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REVIEW ARTICLE

# Microencapsulation by interfacial polymerisation: membrane formation and structure

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**Abstract**

Interfacial polymerisation was mainly developed toward the end of the 1960s, leading to applications in microcapsule production by the mid-1970s. The process consists in the dispersion of one phase containing a reactive monomer, into a second immiscible phase to which is added a second monomer. Both monomers react at the droplet surface (interface), forming a polymeric membrane. Over the last 50 years, many studies have been reported, but very few have provided a comprehensive review of this technology. This contribution reviews microcapsule production by interfacial polymerisation from the chemical, physico-chemical and physical perspectives, providing a tool for understanding and mastering this production technology, but also providing guidance toward improvements for future process design.

**Keywords**

Encapsulation, interfacial polymerisation, physicochemical properties, polymer synthesis

**History**

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## Introduction

The principles of interfacial polymerisation were first described in a series of articles published by Morgan's research group at Dupont Nemour (Beaman et al., 1959; Eareckson, 1959; Lyman and Lup Jung, 1959; Morgan and Kwolek, 1959; Schaefgen et al., 1959; Shashoua and Eareckson, 1959; Stephens, 1959; Sundet et al., 1959; Wittbecker and Katz, 1959; Wittbecker and Morgan, 1959). Two reactive monomers that are soluble in their respective immiscible phases, come into contact at the interface. The resulting polymerisation reaction, forms a polymer film at the interface. Morgan and his colleagues described the potential of interfacial polymerisation to reach high polymer yield at ambient temperature and pressure in comparison to classical single-phase polymerisation (Wittbecker and Morgan, 1959). After 50 years, these initial series of articles are still considered to be the main source of reference material on the subject of interfacial polymerisation.

In the 1960s, several groups (Chang et al., 1966; Koishi et al., 1969) described interfacial polymerisation at the surface of emulsified droplets as illustrated in Figure 1. The resulting microcapsules consisted of liquid droplets enveloped within a polymeric membrane. In the formulation, generally one phase is an aqueous phase and the second consists of an organic solvent. As the aqueous phase is the dispersed phase, the core of the capsules will be hydrophilic, while inverting the phases would lead to a hydrophobic core. As the initial conditions of formulation were relatively harsh (high pH, toxic monomers, solvents and reaction products), applications were limited to the microencapsulation of stable active ingredients. However, improving the formulation process enables application of the technology to areas such as the biomedical field. For example, the encapsulation of enzymes and cofactors in semi-permeable nylon membrane microcapsules, leads to the concept of the artificial cell (Chang, 1964).

The basics of interfacial polymerisation to form microcapsules are known and as such there is an incremental nature to advancements in the study of the microencapsulation process. As a result, in the last two decades, most publications have been more related to optimisation of microcapsules and their formulation for applications such as agrochemicals, self-healing, pharmaceutics and cosmetics (Zhang and Rochefort, 2012), than developing basic knowledge about membrane formation. Moreover, to optimise the process, complex formulation (mix of different monomers) has been used.

In the case of self-healing applications, control of the process parameters enable the formulation of microcapsules with specific diameters and membrane thickness, required in order to optimise the rupture of microcapsules, improving on the efficiency of the self-healing materials (Brown et al., 2002; Yang et al., 2008; McIlroy et al., 2010). In the area of agriculture, the structure of the membrane is adapted to obtain a controlled release of microencapsulated agrochemicals and promote their efficiency (Hirech et al., 2003). This is also the case for pharmaceutical and phase change material applications. In the cosmetic field, controlled properties of the membrane support the protection of essential oil and fragrances against degradation caused by environmental factors (Magdassi, 1997).

Readers are invited to consult the excellent paper from the group of Rochefort at the Université de Montréal (Zhang and Rochefort, 2012) for an overview of the industrial applications. At the time of the writing of this present contribution, the authors were requested to develop a microencapsulation process with production of 2 tons/h (i.e. 1000 tons/year) showing that the

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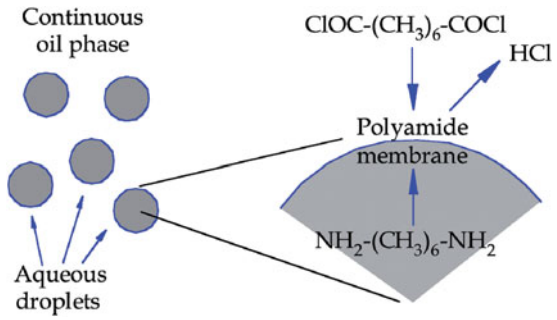



Figure 1. Microcapsule formation by interfacial polymerisation.

subject is still open for large process and new product development. The benefits of interfacial polymerisation are summarised as:

- Simple and reliable process,
- Direct control of capsule mean size and membrane thickness possible,
- High active loading and tunable delivery processes,
- Versatile and stable mechanical and chemical properties of the membrane, as well as membrane permeability and
- Relatively low cost and conducive to scale-up.

Despite its industrial importance, the literature on interfacial polymerisation is still limited. Most research has been conducted inside or in collaboration with industry, and linked to specific applications resulting in protection of intellectual property.

Several reviews were published (Chang et al., 1972; Madam, 1978; Koestler, 1980; Deasy, 1984; Arshady, 1989) but mainly devoted to encapsulation of proteins and pharmaceuticals. In the last 25 years, while the technology is still largely developed in the industry, only two main reviews were published, one in French (Frere and Danicher, 2007) and the other mainly focused on applications (Zhang and Rochefort, 2012). Moreover, no real advance has been done to better understand the process of microencapsulation by interfacial polymerisation except through the development of complex models at the molecular or nanoscale. Lack of a comprehensive and analytical paper describing the basis of interfacial polymerisation has limited the development of new understanding and real innovation in this process.

Covering all aspects of the technology is not possible through a single article. It was then decided to focus on the mechanism of membrane formation and the resulting structure. Future contributions may relate to the production conditions on microcapsule properties and impact on the encapsulated active ingredient integrity, protection and release. However, the data related to these subjects are quite dispersed, treated case by case and often controversial. It was decided then that combining all aspects of microencapsulation by interfacial polymerisation within a single contribution would be too complex.

In summary, the objective of this article is to provide a comprehensive analysis of both chemical and physical processes involved in microencapsulation by interfacial polymerisation and the impact on membrane formation and structure.

