

Elaboration of Microspheres' Capsules Based on Ethylcellulose and Synthesized Poly (Butylsuccinate) as Biodegradable Matrices for Drug Delivery of an Antithyroidian Agent

Soumia Chirani^{1,2}, Mohamed Oussama Lebig¹, Sarah Bouameur^{2,3}, Meriyem Mouffok¹, Naziha Chirani^{4,5}, Nafa Chafi^{1,4}, Kaddour Guemra^{1,4}

¹ Laboratory of Organic Physical and Macromolecular Chemistry, Faculty of Exact Sciences, University Djillali Liabes of Sidi Bel-Abbes, ALGERIA.

² Department of Pharmacy, Faculty of Medicine Sciences, University Djillali Liabes of Sidi Bel-Abbes, ALGERIA.

³ Hospitalo-University Center C.H.U of Sidi Bel-Abbes, 22 000 ALGERIA.

⁴ Department of Chemistry, Faculty of Exact Sciences, University Djillali Liabes of Sidi Bel-Abbes, ALGERIA.

⁵ Laboratory of Innovation and Bioperformance Analyse -LIAB, Polytechnic School, University of Montreal Quebec, CANADA.

ABSTRACT

Introduction: The present paper provides details of preparation of hardcapsules based on microspheres containing 2-aminothiazole as an antithyroidian agent and synthesized poly(butylsuccinate) (PBS) or ethylcellulose(EC10) as biodegradable matrices as well as the study of the drug delivery. **Methods:** A disintegration tests of these gelatinous capsules were done. The biodegradable synthesized polyester was characterized by infrared spectroscopy, nuclear magnetic resonance (mono and bidimensional ¹H NMR, ¹³C NMR) and by Differential Scanning Calorimetry (DSC). A viscosimetric study has been done in order to evaluate viscosimetric PBS's weight which was calculated from Mark-Houwink equation. The microencapsulation of 2-aminothiazole was done using solvent evaporation technique. **Results:** Microspheres were spherical and the effects of varying emulsifiers and blades number on microspheres encapsulation efficiency were evaluated. A kinetic studies of releases of 2-aminothiazole in gastric pH were done in order to evaluate the best late effect and then the best formulation.

Key words: Antithyroidian agent, Microspheres, Biodegradable polymer matrix, Capsules, Drug release, Kinetic study.

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Correspondence:

Prof. Nafa Chafi,

Laboratory of Organic Physical and Macromolecular Chemistry, Faculty of Exact Sciences, University Djillali Liabes of Sidi Bel-Abbes, BP 89 Larbi Ben M'HIDI City, Sidi Bel Abbes 22 000 ALGERIA.

Ph.no: +213 771 735 887

E-mail: nafachafi@yahoo.com

INTRODUCTION

Antithyroid drugs (ATD) have long been used for the drug therapy of graves' disease¹ 2-Aminithiazole is among the first synthesized antithyroid drugs. It inhibits thyroperoxydase that catalyzes iodination and thyroid hormone biosynthesis.

Biodegradable polyesters and co-polyesters have been the focus of extensive research for several decades as a result of their ease of manufacturing and desirable characteristics. A long with the appropriate physical and mechanical properties, the biocompatibility of degradable polymers and their

degradation products play an important role in determining their potential applications.² Then, their ranges of physical properties and hydrolytic degradation profiles have made them attractive candidates for human use as surgical sutures, implantable devices, and drug delivery systems by the US Food and Drug Administration (FDA).³⁻⁸ The biocompatibilities of various biodegradable polymers such as poly(α -hydroxyesters), polyanhydrides and poly(anhydride-co-imides) as candidate materials for various biomedical applications have been extensively investigated.⁹⁻¹¹



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Aliphatic polyester polymers degrade in to non-toxic monomers by bulk hydrolysis of the ester bonds, then avoiding the need for surgical removal so the risk of long term toxicity or a probable immunological reaction when compared with non degradable systems is also minimized.¹²

Micro-encapsulation is a method of fabricating materials with valuable new properties in the pharmaceutical industry^{13,14} and other fields;¹⁵⁻¹⁷ it is one of the quality preservation techniques of sensitive substances. In current pharmacology, micro-encapsulation is employed as a masking technique and, in particular, to control and modify drug release. Further, microspheres formulated from biodegradable polymers are interesting for sustained drug delivery of pharmaceuticals.¹⁸

Initially, in our research, we were focused on aliphatic polyesters because of their physical properties and non-toxic hydrolytic degradation; then we have synthesized and characterized biodegradable matrix:

Poly (buthylsuccinate) (PBS) and evaluated its viscosimetric weight using Mark-Houwink equation. The solvent evaporation technique of micro-encapsulation was used for the preparation of solid microspheres based on our synthesized PBS and ethylcellulose as a matrices and 2-aminothiazole as an antithyroid agent. Ethylcellulose was used as matrix polymer in which drug was dispersed because of its biodegradability and hydrophobic characteristic. The method is based on an oil-in-water (O/W) emulsion followed by solvent evaporation which leads to monolithic systems known as microspheres.¹⁹ This technique has been the method most commonly used to prepare controlled-release pharmaceuticals.²⁰⁻²³ We have chosen to our microspheres a gelatinous capsules as a solid oral pharmaceutical form according to the European pharmacopeia.²⁵ In order to prove the best formulation a kinetic studies of drug delivery in reconstituted gastric media was done and then several release rates were evaluated and mathematically modeled to determine the release mechanism.

MATERIALS AND METHODS

The IR spectrum of PBS was obtained on Shimadzu FTIR-83 instrument on 1% potassium bromide disks. Its ¹H NMR, RMN 2D (cosy¹H-¹H) and ¹³C NMR spectra were obtained at the University of Rennes-1 (in France) on a bruker WM500. The differential scanning calorimetry (DSC)'s spectrum of PBS was recorded on a setraram DSC apparatus at Rennes-1 University (Pr J. F. Carpentier Services, UMR 6226 CNRS). Molecular weight of our polyester was obtained using a capillary

viscosimeter: Thermovisc 100-B125 (Ubbelohde) instrument.

