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## Comparative study of two ethylcellulose forms (raw material and microspheres) carried out through thermal analysis

C. Dubernet<sup>1</sup>, J.C. Rouland<sup>2</sup> and J.P. Benoit<sup>3</sup>

<sup>1</sup> Laboratoire de Pharmacie Galénique et Biopharmacie, Université de Paris XI, UA CNRS 1218, 5 rue J.B. Clément, 92296 Châtenay-Malabry cedex (France), <sup>2</sup> Laboratoire de Chimie minérale, Université de Paris XI, 5 rue J.B. Clément, 92296 Châtenay-Malabry cedex (France) and <sup>3</sup> Laboratoire de Pharmacie Galénique, Faculté de Pharmacie, 16 Boulevard Daviers, 49100 Angers (France)

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### Summary

The solvent evaporation method has been applied to ethylcellulose to prepare microspheres. The integrity of the polymer during the formulation has been followed by monitoring the physicochemical properties before and after the making of microspheres. Thermal analysis allowed the investigation of three factors: (i) polymer sorption, (ii) the glass transition and (iii) its aging — the oxidative degradation process. All the observations are consistent with the view that ethylcellulose microspheres differ mainly from the raw material in their surface state.

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### Introduction

In the pharmaceutical field, ethylcellulose is a widely used polymer. It allows one to prepare sustained release medications of varying types: for example, matrix tablets (Boymond et al., 1981), film-coated tablets (Rowe and Forse, 1980), films (Donbrow and Friedman, 1975), transdermal patches (Ibrahim et al., 1985), microcapsules obtained by a phase separation process (Deasy et al.,

1980), either filling capsules or compressed into tablets (Agyilirah and Nixon, 1980).

In addition to its lack of toxicity for patients, ethylcellulose is chemically stable under storage. Nevertheless, at high temperatures, its stability decreases in the presence of acids or oxygen. Although it does not react with water, it can adsorb it in large amounts when maintained under sufficient humidity. Ethylcellulose is also able to adsorb organic solvents, but has only a weak affinity for methylene chloride (Winkel and Hendrick, 1984). This last property makes ethylcellulose particularly suitable for the preparation of microspheres according to the solvent evaporation method. In addition, the presence of additives may plastify the polymer and decrease the amount

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*Correspondence:* C. Dubernet, Laboratoire de Pharmacie Galénique et Biopharmacie, Université de Paris XI, UA CNRS 1218, 5 rue J.B. Clément, 92296 Châtenay-Malabry cedex, France.

of residual solvent (Lindholm et al., 1984). In this work, the physicochemical properties of ethylcellulose were studied before and after the making of microspheres, in order to follow the integrity of the polymer during the formulation.

## Materials and Methods

### Materials

The ethylcellulose used was Ethocel<sup>o</sup> 20 standard premium grade (Dow Chemical, Paris, France). It is characterized by a substitution degree of 2.5 and an intrinsic viscosity of 20 mPa s (5% toluene/ethanol 80:20 solution at 25°C). Two commercial batches have been studied (batch nos 1 and 2). For the purpose of microsphere preparation, the methylcellulose used was Methocel<sup>o</sup> A15LV (Dow Chemical). Methylene chloride was provided by Prolabo (Paris, France) and used without further purification.

### Preparation of the microspheres

Ethylcellulose microspheres were prepared according to the solvent evaporation procedure. A sample of 2 g of polymer was dissolved in 20 ml methylene chloride. This organic phase was then emulsified in 250 ml of a 0.25% (w/v) methylcellulose aqueous solution, at 350 rpm. Stirring was maintained until the solvent had evaporated completely. Microspheres were then washed with de-ionized water, filtered and dried under vacuum for 12 h.

### Mechanical sieving

For the purpose of thermal analysis experiments, ethylcellulose was sieved into different fractions:

0–150, 150–250, 250–355 and 355–500  $\mu\text{m}$  for the raw material

0–150, 150–250 and 250–355  $\mu\text{m}$  for the microspheres.

