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Elaboration of microspheres and coated microspheres for the controlled release of the herbicide 2,4-D

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Summary

Controlled release systems loaded with 2,4-D were prepared by double encapsulation using solvent evaporation technique followed by the complex coacervation method. The production of these systems was aimed at modifying the release rate of the active agent and at reducing the herbicide risks by dermal contact. The coated microspheres are composed of Ethylcellulose or Cellulose acetate butyrate butyryle as microsphere matrix and with Gelatin–Arabic gum complex as envelope. The microparticles were characterized by scanning electron microscopy and the size and size distribution were determined. The drug release from the coated microspheres was established in water at 25 °C and it was compared with those of microspheres without envelope. The release mechanism of the active agent from microspheres was investigated according to Fick's law. So the present paper completes the characterization of microspheres by the calcul of the effective diffusion coefficients.

Introduction

Controlled release formulations give a high promise for enhancing the efficacy of biological active agents [1]. In the grochemical domain, these systems are developped in order to diminish the harmfull effects of pesticides and to reduce their environmental pollution [2-7]. Microencapsulation becomes the most industrial process used for the production of controlled release agricultural formulations [7-9]. In fact, various agrochemicals such as norfluazon [10], atrazine and metribuzin [11], diuron [12], dicamba [13] were formulated by different microencapsulation techniques. These formulations permit the protection of the active agent from evaporation and degradation by photolytic, hydrolytic or microbial reactions. Furthermore, the release rate of herbicide can be controlled and its concentration is maintained within optimum limits over a long period [4, 8]. In our previous research [14-15], we have used the microencapsulation by solvent evaporation technique to produce cellulose derivatives (ethylcellulose and cellulose acetate butyrate butyryl) microspheres loaded with 2,4-dichlorophenoxyacetic acid (2,4-D). The 2,4-D is a phenoxy compound and it is one of the most widely used herbicides for control of weed growth. However, it can be considered as a potential pollutant of soils and ground water [16-18]. Then,

these microparticles are prepared and optimized to control the release of herbicide and to reduce his potential toxicity for humans. Different process parameters such as the polymer matrix, the stirring speed, the polymer and emulsifier concentrations and aqueous phase pH are studied in order to show their influences on the microparticles characteristics (size, surface morphology and drug content) and on the release rate of the herbicide. Some empirical relations between the stirring speed and the mean diameter of microspheres and also between the release rate and the mean diameter have been obtained [14-15]. In these systems, the release mechanism was investigated according to the diffusion process. So, in the present paper, we complete the research by the calculation of diffusivities of 2,4-D in these matricial devices by applying Fick's diffusion equations [19].
In addition, this work develops new formulations which permit more protection of the herbicide and a modification of the release rate. Therefore, we have combined two microencapsulation processes namely solvent evaporation and complex coacervation to produce coated microspheres. The envelope is composed of gelatin-arabic gum complex and the preparation conditions were optimized to get spherical microparticles with a continuous coat.

Materials and methods

Chemicals

2,4-dichlorophenoxyacetic acid (2,4-D), from ACROS Organics , used after grinding in mortar. Ethylcellulose (EC) ethoxylate at 48% (viscosity: 0.100 Pa s at 5% in solution of 80/20 toluene/ethanol) from Aldrich, cellulose acetate butyrate(CAB) butyryle content 35–39% (M_w=70000) from ACROS Organics, gelatin type B from bovine skin 225 bloom from Aldrich, arabic gum (acacia) from Aldrich, polyvinylalcohol (PVA) 88% hydrolysed (M_w=22000) from ACROS Organics, dichloromethane (DCM) for pesticide analysis at purity of +99.9% from ACROS Organics, glutaraldehyde solution at purity of 50% from Aldrich are used as received.

Microspheres preparation

The cellulose derivatives microspheres were prepared by the O/W emulsion solvent evaporation technique as reported in previous papers [14-15], in a cylindrical glass reactor (600 mL, ϕ= 80 mm) with a six-blade turbine impeller (bladelength =50 mm, blade width =10 mm, type IKA RW 20 DZM.n). Ethyl cellulose (EC) and cellulose acetate butyrate butyryl (CAB) are used as matrixes.

