Preparation and Optimization of 2,4-D Loaded Cellulose Derivatives Microspheres by Solvent Evaporation Technique

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ABSTRACT: Controlled release herbicide formulations were prepared by microencapsulation using solvent evaporation technique. 2,4-D was chosen as core material, which was microencapsulated in two cellulose derivatives as matrices: cellulose acetate butyrate butyryl (CAB) and ethylcellulose (EC). The work is intended to produce systems containing the herbicide to reduce its risks by dermal contact, evaporation, or degradation and to control the release of the active agent. The microspheres loaded by 2,4-D were characterized by scanning electron microscopy and infrared spectroscopy. We have obtained microparticles in the range of D_{32} of 42–277 μm with CAB and 88–744 μm with EC by varying the process parameters. The drug entrapment was improved by controlling certain factors such as polymer/solvent ratio, pH of continuous phase, and organic phase solvent. The drug release was established in deionized water at pH = 5.5 and 25°C and the 2,4-D concentrations were estimated by UV analysis. The release data were analyzed according to Fick's law and the results demonstrate that the release rate can be controlled by modifying the process parameters. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 103: 2742–2751, 2007

Key words: microencapsulation; drug delivery systems; cellulose derivative; diffusion

INTRODUCTION

In the last decade, it has been seen that the controlled release agricultural formulations offer great promise for enhancing efficacy of herbicides and reducing the environmental impact arising from their conventional applications.[1–3] The microencapsulation is one of the most used formulation techniques to elaborate controlled release pesticide systems. This process aims to protect the active agent from evaporation and degradation by photolytic or hydrolytic or microbial reactions. Furthermore, it maintains the herbicide concentration within optimum limits over a specified period.[4,5]

The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) is one of the most widely used herbicides for control of weed growth. However, it can be considered as an anionic organic pollutant, a potential pollutant of soils and ground water.[6] It was identified in multiple environmental media such as air, dust, and soil.[7,8] The 2,4-D and its degradation products are classified among the potential toxic compounds for humans. For example, an acute exposure to 2,4-D by dermal contact has resulted in nervous system damage. The ingestion of high doses of 2,4-D formulations has led to death and the low doses to neuromuscular problems.[9,10] In addition, it was reported that 80% of 2,4-D can be degraded by UV and the percentage of degradation can be increased either by increasing the light intensity or by irradiating for a long time.[11]

Therefore to reduce the disadvantageous part of this systemic herbicide and diminish its risks as a potential pollutant, some of the formulation processes were used. For example, controlled release formulations based on crosslinked acrylamide gel derivatives were prepared by acylation reaction of transaminated polyacrylamide derivatives with 2,4-dichlorophoxyacetylchloride.[12] It has been noticed that the polyacrylamide gels are good carriers for the active agent, and the length of the side-chain spacer group is an important factor in the release rate. Solid complexes of 2,4-D with β-cyclodextrin were also made by three methods: coprecipitation, kneading, and spray-drying. It was found that the dissolution rate of complexed 2,4-D in aqueous solutions was considerably increased.[13]

We have cited earlier the microencapsulation as a formulation process. In fact, 2,4-D loaded microspheres in the size range of D_{32} (mean diameter of Sauter) of 88–744 μm were prepared by microencapsulation by solvent evaporation technique in ethylcellulose (EC) as matrix.[14] Using this technique we have found that the release rate of the active agent

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from these systems can be controlled by modifying the process parameters. The microencapsulation process was used to formulate other core materials[15,16] and pesticides such as norfluazon[17] and dicamba,[18] and the influence of the process parameters on the encapsulation yield and the release rate was largely discussed.[19] The influence of the matrix was also studied by other authors.[2,18,19] For example, Dailay et al. have studied the encapsulation of Atrazine and Metribuzine in three matrices: EC, acetate butyrate butyryl, and poly(methyl metacrylate).[2]

The principal objective of the present work was to prepare controlled release formulations of 2,4-D using microencapsulation by solvent-evaporation technique and to study the influence of the matrix on microspheres' characteristics, encapsulation yield, and release rate. 2,4-D was microencapsulated in two cellulose derivatives polymers: EC and cellulose acetate butyrate butyryl (CAB); these are chosen for their safety and biodegradability. The influence on microencapsulation of changes of some parameters such as herbicide/polymer, polymer/solvent, emulsifier/water ratios and stirring speed, pH of continuous phase and organic phase solvent was studied. The release of 2,4-D from these matricial systems was performed in deionized water at 25°C and the influence of the process parameters on the release rate was also discussed. In EC, the encapsulation of 2,4-D was already investigated and some of the relations between parameters and drug entrapment, parameters and release rate were obtained.[14] In the present work we have to complete the study and to compare the EC encapsulation results to the CAB encapsulation results.

METHODS

Chemicals

2,4-Dichlophenoxyacetic acid (2,4-D), and cellulose acetate butyrate butyryl (CAB) content 35–39% from ACROS Organics, ethylcellulose (EC) ethoxylate at 48% (m/m) (viscosity, 0.100 Pa s at 5% (m/m) in 80/20 toluene/acetone solution) from Aldrich, poly (vinyl alcohol) (PVA; 88% hydrolyzed, Mw = 22 kDa), dichloromethane (DCM), and acetone 99% from ACROS Organics, and 99% absolute ethanol from SDS were used as received. An acidic solution at pH = 1.1 was prepared with hydrochloride acid (0.1*M*) for the continuous phase.

