Colloid & Polymer Science Colloid Polym Sci 272:211–219 (1994)

Study of the interfacial polycondensation of isocyanate in the preparation of benzalkonium chloride loaded microcapsules

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Abstract: The preparation of benzalkonium chloride loaded microcapsules was performed by interfacial polycondensation of isocyanates. The present study was made in order to clarify parameters affecting microcapsule wall formation during the course of polymerization. The results presented here show that many interrelated parameters are involved during the microcapsule formation. Each individual component introduced in the preparation was shown to have an effect either on the morphology of the microcapsules or on the mechanical resistance. Benzalkonium chloride seemed to interact mainly in the interfacial polymer precipitation step through a salt effect, or influence the polycondensation reaction rate acting as a catalyst. A contribution of the hydroxylic functions of the surfactant in the polycondensation reaction of the isocyanate was also highlighted. Finally, the organic phase composition was found to be able to modulate the reactivity of hydroxylic functions of the surfactant, leading to very slow reactions in pure xylene. These effects were related to the characteristics of the microcapsules obtained according to different compositions of the formulation system.

Key words: Isocyanate – benzalkonium chloride – interfacial polycondensation – microcapsules

Introduction

Microcapsules consist of hollow polymeric spheres with a range of diameters from nanometers to millimeters, and which exhibit a reservoir structure [1]. They are widely used in various processes, but one common aim is the separation of a component from its environment. This can be achieved by the entrapment of the active ingredient in the cavity of the microcapsule which is surrounded by a polymeric shell. Many methods for the preparation of microcapsules have been reported in the literature [2–6] since Green and Schleicher [7] patented the first process in 1956. One of the most feasible and widely used techniques is based on interfacial polycondensation [8]. In general, this procedure consists firstly of preparing an emulsion of two immiscible phases, each containing one complementary monomer. Following emulsification, the polymeric shell of the microcapsule is then formed at the surface of the droplets of the dispersed phase through a polycondensation reaction [9]. This technique was described for different types of monomers and led to microcapsules with different shell properties [4, 9, 10–12].

One crucial step controlling the obtaining of microcapsules is emulsification [9]. The formation of the polymeric shell surrounding the material to be encapsulated nevertheless remains the key step in the case of the interfacial polycondensation process [4]. Interfacial polycondensation reactions can be affected by many interrelated variables such as the nature and the composition

of the two immiscible phases, the concentration of reactants, the partition coefficient of each reactant between the two phases, the swelling or solubility of the newly formed polymer, the presence of additives such as salts and surfactants, and the reaction rate between monomers [13]. In the case of the preparation of microcapsules, parameters inherent to the fact that interfacial polycondensation occurs in an emulsion have also to be considered [4]. A first attempt to model the interfacial polycondensation reaction at the interface of a droplet dispersed in a continuous phase was published by Pearson [14].

In previous papers, we have described conditions of preparation of a reacting medium adapted to the microencapsulation of an amphiphilic compound, benzalkonium chloride, by interfacial polycondensation of isocyanates [15, 16]. In this paper, we report a study of the effect of different factors inherent to the interfacial polycondensation reaction of isocyanates in terms of their effect on the formation and on the properties of the benzalkonium chloride loaded microcapsules obtained by this method. The microscopic aspect of the microcapsules obtained from different batches was investigated after preparation under various conditions. Mechanical resistance of the microcapsules was described in terms of the resistance to a shear stress. Finally, studies of the influence of the surfactant type and of the solvent composition on the rate of the polycondensation reaction were made using viscosity measurements.

Experimental section

Materials

The isocyanate used in this work was methylene diphenyl diisocyanate (Desmodur 44V20) purchased from Bayer (Puteaux, France). Polyoxyethylene sorbitan trioleate (Tween 85) from Sigma (St. Louis, USA) and modified polyesters (Hypermer A60, Hypermer B246) from ICI (Kortenberg, Belgium) were used as surfactants. Coconut oil-derived triglycerides C8-C10 (Miglyol 812) from Hüls (RFA) and xylene from Prolabo (Paris, France) were employed as lipophilic phases without further purification. Benzalkonium Chloride (Barquat MS 100) was kindly supplied by Lonza Co. (Puteaux, France).