Coated microspheres preparation

The coated microspheres were prepared using a solvent/evaporation technique followed by complex coacervation in the same reactor plunged in a bath at 40 °C.
First, 2,4-D and matrix (EC or CAB) were dissolved in 32 g of DCM under light heating (30–35 °C) using 25.33% of %2,4-D_i and 2.34% of % Polymer. At the same time, two aqueous solutions were prepared at 40 °C; the first one was composed of 2% of gelatin dissolved in 200 g of deionised water and the second was prepared with 2% of Arabic gum dissolved in 200 g of deionised water. Then the DCM solution (organic phase) was emulsified in the gelatin solution at 40 °C under stirring at 300 rpm. After 30 min of stirring, the Arabic gum solution was added; at this moment the microspheres were

semi-solids. The stirring of emulsion continued for a further 5 min for homogenization and then coacervation occurred by adding hydrochloride solution (1M) in order to reduce pH to pH=4.1, and the stirring speed was reduced to 250 rpm. After one hour, 0.4 mL of Glutaraldehyde was added to cross-link the gelatin and the temperature was reduced quickly to 5 °C for gelification. Solid suspension was also stirred for approximately 4 hours, and then the microcapsules were filtered, washed with 50/50 (w/w: cold water/isopropanol) solution and dried in a dessiccator. The powder of microparticles was recovered after slight grinding.

UV spectroscopy analysis

The drug loading and drug release are determined using a UV-Vis spectrophotometer (JASCO-530). The 2,4-D aqueous or alcoholic solutions are analyzed at λ_{max} =229 nm where ε is equal to 10255.8 $L.mol^{-1}.cm^{-1}$ in water and 10971.0 $L.mol^{-1}.cm^{-1}$ in ethanol.

Microparticles characterisation

Coated microspheres formation

The formation of coated microspheres is followed by using an optical microscope (Motic microscope B serial) adapted with a Moticam 1000 camera. The images are exploited with « Motic Images Plus 2.0 ML » software.

Surface morphology

The surface morphology of microparticles 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 diameters and size distribution of microparticles were calculated from the results of optical microscopy (Vickers instruments), by counting more than 500 microparticles using appropriate lenses. This method permits us to avoid counting aggregate microparticles.

Drug content

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

$$\%2,4\text{-}D_{loaded} = \frac{weight.of.herbicide.in.microparticles}{weight.of.loaded.microparticles} x100 \quad (1)$$

$$Yield\% = \frac{weight.of.herbicide.in.microparticles}{initial.weight.of.herbicide} x100 \quad (2)$$

Drug release

The release kinetics of 2,4-D from cellulose derivatives microspheres and the coated microspheres were followed in an appropriate dissolution reactor as described in previous papers [14-15], plunged in a bath regulated at 25°C. This reactor permits us

to withdraw solution without microparticles. At initial time, 100mg of powder are soaked in the reactor containing 1000 g of deionized water (pH =5.5 as the pH of rain) as release medium under a stirring rate of 250 rpm. At the desired time, 3 mL of solution is withdrawn, analyzed by UV spectroscopy without dilution, and replaced in the Erlenmeyer flask.

Result and discussion

Coated microspheres formation

The experimental conditions were optimised to get spherical microparticles with a continuous envelope of gelatin-arabic gum. It was found that the moment of addition of the arabic-gum solution and the moment of coacervation are the important factors controlling the sphericity of microparticles and the deposit of coacervats on the microsphere surface. In addition, separation of microparticles starts during the cooling step when a temperature is about 16°C.
The optimum conditions of preparation of the coated microspheres are given in the last part (material and methods). Using this process, we achieved a double encapsulation of the active agent in one experiment. The figures 1 and 2 show the steps of the formation of coated EC microspheres and CAB microspheres respectively. The gelatin-arabic gum envelope appears clearly in the optical microscopy images.