Preparation of microspheres

As reported in Ref. 14 the cellulose derivatives microspheres were prepared by solvent evaporation technique in a cylindrical glass reactor (600 mL, ø = 80 mm) with a six-blade turbine impeller (blade length = 50 mm, blade width = 10 mm, type IKA RW 20 DZM.n).

2,4-D was dispersed or dissolved in 32 g of DCM or mixture of DCM and acetone in the ratio of 90/10 (w/w); then the cellulose derivative was added and the organic solution was heated under light reflux (30–35°C) and stirred for the homogenization. At the same time, the continuous phase was prepared by dissolution of stabilizer PVA in 250 g of deionized water under heating and stirring. After cooling to room temperature, the organic phase was emulsified in continuous phase under mechanical stirring for 6 h for a complete solvent evaporation. Microspheres were recovered by filtration and vacuum dried in a desiccator in the presence of $CaCl_2$. The parameters that were modified were as follows: stirring speed of emulsion "*N*", polymer/solvent (% pol./sol., % w/w), drug/polymer (% 2,4-D/Pol., % w/w or % 2,4-D_i), stabilizer/water (% PVA, % w/w) ratios, aqueous phase pH (5.5 and 1.1), organic phase solvent (DCM or DCM/acetone, 90/10 % w/w).

Organic phase viscosity

To get more information about the internal phase, the viscosity has been measured at 25.4°C using a Brookfield DV-II + Pro programmable viscosimeter equipped with a SC4-18 type spindle. The given viscosities represent the averages of five measures taken each minute of a 5-min viscosity measurement program.

UV spectroscopy analysis

The drug loaded and released were estimated using UV–vis analysis by a JASCO-530 spectrophotometer at the maximum absorbency of 2,4-D: $\lambda_{max} = 229$ nm, where ε in deionized water at pH = 5.5 is equal to 10,255.8 L $mol^{-1} \cdot cm^{-1}$ and ε in ethanol is 10,971.0 L mol^{-1} cm^{-1}.

Characterization of microspheres

IR spectroscopy

The microspheres were characterized by infrared spectroscopy, and so the infrared spectra of pure 2,4-D and matrices (EC and CAB) and corresponding microspheres were compared. The FTIR spectra were recorded from 500 to 4000 cm^{-1} using an FTIR-8300 Shimadzu spectrophotometer. The samples in disk form were prepared with about 1% of solid compound mixed and grinded in dried KBr.

Scanning electron microscopy

The microspheres' surface was characterized by SEM using a Hitachi S3000 scanning electron microscope

at 70 Pa s and 5°C under 12 kV of accelerated tension. The microspheres were deposited on double scotched carbon film fixed on a metal support.

Size and size distribution

The mean diameter of microspheres and size distribution were determined by optical microscopy (Vickers Instruments), and not by the laser diffract meter technique, to avoid counting aggregate microparticles. More than 500 microparticles were observed and counted with appropriate lenses and the mean diameter and distribution were calculated.

Drug content

Extractions of drug from microspheres were performed in triplicate in an appropriate solvent; 50 mg of dried microspheres was soaked in 20 mL of absolute ethanol under stirring in a corked bottle for 4 h. The resulting solution was analyzed by UV spectroscopy after appropriate dilution with ethanol. The drug entrapment (% 2,4-D loaded) and the encapsulation yield (Yield) were calculated by the following equations:

$$\%2,4\text{-D}_{\text{loaded}} = \frac{\text{Weight of herbicide in microspheres}}{\text{Weight of loaded microspheres}} \times 100 \quad (1)$$

$$\text{Yield} = \frac{\text{Weight of herbicide in microspheres}}{\text{Initial weight of herbicide}} \times 100 \quad (2)$$

Dissolution studies

The release kinetics of 2,4-D from cellulose derivatives microspheres were followed in an appropriate dissolution reactor (Fig. 1) plunged in a bath regulated at 25°C. This reactor permits us to withdraw solution without microparticles. At the desired time, the cap 1 is removed and solution rises in the filter tube. Then 3 mL of solution is withdrawn, analyzed by UV spectroscopy without dilution, and replaced in the Erlenmeyer flask. At time $t = 0$, 100 mg of microspheres were soaked in the reactor containing 1000 g of deionized water (pH = 5.5) as release medium under a stirring rate of 250 rpm.

Release data analysis

The release of the herbicide from this system involves four steps:

1. Penetration of water into the microspheres
2. Dissolution of the herbicide

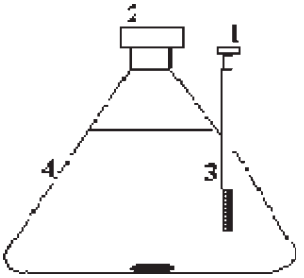

Figure 1 Dissolution reactor: 1,2 – caps, 3 – filter tube, 4 – Erlenmeyer flask.

3. Diffusion of the herbicide into the matrix
4. Transfer of the herbicide in solution.

The whole process is probably governed by the slowest stage, which is inevitably the diffusion of the herbicide throughout microspheres.

Consequently, the release of the active agent can be described by the basic equation for unsteady state diffusion, i.e. Fick's second law. If we suppose that microspheres of radius R are isotropic, the equation of diffusion of active agent into polymeric matrix is

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[Dr^2\ \frac{\partial C}{\partial r}\right] \quad 0 < r < R \quad (3)$$

where C is the concentration, D the diffusivity, and r the distance. The solution of eq. (3) depends on initial and boundary conditions. But the cumulative amount of the active agent M_t released in the earlier stages of the process is always given[20] by

$$\frac{M_t}{M_\infty} = 6\sqrt{\frac{Dt}{\pi R^2}} = Kt^{0,5} \quad (4)$$

where M_∞ is the total amount released at equilibrium. The result is analogous to Higuchi's law, which states that M_t is proportional to $t^{0,5}$ if we suppose that K is constant.