Microparticles were prepared in a cylindrical glass reactor (volume of 600 mL, external diameter= 80 mm) with six and four-bladed turbine impellers (type Velp Scientific as.r.l ISO 9001, ISO 14001; Italy) plunged in a bath adjusted to 25°C; (blade length=12 mm for six blades and 18 mm for the fourth one; blade width=10 mm)

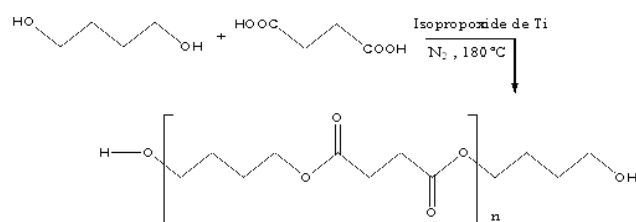
The mean diameters and size distribution of micro particles were calculated from results of optical microscopy (Optika zoom stereo microscopes SZM).

The filling of capsules was done using a semi-automatic filler machine type CAPSUNORM®2000, TECNY-FARMA GROUPE in Laboratory of Galenical Pharmacy in the Department of Pharmacy of the Faculty of Medical Sciences of the Djillali liabes University of Sidi Bel-Abbes in Algeria.

Synthesis of poly (buthylsuccinate) (PBS)

It was successfully done by the application of the “ring opening polymerisation”²⁴

A mixture of buthan1,4diol (0.12 mol.) and succinic acid (0.10 mol.) in presence of catalytic amount of 1 to 2% of titaneisopropoxide was refluxed during two hours at 180°C with high stirring under a nitrogen draught. In order to purify the obtained polymer (to eliminate residual monomers) it was heated at 200°C under reduced pressure (max= 10⁻³mmHg) during three hours.



Microspheres preparation

The monolithic systems were obtained by the emulsion solvent diffusion method using de-ionized water as an external phase in which 0.5% of the emulsifier (PVA or Tween 80) was dissolved. The internal phase was composed of 2-aminothiazole with EC or PBS as matrices (2-aminothiazole/matrix=50 mass%) and dichloromethane (DCM) as the organic solvent (polymer matrix/DCM=6 mass %).

First, the drug and polymer were co-dissolved in the organic solvent by heating them under slight reflux (30–35°C) and stirred to get homogenization. At the same time, the emulsifier was dissolved in 250 g of deionized water under heating and stirring. After cooling to laboratory temperature, the organic phase was emulsified with the continuous phase under mechanical

stirring (600 rpm) for 3 h to complete solvent evaporation. Then, the dispersion was filtered and microspheres were vacuum-dried in a desiccator in the presence of CaCl_2 .

Filling of microspheres in gelatin capsules

We have chosen gelatin capsules as a solid oral pharmaceutical form for our elaborated microspheres because of its disponibility and its ease of development. Then, in the first we've determined the apparent volume of microspheres to determine the capsules size as well as the volume of diluent²⁵ We have determined diluent volumes (lactose or saccharose) using the Table 1 which gives the total volume of the capsule too.

However, we gave for each formulation of microspheres: the apparent volume, the number of capsule and the diluent volume.

Drug release study

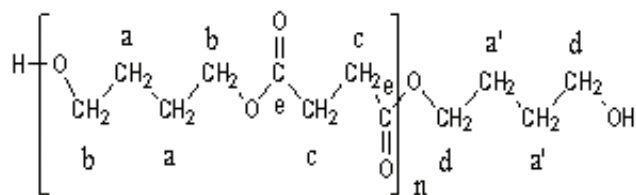
The release kinetic studies of the active agent from microspheres were performed in a cylindrical double-wall glass reactor (100mL), kept at a temperature of $(37 \pm 0.5)^\circ\text{C}$. 100 mg of microspheres were dispersed in 100 mL of simulated gastric medium (pH 1, 2). The dissolution medium was stirred magnetically at a rotation speed of 500 min^{-1} to achieve good homogenization. A sink method was followed: Samples (3 mL) of the

solution were collected for analysis at different time intervals and replaced simultaneously by 3ml of the gastric pH. The samples were analyzed using a UV-VIS spectrophotometer at $\lambda_{\text{max}} = 268 \text{ nm}$ of 2-Aminothiazole. The value of molar extinction co-efficient ϵ_{max} ($\text{l.mole}^{-1} \cdot \text{cm}^{-1}$) = 3038 is calculated from the slope of the plot of $\text{Abs} = f(C)$ at $\text{pH}=1.2$.

The release studies were carried out in a buffered solution at pH 1.2 and 37°C and the influence of the matrix on the ATD's release was studied.

RESULTS

Poly (buthylsuccinate) characterization



- From the ^1H NMR spectra of poly (buthylsuccinate) (Figure. 1) we confirmed $\delta\text{H}(\text{CDCl}_3)$ (ppm): 1.65 ($\text{CH}_2(\text{a})$); 1.55 ($\text{CH}_2(\text{a}')$); 2.55 ($\text{CH}_2(\text{c})$); 4.05 ($\text{CH}_2(\text{b})$); 3.55 ($\text{CH}_2(\text{d})$).
- 2D NMR ($\text{cosy}^1\text{H}-^1\text{H}$, CDCl_3 , 500Mhz) of poly (buthylsuccinate) was done (Figure. 2)

Table 1: Approximate capacities of gelatin capsules

	Capsules size							
	000	00	0	1	2	3	4	5
Volumes ml	1.40	0.95	0.70	0.50	0.40	0.30	0.20	0.125

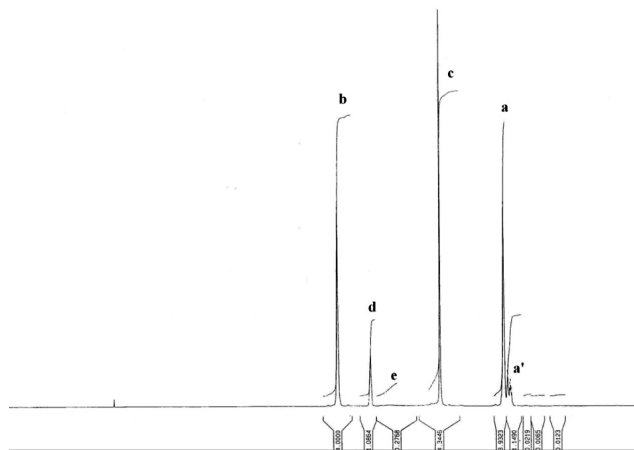


Figure 1: ^1H NMR spectra of poly(buthylsuccinate)

