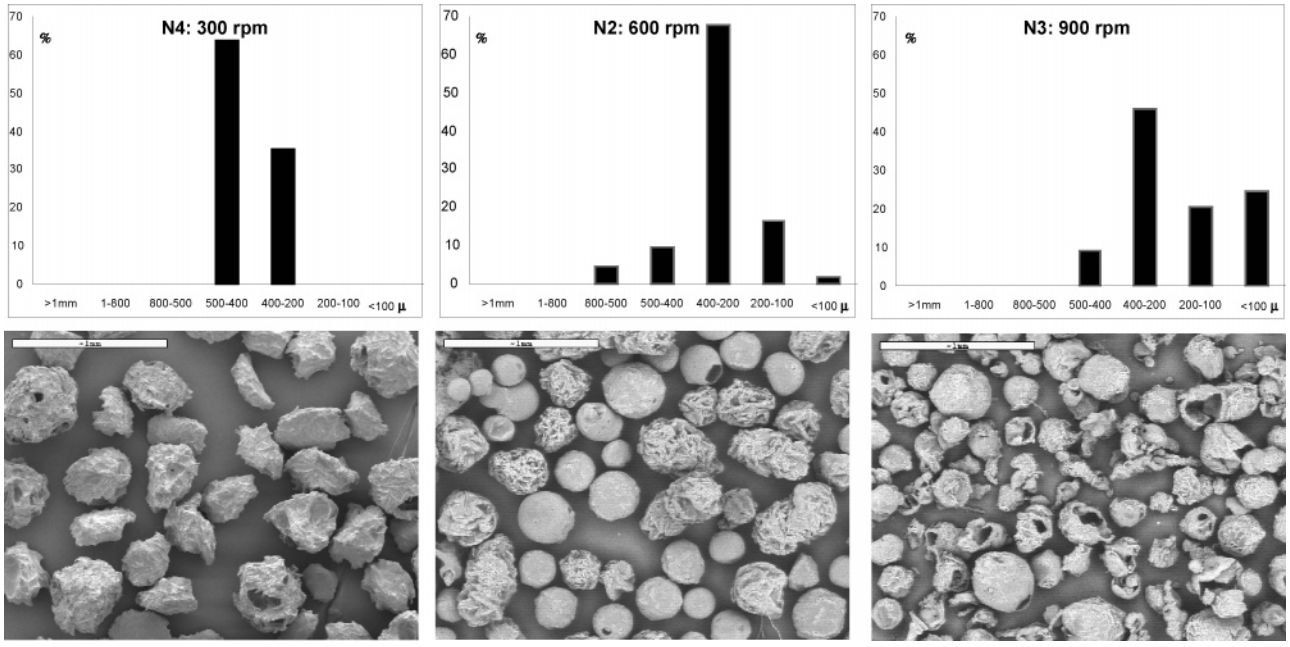

Figure 5. Particle size distribution (% vs size μm) and SEM observation (×50) of microspheres N4, N2, and N3 prepared with different stirring speeds.