RESULTS AND DISCUSSION

Microspheres' characteristics

Evidences on the entrapment of 2,4-D in cellulose derivatives matrices were provided using IR spectroscopy; the FTIR spectrum of microspheres was compared with a pure 2,4-D and cellulose derivatives spectra. In the FTIR spectra of EC and CAB microspheres [Figs. 2(c) and 3(c)] respectively, we found the characteristic bands of 2,4-D at 1732 cm^{-1} corresponding to carboxylic group (C=O) and at 1584 cm^{-1} corresponding to C=C aromatic ring.

The SEM photomicrographs of 2,4-D loaded microspheres (Fig. 4) show spherical microparticles

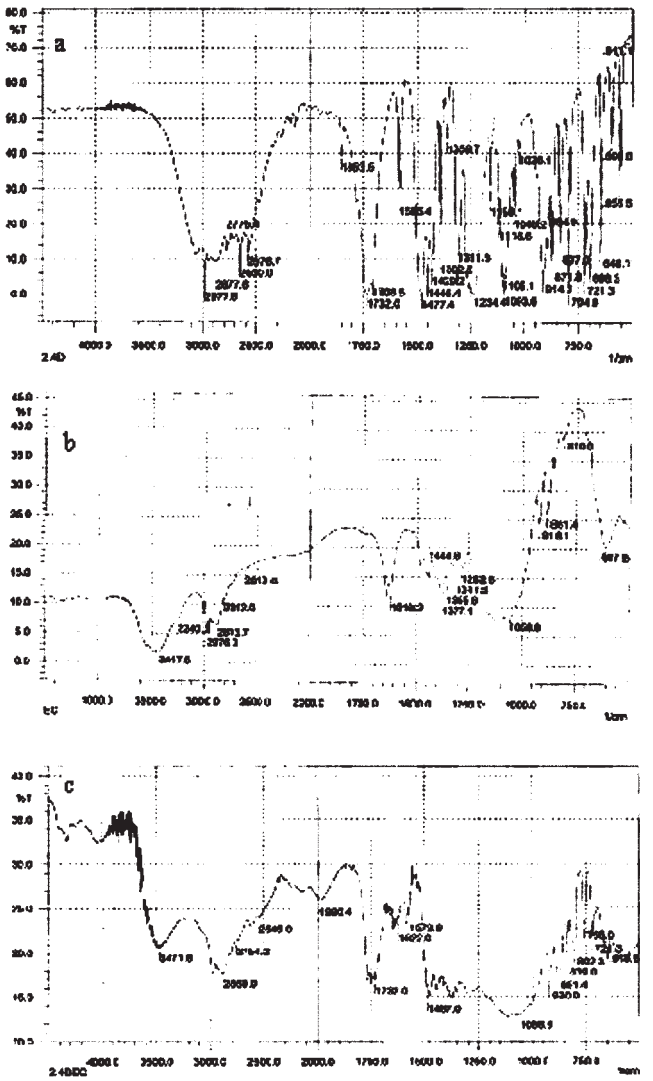

Figure 2 Infrared spectra of (a) pure 2,4-D, (b) ethylcellulose, (c) ethylcellulose microspheres.

with a rough and porous surface. During the phase-separation process, both the polymer and herbicide precipitate after the diffusion of solvent into the aqueous phase and its evaporation. We have remarked formation of visible 2,4-D crystals when we used 50.66% of initial drug/polymer ratio [Figs. 4(4a) and 4(4b)]. It could indicate that the herbicide precipitates before the polymer, as was demonstrated by Bodmeier and Chen.[21] An increase of % PVA led to a rougher and more irregular surface. However, the other parameters had no significant influence on the surface and shape of microspheres.

From the results of the size (Table I) we have noted that under the same conditions of microencapsulation, CAB microspheres are smaller than EC microspheres. Indeed we have obtained micropsheres with a mean diameter of Sauter (D_{32}) in the range of 88–744 μm with EC and in the range of 42–277 μm with CAB. On the basis of the viscosity values, at the same % pol./sol., % 2,4-D/Pol., and solvent, the viscosities of the CAB organic phase are lower than those of the EC. For example the viscosity of the EC organic phase is about three times higher than CAB's when we use 2.34% of pol./sol. and 25.33% of 2,4-D$_i$. So evidently the break-up of the EC phase is more difficult than that of CAB and this is the reason why we have obtained bigger microparticles with EC.

From Table I, the parameters that have considerably affected the microspheres' size are the polymer/solvent ratio and the stirring speed. As shown in Figure 5, at different stirring speeds, we have seen that the mean diameter D_{32} increased by a factor of 3.1 ± 0.3 by doubling the pol./sol. ratio for EC microspheres and by a factor of 2.2 ± 0.2 for CAB microspheres. On the other hand, by comparing the mean diameter of Sauter as a function of stirring speed N (rpm) (Fig. 6), we have obtained a relationship between $\ln(D_{32})$ and $\ln(N)$; straight lines have been drawn with a slope of −0.75 and −0.63 for EC microspheres and −0.63 and −0.68 for CAB microspheres at 4.68 % and 2.34 % of pol./sol. ratio, respectively. The results of the variation of the size with stirring speed for the two cellulose derivatives microspheres are in agreement with initial break up theory.[22,23] Similar to other authors,[24,25] we have obtained a deviation of the experimental slope from the theoretical one (−6/5).