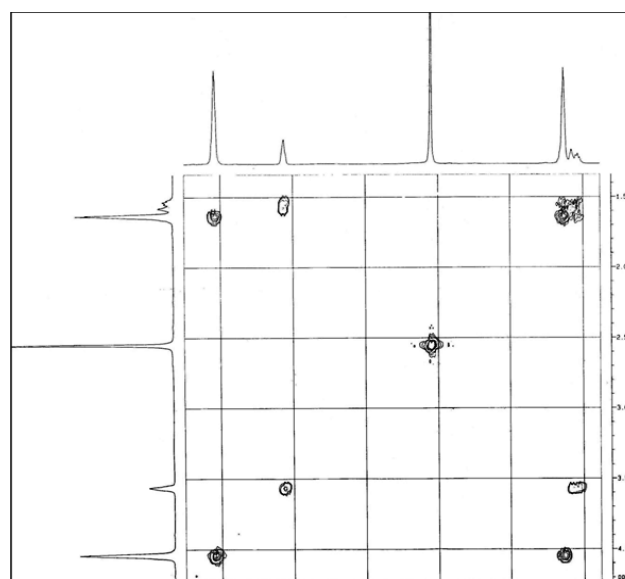


Figure 2: 2D NMR ($\text{cosy}^1\text{H}-^1\text{H}$, CDCl_3 , 500Mhz) of poly(buthylsuccinate)

- FT-IR spectrum (Figure. 3) (KBr pellet) ν (cm⁻¹): (1716-1732) (ester C=O); (2945-2956) (CH₂); (1100-1200) (ester C-O-C); (3429-3552) (terminal O-H).
- The glass temperature of our biopolymer was been picked on heating and cooling temperatures between 30 and 250°C on 10.4 mg of PBS sample (Figure 4).
We used two “heating/cooling” cycles separated by 10 to 50°C bearing. The used speeds are +10°C/mn for heating and -20°C/mn for cooling.
The glass temperature depends on the speed; it's increased with heating/coldling speed and it's the same with melting temprature. Exemple: T_f PBS (coldling)>T_f PBS (heating). We note an average glass temperature T_g_{PBS} = 65°C.
The heating and coldling were been done under an argon atmosphere.
- Viscosimetric study of the polymer matrix (PBS) was done in chloroform at (20°C±1); the flow time of solvent was t₀=16.91sec.

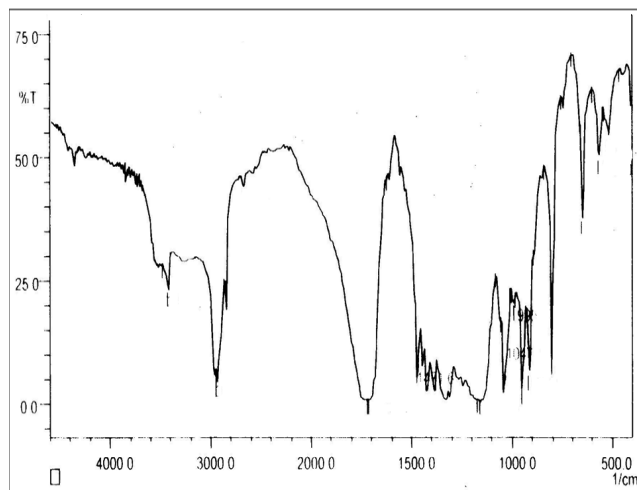


Figure 3: FTIR spectra of poly(buthylsuccinate)

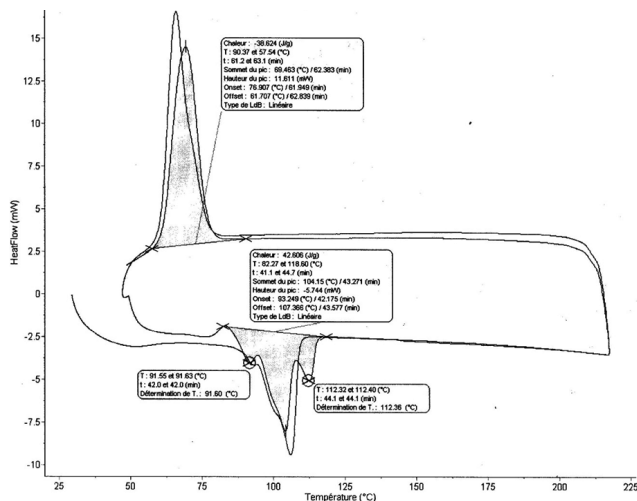


Figure 4: DSC thermogramme of poly(buthylsuccinate)

Microparticles characterization

The mean diameters and size distribution of microparticles were calculated from the results of optical microscopy (OPTIKA STEREOMICROSCOPES / SZM (SZM 1)), by counting more than 500 micro particles using appropriate lenses. Then, the classification of each microspheres' formulation was illustrated by the histograms shown in Figure 5.

The extractions of ATD agent from dried microparticles by absolute ethanol were performed in triplicate under stirring in sealed bottles for 24 h (Table 2).

The resulting solution was analyzed by UV-VIS spectroscopy (Shimadzu UV-2401 PC, Shimadzu, Japan) after an appropriate dilution with ethanol. The loading efficiency (2-aminothiazole loaded %) and the encapsulation efficiency (Yield, %) were calculated according to the following equations:

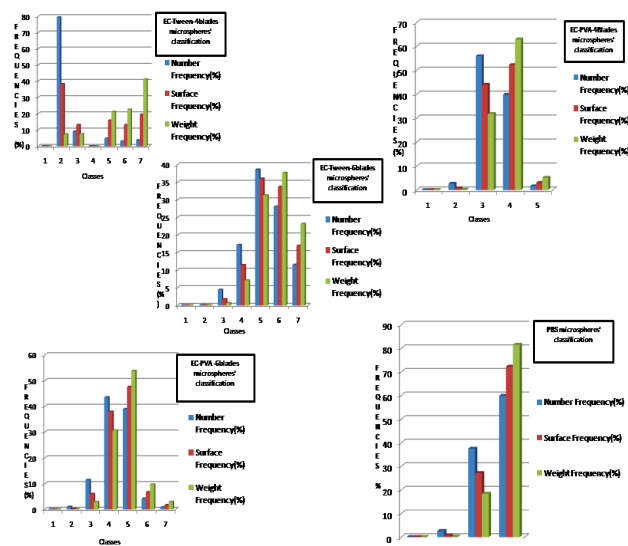


Figure 5: Classification of size distributions of all microspheres' formulations

Table 2: Extractions of ATD agent from dried microparticles by absolute ethanol

Microspheres' formulation	Microspheres' weight(mg)	Absolute ethanol's volume(mL)
PBS microspheres	10	20
EC-Tween-6blades	10	50
EC-Tween-4blades	15	10
EC-PVA-4Blades	10	30
EC-PVA-6Blades	10	50

$$\text{ATD loaded} = \frac{\text{mass of ATD in microparticles}}{\text{mass of microparticles}} \times 100$$

$$\text{Yield} = \frac{\text{mass of ATD in microparticles}}{\text{initial mass of ATD}} \times 100$$

The microspheres were characterized by infrared spectroscopy and the infrared spectra of pure 2-aminothiazole,

EC, PBS and corresponding microparticles so obtained were compared. The FTIR spectra were recorded from 500 cm^{-1} to 4000 cm^{-1} using a Bruker FTIR ALPHA Spectrometer.