### Thermal analysis

Thermogravimetric analysis was performed on a Dupont analyzer (Wilmington, DE, U.S.A.). The samples (5–10 mg) were heated from 20 to 250°C at 5°C/min, under air or nitrogen. Differential

scanning calorimetry was carried out with three analyzers:

Setaram modele (Lyon, France): allows analysis of the samples (80 mg) from –30 to 300°C. Heating was carried out under nitrogen at 4°C/min.

Dupont 990 analyzer: samples (5–10 mg) were heated from 20 to 300°C at 5°C/min, under air or nitrogen.

Mettler (FP80) equipped for DSC (FP85) and hot-stage microscopy (FP84) (Mettler, Paris, France). The samples (2–15 mg) were heated from 20 to 300°C, under air only.

### Gel permeation chromatography (GPC)

A 2% (w/v) ethylcellulose solution in tetrahydrofuran (THF) was injected into two Ultrastyrigel<sup>o</sup> columns (500 Å and 10<sup>4</sup> Å). The solvent flow (THF) was maintained at 1 ml/min. The polymer was analysed by refractometry. Calculations were performed with the help of an integrator (Waters, Saint Quentin en Yvelines, France), polystyrene lattices being taken as references.

### Infrared spectrophotometry

Infrared spectra were recorded on powdered samples, compressed with KBr, using a Pye Unicam SP3-200 spectrophotometer (Cambridge, U.K.).

## Results and Discussion

In the first step, each of the two ethylcellulose preparations was investigated by DSC in order to compare their behaviour under heating. Differences were immediately apparent and prompted us to study three particular properties of the polymer: (1) water sorption, (2) glass transition and (3) oxidative degradation at high temperatures.

### Water sorption

The DSC profiles, for both ethylcellulose raw material and microspheres, show a slight and broad endothermic event between 30 and 100°C. Experiments were performed on a Setaram analyzer from –30°C, which allowed the samples to attain full equilibrium at room temperatures. Under these

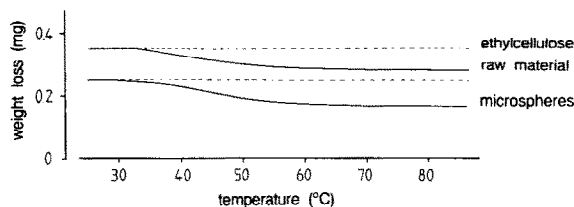


Fig. 1. TGA profiles of ethylcellulose, raw material and microspheres, between 20 and 90 °C.

conditions, the event appeared like a glass transition with a pseudo glass transition temperature  $T$  measured at 42 °C, in good agreement with the published value (Polymer Handbook, 1975). Nevertheless, TGA performed on the same samples showed a weight loss between 30 and 100 °C (Fig. 1), varying from 0.5 to 1.5% of the initial weight, but of similar extent for the raw material and the microspheres when the experiment is carried out on the same day for both samples. In addition, the morphological characteristics of the samples were unchanged after heating at 100 °C.

Consequently, the endotherm observed between 30 and 100 °C is attributed to a loss of volatiles rather than to a glass transition.

The relationship between the weight loss recorded in TGA and the atmospheric conditions leads one to believe that the exchanged volatile is a major component of the air: it must be water. The appearance of the peak and the temperature range in which the phenomenon occurs both show that it might be due to adsorbed water. In such a case, the amount of water fixed by ethylcellulose and released during the DSC experiments will depend upon the relative humidity in which the

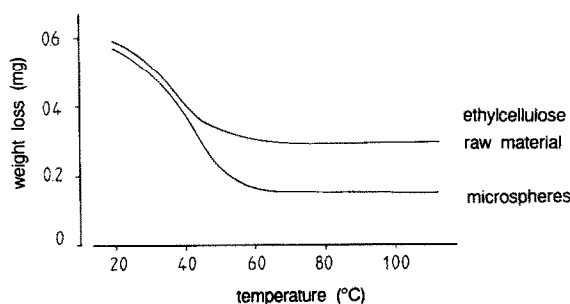


Fig. 2. TGA profiles obtained after 1 week storage of ethylcellulose in a high humidity atmosphere.

samples are stored. To confirm this hypothesis, the following experiments were carried out.