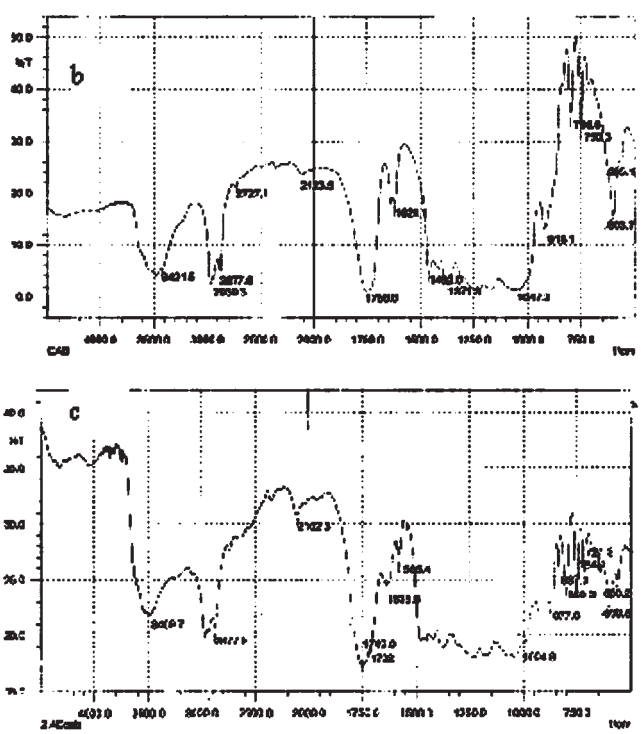

Figure 3 Infrared spectra of (b) CAB and (c) CAB microspheres.