## Types of polymers considered for interfacial polymerisation

Many chemistries have to be considered to produce microcapsules by interfacial polymerisation, but mainly four types of polymers have been developed thus far, consisting of polyamides, polyurethanes, polyureas and polyesters. This section will then be concentrated on the reactions leading to these classes of polymers.

### Polyamides

The reaction of a diamine and a diacid chloride at the water/solvent interface, leading to polyamides is the method most extensively described in the literature (Table 1A). It was one of the reactions initially proposed by Morgan's group (Beaman et al., 1959; Morgan and Kwolek, 1959).

The reaction is conducted at room temperature and governed by a second order reaction:

$$r = k[\text{Diamine}][\text{Diacid Chloride}] \quad (1)$$

The chemical reaction constant is very high ($10^4$–$10^5$ l mol$^{-1}$ s$^{-1}$) (Odian, 2004). However the overall process is controlled by diffusion of the diamine through the membrane (see ''Discussion'' section below). Fast membrane formation involves working at high pH (12–14) and use of polar solvents, such as chloroform.

Diacid chloride containing an aromatic group has a higher reactivity due to better delocalisation of the electrons on this aromatic group leading to a higher electrophilic character of the carbonyl group. However, the presence of an aromatic ring would make diacid chloride difficult to assume advantageous orientations to the reactions with diamine, compared to linear diacid chloride which can form favourable conformations thanks to flexible linear carbon chains (Wakamatsu et al., 1974). This difference in chemical structure will also have an impact on the final membrane of the resulting microcapsules: the aromatic structure of the monomer gives more rigidity to the membrane compared to linear diacid chloride which gives more flexibility to the membrane. In contrast, the presence of an aromatic cycle in the diamine reduces reactivity of the diamine by decreasing the nucleophilic character of the amine. Then, for an optimal reactivity between the two monomers, linear diamine with aromatic diacid chloride is the best choice.

Selecting some monomer derivatives enables formation of other polymeric structures. Sundet et al. (1959) proposed to replace the diacid chloride by a disulfonyl chloride to form polysulfonamides, illustrated in Table 2(D). Manfred (1959) formed polyphtalamides using aromatic diacid chloride and piperazine (cyclic secondary diamine), shown in Table 2(A). Kondo's group proposed replacing the diamine with amino acids (Shigeri et al., 1971), enabling reaction at lower pH.

One drawback of polyamide synthesis is the release of hydrochloric acid (Table 1A). This will affect the integrity of some encapsulated material but also strongly reduce reactivity of the diamine (see ''Discussion'' section below), which could be compensated using alkaline buffer. On the other hand, the reaction is mainly irreversible.

### Polyurethanes

Polyurethanes are produced by combining a diisocyanate with a diol (Table 1B). While this reaction will proceed slowly at room temperature, higher polymerisation rates require higher temperatures (120–150 °C) (Wittbecker and Katz, 1959) and a catalyst such as tin dibutyl-dilaurate (Hepburn, 1991). The higher the temperature, the more linear will be the polymer formed (Hepburn, 1991).

The aromatic diisocyanates are more reactive than the linear forms, as the nucleophilic character is enhanced by delocalisation of the nitrogen electron doublet on the aromatic group. The diols with primary alcohol functions are 10 times more reactive than secondary alcohol functions (Woods, 1987). Aromatic diols are less reactive than linear diols and the resulting polymers are less stable when temperature is raised (Woods, 1987).

A particular characteristic of polyurethanes is that they still have some free hydrogen on the nitrogen that could react with

Table 1. Polymerisation and cross-linking reactions.