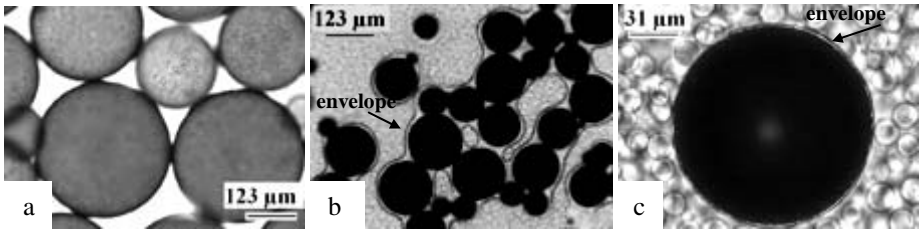

Fig. 1: Formation of the coated microspheres prepared with EC as matrix (a: organic phase globules “x100”, b: coacervation, solidification of microparticles and formation of the envelope “x100”, c: separation of the coated microspheres “x400”).

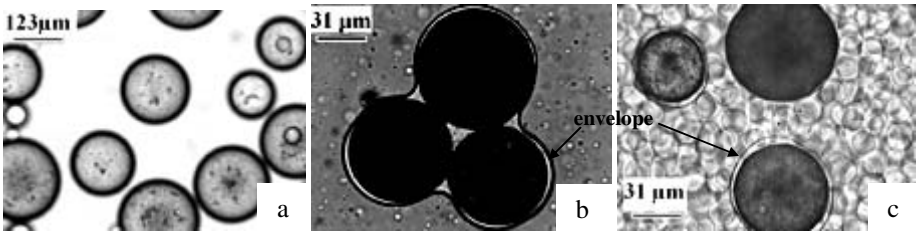

Fig. 2: Formation of the coated microspheres prepared with CAB as matrix (a: organic phase globules “x100”, b: coacervation, solidification of microparticles and formation of the envelope “x400”, c: separation of the coated microspheres “x400”).

Final microparticles characterization

The microspheres are characterized by SEM and infrared spectroscopy as shown in the reference [15]. At the same time, in the present paper, we show the shape and

surface morphology of coated microspheres compared with microspheres. The figures 3 and 4 give the SEM photographs of microparticles. Both microspheres and coated microspheres are spherical with different surface morphologies. The EC microspheres (Fig. 3-a) have a surface which is both rough and porous. The CAB microspheres (Fig. 4-a) surface has slight pores. Regarding the coated microspheres, the photographs (Fig. 3-b et 4-b) show that microspheres are covered with a transparent polymeric film. We should indicate that the envelope appears clearly when we observe the microparticles separated by a slight grinding. In fact, as shown in figure 5, the imperfections, caused by separation, permit us to distinguish the envelope.

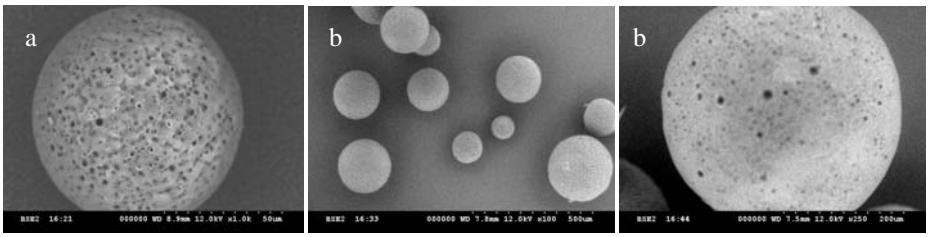

Fig. 3: SEM photographs of EC microparticles (a- microsphere, b-coated microspheres).

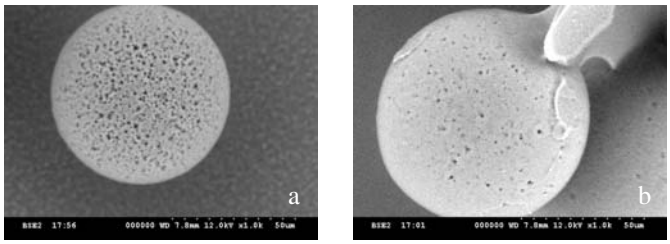

Fig. 4: SEM photographs of CAB microparticles (a- microsphere, b-coated microsphere).