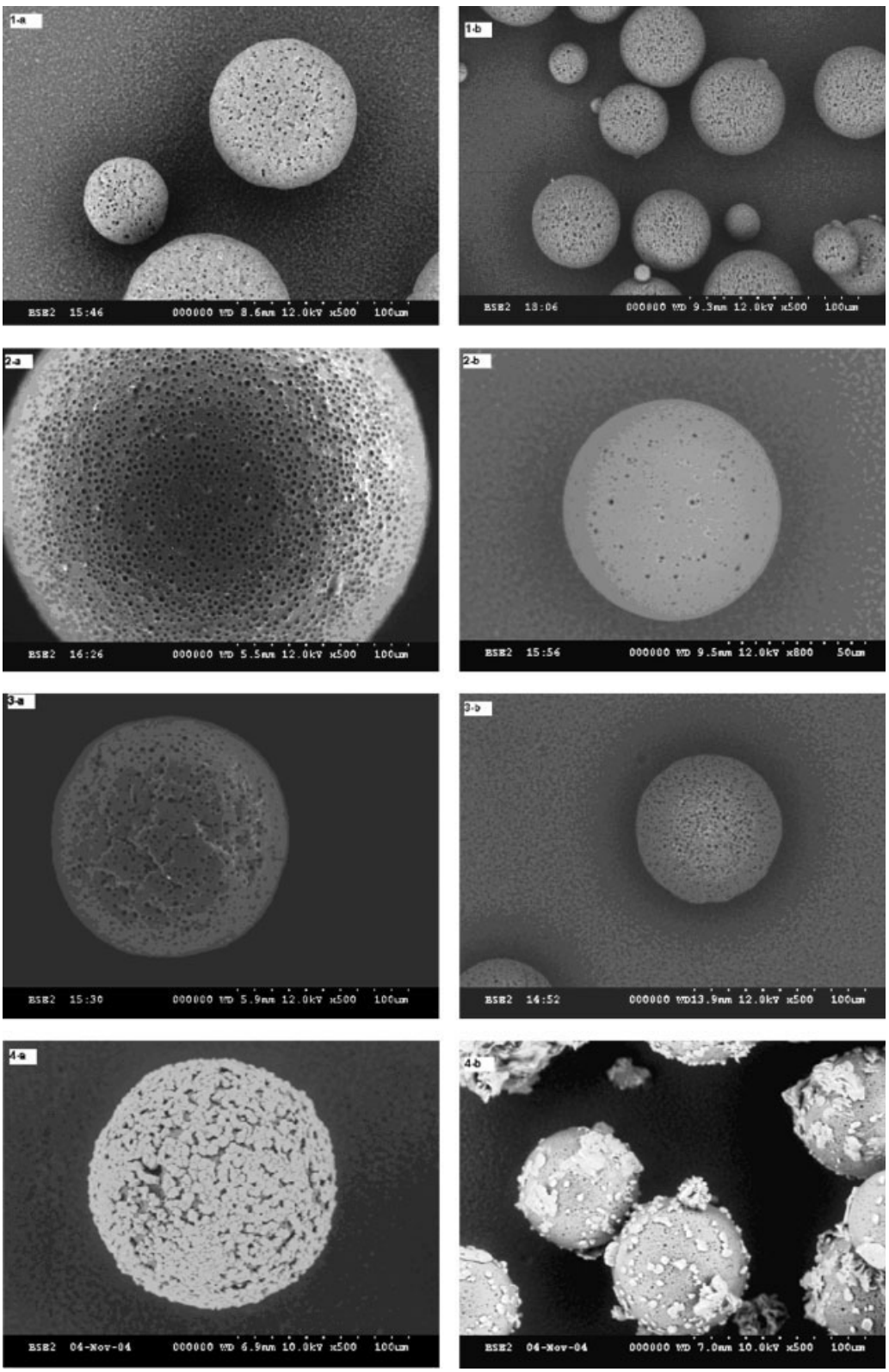

Figure 4 SEM photomicrographs of 2,4-D loaded microspheres. 1 – Conditions: 2.34% pol., 25.33% 2,4-D_i., 0.25% PVA, 800 rpm, pH = 5.5; 2 – Conditions: 4.68% pol., 25.33% 2,4-D_i, 0.25% PVA, 600 rpm, pH = 5.5; 3 – Conditions: 2.34% pol., 25.33% 2,4-D_i, 1% PVA, 300 rpm, pH = 5.5; 4 – Conditions: 2.34% pol., 50.66% 2,4-D_i, 0.25% PVA, 300 rpm, pH = 1.1. (a) EC microspheres; (b) CAB microspheres.

TABLE I
Experimental Results of the Effect of the Process Parameters on the Microspheres' Size, %2,4-D Loaded, and Encapsulation Yield

Process parameters						EC microspheres				CAB micrpspheres			
% 2,4-D_i/Pol.	% Pol./sol.	% PVA	Solvent	pH	Stirring (rpm)	η_{EC} (mPa s)	D_{32} (μm)	%2,4-D loaded	Yield	η_{CAB} (mPa s)	D_{32} (μm)	% 2,4-D loaded	Yield
25.33	2.34	1	DCM	5.5	300	21.70 ± 0.15	118.0	7.77 ± 0.92	31.80 ± 3.70	07.49 ± 0.60	80.1	7.40 ± 0.71	30.73 ± 2.78
25.33	2.34	0.25	DCM	5.5	200	21.70 ± 0.15	220.9	10.20 ± 0.04	42.47 ± 0.17	07.49 ± 0.60	134.7	09.48 ± 1.50	39.12 ± 6.17
25.33	2.34	0.25	DCM	5.5	300	21.70 ± 0.15	125.7	10.36 ± 0.70	43.50 ± 3.30	07.49 ± 0.60	73.9	09.83 ± 0.03	40.68 ± 0.20
25.33	2.34	0.25	DCM	5.5	600	21.70 ± 0.15	93.3	10.05 ± 0.67	41.33 ± 2.78	07.49 ± 0.60	68.2	09.91 ± 0.40	39.94 ± 1.40
25.33	2.34	0.25	DCM	5.5	800	21.70 ± 0.15	87.7	10.52 ± 0.57	41.53 ± 2.27	07.49 ± 0.60	42.6	09.80 ± 1.25	39.02 ± 4.90
25.33	4.68	0.25	DCM	5.5	200	192.56 ± 0.90	743.5	13.91 ± 0.71	55.64 ± 2.70	45.89 ± 0.75	277.6	12.24 ± 1.60	50.40 ± 6.80
25.33	4.68	0.25	DCM	5.5	300	192.56 ± 0.90	422.4	13.04 ± 0.30	52.60 ± 1.50	45.89 ± 0.75	182.2	12.40 ± 0.35	52.30 ± 1.50
25.33	4.68	0.25	DCM	5.5	600	192.56 ± 0.90	283.6	14.00 ± 0.10	54.20 ± 4.70	45.89 ± 0.75	143.5	13.72 ± 1.40	57.02 ± 5.70
25.33	4.68	0.25	DCM	5.5	800	192.56 ± 0.90	248.4	14.11 ± 0.17	53.29 ± 0.70	45.89 ± 0.75	105.3	12.82 ± 1.42	49.74 ± 5.52
25.33	2.34	0.25	DCM	1.1	300	21.70 ± 0.15	118.5	14.39 ± 2.36	62.79 ± 8.12	07.49 ± 0.60	64.2	12.98 ± 1.70	55.19 ± 7.22
25.33	4.68	0.25	DCM	1.1	300	192.56 ± 0.90	450.5	18.70 ± 1.09	78.73 ± 4.59	45.89 ± 0.75	164.0	15.60 ± 0.51	66.34 ± 2.18
25.33	2.34	0.25	DCM/Ac	5.5	300	18.48 ± 0.27	139.0	12.71 ± 1.60	47.40 ± 3.79	07.30 ± 0.00	76.2	11.87 ± 0.18	50.09 ± 0.76
25.33	4.68	0.25	DCM/Ac	5.5	300	134.82 ± 0.60	449.2	16.30 ± 0.03	68.64 ± 0.10	42.35 ± 0.99	183.0	13.48 ± 1.21	54.30 ± 3.70
25.33	2.34	0.25	DCM/Ac	1.1	300	18.48 ± 0.27	136.1	17.57 ± 0.68	67.22 ± 2.62	07.30 ± 0.00	80.2	14.27 ± 1.12	62.70 ± 4.90
25.33	4.68	0.25	DCM/Ac	1.1	300	134.82 ± 0.60	401.5	19.33 ± 0.70	81.38 ± 3.26	42.35 ± 0.99	183.0	16.13 ± 0.59	67.93 ± 2.50
50.66	2.34	0.25	DCM/Ac	5.5	300	17.02 ± 0.23	121.4	17.57 ± 0.05	41.21 ± 0.12	07.45 ± 0.10	72.5	14.74 ± 1.52	32.39 ± 3.33
50.66	4.68	0.25	DCM/Ac	5.5	300	142.62 ± 0.60	359.1	23.67 ± 1.30	57.88 ± 3.35	42.86 ± 0.33	186.3	19.90 ± 0.10	48.58 ± 0.24
50.66	2.34	0.25	DCM/Ac	1.1	300	17.02 ± 0.23	129.6	20.24 ± 0.36	51.37 ± 0.93	07.45 ± 0.10	70.2	20.85 ± 0.80	51.49 ± 2.00
50.66	4.68	0.25	DCM/Ac	1.1	300	142.62 ± 0.60	376.0	27.74 ± 1.92	70.09 ± 4.86	42.86 ± 0.33	170.8	21.47 ± 0.22	56.00 ± 0.57