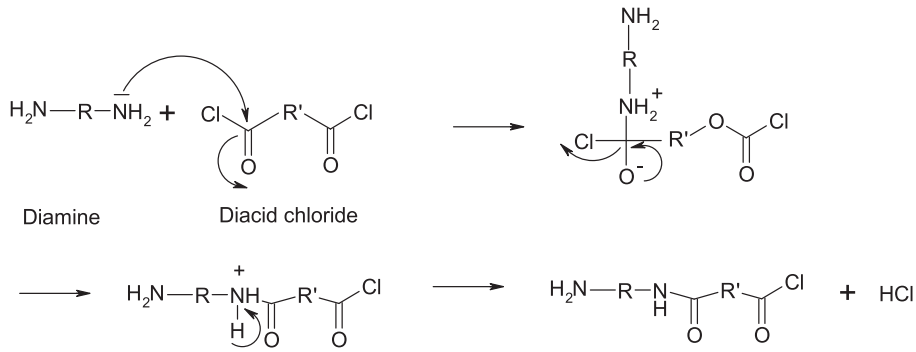
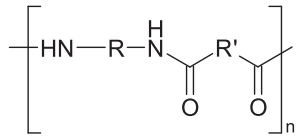
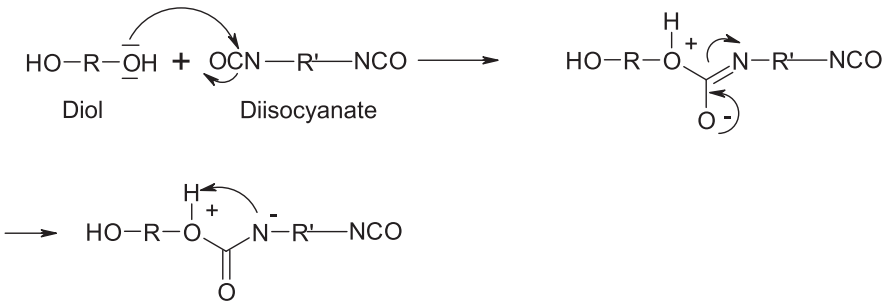
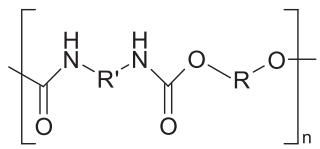
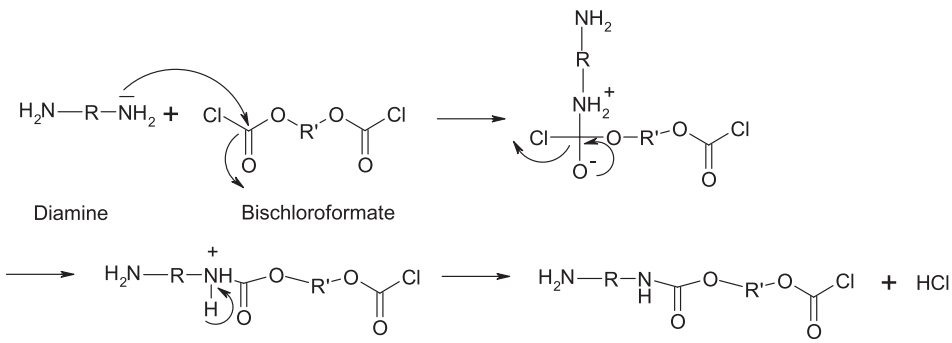
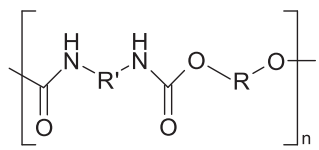
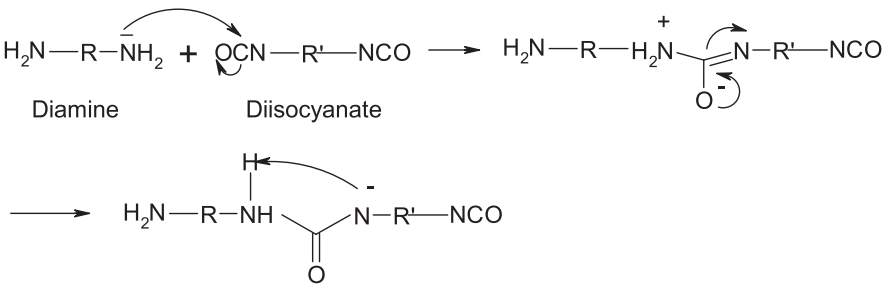
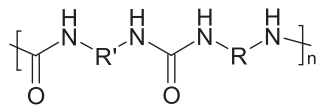
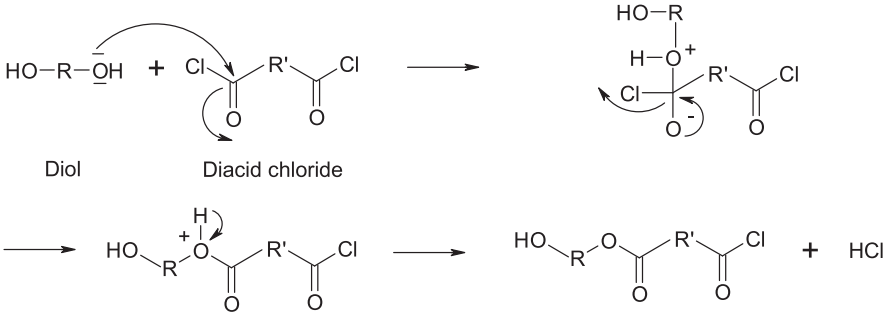
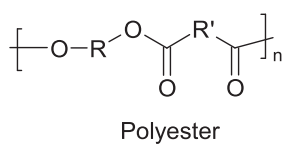
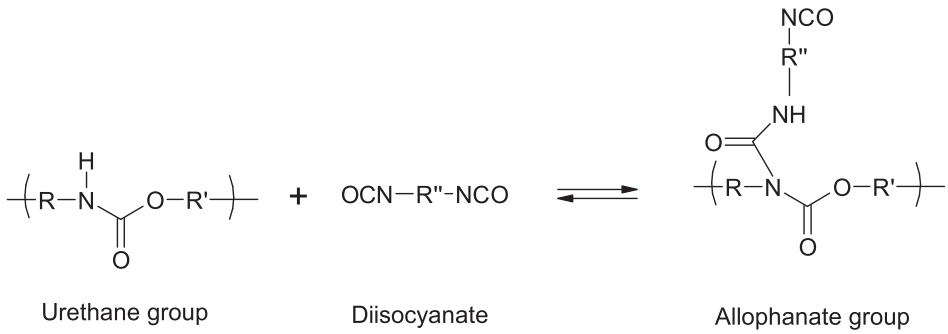
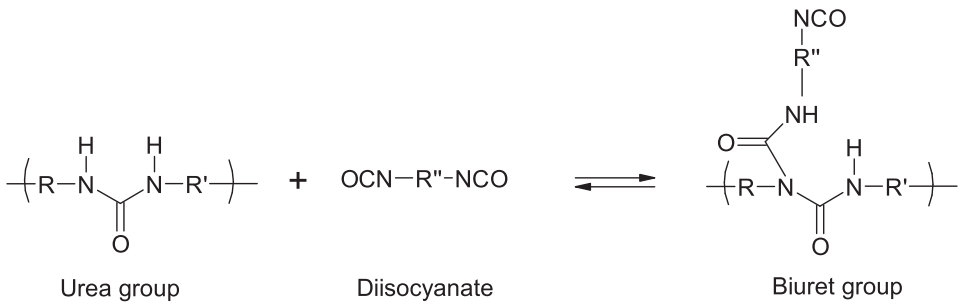
| | Reaction | Products |
|---|---|---|
| A |   |  Polyamide |
| B |   |  Polyurethane |
| C |   |  Polyurethane |
| D |   |  Polyurea |
| E |   |  Polyester |

Table 1. Continued

| | Reaction | Products |
|---|---|---|
| F |   | Polyurethane inter-chain cross-linking |
| G |   | Polyurea inter-chain cross-linking |



new molecules of diisocyanate leading to a cross-linking between the polyurethane chains (Table 1F).

The polyurethane may also be synthesised using a diamine and bischloroformate (Wittbecker and Katz, 1959) (Table 1C). Using this reaction, Wittbecker and Katz (1959) formed polyurethanes inside a water-in-benzene dispersion. The reaction can be conducted at milder temperatures (20–50 °C), and even to as low as 10 °C (Sandler and Karo, 1996). The resulting polyurethanes are higher molecular weight than those found in classical reactions (Wittbecker and Katz, 1959). However, as in the case of polyamides, the reaction releases some hydrochloric acid.

## Polyureas

Polyurea is formed by reacting a diamine with a diisocyanate (Table 1D). This reaction can be performed at room temperature without catalyst.

The diamine has stronger nucleophilic character than diols and a superior reactivity with diisocyanates (Caraculacu and Coseri, 2001). The synthesis of polyurea is then faster by a factor of 100–1000, compared to the synthesis of polyurethanes by classical reaction (Woods, 1987).