Ethylcellulose raw material and microspheres were stored for 1 week in a vial saturated with water.

The TGA profiles demonstrate an instantaneous weight loss, well before the temperature begins to rise. The weight loss at 130 °C reaches 3.5% of the initial mass for the raw material, and 4.2% for the microspheres (Fig. 2).

Secondly, the weight variations of microspheres submitted to a heating/cooling cycle were recorded. When the TGA experiments were performed in the air, the microspheres recovered their initial weight at the end of the cycle. However, under a stream of nitrogen, the particle weight remained constant during cooling. This must be due to a difference in humidity present in the thermobalance: nitrogen is anhydrous. In contrast, the air was of equal humidity to that of the atmosphere in which the microspheres were stored just before the experiment. The volatiles lost by the microspheres on heating undoubtedly consist of water.

All these experiments confirm that the endotherms observed between 30 and 100 °C for both the raw material and the microspheres are due to the volatilization of adsorbed water. In particular, they allow one to conclude that the amount of residual methylene chloride is close to zero, being undetectable in DSC and TGA. This is a very important finding and offers positive prospects in the future therapeutic use of such particles.

#### *Glass transition determination $T_g$*

The glass transition temperatures of ethylcellulose raw material and microspheres were determined by DSC, during the first run. The values determined were +136 and +133 °C for ethylcellulose batches 1 and 2, respectively, and +128 °C for microspheres, irrespective of the original batch (Fig. 3). These values were confirmed by observations made during hot-stage microscopy: in this temperature range, the particles become transparent. In addition, no weight variation was detectable in TGA. The values determined are comparable to those obtained previously by others (Entwistle and Rowe, 1979; Rowe et al., 1984;

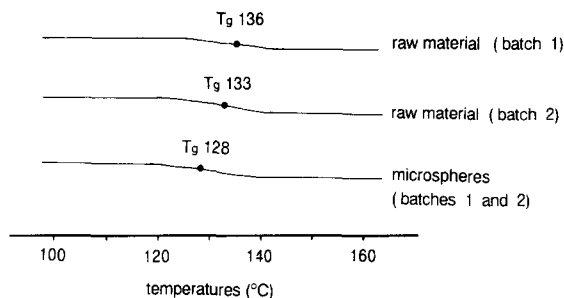


Fig. 3. Glass transition profiles in DSC obtained for two ethylcellulose batches, of the same commercial quality, and for the microspheres prepared from them.

Sakkeliariou et al., 1985), although they measured the  $T_g$  after a repeat run in DSC. We preferred to submit the polymer to a single temperature increase only, degradation of the macromolecular chains increases markedly at temperatures above 130 °C (Kozmina, 1968). The degradation phenomenon involves the fragmentation of the chains, and therefore a decrease in  $T_g$ . As for the results concerning ethylcellulose microspheres, they clearly show that the solvent evaporation process leads to a decrease in  $T_g$  values, from 5 to 8 °C depending on the batch of raw material. We must assume that the polymer undergoes some physicochemical changes during the preparation of microspheres. Previous TGA studies established that the amount of residual methylene chloride is undetectable. Consequently, the residual solvent cannot plastify the polymer and induce a  $T_g$  decrease. On the other hand, a slight decrease in polymer molecular weight is not unlikely. It would be due to the prolonged contact with methylene chloride saturated with acidic water (pH 4.5). GPC analyses have been carried out in order to verify this point, and the results are reported in Table 1. With the consideration that the values are significantly different if the variations exceed 10%, we can state the following conclusions: firstly, the overall molecular masses of raw material batch 1 are greater than those of batch 2. This would explain the 3 °C difference recorded between the  $T_g$  of the two batches; secondly, the molecular mass of ethylcellulose batch 2 remains unchanged after microsphere preparation. In contrast, concerning batch 1, the solvent evaporation process leads to

the partial cleavage of chains, as determined from the slight decrease in molecular mass. The longest macromolecular chains would give lower molecular mass fragments, of the order of 50 kDa. The polydispersity is consequently improved, decreasing from 3.3 to 2.0.