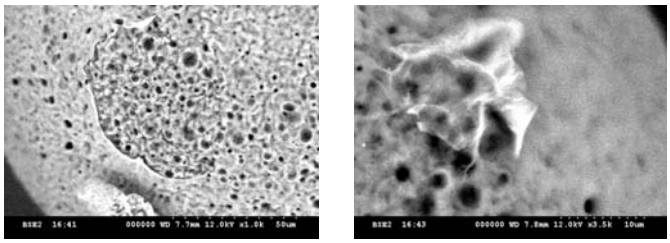

Fig. 5: SEM photographs of EC coated microspheres separated by grinding.

The mean diameters on number d_{10}, surface d_{32} and weight d_{43} and the dispersion values are given in table 1 for the coated microspheres and microspheres prepared with the same percentages of 2,4-D_i (25.33%) and polymer (2.34%) and at a stirring speed of 300rpm. We noticed that the coated microspheres size is higher than the uncoated ones .The increase in the size of the coated particles is especially due to the fact that the drops of the emulsion are larger with gelatine, instead of the PVA, as emulsifier. Concerning microspheres and for the two matrixes, some empirical

relations between the mean diameter and the stirring rate have been found. All the corresponding results are given in the references [14-15].

Table 1: Microspheres and coated microspheres characteristics

Matrix	System type	d_{10} (µm)	d_{32} (µm)	d_{43} (µm)	δ	%2,4-D_{loaded}	Yield %
EC	µspheres	104.4	125.7	132.6	1.27	10.3 ± 0.7	43.5±3.3
	Coated µspheres	194.9	223.0	235.8	1.21	11.2 ± 1.6	31.2±4,4
CAB	µspheres	62.7	73.9	77.4	1.23	09.8 ± 0.1	40.6±0.2
	Coated µspheres	102.0	107.9	110.8	1.09	08.0 ± 1.6	22.5±6.5

$d_{10}=\sum n_i d_i / \sum n_i$, $d_{43}=\sum n_i d_i^4 / \sum n_i d_i^3$, $d_{32}=\sum n_i d_i^3 / \sum n_i d_i^2$. Dispersion: $\delta=d_{43}/d_{10}$.

The drug content in coated microspheres is almost the same as in microspheres without envelope. Then, we can say that the 2,4-D is encapsulated in biodegradable and non toxic walls and the risk by dermal contact is, in this event, minimized especialy in the coated microspheres.

Drug release studies

The release of 2,4-D from the dried microspheres and coated microspheres was studied in deionised water at 25 °C and pH=5.5 (the pH of rain). Figure 6 shows the release profiles of 2,4-D released from the coated microspheres and the microspheres prepared with 25.33% of 2,4-D_i, 2.34% of %Pol., 0.25% of PVA and 300rpm.

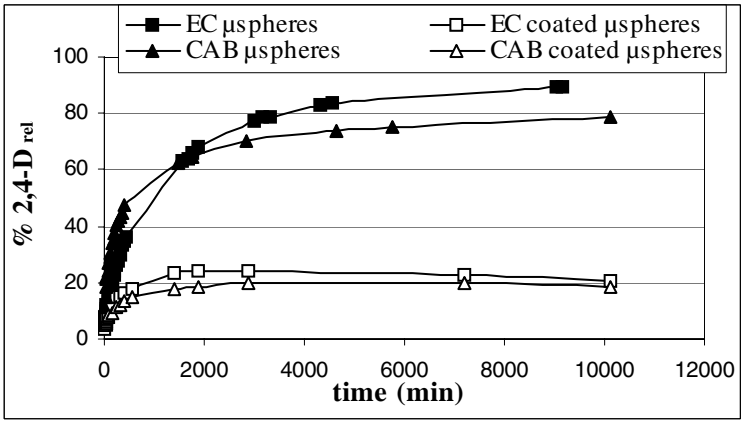

Fig. 6: Release profiles of 2,4-D from microspheres and coated microspheres.

We suppose that the release of the herbicide from this system involves 4 steps:
a. Penetration of water into the microparticles
b. Dissolution of the active agent
c. Diffusion of active agent into the matrixes
d. Transfer of the 2,4-D in solution.

For the microspheres, in order to draw a release model, we have tested the approached analytical solution derived from Fick's law [19] for diffusion in a sphere. The following assumptions are thus made in order to simplify the problem:
– microspheres are considered as spherical isotropic microparticles.
– two mass transfers take place: the liquid entering the microparticles, and the drug leaving the microparticles. We have studied only the second one because it's difficult to measure the first.
– both these transfers are controlled by transient diffusion throughout the microparticles with constant diffusivity.