Preparation of the microcapsules

The preparation of the microcapsules was carried out at room temperature according to the method described previously [15, 16]. Briefly, 30 ml of an aqueous phase containing 0, 0.3, 1.5, or 3 g of benzalkonium chloride was dispersed at 2500 rpm with a Microvortex (Grenier-Charvet, Rennes, France) in 200 ml of a lipophilic phase. The lipophilic phase consisted of different mixtures of xylene and Miglyol 812 in which 15 g of isocyanate and 7 g of surfactant were added. When the desired droplet size of the emulsion was reached, stirring was carried on using a blade stirrer at a lower speed (350 rpm, Digital 2000, Heidolph, RFA) until the polycondensation was complete (18 h). Finally, the microcapsules were recovered by filtration, washed with cyclohexane and dried at room temperature.

Microscopic aspect of the microcapsules

The microscopic aspects of the microcapsules were observed both by light microscopy (Olympus BHS, OSI, France) and scanning electron microscopy (Leica, Rueil Malmaison, France).

Study of the mechanical resistance of the microcapsules

A study of the mechanical resistance of the microcapsules was performed by submitting the microcapsules to a shear stress in a coaxial cylinder of a Couette viscometer (gap: 0.21 cm). Microcapsules were washed twice with distilled water and were then suspended in an aqueous solution containing Dextran 2000 (Sigma, St Louis, USA). The concentration of the microcapsules in the dispersion was 5% (v/v). The viscosity of the dispersion was evaluated with a Brookfield viscometer (Brookfield Eng. Lab., Stoughton, USA) and the density was measured with a pycnometer. The suspension was then placed in the gap of the coaxial cylinder of the Couette viscometer and submitted to a given shear stress for 30 min at 25 °C. Measurements were performed on laminar and turbulent flow rates. Under these conditions, the value of the shear stress can be approximated knowing the number of Taylor

(*TA*), given by

$$TA = \frac{U_i h}{v} \times \left(\frac{h}{R_i}\right)^{1/2}, \quad (1)$$

where h is the thickness of the gap, v, the kinematic viscosity, U_i the rate of rotation of the inner cylinder, and R_i the radius of the inner cylinder.

In the case of laminar flow rates ($TA < 41.3$), the shear stress, τ, is given by

$$\tau = \frac{2\mu\Omega R_i^2 R_e^2}{r^2(R_e^2 - R_i^2)}. \quad (2)$$

In this equation, μ represents the dynamic viscosity, Ω is the angular velocity, R_i is the radius of the inner cylinder, R_e the radius of the outer cylinder, and r is the mean radius.

In case of turbulent flow rate ($TA > 400$), the shear stress can be deduced from the Taylor graph [17]. The maximum shear stress developed under experimental conditions was 20 000 dyn/cm^2. The mechanical resistance of the microcapsules was determined by viewing their microscopic state with an optical microscope before and after the application of the shear stress.

Viscosity measurements

Polymer formation was monitored by measuring the viscosity of systems containing 5% (w/w) of isocyanate, 4.5% (w/w) of surfactant in different solvents. The solvents consisted of mixtures of xylene and Miglyol 812 in different proportions (0–100% of each). The viscosity measurements were carried out in a cone and plate (8°) syncroelectric viscometer (Brookfield Eng. Lab., Stoughton, USA).

Visualization of the location of the film formation

Depending on the interfacial polycondensation reaction and the nature of the system, the initial site of polycondensation and subsequent growth of film may occur at either interface [4, 18]. The method described by Morgan and Kwoleck [18] was used here in order to clarify the loci of the polycondensation reaction during the formation of the polymer constituting the microcapsule wall.