Urea groups offer reactive hydrogens, and polyureas are then susceptible to be cross-linked by new diisocyanate molecules as illustrated in Table 1(G). This reaction is faster and takes place at lower temperature than for polyurethanes (Woods, 1987). Low temperature for polymer synthesis and cross-linking leads to compact and resistant microcapsules formed under mild conditions explaining the interest of industry for this type of microcapsule.

## Polyesters

Little interest has been devoted to polyester synthesis by interfacial polymerisation. The classical reaction between a dicarboxylic acid and a diol is not applicable because the reaction is reversible and slow. This is why polyesters are produced by reaction between a diacid chloride and a diol (Table 1E).

The diacid chloride is more reactive than the dicarboxylic acid and the release of hydrochloric acid leads to irreversibility of the reaction. However, Morgan and Kwolek (1959) found that the reaction is $10^6$ times slower than polyamide synthesis ($10^{-2}$ l mol$^{-1}$ s$^{-1}$ reported by Hodnett and Holmer, 1962).

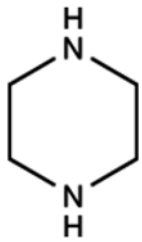
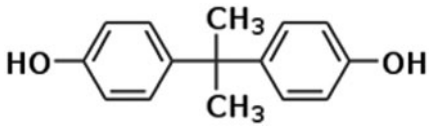
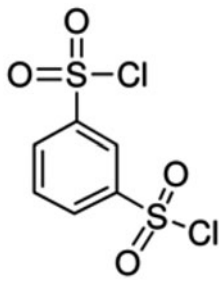
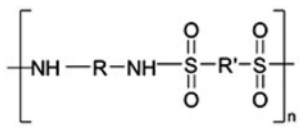
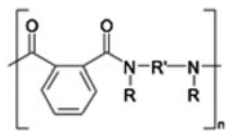
Eareckson (1959) enhanced the reaction by recommending the use of aromatic diols such as bisphenol A (Table 2B). This reaction has been applied by the group of Kondo in Japan to form microcapsules (Suzuki et al., 1968; Wakamatsu et al., 1974). However, recently the European commission totally prohibits the use of bisphenol A due to the risk of cancer.

To reinforce the nucleophilicity of alcohol groups and to speed up the reaction (Morgan and Kwolek, 1959), a strong base must be added to convert to alcoholate form, leading to a pH >12 (Eareckson, 1959). Morgan and Kwolek (1959) reported that the reaction starts in the aqueous phase, then proceeds toward the organic phase. Slow reaction then favours a risk of diacid chloride hydrolysis. However, the use of aromatic diacid chloride minimises such hydrolysis and allows formation of high molecular weight polymers (Eareckson, 1959; Morgan and Kwolek, 1959).

## Selection of polymer synthesis

One criterion in selecting a reaction to form microcapsules is a high reactivity allowing rapid membrane formation under mild conditions. Fast reaction is required to rapidly form a membrane able to resist shear in the reactor. Irreversibility of the reaction leads to more stable microcapsules but is generally linked to the release of hydrochloric acid, reducing pH, slowing the reaction. Table 3 presents a sampling of polymerisation reactions with rate constants and usual polymerisation conditions. Also indicated is whether acid is formed during the reaction or not. Monomer

Table 2. Chemical structure of different molecules used in interfacial polymerisation reactions.

| | Name | Chemical structure |
|---|---|---|
| A | Piperazine |  |
| B | Bisphenol A |  |
| C | Disulfonyl chloride |  |
| D | Polysulfonamide |  |
| E | Polyphtalamide |  |

reactivity also plays a role in driving polymerisation kinetics. The monomer reactivities may be classified as follow:

Aqueous soluble monomers
Linear amine >> Aromatic diamine >> Linear alcohol (primary >> secondary) >> Aromatic alcohol (Phenol)

Organic soluble monomers
Aromatic diacid chloride ≈ Aromatic diisocyanate >> Linear diacid chloride ≈ Linear diisocyanate >> Dicarboxylic acid

While high reactivity in these cases can be desirable in microcapsule formulation, other criteria can also be important when selecting a chemistry, such as membrane strength, thickness and structure, degradability and permeability.

## Membrane formation mechanism

Forming a polymer membrane at an interface involves a complex mechanism that is not completely understood. The reaction starts at the liquid interface, and as the membrane begins to form, the reaction site evolves toward the bulk phase (Figure 2). When oligomers are largely insoluble in the dispersed droplet phase, polymer will quickly precipitate near to the interface and membrane bound microcapsules are obtained (Arshady, 1989). In function of the solubility of oligomers, a more or less thick membrane is formed.

### SEM observations of the membrane

*Polyamide membrane*

Morgan and Kwolek (1959) were first to observe polyamide film formation using coloured powders. They observed that powders dispersed in the aqueous phase were not incorporated in the membrane while powders dispersed in the organic phase were incorporated in the membrane. By electron scanning microscopy, they also showed that the surface of the membrane on the aqueous side was smooth while the organic side was rough. Janssen and TeNijenhuis (1992) observed the membrane at different times of reaction while forming organic core microcapsules. The surface of the capsules (aqueous side of the interface) was smooth while the internal side (organic side) was irregular (Figure 3A–C). When forming aqueous core capsules, the microcapsule surface was rough while the internal side was smooth (Danicher et al., 1999). This observation supports the point that the membrane grows in the organic phase. Polyamide membrane contains pores and the

Table 3. Polymerisation kinetics.

| Reaction | Polymer type | Reaction constant at room temperature ($l\ mol^{-1}\ s^{-1}$) | Usual polymerisation temperature | Hydrochloridric acid production |
|---|---|---|---|---|
| Diamine+diacid chloride | Polyamide | $10^4$–$10^5$ (Odian, 2004) | Room temperature (Odian, 2004) | Yes |
| Diol+diisocyanate | Polyurethane | $10^3$–$10^4$ (Odian, 2004) | 25 °C–150 °C (Odian, 2004) | No |
| Diamine+bischloroformate | | – | 10 °C–50 °C (Odian, 2004) | Yes |
| Diamine+diisocyanate | Polyurea | 100–1000 (Wood, 1987) | Room temperature (Hong and Park, 2000; Dhumal and Suresh, 2009) | Non |
| Diol+diacid chloride | Polyester | $10^{-2}$ (Hodnett and Holmer, 1962) | Room temperature (Eareckson, 1959) | Yes |