The whole process is probably governed by the slowest stage which is inevitably the diffusion of the active agent 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 [19]. If we suppose that microspheres of radius R are isotropic and the diffusivity D is constant, the equation of diffusion of active agent into polymeric matrix is:

$$\frac{\partial C}{\partial t}=\frac{D}{r_2}\frac{\partial}{\partial r}\left(r_2\frac{\partial C}{\partial r}\right), \quad 0 < r < R \tag{3}$$

Taking into account the following initial and boundary conditions:

Within the sample:	t=0	$0 \le r \le R$	$C=C_0$	C_0 = initial concentration
	t>0	$0 \le r < R$	C=f(t, r)	
On the surface:	t>0	r = R	$C=C_\infty$	C_∞=Concentration at equilibrium

In the earlier stages of the process [19], the analytical solution of the equation (3) is given by:

$$\frac{C-C_0}{C_\infty-C_0}=\frac{R}{r}\sum_{n=1}^{\infty}\left\{erfc\frac{(2n+1)R-r}{2\sqrt{Dt}}-erfc\frac{(2n+1)R+r}{2\sqrt{Dt}}\right\} \tag{4}$$

and the amount of diffusing substance at time t (M_t) is given by:

$$\frac{M_t}{M_\infty}=6\left(\frac{Dt}{R^2}\right)^{1/2}.\left\{\pi^{-1/2}+2\sum_{n=1}^{\infty}ierfc\frac{nR}{\sqrt{Dt}}\right\}-\frac{3Dt}{R^2} \tag{5}$$

where M_∞ is the amount of diffusing substance at infinite time (equilibrium) and n is an integer.
For the very short times, the equation (5) is more simplified and the diffusivity can be calculated by applying the following equation:

$$\frac{M_t}{M_\infty}=6\sqrt{\frac{Dt}{\pi R^2}}=k.t^{0,5} \tag{6}$$

For long times, another approached solution which is also interesting for calculating the diffusivity is :

$$Ln\left(1-\frac{M_t}{M_\infty}\right)=-\frac{D\pi^2 t}{R^2}+Ln\frac{6}{\pi^2} \tag{7}$$

The values of diffusivities are obtained from the straight lines expressed either by equation (6) for short durations or equation (7) for long periods.

Concerning microspheres, we have noted that the fractional release of herbicide is proportional to the square root of time during the short time as reported in our previous research [14-15]. The coefficients of diffusion of the active agent in each matrix are calculated and discussed in the next section of the present paper.
Although we have obtained linear relation of the 2,4-D released from the coated microspheres versus the square root of time as shown in Figure 7, we can not calculate the diffusivities in this case. Indeed, these devices are more complex and the diffusion is realized through the two wall materials (EC or CAB matrix and gelatin-arabic gum envelope). Nevertheless, we can compare the release constant (the slope of the straight line of the equation of $\%2,4\text{-}D_{released}=f(t^{0.5})$) of the coated microspheres with those of microspheres. The release results for each batch of microparticles (the coated microspheres and microspheres prepared with same percentages of $2,4\text{-}D_i$ (25.33%) and polymer (2.34%) and at a same stirring speed (300rpm)) are given in table 2.

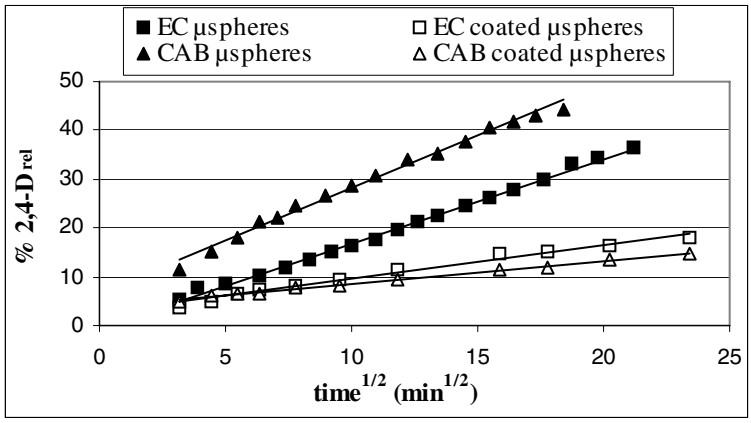

Fig. 7: %2,4-D released from microspheres and coated microspheres as function of square root of time.