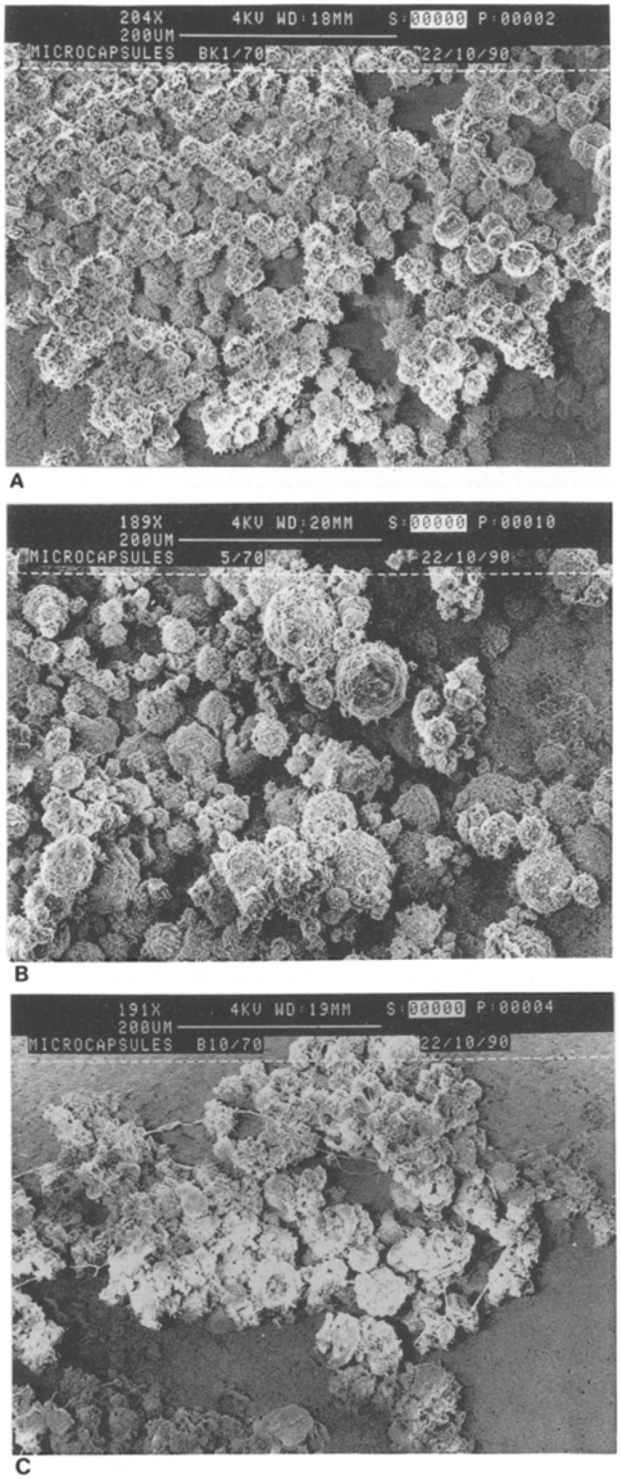
Finely divided carbon black powder was introduced at the interface of a two-phase unstirred liquid/liquid system. The upper organic phase consisted of a mixture of 20% xylene and 80% Miglyol 812 containing 1% (w/w) isocyanate. The lower aqueous phase consisted of demineralized water. Carbon black powder is insoluble in both phases, but is wetted by water. Following polycondensation, its location, with respect to the polymeric film, indicates the phase in which the film is formed and grown depending on the time of observation.