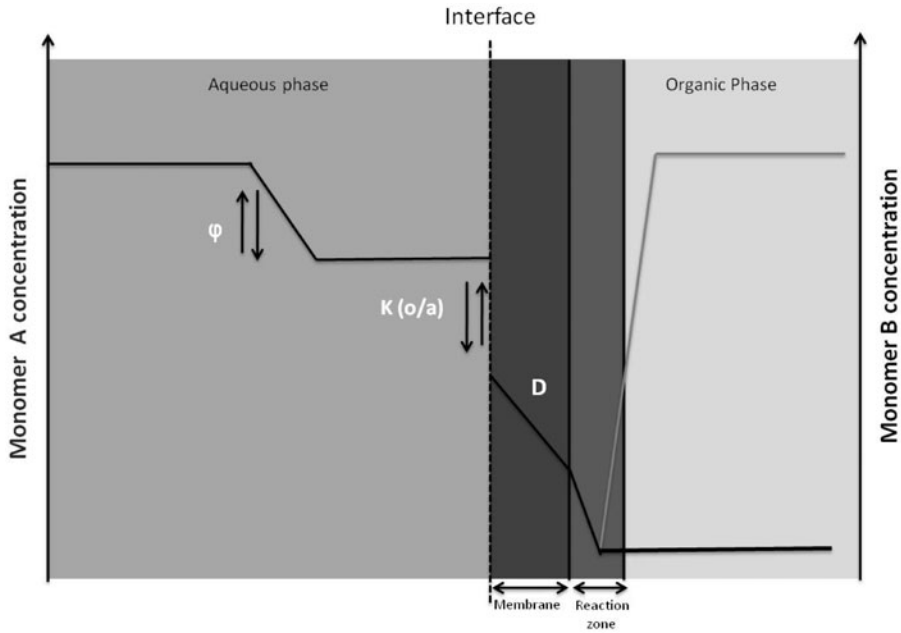



Figure 2. Evolution of monomer concentration over the membrane.

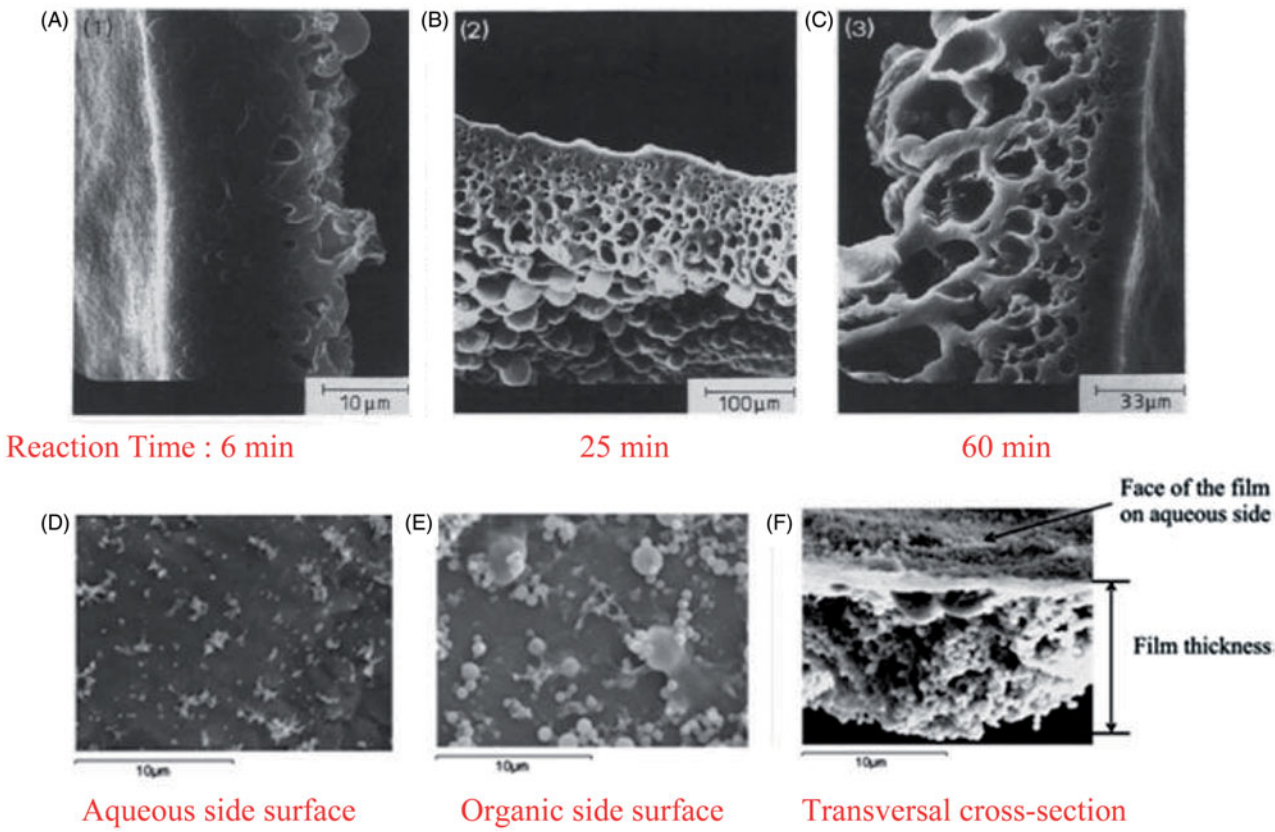



Figure 3. (A–C) Oil core polyamide microcapsule membrane observations by scanning electron microscopy (from Janssen and TeNijenhuis, 1992) and (D–F) polyurea membrane structure by scanning electron microscopy (from Dhumal and Suresh, 2010).

size of the pores increase from the aqueous side to the organic side (Figure 3B and C).