D_{32}, mean diameter of Sauter; mean diameter in surface = $\Sigma n_i d_i^3 / \Sigma n_i d_i^2$ (n_i, number of microparticles with a mean diameter of d_i); η is the organic phase viscosity in mPa s or cP.

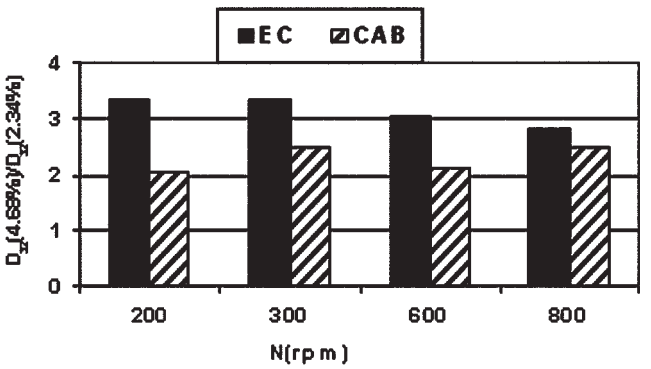

Figure 5 Effect of the % pol./sol. on the mean diameter of Sauter of microspheres.

The other parameters such as PVA/water and drug/polymer ratios, pH of continuous phase and organic phase solvent did not have an appreciable influence on the microspheres size, especially for the CAB microspheres.

Drug content

The 2,4-D was encapsulated in biodegradable polymeric matrices, and so the first purpose, which was to minimize the risk by dermal contact, has been achieved. The second purpose is to optimize the experimental conditions to get high efficiency on drug entrapment by modifying and adjusting the process parameters.

We have noted that under the same conditions, the drug loaded is lower in CAB microspheres than in EC ones (Table I); this can be explained by the size of microspheres. In the emulsion step, when the microspheres are smaller, the surface contact with continuous phase is larger and so the loss of the active agent is more important.

For both the polymers, the drug entrapment can be increased by increasing % pol./sol. Indeed, for

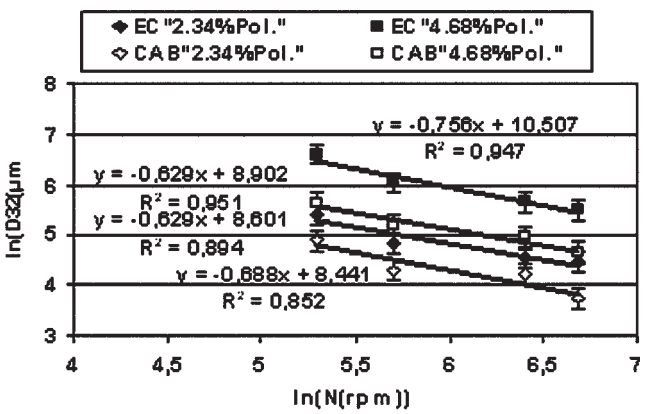

Figure 6 Relationship between mean diameter of Sauter and stirring speed.

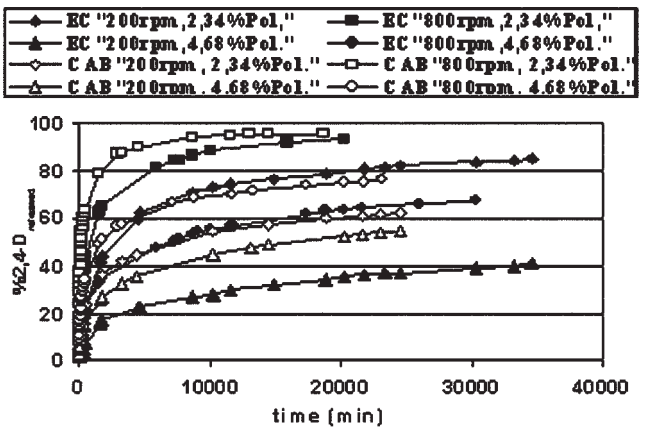

Figure 7 Release profiles of 2,4-D from ethylcellulose and CAB microspheres (0.25% PVA, 25.33% 2,4-D_i, pH = 5.5, DCM).

EC microspheres the % 2,4-D loaded increased from 10.36 to 13.04% when we doubled the % polymer from 2.34 to 4.68%; and for CAB microspheres the % 2,4-D loaded increased from 9.83 to 12.40%. The encapsulation yield was also improved in this case and exceeded 50%.