Table 2: Release results of 2,4-D from microspheres and coated microspheres.

Matrix	Type of système	Release equation: $\%2,4\text{-}D_{released}=k.t^{0.5}+A$	R^2	% 2,4-D *	% $2,4\text{-}D_\infty$
EC	µspheres	$\%2,4\text{-}D_{rel.}=1.73\ t^{1/2}-0,48$	0.996	36.3	95.2
	Coated µspheres	$\%2,4\text{-}D_{rel.}=0.70t^{1/2}+2.54$	0.984	18.0	25.8
CAB	µspheres	$\%2,4\text{-}D_{rel.}=2.13\ t^{1/2}+6.77$	0.990	44.5	82.7
	Coated µspheres	$\%2,4\text{-}D_{rel.}=0.47t^{1/2}+3.76$	0,994	14.9	20.2

* The kinetic equation is valid up to this value of % 2,4-D released.

The release constant of 2,4-D discharged by the coated microspheres is lower than that released by the microspheres. Indeed an additional coating increases the course of diffusion and consequently the time of release because this time is proportional to the square of this diffusion distance according to Fick's law . Therefore the double encapsulation aim was achieved since the release of herbicide is slower through these systems.

Calculation of the diffusivities

In the microspheres, the herbicide is dispersed in the polymeric matrix (EC or CAB), and then the release of the active agent involves four stages as reported in the previous section. The values of diffusivities are characteristic of the mobility of the active agent in a known matrix. For example, as reported in Mogul and al. research [8], the diffusion coefficients of 2,4-D in gelatin microspheres calculated in short times (M_t/M_∞<15%) are in the range of $1.2*10^{-14}$ to $2.8*10^{-16}cm^2sec^{-1}$ and depend on the swelling properties of the matrix. However, in the present study, some microspheres have a porous structure so the diffusion coefficient calculated corresponds to an effective diffusion coefficient (D_{eff}) of drug in the porous network microspheres. The D_{eff} includes the drug diffusion through both the pure matrix and the liquid present in the pores.

Therefore, the diffusivities are calculated by applying equation (6) for the short times ($D_{s,t}$) and using the three mean diameters (on number d_{10}, on surface d_{32} and on weight d_{43}). The corresponding results are given in table 3 for EC and CAB microspheres.

Table 3: Values of effective diffusivities of 2,4-D in EC and CAB microspheres.