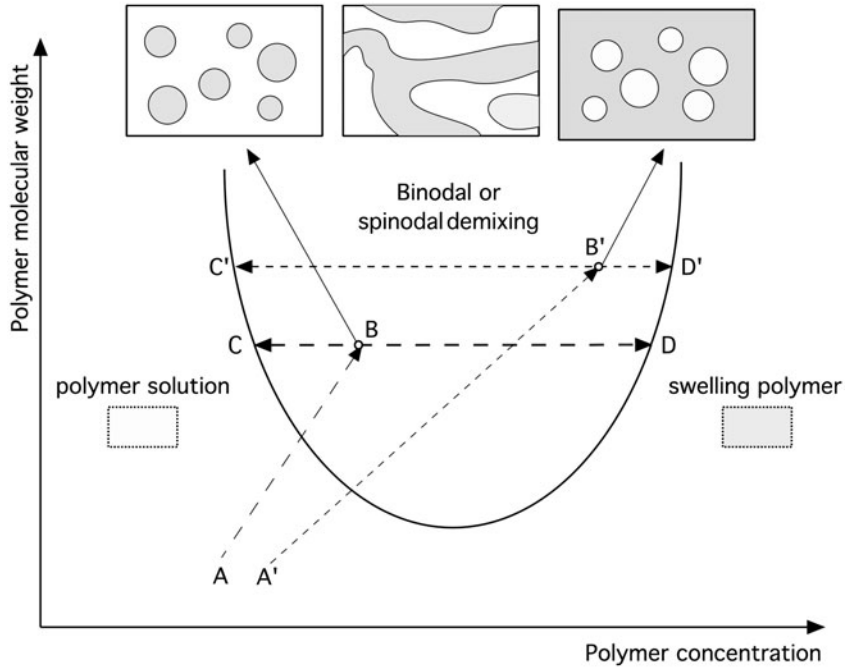
*Polyurethane membrane*

As a polyamide, the organic solvent side of the polyurethane membrane is irregular (Frere et al., 1998) and the pore size is larger on the organic side. These observations also confirm that the membrane grows in the organic phase.

*Polyurea membrane*

In regard to the transversal cross-section of the membrane (Figure 3D–F), the growth of the membrane is also in the organic

Figure 4. Polymer precipitation processes.




side. However, the structure can be different as pores were observed, which seem more homogeneously dispersed in the membrane (Figure 3D–F) (Dhumal and Suresh, 2010).

*Polyester membrane*

In the case of polyester, its higher oligomer solubility in water may lead to an initial growth in the water phase, followed by a precipitation at the interface. Once this primary membrane has been formed, the growth will take place in the organic phase (Arshady, 1989).

## Theoretical mechanisms of membrane formation

In all cases, a thin dense membrane is observed along the interface. Once the reaction starts, the interface is liquid allowing mixing and rapid contact between the monomers. Polymerisation is controlled by chemical kinetics, which is rapid compared to diffusion. The progressive insolubilisation of the polymer is then very fast, leading to dense membrane (Wijmans et al., 1985; Kamide et al., 1993; Karode et al., 1997).

As the initially formed membrane solidifies, the diamine must be transferred by diffusion. The reaction is then slowed down and the formation of a porous structure is observed. Two theories have been proposed to explain this structure of the polymer membrane:

- The transfer of the diamine will be done in solvated form, thus entraining some water in the organic phase (Janssen and TeNijenhuis, 1992; Danicher et al., 1999). As polymerisation takes place, water would be released forming small droplets inside the membrane. As the thickness of the membrane increases, the transfer is slower, which takes more time to reach a precipitation of the polymer, leading to higher water accumulation and formation of larger pores.
- The polymer grows in the organic phase. Simultaneously, its concentration and molecular weight increase, leading at some stage to a demixing, forming two phases, one rich in polymer and one poor in polymer. Two situations could appear (Figure 4):
  - In the first situation, if demixing takes place while the polymer concentration is low (Figure 4, point A, B, C and D), small swollen polymer droplets or coacervates can be formed that could coalesce to form the membrane.
  - In the second situation, if demixing takes place while polymer concentration is high (Figure 4 point A′, B′, C′ and D′), droplets of solvent will be included in the polymer membrane. The slower the process of demixing, the larger will be the size of the included pores.
  - In fact, all intermediate situations may exist.

It is difficult to determine which process is taking place. The pore content nature (water or solvent) has not been determined. Diamine must be neutral and more hydrophobic to diffuse easily in the membrane, thus the water transport hypothesis does not seem favoured. If the pore structure is linked to a demixing process, this can be influenced by many factors such as solubility, reactivity and swelling leading to a more or less porous membrane.

It should be noted that spinodal demixing assumes that free energy is positive and the process is spontaneous while in binodal conditions, some energy is needed to provoke polymer precipitation.

## Theoretical modelling of membrane formation

In the last 15 years, several models have been developed to explain the formation of membrane by interfacial polymerisation, based on theoretical approaches and powerful mathematical tools (Karode et al., 1997, 1998; Ji et al., 2001; Yashin and Balazs, 2004; Berezkin and Khokhlov, 2006; Dhumal and Suresh, 2009; Oizerovich-Honig et al., 2010). The models are based generally on molecular interactions using statistical simulation. The most advance model is based on computational fluid dynamic analysis (Berezkin and Kudryavtsev, 2013). In light of the complexity of these models, a detailed description is outside the scope of this article.

These models and approaches likely represent the future for developing our knowledge base around microencapsulation via interfacial polymerisation. They provide useful information such as molecular weight distribution through the membrane, presence of residual functional groups and porosity. Such parameters will strongly influence the behaviour of the capsules in terms of permeability, mechanical strength or surface charge. However, these models have certain drawbacks, limiting their applicability:

- The models are generally based on numerous constants, assumptions and hypotheses that need to be identified and demonstrated to validate the model.

- Despite the sophistication, the models cannot include all aspects of the phenomena involved in interfacial polymerisation. They generally neglected influence of pH, microcapsule size and distribution, monomer consumption and release of secondary product, which play an important role in membrane formation.
- Experimental data needed to validate these models are not easily accessible. For example, it is difficult to verify the molecular weight distribution over a thin membrane and porosity in a non-homogeneous membrane.

## Membrane formation kinetics

The evolution of the monomer concentrations can be represented as illustrated in Figure 2. As stated earlier, the growth of the membrane takes place in the organic phase. This implies that the diamine (or more generally the aqueous monomer) must be transferred from the aqueous phase to the organic phase, and cross the membrane to reach the reaction site.