Nevertheless, such variation in molecular mass was not recorded for batch 2 whereas a difference in  $T_g$  approaching 5 °C exists between the raw material and the corresponding microspheres. Consequently, even if in some cases, ethylcellulose undergoes a slight molecular mass reduction, the reason for the  $T_g$  decrease has to be sought elsewhere.

We propose the process of polymer aging to be the cause. Indeed, polymer dissolution in methylene chloride destroyed the organization of the chains. Solvent evaporation leads to a solid mass in which chains are very unlikely to recover their previous physical state. The energy level of ethylcellulose in the microspheres cannot be the same as that of the raw material, obtained via a different route and a long time ago. In addition, at ambient temperature, ethylcellulose is in a glassy state, i.e., very viscous. If chains are set in a conformation far from their equilibrium state, they will readopt their stable state very slowly.

Annealing experiments carried out at 115 °C demonstrated that the raw material itself is not at equilibrium (Fig. 4). Storage at 115 °C led to the modification of the endothermic transition, and to an increase in  $T_g$  values (more than 10 °C after 40 h). In these experiments, equilibrium is not

TABLE 1

GPC analyses performed on two ethylcellulose batches of the same commercial product, and on the microspheres obtained from them

	MW <sub>N</sub>	MW <sub>w</sub>	MW <sub>Z</sub>	MW <sub>v</sub>	Dispersity
Raw material batch 1	36862	121082	266378	121072	3.3
Microspheres batch 1	51864	104158	178840	104130	2.0
Raw material batch 2	28248	86035	215425	86023	3.3
Microspheres batch 2	33158	83066	202678	83047	2.5

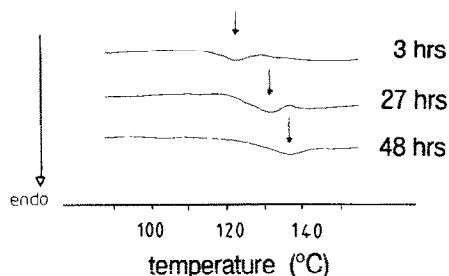


Fig. 4. Annealing experiments carried out on ethylcellulose raw material, at 115°C, showing the progressive change of the glass transition.

reached, and storage cannot be prolonged owing to rapid oxidation of the polymer at this temperature. In conclusion, we state that the slight decrease in  $T_g$  recorded for ethylcellulose microspheres compared to that of the raw material does not reflect a chemical change in the polymer, and only provides information about polymer aging. The process of solvent evaporation is too rapid to allow the macromolecules to organize themselves into a stable state before solidification. The high energy level of the microspheres involves the measurement of a lower  $T_g$ .

#### *Oxidative degradation phenomenon study*

At high temperatures, both the raw material and the microspheres exhibit exothermic DSC peaks. The overall profile is similar for both samples, but the temperature range is 5–8°C lower in the case of the microspheres (Fig. 5).

After the glass transition, the DSC curves recover their baseline. Then, around 165°C, a distinct exotherm appears (A), immediately followed by another, less high and broader (B). When the DSC analysis is performed under a stream of nitrogen, at the same temperatures as used previously, two endothermic peaks can be visualized (Fig. 5). The energy involved is then low, compared to that of the exotherms observed in the air.

TGA experiments carried out in parallel demonstrate a continuous weight loss. The reduction in weight which is low and constant in a nitrogen atmosphere, is enhanced above 170°C in the air. Furthermore, two steps can be identified: the first, between 170 and 187°C, indicates the temperature corresponding to the maximum of peak (A) in

DSC, and the second step marks the stage at which the weight loss increases markedly.

Finally, hot-stage microscopy experiments clearly show the modifications of the polymer structure. In particular, they allow one to associate peak (A) with the coalescence and spreading of the particles (both raw material and microspheres) leading to a fluid at 190°C.