Process parameters of the microspheres preparation						**EC microspheres**				**CAB microspheres**			
						d_{10} (µm)	**Ds,t *10^{11} (cm^{2}sec^{-1})**			d_{10} (µm)	**Ds,t *10^{11} (cm^{2}sec^{-1})**		
% 2,4-D$_i$	**% pol.**	**N rpm**	**Solvent**	**PH**	**% PVA**		**D_1**	**D_2**	**D_3**		**D_1**	**D_2**	**D_3**
25.33	2.34	300	DCM	5.5	1	88.3	0.9	1.6	1.9	61.8	1.0	1.7	2.1
25.33	2.34	200	DCM	5.5	0.25	175.3	1.4	2.2	2.4	116.6	2.2	2.9	3.2
25.33	2.34	300	DCM	5.5	0.25	104.4	1.0	1.4	1.6	62.7	1.3	1.9	2.1
25.33	2.34	600	DCM	5.5	0.25	75.0	1.1	1.8	2.1	59.0	1.3	1.8	1.9
25.33	2.34	800	DCM	5.5	0.25	56.6	0.7	1.7	1.7	31.3	0.6	1.1	1.3
25.33	4.68	200	DCM	5.5	0.25	542.9	4.6	8.7	9.9	237.1	4.4	6.1	6.6
25.33	4.68	300	DCM	5.5	0.25	280.4	2.6	6.0	7.2	155.1	2.1	2.9	3.2
25.33	4.68	600	DCM	5.5	0.25	186.5	2.8	6.4	7.9	105.6	1.3	2.4	2.7
25.33	4.68	800	DCM	5.5	0.25	135.1	2.4	8.2	10.7	72.8	0.8	1.8	2.1
25.33	2.34	300	DCM	1.1	0.25	80.7	3.1	6.8	7.6	46.3	0.5	1.0	1.2
25.33	4.68	300	DCM	1.1	0.25	326.2	7.7	14.7	16.8	136.3	1.4	2.1	2.4
25.33	2.34	300	DCM/Ac	5.5	0.25	110.7	1.3	2.1	2.3	56.6	0.8	1.5	1.7
25.33	4.68	300	DCM/Ac	5.5	0.25	333.5	3.9	7.1	8.3	146.7	2.2	3.4	3.8
25.33	2.34	300	DCM/Ac	1.1	0.25	116.9	3.9	5.3	5.8	65.1	1.1	1.7	1.8
25.33	4.68	300	DCM/Ac	1.1	0.25	288.1	3.1	6.1	7.0	155.3	1.6	2.2	2.5
50.66	2.34	300	DCM/Ac	5.5	0.25	95.9	1.3	2.1	2.3	55.8	0.8	1.4	1.6
50.66	4.68	300	DCM/Ac	5.5	0.25	271.8	1.5	2.7	3.1	163.2	1.0	1.3	1.4
50.66	2.34	300	DCM/Ac	1.1	0.25	114.6	3.1	4.0	4.4	61.3	0.5	0.7	0.7
50.66	4.68	300	DCM/Ac	1.1	0.25	292.9	2.2	3.7	4.4	145.8	0.3	0.4	0.5

$D_{s,t}$ calculated when M_t/M_∞ < 25-30% , D_1: diffusion coefficient calculated with d_{10},
D_2: diffusion coefficient calculated with d_{32}, D_3: diffusion coefficient calculated with d_{43}.

From the diffusivity results, we remarked that, in short times, the values of effective diffusivity of 2,4-D calculated with d_{10} are in the range of 0.7 to $7.7*10^{-11}$ cm^2sec^{-1} for EC microspheres and in the range of 0.3 to $4.4*10^{-11}cm^2sec^{-1}$ for CAB microspheres. We can see that diffusivities of the herbicide in cellulose microspheres are higher than in gelatin microspheres [8].

We noticed that the diffusion coefficients of 2,4-D in ethylcellulose are slightly superior than in CAB because of the porosity of microspheres. The diffusion in pores is

easier than in the matrix network and from the SEM photographs (fig.3 and 4), the EC microspheres appear more porous than the CAB ones.
Under the same experimental conditions of microspheres preparation, the effective diffusion coefficient calculated with the mean diameter d_{43} is higher than d_{32} and d_{10}, but its relative variation with the experimental conditions is the same.
Regarding the diffusion coefficients calculated with long time (equation 7) and with d_{10}, we have noticed that the values of $D_{l,t}$ of EC microspheres are in the range of 0.1 to 2.3 $*10^{-11}$ cm^2sec^{-1} and in the range of 0.1 to $1.2*10^{-11}$ cm^2sec^{-1} for CAB microspheres. Taking into account the whole approximations necessary for the simplification of the diffusion equations and the required consideration of isotropic and uniform microspheres, we can consider that the diffusion coefficient decreases slightly during the diffusion process.

Conclusion

Cellulose derivatives microspheres loaded with the herbicide 2,4-D are prepared using the solvent evaporation technique. In the present paper, other systems consisting of coated microspheres are obtained using the solvent evaporation technique coupled with complex coacervation. The experimental conditions are optimised and the envelope is formed with gelatin-arabic gum complex. These new devices make herbicide safer for users and promise more protection from evaporation. The release of herbicide from the coated microspheres is much slower compared with microspheres. Taking into account the presence of pores in the microspheres structure and by applying the analytical equation derived from Fick's second law, the effective diffusivities of 2,4-D calculated in short times and with the number mean diameter are in the range of 0.7 to $7.7*10^{-11}$ cm^2sec^{-1} for EC microspheres and 0.3 to $4.4*10^{-11}cm^2sec^{-1}$ for CAB microspheres.

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