Results and discussion

As shown in previous papers, microencapsulation of benzalkonium chloride was performed by interfacial polycondensation of isocyanates [15, 16]. In this case, a facile understanding of the mechanism of the polycondensation of the isocyanate at the oil-water interface can be gained through the following reaction scheme. Isocyanate solubilized in the continuous lipophilic phase of the emulsion is first hydrolyzed to an amine due to the presence of water in the dispersed phase. In turn, amine molecules react with neighboring isocyanate molecules to form the microcapsule wall at the end of the preparation [18]. This very simple scheme really should not occur during the formation of the benzalkonium chloride loaded microcapsules since the microencapsulation medium is much more complex than a simple mixture containing water, pure solvent, and pure monomer. The medium, in fact, contained benzalkonium chloride, one surfactant, one or two organic solvents, and water. Under such conditions many side reactions may occur [18]. Furthermore, interfacial polycondensation reactions are affected by many variables inherent to the method of microencapsulation such as the agitation rate and the curvature of the interface [4, 14]. This last parameter is directly related to the droplet size of the emulsion.

To gain a better understanding of particle formation in the case of the preparation of benzalkonium chloride-loaded microcapsules, we have studied the influence of the concentration effect of benzalkonium chloride on the microcapsule morphology and on the microcapsule mechanical resistance. The scanning electron microphotographs

are given in Fig. 1. Microcapsules prepared without benzalkonium chloride (Fig. 1A) were spherical, individual entities with irregular surfaces. When 5% (w/w) of benzalkonium chloride were added into the aqueous phase of the emulsion, the recovered microcapsules became less spherical. Notably, holes appeared on the surface as shown in Fig. 1B. This phenomenon was enhanced when benzalkonium chloride concentration was even increased (Fig. 1C). Some fragments of polymer could be observed for the highest tested benzalkonium chloride concentration (10% w/w in the aqueous phase) (Fig. 1C). However, for the same benzalkonium chloride concentration (10% w/w) together with a higher quantity of the surfactant (Hypermer A60) (4.5% w/w instead of 2.4% w/w) and by increasing the temperature of the preparation (45 °C instead of room temperature), spherical microcapsules with a regular shape could be recovered (Fig. 2). These results clearly demonstrate that the composition of the encapsulation system in terms of benzalkonium chloride concentration and the process variables affect the morphology of the microcapsules. Thus, this means that these modifications of the schedule have significantly affected the course of the polymer wall formation during the microencapsulation process.



The mechanical resistance was studied for microcapsules prepared with different benzalkonium chloride concentrations and with two ratios of xylene and Miglyol 812 (15% xylene, 85% Miglyol 812 and 30% xylene, 70% Miglyol 812). Hypermer A60 concentration was kept constant (2.4%). The results reported in Fig. 3 show that an increase of the benzalkonium chloride concentration decreases the mechanical resistance of the microcapsules. Microcapsules prepared with an aqueous solution containing 1% (w/w) of benzalkonium chloride were not broken even after the highest shear stress application (30 min, 20000 dyn/cm^2). In contrast, microcapsules obtained in the presence of higher concentrations of benzalkonium chloride (5 and 10% w/w) were more brittle and could be broken after the application of the lowest shear stress. The nature of the organic phase did not significantly affect the minimum shear stress which induced the breakage

Fig. 1. Microphotographs of microcapsules prepared at room temperature in a system containing Hypermer A60 (2.4%) and Desmodur 44V20 in the organic phase composed by 30% xylene and 70% Miglyol 812 and different concentrations of benzalkonium chloride in the aqueous phase. Benzalkonium chloride concentrations were A) 0% B) 5% and C) 10% w/w in the aqueous phase