All these experiments provide evidence of the degradation of ethylcellulose. Part of the phenomenon does not need oxygen and is endothermic. In the air, oxidative degradation is superimposed on that observed under nitrogen. Two main processes characterize this overall phenomenon:

scission of the chains, as indicated by the clearly evident viscosity decrease in hot-stage microscopy and reported elsewhere (Kozmina, 1968; Brown and Tipper, 1978);

the loss of volatiles (TGA).

The slight difference in temperature between the raw material and microspheres must be related to the variation in  $T_g$  previously recorded. Never-

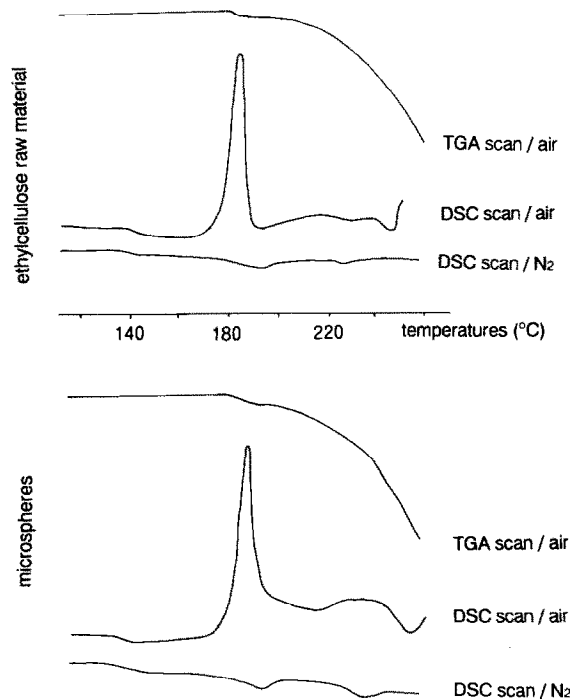


Fig. 5. DSC profile of ethylcellulose raw material and microspheres at high temperatures.

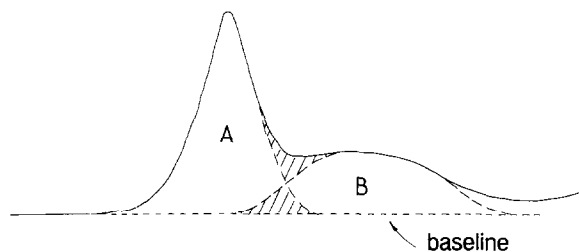


Fig. 6. Drawing of peaks (A) and (B) from the DSC profile, for the purpose of area measurements.

theless, the two samples differ in at least one aspect: the energy involved in the degradation process which is around 2.5-times greater for the microspheres as compared to the raw material. The main difference appears in peak (A). For the purpose of a more precise analysis of the peaks, the exotherms were separated into their two components (A) and (B). Since the curves of the two phenomena overlap, the decreasing curve for peak (A) and the increasing trace for (B) must be drawn as if the exotherms were well isolated and symmetrical. In Fig. 6, care must be taken to ensure that the hatched surfaces are equal. Peak (B) is expected to begin at the temperature corresponding to the peak (A) maximum. Finally, it should be noted that the baseline is drawn according to the one obtained after the glass transition. Under these conditions, the curves do not recover the baseline at 225 °C for all samples. The reason for this lack of baseline recovery is due to a third phenomenon which partially overlaps process (B), and leads to complete carbonization of the polymer.

Evaluation of the areas (A) and (B) allows one to calculate the energy involved in each of the two phenomena for every sample. The values of  $\Delta H_A/m$  concerning peak (A), and  $\Delta H_B$  for peak (B) are reported vs the nature and size of the samples in Figs 7 and 8.