Considering Equation (1), the site of the reaction is located in the zone where the product of the monomer concentrations is maximum. However, one has to consider the local concentration at the reaction site (index *r*).

$$r = k[\text{Diamine}]_r[\text{Diacid Chloride}]_r \tag{2}$$

The diacid chloride concentration profile is relatively simple. One may assume a constant concentration, which will drop over the reaction zone. It can then be assumed that the diacid chloride concentration at the reaction site is near to the bulk concentration.

In case of the diamine, the profile is more complex. The diamine (*A*) in water splits in different acid–base forms:

$$H_2A^{2+} \rightleftharpoons HA^{+} + H^{+} \rightleftharpoons A + 2H^{+} \tag{3}$$

Only the neutral fraction of the diamine, $\varphi_0$, would be transferred to the organic phase. This fraction is given by (Poncelet et al., 1985):

$$[A]_a = \varphi_0 C_A \tag{4}$$

and

$$\varphi_0 = \frac{K_{a1}K_{a2}}{K_{a1}K_{a2} + K_{a1}[H^+] + [H^+]^2} \tag{5}$$

where the index a refers to the aqueous phase. $C_A$ is the total concentration of diamine in the water phase and $K_{ax}$ is the dissociation constant of the diamine.

At the interface, diamine is in equilibrium between the water and organic phase:

$$K_{o/a} = \frac{[A]_{oi}}{[A]_{ai}} \approx \frac{[A]_{oi}}{[A]_a} \tag{6}$$

where $K_{o/a}$ is the partition constant, oi and ai index refers, respectively, to the concentrations at the organic and water side of the interface. As diffusion in the membrane is likely to be the slower process, one may assume that the concentration at the water side interface is equal to the water bulk concentration.

As the diamine is transferred in the organic phase, it must diffuse through the membrane following Fick's diffusion flux, J:

$$J = -D\frac{[A]_r - [A]_{oi}}{\partial} \tag{7}$$

where D is the diffusion coefficient and $\partial$ is the membrane thickness. The diffusion coefficient varies between $10^{-11}$ and $10^{-15}$ $m^2$ $s^{-1}$ (Poncelet et al., 1990; Karode et al., 1997; Dhumal et al., 2008). Equations (2) and (7) show that the process is mainly controlled by diamine diffusion. In such conditions, the diamine concentration at the reaction site will be very low and Equation (7) can be simplified and combined with Equations (4) and (6) to result in:

$$J = D\frac{K_{o/a}\varphi_0 C_A}{\partial} \tag{8}$$

The growth of the membrane may then be described by:

$$\frac{d\partial}{dt} = \alpha D\frac{K_{o/a}\varphi_0 C_A}{\partial} \tag{9}$$

where $\alpha$ is a coefficient function of the membrane concentration expressed in $m^3$ $mol^{-1}$ of diamine monomer. This coefficient is largely a function of the membrane porosity and then will decrease with the membrane thickness. However, in most modelling, $\alpha$ is considered constant using a mean value.

For microcapsules to form, an initial membrane must be quickly established to resist shear forces from the mixing necessary to maintain the emulsion. During this step, the reaction takes place at the interface as no membrane exists. Diamine molecules react quickly with the diacid chloride, resulting in oligomers (Morgan and Kwolek, 1959). Due to their amphiphilic character, oligomers accumulate at the interface and the diamine will react faster with the oligomers than with new diacid chloride molecules. At this stage, the reactivity of the monomers is then the most important parameter controlling the reaction (Equation 1). This explains why it is easier to form polyamide membrane than, for example, polyurethane (Table 3).

As the primary membrane is formed, diamine (or aqueous soluble monomer) must cross the membrane and diffusion becomes the controlling factor (Equation 9). The reactivity is still probably important but the acidity constant, $pK_a$ and partition coefficient, $K_{o/a}$, may play a major role in membrane formation rate.

## Influence of process parameters on the kinetics

### Influence of the pH

Figure 5 presents the neutral fraction of different diamines determined by Equation (5) using data from Table 4. To obtain a high neutral diamine fraction and a high membrane formation speed, the pH must be at least one unit higher than the second acidity constant, $pK_{a2}$ (Table 4). For most diamines, this implies a pH >11. Using diamine with lower $pK_a$ values, the pH can be fixed at a lower value (in case of piperazine, pH 10 will still be acceptable).

Using a pH computational model by Poncelet et al. (1985), different conditions of microcapsule production were simulated. Figures 6 and 7 present the pH and neutral diamine fraction in function of the consumption of diamine, respectively. Four cases have been considered:

(A) Reaction of hexamethylenediamine 0.4 M with a diisocyanate
(B) Same reaction but with the addition of 0.4 NaOH to the aqueous solution (buffer)
(C) Reaction of hexamethylenediamine 0.4 M with diacid chloride
(D) Same reaction but with the addition of 0.4 M NaOH to the aqueous solution (buffer)

The first observation from Figures 6 and 7 is that dissolving diamine in water increased pH to 12.7 (Figure 6, curve A) and only 88% of the diamine is in neutral form (Figure 7, curve A). To move closer to 100% neutral diamine fraction, 0.4 M of NaOH must be added to the solution (Figure 7, curve B).

When a polyurethane is formed by reacting a diol with a diisocyanate, the pH remains almost constant during the entire

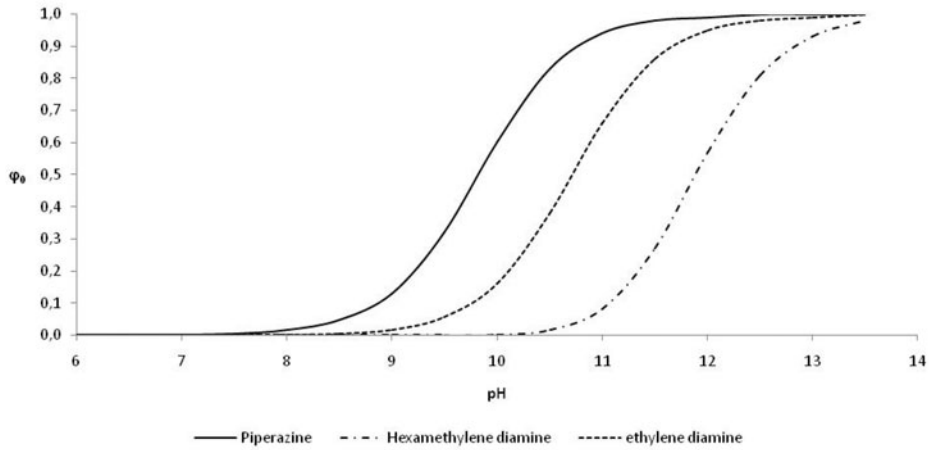



Figure 5. Neutral diamine fraction versus pH.