From the results, the drug entrapment and the encapsulation yield increased by reducing the pH of continuous phase or using the mixture of DCM and acetone as organic phase solvent. In fact for CAB microspheres prepared with 2.34% of pol./sol. and 25.33% of drug/pol., the % 2,4-D loaded increased from 9.83 to 12.98% when we emulsified the internal phase in a more acidic continuous phase (pH = 1.1). Likewise, for EC microspheres prepared under the same conditions, the drug loaded was improved from 10.36 to 14.39%. The result is due to the solubility of 2,4-D in the acidic medium; at pH = 1.1, the 2,4-D is less soluble than in a neutral aqueous phase (311 mg L^{-1} at pH = 1.1 and 620 mg L^{-1} in neutral pH). Therefore the use of an aqueous phase pH equal to 1.1 has diminished the loss of 2,4-D and consequently favored the drug entrapment and the encapsulation yield. On the other hand, for both

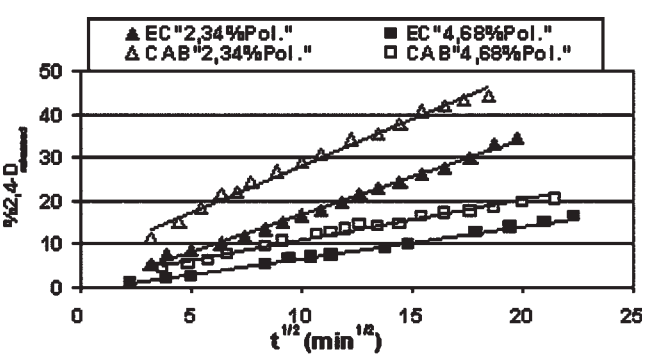

Figure 8 Fickien behavior of 2,4-D released from microspheres (0.25% PVA, 25.33% 2,4-D_i, 300 rpm, pH = 5.5, DCM).

TABLE II
Release Results of 2,4-D from CAB and EC Microspheres[a]

Matrix	Process parameters					D_{32} (μm)	% 2,4-$D_{released}$ [$= f(t^{1/2})$]	R^2	% 2,4-D[b]
	% 2,4-D_i	% Pol.	Stirring (rpm)	Solvent	pH				
CAB	25.33	2.34	200	DCM	5.5	134.7	$1.34\ t^{1/2} + 0.34$	0.9871	20
	25.33	2.34	300	DCM	5.5	73.9	$2.14\ t^{1/2} + 6.77$	0.9906	44
	25.33	2.34	600	DCM	5.5	68.2	$2.80\ t^{1/2} + 6.99$	0.9905	52
	25.33	2.34	800	DCM	5.5	42.6	$3.49\ t^{1/2} + 9.19$	0.9847	46
	25.33	4.68	200	DCM	5.5	277.6	$0.93\ t^{1/2} - 0.38$	0.992	16
	25.33	4.68	300	DCM	5.5	182.2	$1.21\ t^{1/2} - 0.22$	0.9944	16
	25.33	4.68	600	DCM	5.5	143.5	$1.37\ t^{1/2} + 0.80$	0.9970	19
	25.33	4.68	800	DCM	5.5	105.3	$1.76\ t^{1/2} + 3.15$	0.9888	21
	25.33	2.34	300	DCM	1.1	64.2	$2.04\ t^{1/2} + 7.05$	0.9945	42
	25.33	4.68	300	DCM	1.1	164.0	$1.02\ t^{1/2} + 8.22$	0.9911	23
	25.33	2.34	300	DCM/Ac	5.5	76.2	$1.63\ t^{1/2} + 3.67$	0.9936	33
	25.33	2.34	300	DCM/Ac	1.1	80.2	$2.13\ t^{1/2} + 3.35$	0.9940	36
	25.33	4.68	300	DCM/Ac	5.5	183.0	$1.09\ t^{1/2} + 0.79$	0.9954	17
	50.66	2.34	300	DCM/Ac	5.5	72.5	$2.29\ t^{1/2} + 18.79$	0.9926	46
EC	25.33	2.34	300	DCM	5.5	125.7	$1.73\ t^{1/2} - 0.48$	0.9960	36
	25.33	4.68	300	DCM	5.5	422.4	$0.76\ t^{1/2} - 1.01$	0.9957	16
	25.33	2.34	300	DCM/Ac	1.1	136.1	$2.10\ t^{1/2} - 0.47$	0.9881	28
	25.33	4.68	300	DCM	1.1	450.5	$0.65\ t^{1/2} + 0.65$	0.9930	11
	25.33	4.68	300	DCM/Ac	5.5	449.2	$0.59\ t^{1/2} - 5.25$	0.9888	07
	50.66	2.34	300	DCM/Ac	1.1	129.6	$2.19\ t^{1/2} + 15.70$	0.9894	46

[a] The complete results of EC microspheres are reported in Ref. 14.
[b] The kinetic equation is valid until this value of % 2,4-D released.

polymers the % 2,4-D loaded increased by adding acetone as cosolvent in the internal phase. For example, for the EC microspheres prepared with 4.68% of pol./sol. and 25.33% of drug/pol. and at pH = 5.5, the 2,4-D loaded increased from 13.04% (in DCM) to 16.30% (in DCM/acetone). Then the use of acetone as cosolvent probably renders both the solvent evaporation and the precipitation of polymer at the droplet surface more rapid. So this factor, which has also been studied by other authors,[26] is very important for the successful encapsulation of the herbicide.

By increasing initial drug/polymer ratio the drug loaded was increased. Nevertheless the encapsulation yield was decreased. In this case we have to be careful because the SEM photomicrographs show presence of crystal of 2,4-D on the surface of microspheres.

The concentration of the emulsifying agent can increase the solubility of the active agent in continuous phase and thereby influence the drug loading. In our research, an increase in % PVA led to a decrease in herbicide loaded and encapsulation yield.