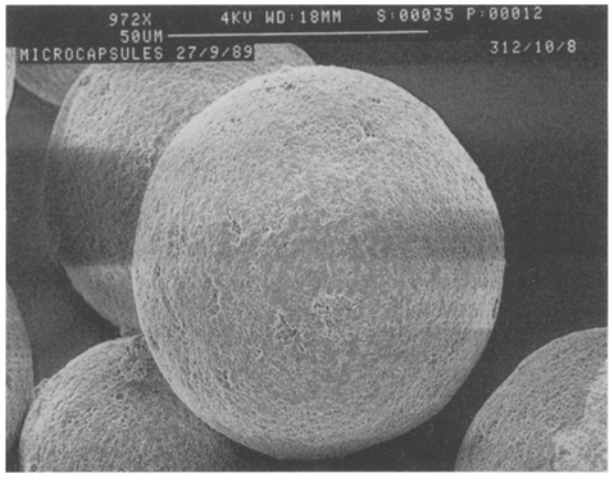


Fig. 2. Microphotograph of microcapsules prepared at 45 °C in a system of the same composition as in Fig. 1C except that Hypermer A60 concentration was 4.5%

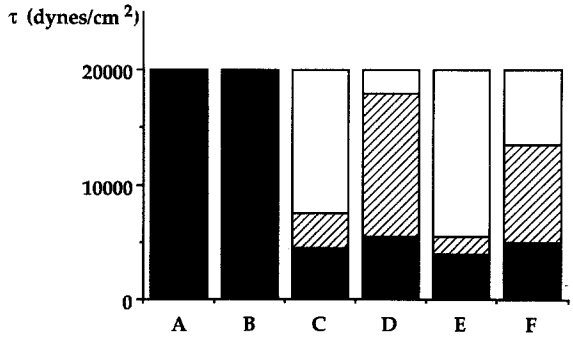


Fig. 3. Evaluation of the mechanical resistance of the microcapsules after a shear stress for 30 min at 25 °C. Benzalkonium chloride concentrations were 1% (A, B), 5% (C, D) and 10% w/w (E, F) in the aqueous phase. The organic phase composition was 15% xylene and 75% Miglyol 812 for the microcapsules A, C and E, and was 30% xylene and 70% Miglyol 812 for the microcapsules B, D and F. □ microcapsules were all broken, for ▨ only a slight proportion of the microcapsules was broken, and ■ microcapsules were not broken

of microcapsules. This parameter seems to have a greater effect on the threshold in which almost all the microcapsules were broken. Results obtained from the mechanical resistance study were consistent with the change of the microcapsule morphology observed with increasing concentrations of benzalkonium chloride. It seems that the microcapsule wall became more porous and brittle when the benzalkonium chloride concentration was increased. This effect can be related to an increase of the rate of precipitation of the polymer at the surface of the dispersed droplets during the early stage of the formation of the microcapsule wall corresponding to the formation of the primary membrane. It suggests that the higher the rate of precipitation, the higher the porosity and the worse the uniformity of the polymer film formed [4]. In the similar way, the rate of the polymer precipitation can be related to the rate of the formation of the polymer and to its solubilization in the medium.

In the present case, benzalkonium chloride should act in both levels. Quaternary ammonium compounds are known to be accelerators in many polycondensation reactions [19–22]. They are also used as catalysts in polyurethane synthesis [23]. Furthermore, in some cases they have been described as promoters of the formation of high molecular weight polymers [21]. Benzalkonium chloride should thus act as an accelerator of the rate of the polymer formation and also influence the molecular weight of the polymer formed. These two combined effects result in an increase of the polymer precipitation rate and the formation of badly shaped microcapsules for the highest benzalkonium chloride concentration tested. Another parameter which has to be taken into account in order to interpret the results of the change of both morphology and mechanical properties of the microcapsules is the polymer swellability. This parameter can be affected by many factors such as the nature of the organic phase and the presence of salts [4]. Benzalkonium chloride should also act through a salt effect on the solubility of the polymer and on the swellability of the polymer film after its deposition on the surface of the dispersed phase. Following this rationale, both the precipitation rate and the polymer growth should be affected [4]. The morphology of the microcapsules may be altered as a consequence of these effects.