Capsules filling

Using the European Pharmacopeia, we gave for each formulation of microspheres (Table 4)²⁵ the appearing volumes, the number of capsule and the diluent volumes.

Table 3: Microparticle characteristics and encapsulation results

Microparticles	$d_{10}(\mu\text{m})$	$d_{32}(\mu\text{m})$	$d_{43}(\mu\text{m})$	Dispersion ^a	ATD _{loaded} (%)	Yield(%)
PBS _{microspheres}	27.69	33.24	34.70	1.25	14.70	16.90
EC _{Tween-6blades}	68.13	80.51	85.11	1.24	13.70	32.90
EC _{Tween-4blades}	05.96	26.10	41.80	7.01	12.40	16.10
EC _{PVA-4Blades}	70.00	70.00	70.00	1.00	15.23	21.88
EC _{PVA-6Blades}	51.00	61.90	65.80	1.29	14.74	25.40

a) calculated as : the number mean diameter calculated as $\sum n_i d_i / \sum n_i$; d_{32} : the surface mean diameter calculated as $\sum n_i d_i^2 / \sum n_i d_i$; d_{43} : the weight mean diameter calculated as $\sum n_i d_i^3 / \sum n_i d_i^2$

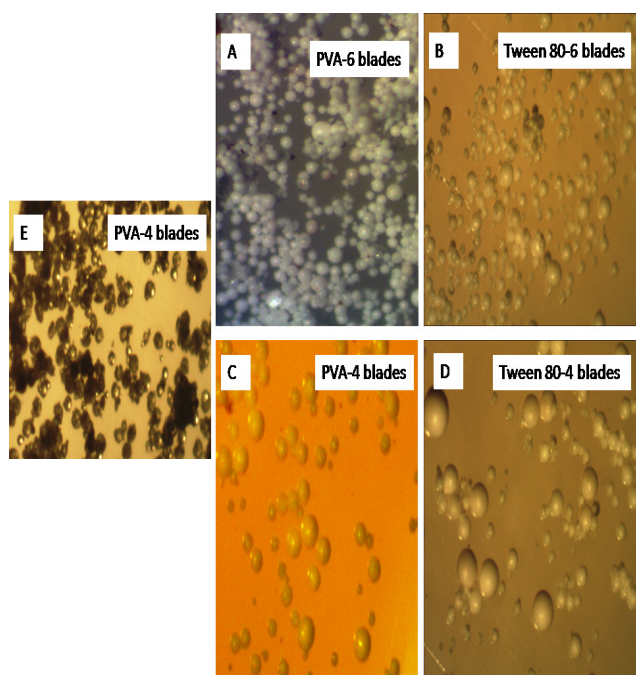


Figure 6: Microscopic images of 2-amiothiazole-loaded ethylcellulose's microparticles spherical form (A, B, C, D) and PBS one(E)

Table 4: Parameters of microspheres' gelatin capsules

mixture	Apparent Volume (mL)	Capsule N°	Diluent Volume (mL)
EC _{Tween80-6blades}	1,1	000	0,26
EC _{Tween80-4blades}	0,4	1	0,08
EC _{PVA-4blades}	0,4	1	0,08
PBS _{PVA-4blades}	0,1	5	0,03

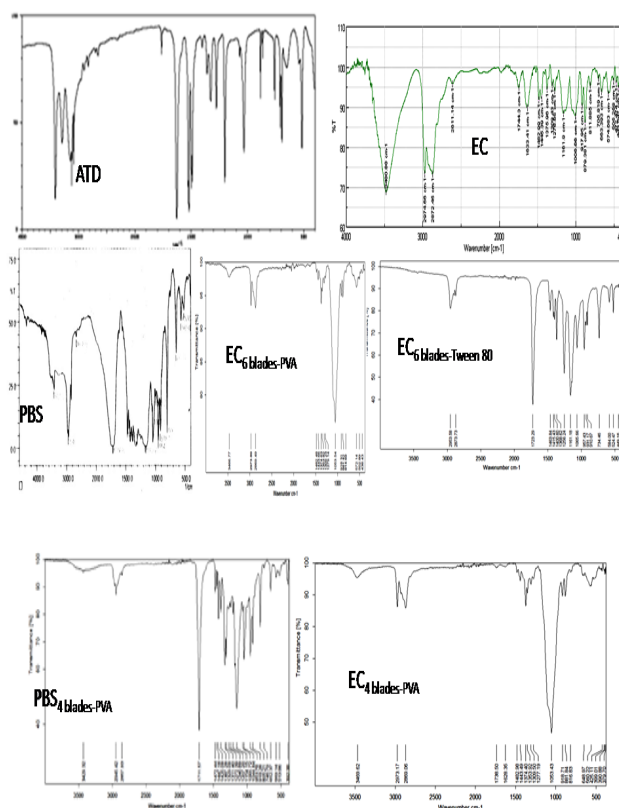


Figure 7: Infrareds pectra of the diffrent microparticles formulations, polymers matrices and 2-aminothiazole

Table 5: Viscosimetric molecular weight of PBS

polymer	$[\eta](\text{ml/g})$ (a)	Mv(b)
PBS	8.445	1648

where: (a) represents the intrinsic viscosity of the polyester measured in chloroform at 20°C; and (b) the viscosimetric molecular weight of PBS calculated from Mark-Houwink equation.

Drug release

The disintegration tests of these gelatinous capsules improved that their degradation take few minutes (4 mn); thing which allow us to consider and study directly the release from micro particles.

All formulations were seen to be intact throughout the dissolution studies. The percentage of drug released from microspheres relative to time is shown in Figure 8.