To resume, for both polymers the drug entrapment can be improved by modifying one or some of the process parameters: by increasing pol./sol. ratio, by reducing pH of continuous phase, or by using a cosolvent in organic phase.

Release studies

The release studies were carried out in deionized water at pH = 5.5 and 25°C and the influence of microencapsulation variables and the nature of matrix on the herbicide release were studied. The plots of % 2,4-D released from EC and CAB microspheres against time are shown in Figure 7. When we tested the approached analytical solution of Fick's law [eq. (4)], we obtained a straight line relation between the fractional release of 2,4-D and the square root of time (Fig. 8). Good fits (R^2 = 0.984–0.997) were obtained during the short times (indicated by the values of % 2,4-D released) where the equation is valid (Table II). The results give information about the release model. The release mechanism seems to be governed by diffusion process according to Fick's laws.[20]

The objective of the work is to produce controlled release devices by emulsion-solvent evaporation technique. The aim was achieved by modifying the process parameters. Table II shows the effect of some of the formulation factors on the release rate. We have given equations of % 2,4-D released related to the square root of time. In Table II we have indicated the majority of the results of the drug release from CAB microspheres and we have summarized the results of 2,4-D released from EC microspheres.[14]

By comparing the two matrices, under the same conditions of microspheres preparation, we have obtained fast release from CAB microspheres. This is illustrated in Figure 8.

For both cellulose derivatives, we have noted that the release rate of the active agent from microspheres was decreased when we increased the percentage of polymer (% pol./sol.) at the different process parameters. However, we have noticed that the stirring speed had an important effect on the size of microspheres.

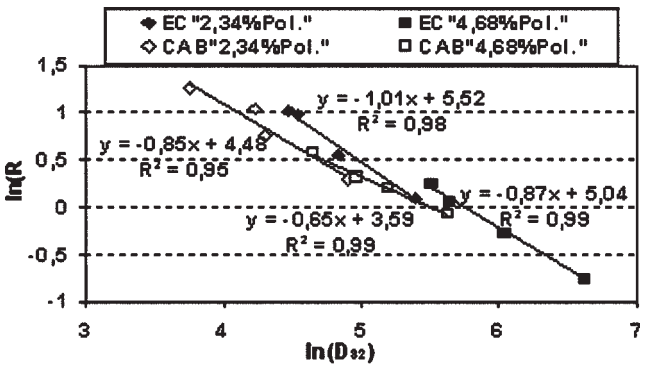

Figure 9 Relationship between the release rate and particle size (0.25% PVA, 25.33% 2,4-D$_i$, pH = 5.5, DCM).

At the same time it had an important effect on the release rate. In Figure 9, we have drawn a relationship between the logarithm of the release rate of 2,4-D (ln R) and the logarithm of mean diameter of Sauter (ln D_{32}) of microspheres for both polymers and both percentages; the absolute values of slopes of EC microspheres are superior to those of CAB microspheres.

So, a correlation between the mean diameter and release rate has been found and the release of the active agent is inversely proportional to the size of microspheres.

In Figure 10 we have shown the effect of the initial drug/polymer ratio on the herbicide release. When we used 50.66% of % 2,4-D$_i$, we have noticed that the release rate is slightly increased, especially for CAB microspheres. Nevertheless, we have remarked an important burst effect for the two matrices. The result can be explained by the presence of crystals of 2,4-D on the surface of microspheres which have been seen by SEM characterization.

The % PVA did not have a notable effect on the release rate but the microspheres prepared in acid medium have yielded a higher release rate, especially for EC microspheres.

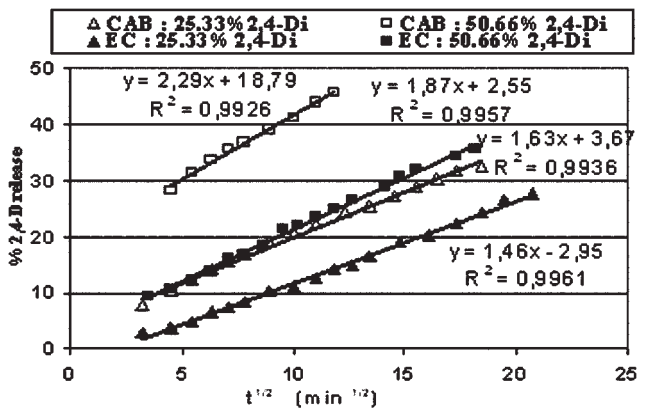

Figure 10 Effect of initial drug/polymer ratio (% 2,4-D$_i$) on the release kinetics (0.25% PVA, 2.34% Pol., 300 rpm, pH = 5.5, DCM/acetone).

CONCLUSIONS

The work was intended to prepare herbicide controlled release formulations consisting of cellulose derivatives by the encapsulation method using emulsion-solvent evaporation technique. The 2,4-D was chosen as core material and EC and CAB as matrix. The risks of 2,4-D by dermal contact must be controlled using these formulations and consequently the active agent is protected from degradation by the external aggressions. The two matrices are biodegradable and can be used without inconvenience. We have obtained systems with large ranges of size (D_{32}, 88–744 μm with EC; and D_{32}, 42–277 μm with CAB) by modifying the process parameters. The mean diameter can be controlled particularly by stirring speed of emulsion and the pol./sol. ratio. The drug entrapment can be improved especially by increasing pol./sol. ratio, or by using acidic continuous phase pH (pH = 1.1), or by adding a cosolvent. The release kinetics seem to be governed by the diffusion process and the release rate can be controlled by modifying the encapsulation parameters that have an important effect on the particle size.

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