The changes in mechanical resistance observed with increasing benzalkonium chloride concentrations can be interpreted in the same way as the modification of the morphology of the microcapsules. Benzalkonium chloride was believed to be responsible for inducing crucial modifications during the course of the wall formation. In addition, benzalkonium chloride can affect the polymer characteristics and thus microcapsule wall properties. The effect of the organic phase

composition is less evident. It may be hypothesized that the nature of the organic phase influences microcapsule wall swellability, changing its rheological properties and, consequently, the mechanical behavior. The major parameter, affecting the mechanical resistance of microcapsules remained, nevertheless, the concentration of benzalkonium chloride.

In a second study, the location of the formation of the polymer film was determined and the influence of the composition of the organic phase examined in a two-phase unstirred system and a one-phase system, respectively. These conditions were not exactly the same as in microcapsule preparation. They do, however, permit observable effects which give a better understanding of microcapsule wall formation. The method used to locate the interface where the polymer was formed and grown was first described by Morgan and Kwolek [18] . Carbon black powder, spread on the aqueous side of the interface of the unstirred medium of microencapsulation, was not included in the thickness of the polymeric film after recovering. This result indicates that the polymeric film was formed and grown in the organic phase. By analogy, during the formation of benzalkonium chloride loaded-microcapsules, the same phenomenon should occur. This hypothesis can be supported by the fact that both the isocyanate and the derived amine entities formed at the interface by water hydrolysis are both liposoluble [24].

Since the polymer was formed and grown in the organic phase, the nature of the components and composition of this phase should affect the course of the polycondensation reaction. In order to follow progressively the appearance of the polymer in the organic phase, viscosimetric measurements were performed as a function of time. In experiments performed with reactants carrying at least two functional groups per molecule, a sudden increase of the viscosity medium, measured as a function of time, indicates that a polymer is formed [25]. This behavior is characteristic of polycondensation reactions. In our systems containing organic solvents, monomer and surfactant, no polymer should appear, as a result of the absence of complementary monomers. However, the surfactant Hypermer A60 used for the preparation of the microcapsules is known to possess free hydroxylic functions [26]. Consequently, this compound is able to react with isocyanates and induce the formation of a polymer [27]. It should thus be incorporated into the polymer structure. The data depicted in Figs. 4 and 5 clearly show a sudden increase of the medium vicosity. This implies that a polycondensation reaction occurs in these systems. For systems with different compositions of the organic phase (Fig. 4) this effect was obtained only for mixtures of Miglyol 812 and xylene and pure xylene. In contrast, no significant increase of the viscosity of the medium was detectable for the system containing 100% of Miglyol 812. In this case, there was no induction of polycondensation during the time of the experiment. This difference can be attributed to the ability of the solvent to establish hydrogen bonds

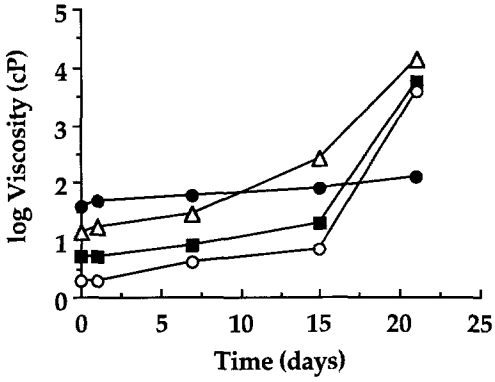


Fig. 4. Variation of the viscosity of media containing isocyanates, Hypermer A60 and various mixtures of xylene and Miglyol 812. The ratios between xylene and Miglyol 812 were respectively: ● 0/100, ■ 50/50, △ 20/80, ○ 100/0