DISCUSSION

- The reduced viscosity of PBS was calculated using the next equation:

$$\eta_{sp} = \frac{(t - t_0)}{t_0}$$

and the Huggins equation

$$\eta_{red} = \frac{\eta_{sp}}{C} = [\eta] + k_H [\eta]^2$$

Where t and t_0 are the flow times taken for polymer solution and solvent respectively and C is the concentration (g/cc) of solution.

In chloroform solution our polymer has a regular viscosimetric behaviour in a concentration interval from 10^{-3} to 10^{-2} g/cc.

Since the $[\eta]$ is directly proportional to the molecular weight of the polymer by Mark Houwink equation,

$$[\eta] = K \cdot \overline{M}_v^a$$

Where k and a are constants depends on solvent, polymer and conditions

Therefore

$$[\eta] \propto \overline{M}_v^a$$

For our polyester:

$$k = 24.4 \times 10^{-3} \text{ mL/g and } a = 0.79 \text{ at } 20^\circ\text{C.}$$

However the equation 5 will be:

$$[\eta](\text{dL/g}) = 24.4 \times 10^{-3} \overline{M}_v^{0.79}$$

Then, intrinsic viscosity was been determined by extra polling (at a null concentration) the graphic representation of $\eta_{red} = f(C)$ (Figure 9)

Therefore, Viscosimetric molecular weight of PBS is given in Table 5.

- By means of the optical microscope, the surface and morphology of the micro particles were characterised and the size and size distribution were determined. In Figure 7 we note that the populations of micro particles have a homogeneous spherical shape. Taking the micro particles forms into account, the micro particle mean diameter was measured and finally the number mean diameter, the weight mean diameter and the surface mean diameter were calculated by examining 500 micro particles for each formulation. The characteristics of micro particles including the mean diameter, the percentage of 2-aminotiazole-loaded micro particles and the encapsulation yield obtained by extractions are given in Table 3.
- In the IR spectra of the different micro particle's formulations with polymers matrices and pure 2-aminotiazole (Figure 9), we noted the presence of some significant IR bands of 2-aminotiazole in all microspheres formulations spectra at the same wave numbers.

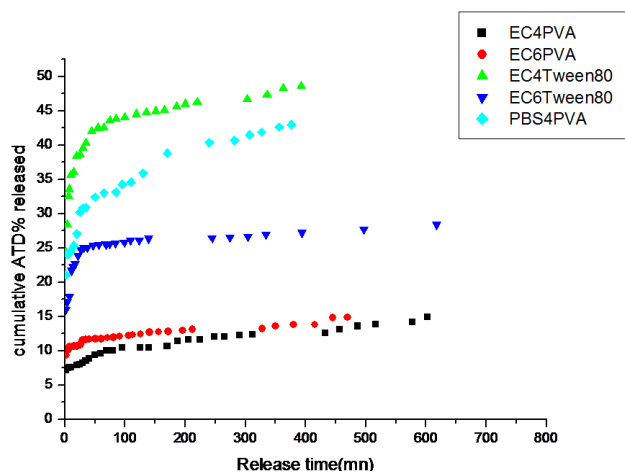


Figure 8: Cumulative release of ATD% from the different microspheres in pH=1.2 at 37°C

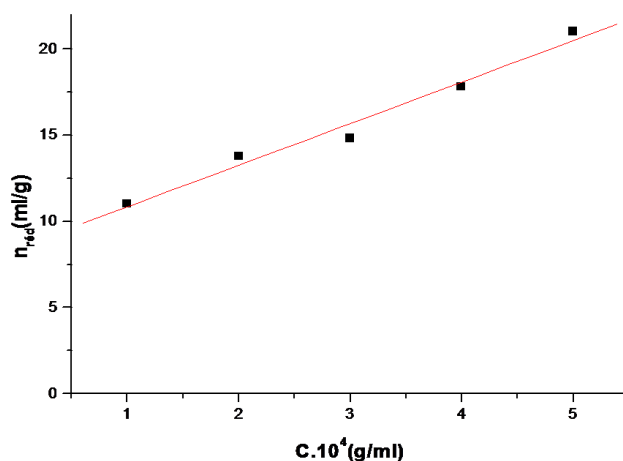


Figure 9: Evolution of reduced viscosity of PBS with concentrations

However, we can consider that microspheres formulations spectra as a sum of pure 2-aminothiazole and polymers matrices spectra. Then, the FTIR analysis confirms the presence of 2-aminothiazole in our different elaborated micro particles.

- We can deduce from the results (see Table 3) that microspheres elaborated from EC with PVA as emulsifier and using 4 blades are mono dispersed but not when increasing the number of blades ($EC_{PVA-6blades}$) where the dispersion increased with 0.29 degrees which is not so far but with Tween 80 and the same number of blades (4 blades) dispersion increased until 7.01 which is so worst. Also from the ATD loaded and the yield values we can deduce that the best formulation is well with the $EC_{PVA-6blades}$ (unitary convergence of dispersion, the best ATD loads and the best yield). However, the effect of the number of blades is well marked. When about the PBS polymer matrix formulations, the only successful one is with PVA emulsifier and four blades which was characterized with its good dispersion (1.25). Then the great effect of emulsifier can be explained by their chemical structures (Figure 10).

Moreover, the encapsulation with PBS has succeeded only with PVA and using 4 blades; which can be explained with emulsifiers chemical structures too as well as when increasing the number of blades microspheres elated.

- From the drug releases studies we can notice the effect of: matrix, emulsifier and blade number (Figure 8) on the drug release from microspheres. The results demonstrated that in the case of EC as matrix and PVA as an emulsifier, the effect of blade number on the release of 2-Aminothiazole is not remarkable. However, its releases using the Tween 80 as an emulsifier depends largely on blade numbers: after 2 h (the time corresponding to the drug retention in the human stomach), the percentages of the drug released from EC4Tween80 and EC6Tween 80 are 45% and 25%, respectively. Then in this case when the number of blades increases the amount of the active agent released decreases; thing which can be explained by the structure of

Tween 80 which favors the formation of more microspheres if we increase the number of blades, then the release from the same pores of the same micro particle is slower than its release from different pores of several microspheres. Also, in the same conditions of emulsifier and blade numbers, the release from PBS's microspheres is faster than from EC's ones. It can be explained by the interactions between the polymer matrix and the enveloped molecules of 2-Aminothiazole due to their polarity as well as the size of micro particles (d_{32}). However, we have noted the significant effect of polymer type on microspheres sizes and the drug release rate from the obtained microspheres. Figure 8 shows that the cumulative release is more speed from the smaller microspheres prepared with PBS' ($33.14 \mu m$) than the EC ones ($70.00 \mu m$). It was reported that for the smaller microspheres, a larger effective area produces a greater number of drug molecules in the surface of the microspheres, which leading to a faster drug release.²⁶⁻³³

Release mechanisms and mathematical analysis

The mathematical description of drug diffusion is often based on Fick's second law.³⁴ In the literature, many theoretical or empirical models are described to explain this process of mass transfer. In our study, we chose four of them for quantitative prediction of controlled drug delivery. The selected models are: the first order, the Higuchi's³⁵ and the Hixson-Crowell's.³⁶ Thus the choice of the best model is based on the value of r^2 , correlation coefficient obtained after tracing experimental results according to the equations corresponding to the selected models.