As regards peak (A), it is clearly evident that the  $\Delta H_A/m$  values measured for the microspheres are greater than for the raw material, the respective ranges being 50–110 J/g vs 20–50 J/g. In addition, whereas  $\Delta H_A/m$  does not vary with particle size in the case of the raw material, it is found to increase with decreasing particle size in the case of microspheres. The effect is particularly

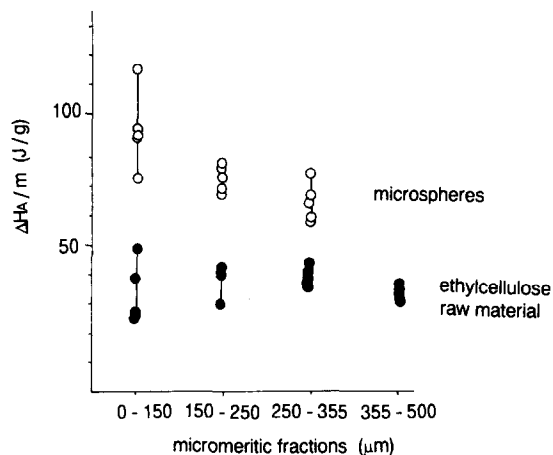


Fig. 7. Values of  $\Delta H_A/m$  measured for each micromeritic fraction, for both the raw material and the microspheres. Five different sample masses have been analysed for a given particle size, ranging from 2 to 10 mg.

pronounced for the two lower particle size fractions. This is consistent with the particle size distribution: the largest particles do not exceed 280  $\mu\text{m}$  which is very close to the upper limit of the 150–250  $\mu\text{m}$  fraction.

As for peak (B), the values determined for the microspheres are higher than with the raw material.

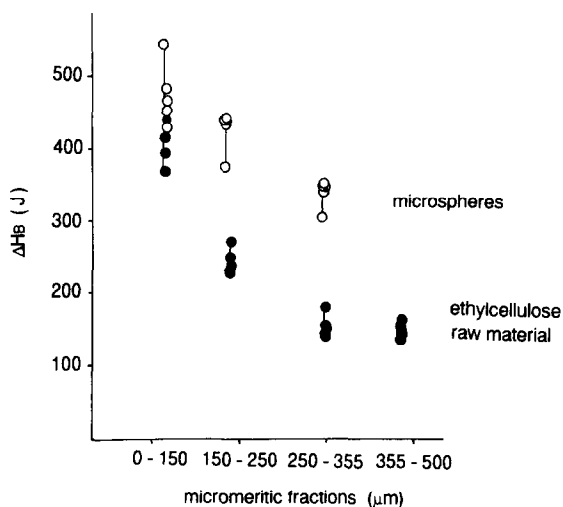


Fig. 8. Values of  $\Delta H_B$ , heat of reaction measured in peak (B), for each micromeritic fraction of the two ethylcellulose samples (raw material and microspheres). The different spots for a given sample correspond to different sample masses (ranging from 2 to 10 mg).

The heats of reaction measured,  $\Delta H_B$ , are unaffected by sample mass for both the raw material and microspheres. On the other hand, the values decrease markedly with increasing particle size for both ethylcellulose forms.

These initial results show a close relationship between the  $\Delta H_B$  values and the spread sample area at  $190^\circ$ , being constant for a given particle size, from one sample weight to another. The chemical process involved in phenomenon (B) must be limited to the sample surface.

From all of the experiments described here, it appears that the difference in behaviour between the microspheres and the raw material rests in the initial stages of the oxidative degradation process, namely (A). Therefore, a difference in chemical nature must exist between the two ethylcellulose presentations. In order to identify the step responsible for the alteration of the polymer during microsphere preparation, two experiments were carried out as follows:

(1) A quantity of 2 g of ethylcellulose raw material was suspended in a 0.25% methylcellulose aqueous solution for 3 h, thereby simulating the microsphere preparation. After drying, the polymer was analysed by DSC. The energy involved during the exothermic degradation between 160 and  $225^\circ\text{C}$  was of the same order of magnitude as that of the initial raw material, and not that of the microspheres (64.3 J/g for a 9.2 mg sample).

(2) A 10% (w/w) ethylcellulose methylene chloride solution was stored for 2 days in a well-closed vial. At repeated intervals, 1 ml was allowed to evaporate on a glass surface, leading to a thick film. DSC analyses showed no change in the energy involved in the exothermic degradation between 160 and  $225^\circ\text{C}$ , even after 2 days.