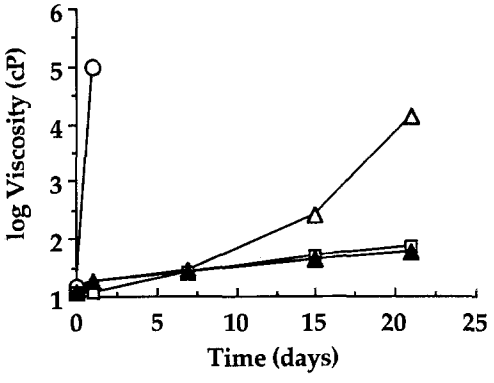


Fig. 5. Variation of the viscosity of media containing isocyanates, a mixture of 20% xylene and 20% Miglyol 812 and different types of surfactants: △ Hypermer A60, ▲ Hypermer B246, ○ Tween 85, □ no surfactant

with the hydroxylic groups borne by the surfactant [27]. This interaction led to alcohol-solvent complexes with different reactivities towards isocyanate. Oberth and Bruenner [27] have demonstrated the enhancement of alcohol-solvent complex formation diminishes isocyanate reactivity with surfactant. The extent of complex formation between alcohol and solvent was shown to be related to the mutual solubility parameters of the two components [27]. We have found, according to data given by Oberth and Bruenner [27] and by Burrell [24], that this effect is even more dependent on the partial solubility parameter due to the hydrogen bonding. The partial solubility parameter due to the hydrogen bonding of Miglyol 812 was calculated according to Hansen formula [28]. It was found to be equal to 3.05 $(cal/cm^3)^{1/2}$, whereas the partial solubility parameter due to the hydrogen bonding of xylene is equal to 1.5 $(cal/cm^3)^{1/2}$ [24]. This indicates that Miglyol 812 should have a higher affinity for the hydroxylic groups of the surfactant than xylene and should form complexes more easily. Thus, this effect reduces the reactivity of the hydroxylic groups of the surfactant with the monomer leading to slower polycondensation reaction rate. This was clearly demonstrated by the slow increase in the viscosity obtained for the system containing 100% Miglyol 812 (Fig. 4). In medium containing xylene, the interactions between the hydroxylic groups of the surfactant and the solvent were decreased, indicating that the hydrophilic groups were more reactive towards isocyanates, leading to faster polycondensation reactions. Very notable increases in viscosities of systems containing xylene were found (Fig. 4).

The reactivity of the isocyanate in different organic media alone cannot account for the formation of very brittle microcapsule in some instances and readily isolatable, well formed microcapsules in others (Table 1). In the microencapsulation medium, surfactant molecules are highly concentrated at the surface of the droplets of the aqueous dispersed phase. The polycondensation reaction takes place at this site and requires the diffusion of monomer molecules from the bulk of the organic phase to the droplet surface. This phenomenon should occur more slowly in a good solvent than in a poor solvent of the monomer. This is another parameter which should control the formation of the microcapsule wall acting on the growth of the thickness of the polymer film. In the present case, isocyanate monomers were found to be much more soluble in xylene than in Miglyol 812. As a result of all these combined effects, the organic phase composition can play an important role during the two steps of the polymeric film formation. The first step consists of the formation of the primary membrane by precipitation of the growing polymer. The way in which precipitation is induced affects the permeability properties of this membrane and is of paramount importance for the success of the second step, the formation of the film [4]. The formation of a non-porous primary membrane can stop the growth of the polymer film thickness, leading to very brittle polymer films and, in turn, to brittle microcapsules. This phenomenon could have persisted in the systems containing 0 to 50% Miglyol 812. In such systems the appearance of the polymer at the surface of the droplet is enhanced due to the high percentage of xylene in the medium and, in turn, to the high reactivity of the hydroxylic groups of the surfactant. By contrast, the growth of the polymer is probably slow because of the good solubility of the monomer in xylene. The appearing polymer should slowly precipitate at the interface of the droplet, leading to a non-porous film inhibiting subsequent growth of the polymeric film. In systems containing higher percentages of Miglyol 812, the local polymer formation at the surface of the droplet occurred slowly. In contrast, the growth of the polymer should be fast because of the low solubility of the monomer in Miglyol 812. Following this argument, polymer precipitation should be more rapid, leading to a more porous primary membrane and then to the growth of the