First Order

$$\log Q_t = \log Q_0 + \frac{K_1 \cdot t}{2.303}$$

Higuchi

$$Q_t = K_H \sqrt{t}$$

Hixson-Crowell

$$\sqrt[3]{Q_t} - \sqrt[3]{Q_r} = K_s \cdot t$$

Where Q_t is the amount of drug dissolved in time t ; Q_0 is the initial amount of drug in the solution (most times $Q_0=0$); Q_i is the initial amount of drug in the

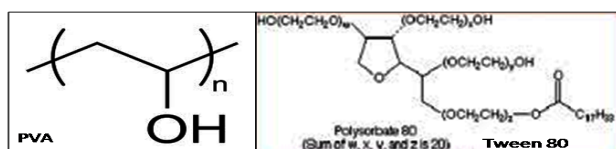


Figure 10: Emulsifiers structures

pharmaceutical dosage form; Q_r is the amount of drug remaining as a solid state at time t ; M_t/M_∞ is the fraction of drug released; K_1 , K_H and K_s are, respectively the first order, the Higuchi's and the Hixson–Crowell's release constants; and n the release exponent that indicates of the mechanism of release.^{35–40}

The Hixson–Crowell model assumes that the drug release is limited by the dissolution rate of the particles, and not by diffusion through the polymer matrix,³⁷ and the Higuchi model able to describe the release of soluble or poorly soluble drug in water from a semi-solid or solid matrix system.³⁵ Therefore, the value of n was used by Peppas⁴⁰ in order to characterize the various release mechanisms. When $n=0.5$ the release mechanism as Fick diffusion, and as a non-Fickian model if n is between 0.5 and 1.0 or $n=1.0$. When $n=0.5$, the drug release is controlled by diffusion and is time-dependent while when $n=1.0$, the drug release is controlled by

swelling and is time-independent with zero order kinetics. Values of n between 0.5 and 1.0 indicate superposition of both phenomena, known as anomalous transport. It is necessary to consider that the exponent values are valid for certain slab geometry, and different values can be derived for spheres and cylinders.³⁴ The model which gave the highest coefficient of correlation r^2 was considered to be the most suitable kinetic model for describing the release of ATD from the microspheres.

Figure 11 gives plots of the fractional drug release as a function of the square root of time, and Table 6 shows the coefficients of correlation and dissolution rate constants of 2-Aminothiazole according to the models studied. We have noted that the fractional release of ATD is proportional to the square root of time during the short time as shown in Figure 11.

Figures 12, 13, 14, 15 and 16 represents the Hixson–Crowell mathematical modeling.

Table 6: Coefficients of correlation and dissolution rate constants of ATD from microspheres

Formulation	Higuchi		Hixson-crowell	
	r^2	K_H	r^2	K_s
PBS _{PVA-4 blades}	0.96509	0.69031	0.96929	4.63109
EC _{PVA-4 blades}	0.99343	0.17406	0.97698	0.2196
EC _{PVA-6 blades}	0.965	0.39283	0.99800	1.11574
EC _{Tween80-4 blades}	0.9900	2.48058	0.98815	5.20217
EC _{Tween80-6 blades}	0.9844	2.12258	0.98752	5.19759

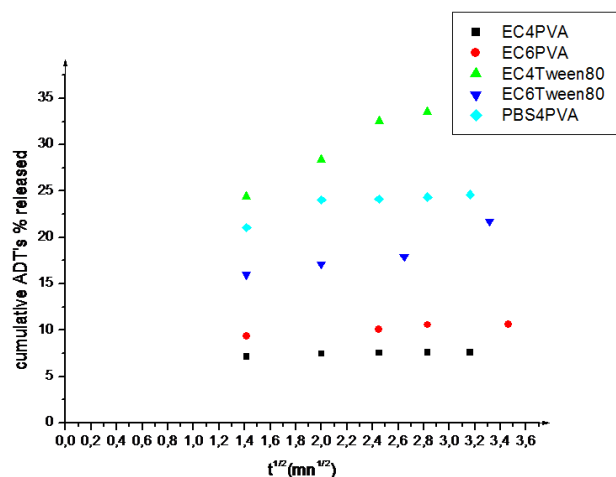


Figure 11: Higuchi plots of ATD% released from microspheres in gastric pH at 37°C