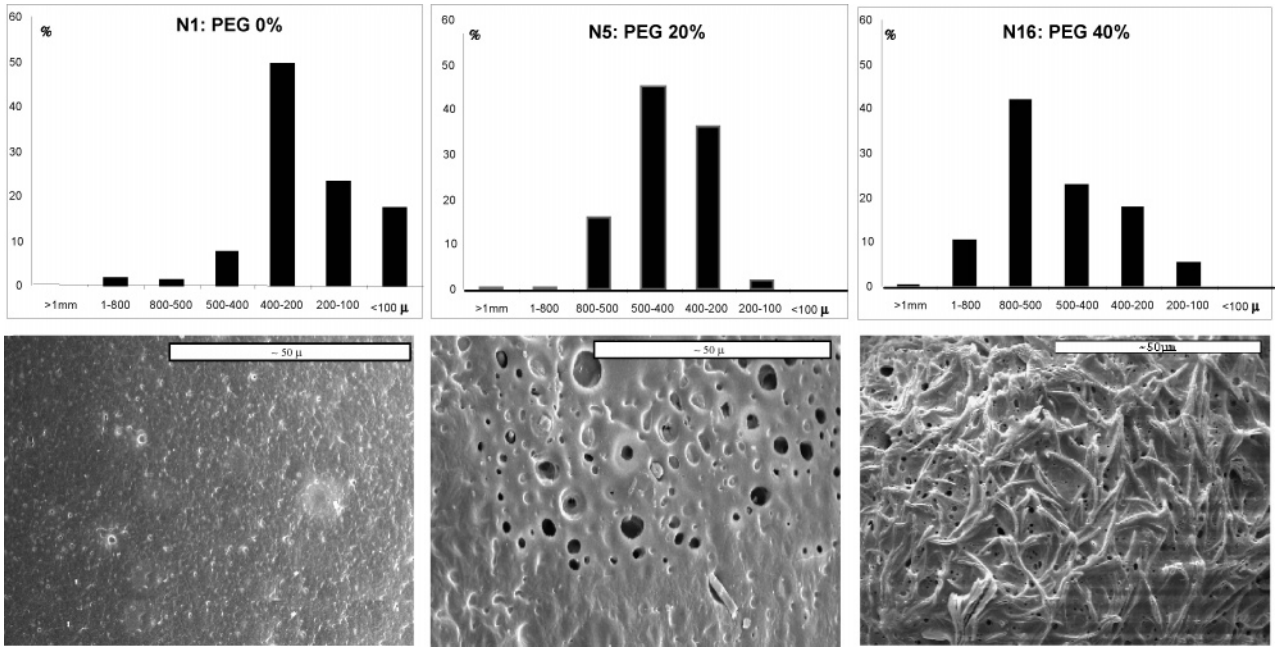

Figure 6. Particle size distribution (% vs size μm) and SEM observation (×1000) of microspheres N1, N5, and N16 prepared with different percentages of PEG.

the microspheres produced was rough with many small pores homogeneously distributed on it, indicating that the leaching of PEG would easily have occurred from the microsphere to the aqueous phase during preparation. By decreasing the amount of PEG used to 20%, microspheres obtained were smoother and many pores were formed but not homogeneously on all of the surfaces of the microspheres. When 10% PEG was used (N5, figure not shown), the microspheres presented a smooth surface with very few small pores, similar to those obtained in microspheres without PEG (N1, **Figure 6**). Probably the amount of PEG used was so low that it was not able to leach to the solution and form pores, remaining largely within the microspheres. This is the reason that the release of norflurazon into water from microspheres N23 and N1 was the same (**Figure 3**), being greater as higher amounts of PEG were used, due to their higher porosity. The effect of such high porosity accounts for the release of the herbicide in the following order: N16 > N5 > N23 = N1. On the other hand, it is interesting to take into account that the particle size of the microspheres prepared with PEG follows a similar order: N16 > N5 > N23 > N1. According to our previous results shown in this paper, the release of norflurazon should be higher the lower the particle size. However, the contrary occurs when PEG is used, indicating that the release of the herbicide from the microspheres is mainly influenced by the quantity and size of the pores rather than by the particle size of the microspheres.

Given that lower HL values were obtained in the microspheres prepared using PEG, the only case in which a lower HL value

could be the reason for a higher T_{50} value is the corresponding formulation N23 (10% PEG) in comparison to N1 (0% PEG). In the cases of 20 and 40%, lower T_{50} values were obtained, indicating that their higher porosity was dominating the herbicide release.

The experimental results demonstrate that Ethocel 40 can be used successfully to prepare norflurazon controlled release microspheres, which show large EE for the herbicide. In the design of these controlled release devices, a very wide range of release rates can be achieved by adjusting different parameters. The increase of shaking speed used to prepare the microspheres gave, as a result, higher release percentages due to the decrease in particle size. However, the increase in particle size obtained when lower EC_{40}/norflurazon ratios were used did not yield lower release rates, because in such cases, higher HL was obtained. Increasing the concentration of PVA (used as emulsifying agent) or PEG (used as pore-forming agent) causes an increase in release percentages, due to the rougher and more porous surfaces of the microspheres obtained.

According to the results obtained, the most suitable formulation for its application in field experiments could be formulation N2, which presents the highest EE, a HL of approximately 16%, a T_{50} value of 4.47 (more than 7-fold higher than the commercial), and almost 70% of the microspheres in the range 200−400 μm.

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