Table 1. Influence of the organic phase composition on the recovery of microcapsules prepared with a concentrated aqueous benzalkonium chloride solution (10% w/w)

Organic phase composition		Microcapsule batches
Xylene (%)	Miglyol 812 (%)	
100	–	very brittle
80	20	very brittle
60	40	very brittle
50	50	very brittle
40	60	readily isolated
30	70	readily isolated
20	80	readily isolated
–	100	some agglomerates formed

polymeric film. The second step of interfacial film formation, corresponding to the thickening of the film, can be affected by the swellability of the polymer by the solvent. No correlations were drawn concerning this effect from our experimental findings.

The data presented in Fig. 5 show the effect of the nature of surfactants on the onset of polymerization followed by viscosimetric measurements. The different surfactants tested were characterized by hydroxylic functions able to react with isocyanates. As shown in Fig. 5, different surfactants used exhibited different reactivities. Tween 85 induced rapid formation of a polymer. Hypermer A60 was able to induce the polycondensation reaction after a delay of 14 days, whereas Hypermer B246 appeared not to have reacted during the time of the experiment. The increase in viscosity obtained in the absence of surfactant was the same as that observed with Hypermer B246. This may be attributed to traces of contaminant water in the system which induced very slow rates of polymerization. The effects of Tween 85 and of Hypermer A60 were clearly different from the latter. These behaviors can be interpreted by the accessibility of the hydroxylic functions in different surfactant molecules. Davis and Farnum [29] have found that the rate of the polycondensation reaction is dependent on the position of the hydroxylic groups and on the chemical structure of molecules. Here, the three surfactants used have completely different chemical structures. Tween 85 is a polyoxyethylene sorbitan ester, whereas Hypermer A60 and hypermer B246 are random copolymers and block copolymers containing polyoxyethylene chains [26]. The steric accessibility of hydroxylic functions of those molecules in relation to their chemical structure can be correlated to their ability to induce the polycondensation reaction. Microencapsulation studies of benzalkonium chloride performed with these surfactants have shown that very brittle microcapsules are formed in the presence of Hypermer B246, whereas strong and nice microcapsules are obtained with Hypermer A60. No microcapsules are formed in the presence of benzalkonium chloride and Tween 85, but in that case the microencapsulation system was not adapted, as shown previously [16]. The recovery of brittle microcapsules, even in the presence of Hypermer B246, can be explained by the action of benzalkonium chloride on the isocyanate polycondensation discussed above. The special characteristics of microcapsules obtained with Hypermer A60 could result from the incorporation of this polymeric surfactant into the polymer forming the microcapsule wall. The result of this incorporation could be the formation of a highly crosslinked network giving increased mechanical resistance and greater chemical stability. Many assays were carried out in order to dissolve and destroy the microcapsule wall to analyze the polymer formed in the different conditions.

Conclusion

This study has attempted to elucidate the roles of the different components used in the preparation of benzalkonium chloride-loaded microcapsules by interfacial polycondensation of isocyanates. The results showed that the course of the preparation is affected by many interrelated parameters. These parameters were observed to control the microcapsule wall formation through various ways. Some could affect polymer precipitation, whereas others could control the polymer rate formation. Modification of one of these parameters can alter either the morphology or the mechanical resistance of the microcapsules. Characterization difficulties were enhanced by the poor solubility of the polymer, consequently, no direct compositional analysis of the polymer forming the microcapsule wall was obtained.

Acknowledgements

The authors wish to thank O. Thomas (Faculty of Pharmacy, Angers, France) for his excellent technical assistance, C. Pesando (Center of Research, Hutchinson, France) for her assistance in scanning electron microscopy, and S. Sutera (Washington University, St Louis, MO., USA) for his helpful discussions. This work was supported financially by Hutchinson, France.

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Received January 11, 1993;
accepted March 1, 1993

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