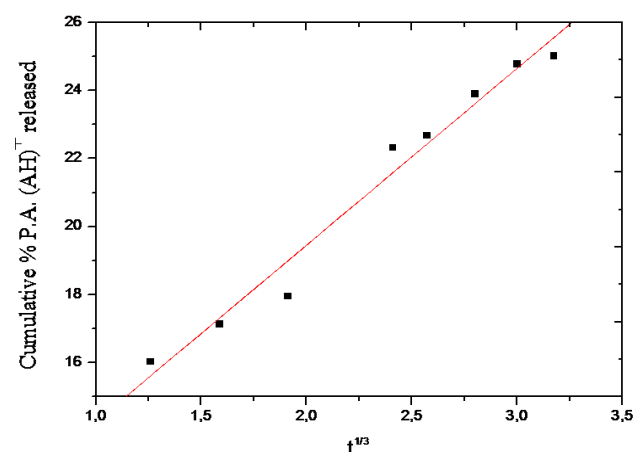


Figure 12: Hixson-Crowell plot of release rate from ECT6 microspheres

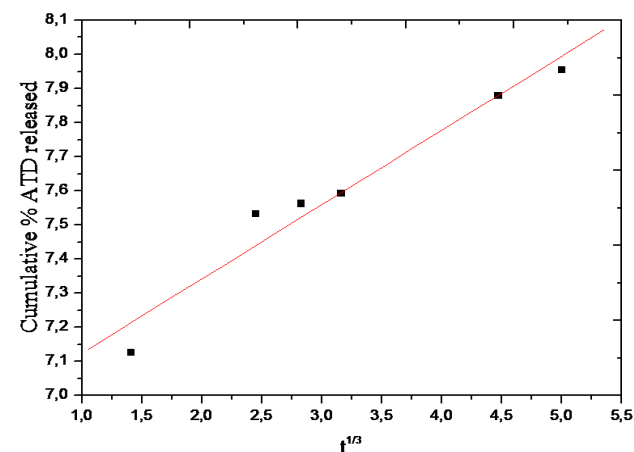


Figure 13: Hixson-Crowell plots of release rate from ECPVA4 microspheres

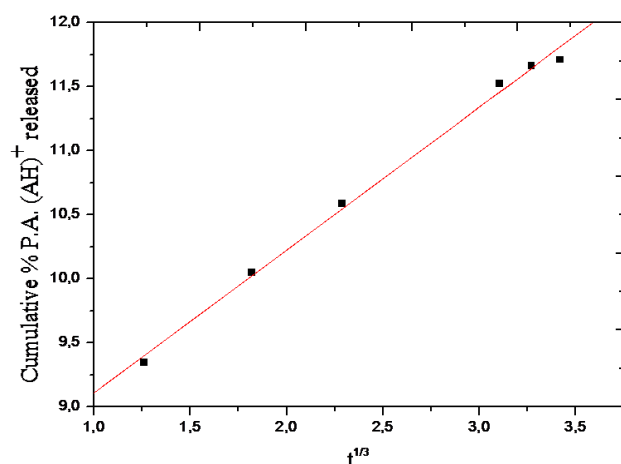


Figure 14: Hixon-Crowel plot of release rate from ECPVA6b-lades microspheres

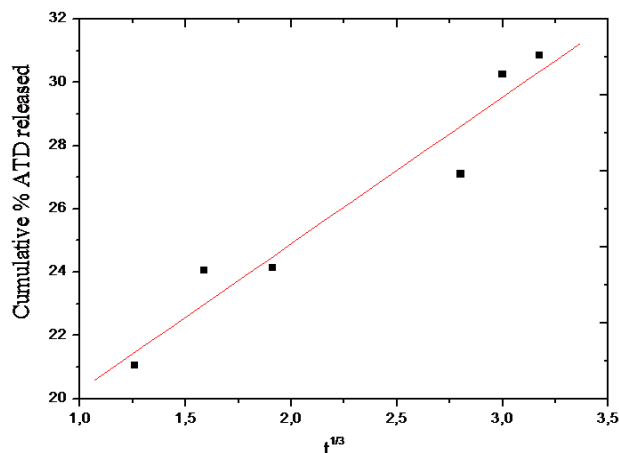


Figure 15: Hixon-Crowel plot of release rate from PBS microspheres

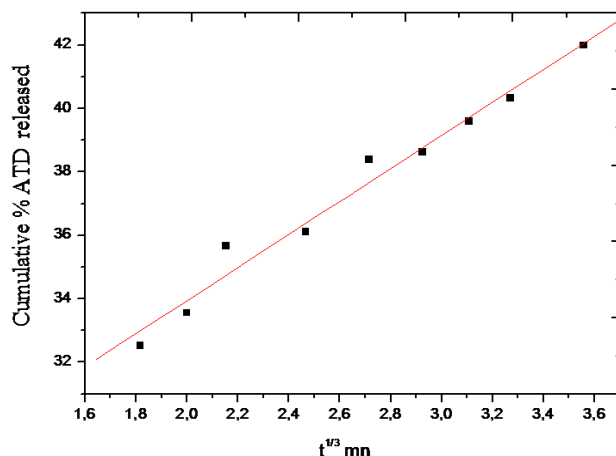


Figure 16: Hixon-Crowel plot of release rate from ECTween80-4blades microspheres

The suitable kinetics model for describing the release of ATD from microspheres was the Higuchi model. The coefficients of correlation r^2 in this model are above 0.96. From the results of Higuchi's equation plots, the dissolution rate constants of drug varied from $0.69031 \text{ min}^{-1/2}$ for PBS, $0.17406 \text{ min}^{-1/2}$ for $\text{EC}_{\text{PVA-4blades}}$, $0.039283 \text{ min}^{-1/2}$ for $\text{EC}_{\text{PVA-6 blades}}$, $2.48058 \text{ min}^{-1/2}$ for $\text{EC}_{\text{Tween80-4 blades}}$ to $0.12258 \text{ min}^{-1/2}$ for $\text{EC}_{\text{Tween80-6 blades}}$. The effect of matrix on the dissolution rate is then notable.

CONCLUSION

This study was focused on the microencapsulation of 2-aminothiazole as an antithyroid agent either by PBS as a biodegradable polyester matrix; which was synthesized and well characterized, its viscosimetric study was done too; and by ethylcellulose (EC_{10}) as a biocompatible

polymer matrix in order to compare micro particles' characteristics (shape, size, dispersion, yield, efficiency, the drug release...). The formulation and the preparation of capsules were studied obeying to the European Pharmacopeia. Also, an important kinetic and mathematical study was been done in order to determine experimentally various release rates.

However, from these studies, we can conclude that the effects of emulsifiers and blades number as physico-chemical parameters have a great impact on the characteristics of the elaborated micro particles (their quality, size, shape, their surface and morphology, the drug loaded...) and then certainly on the drug delivery of the active encapsulated agent. So, in this work all succeeded formulations conduct to a homogeneous spherical shape of micro particles. The only one succeeded formulation with PBS as a biodegradable polyester matrix is with

PVA as an emulsifier and using 4 blades; this formulation conduct to a good dispersion but a low yield. In the other side, among the EC formulations the best one is well with PVA as an emulsifier and using 4 blades (unitary dispersion, good drug loaded as well as a good yield).