In conclusion, neither the prolonged contact of dry polymer with a methylcellulose solution nor polymer dissolution in methylene chloride is responsible for the chemical changes in ethylcellulose microspheres. Nevertheless, nothing is known about the prolonged contact of the polymer in methylene chloride saturated with water, or about the macromolecule's behaviour at the water/oil interface.

In order to aid in the discussion of the DSC results, two physicochemical properties of the

polymer were analysed: (1) the amount of peroxides present before and after microsphere preparation; (2) the molecular mass of the polymer before and after the process of solvent evaporation. Regarding the first point, ethylcellulose is expected to be chemically stable on storage. Nevertheless, a very slight extent of oxidation is always found to occur in air, leading to increasing amounts of peroxides (Kozmina, 1968). These products act as catalysts for the oxidative degradation at high temperature, inducing chain reactions. Infrared spectrophotometry showed no noticeable difference between the raw material and the microspheres. Consequently, the microencapsulation process does not lead to a significant increase in peroxides inside the polymer mass.

As concerns the latter point, two ethylcellulose batches were studied, which differed slightly in molecular mass, although both are Ethocel<sup>®</sup> 20 standard. The GPC analyses are reported above. The DSC experiments showed that the longest chains yielded the highest degradation energy (about 3-fold higher for batch 1, as defined in Table 1). Indeed, the greater the length of the chain, the more numerous are the rupture sites that may exist along the molecules. In such a case, the slight decrease in molecular mass observed in some cases after microsphere preparation (Table 1) cannot explain the increase in exothermic energy.

However, the difference recorded between the different micromeritic fractions for the microspheres could originate from a molecular mass variation limited to the periphery of the particles, therefore increasing with the specific area of the microspheres. GPC analyses were carried out in order to verify this point (Table 2). No difference was found to exist between the molecular mass of the different micromeritic fractions for either the raw material or the microspheres.

In conclusion, chain length is not involved in the variation in oxidative energy. Nevertheless, it can be reasonably assumed that such energy variation arises from a chemical change that increases the polymer reactivity.

It has been demonstrated that the stability of the polymer is related to the degree of substitution of the hydroxyl groups. The greater the extent of

TABLE 2

GPC analyses performed on the different micromeritic fractions of ethylcellulose, under the raw material or the microsphere shape

Size fraction ( $\mu\text{m}$ )	MW <sub>N</sub>	MW <sub>w</sub>	MW <sub>Z</sub>	Dispersity
Raw material				
0-150	18890	65298	186246	3.4
150-250	24794	76446	180835	3.1
250-355	22402	70054	173707	3.1
355-500	20550	69172	186150	3.4
Microspheres				
0-150	23119	69730	172535	3.0
150-250	19067	62316	166469	3.3
250-355	19231	62592	167242	3.3

ethoxylation of a polymer, the more stable it is (Brown and Tipper, 1978). Consequently, to explain the higher reactivity of the polymer, that is to say its lower stability in the presence of oxygen at high temperatures, we can assume that some ethoxyl links have been disrupted during the preparation of microspheres, leading to a decrease in the degree of substitution of ethylcellulose. Formation of peroxides would then be favoured and would enhance polymer degradation during the initial part of the degradation process, namely (A). Nevertheless, to explain the existence of such a relationship between  $\Delta H_A/m$  and microsphere size, since a similar variation was not observed for the raw material, the assumption is made that the chemical change in the polymer is only sensitive at the microsphere surface. Indeed, the reaction would be favoured at the water/oil interface, due to the presence of H<sub>2</sub>O. The fall in the degree of substitution would be more marked for smaller particles, for which the specific area is greater than for larger particles. The stability of the polymer would therefore undergo greater alteration in the case of small microspheres.

In conclusion, recalling that the aim of this work was to determine whether ethylcellulose was altered by the preparation of microspheres, the results of the present investigation lead us to conclude that the major physicochemical characteristics of the polymer remain unchanged (residual solvent content, molecular mass). However, we have demonstrated that the polymer becomes more

sensitive to oxygen when in the microsphere form, and we came to rely upon this property to indicate a chemical change in the polymer, limited to the particle surface.

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