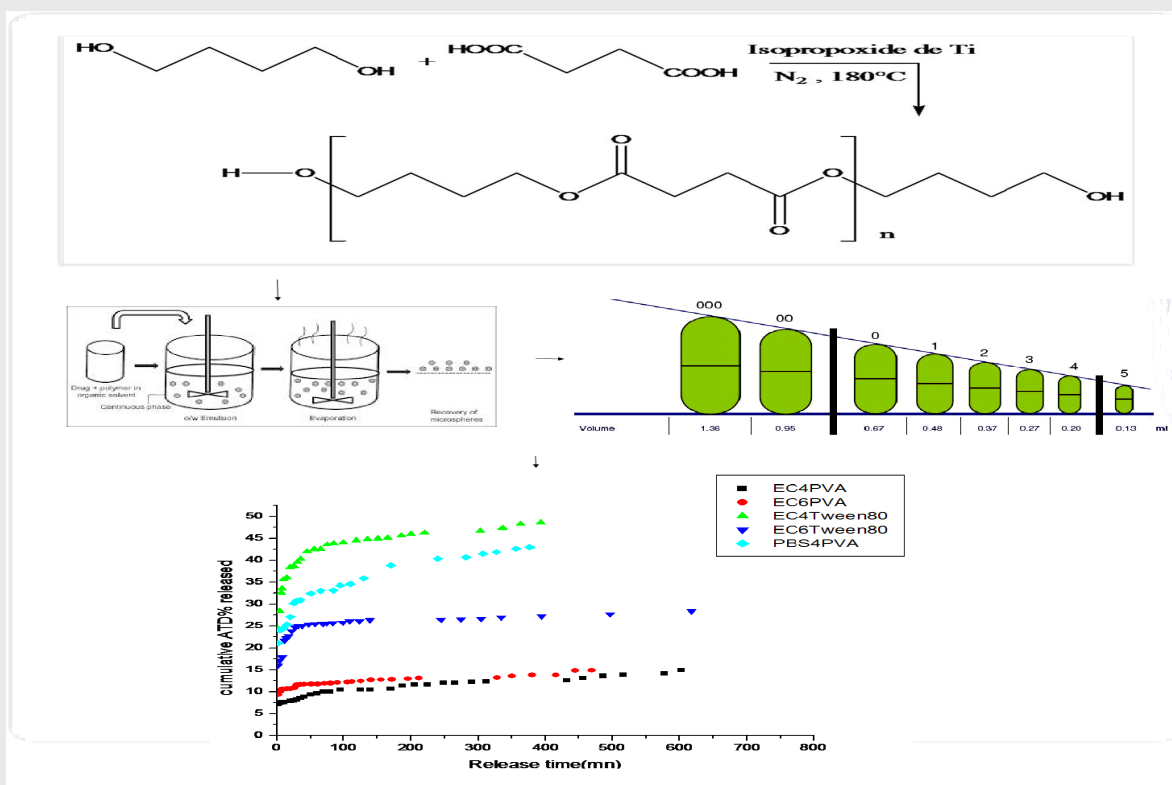
The drug releases are significantly influenced by the nature of matrix. Indeed, the kinetics of drug release obtained by experiment and theory are in good agreement, proving the validity of the chosen model. Diffusion, swelling and dissolution are the governing mechanisms involved in the overall drug release process. Finally, the practical advantage of the models is to identify the mechanism of drug release from our micro particles based on different biodegradable matrices to achieve desired release profiles, thus facilitating the development of a new microencapsulated prodrug.

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PICTORIAL ABSTRACT



SUMMARY

- In order to modify the release rate of our antithyroid agent several microspheres' formulations have been done according to the solvent-evaporation microencapsulation method. In this case, a study of the effect of some physico-chemical parameters on formulations was done.
- In order to eliminate any source of toxicity we have synthesized and well characterized a biodegradable polyester which we used as matrix for microencapsulation. As well as we have used Ethyl cellulose as a biocompatible polymer matrix.
- Elaborated microspheres were well characterized where we calculated the mean diameters and size distribution of microparticles from results of optical microscopy. Best formulations were then marked.
- A kinetic study of the drug delivery was done in gastric pH at 37°C in order to evaluate the release effect and to determine a sustained delivery. All deliveries obey to a Fickian order and are determined by a diffusional step.
- Theoretical analyses of drug release kinetics have been established and Higuchi's and Hixson-Crowell's release models. The suitable kinetics model for describing the release of ATD from microspheres was the Higuchi model. The practical advantage of the models is to identify the mechanism of drug release from our microparticles based on different biodegradable matrices to achieve desired release profiles, thus facilitating the development of a new microencapsulated prodrug.
- The formulation and the preparation of capsules were studied obeying to the European Pharmacopeia.

About Authors

Soumia CHIRANI: Assistant Professor in the Department of Pharmacy, Faculty of Medical Sciences, University Djillali LIABES of Sidi Bel-Abbes, ALGERIA. Researcher member in Laboratory of Organic Physical and Macromolecular Chemistry, in Exact Sciences Faculty, University Djillali LIABES of Sidi Bel-Abbes, ALGERIA.

Mohammed Oussama LEBIG: Doctorant member in Laboratory of Organic Physical and macromolecular Chemistry, Faculty of Exact Sciences, University DjillaliLiabes of SidiBel-Abbes, Algeria.

Sarah BOUAMEUR: Assistant Professor in the Department of Pharmacy, Faculty of Medical Sciences, University Djillali LIABES of Sidi Bel-ABBES. Researcher in Galenic Laboratory, Department of Pharmacy, Faculty of Medical Sciences, University Djillali LIABES of Sidi Bel-ABBES

Meriyem MOUFFOK: Doctorant member in Laboratory of Organic Physical and macromolecular Chemistry, Faculty of Exact Sciences, University DjillaliLiabes of SidiBel-Abbes, Algeria.

Naziha CHIRANI: Doctoral post researcher in Laboratory of Innovation and BioperformanceAnalyse -LIAB, Polytechnic School, University of Montreal Quebec, Canada. Confrence professor in Department of Chemistry, Faculty of Exact Sciences, University DjillaliLiabes of SidiBel-Abbes, Algeria

Nafa CHAFI: Professor in Department of Chemistry, Faculty of Exact Sciences, University DjillaliLiabes of SidiBel-Abbes, Algeria. Researches Chef mumber in Laboratory of Organic Physical and Macromolecular Chemistry, Faculty of Exact Sciences, University DjillaliLiabes of SidiBel-Abbes, Algeria.

Kaddour GUEMRA: Professor in Department of Chemistry, Faculty of Exact Sciences, University DjillaliLiabes of SidiBel-Abbes, Algeria Researches Chef member inLaboratory of Organic Physical and Macromolecular Chemistry, Faculty of Exact Sciences, University DjillaliLiabes of SidiBel-Abbes, Algeria.

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