Table 4. Acidity constants and partition coefficients for different diamines.

| Diamine | Symbol | p$K_{a1}$ (mol/l) | p$K_{a2}$ (mol/l) | $K_{o/a}$ (−)* |
|---|---|---|---|---|
| Hexane-1,6-diamine Hexamethylene diamine | HMDA | 10.76 | 11.86 | 1.023 |
| Butane-1,4-diamine | BDA | 9.53 | 10.8 | 0.617 |
| Propane-1,3-diamine | PDA | 8.9 | 10.6 | 0.038 |
| Ethylene diamine Ethane-1,2-diamine | EDA | 7.56 | 10.1 | 0.015 |
| Piperazine | Pip | 5.68 | 9.82 | 0.008 |

Note: *In cyclohexane/chlorophorm ¼ v/v.

reaction (Figure 6, curves A and B). However, the small variation of pH in the case of non-buffered solution triggers a drop of the neutral diamine fraction, reducing the reaction speed to 50% (Figure 7, curve A).

The reaction between the diamine and diacid chloride forming polyamide, releases some hydrochloric acid. An acidification is observed already when <50% of the diamine is consumed (Figure 6, curve C), even when buffer is added to the solution (Figure 6, curve D). Regarding the neutral diamine fraction and by consequence the polymerisation speed, the situation is even more drastic. The neutral fraction of the diamine decreases even for small diamine consumption (Figure 7, curve C). The addition of a concentrated buffer delays the drop until 50% of the diamine consumption has occurred (Figure 7, curve D).

In fact, the impact of the pH is largely a function of the fraction of consumed diamine. If the aqueous phase forms the core of the capsules, a large part of the diamine is then consumed causing a large decrease of pH by release of hydrochloric acid. This is especially the case if the microcapsules are small due to the fact that surface to volume ratio of the microcapsules is high. If the aqueous phase is the continuous phase, its volume is larger (generally 4 times or more) than the volume of the capsules. Only a small part of the diamine would be consumed, generally <25%, and then the decrease of pH is low.

The problem of the pH is then especially critical for aqueous core capsules. The formulator is confronted with the need to have a very high pH value at the beginning, with potential detrimental effect on the encapsulated material and risk of quick pH drop associated with decrease of the polymerisation rate to a termination of the reaction.

Based on reactivity, one may expect that the use of diacid chloride or bischloroformate as organic reagent will lead to thicker and stronger membrane. However, if the pH drops, the reaction will be stopped before all the monomer is consumed.

### Selection of the aqueous soluble monomer

As the number of carbon atoms of a linear diamine increases, the polarity of the diamine decreases and its solubility in organic solvent increases (Poncelet et al., 1990). Consequently, the partition coefficient increases as the number of carbons increases (Figure 8). The tendency would then be to select a long linear diamine. However, $pK_a$ of the diamine increases with the length of the chain. For pH >13, it has a limited impact on the neutral diamine fraction as seen in Figures 6 and 7. But for lower pH, the neutral fraction of the diamine decreases with the number of carbons as shown in Figure 8. Moreover, the polarity and the molecular weight of the diamine influence the diffusion factor. However, the impact of this factor on membrane formation has not been evaluated.

Based on these different elements, one would prefer short chain (ethylenediamine) versus long chain (hexamethylenediamine). Interesting alternatives are piperazine and cyclohexanediamine providing short distance between the diamine functions ($pK_{a2} = 10$) but low polarity (high $k_{o/a}$). Diaminobenzene has an even lower $pK_{a2}$ (5–6) but a relatively low reactivity.

### Selection of the organic soluble monomer

The organic soluble monomer does not need to be transferred through the membrane. The selection may then be essentially based on its reactivity. Diacid chloride is probably the most reactive but will promote acidification, which could inhibit or even stop the transfer of the diamine.

In the case of polyurethanes and polyureas, secondary reaction may take place leading to branched or even cross-linked polymers. In the case of polyamides and polyesters, the membrane is mainly composed of linear polymers. Several authors have proposed mixing the diacid chloride with triacid chloride to obtain a stronger membrane.

Danicher et al. (1999) observed that the addition of triacid chloride results in a thicker membrane as shown in Figure 9. They proposed that the presence of triacid chloride leads to a denser initial membrane. The diffusion is then slowed down allowing the formation of larger pores. The increase in membrane thickness would then be linked to a higher porosity than a higher polymer mass itself.

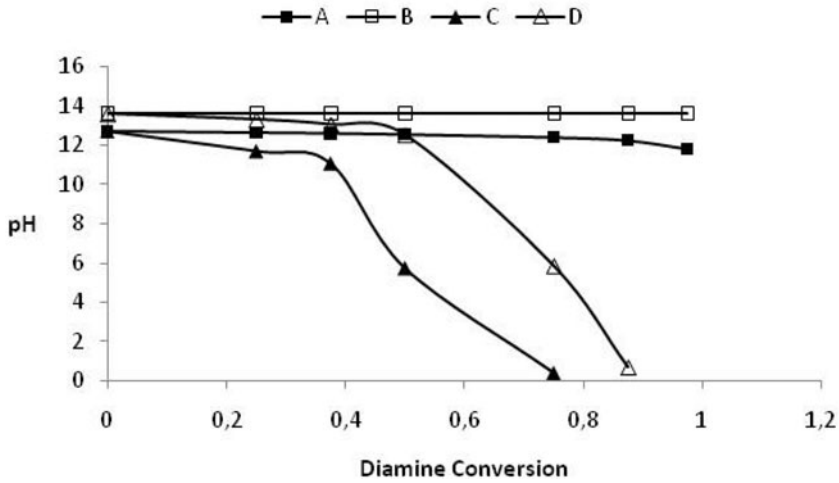



Figure 6. Evolution of the pH in function of the diamine conversion. Hexamethylenediamine concentration 0.4 M. (A and B) Reaction with diisocyanate, (C and D) reaction with diacid chloride and (B and D) aqueous phase buffered by 0.4 M NaOH.

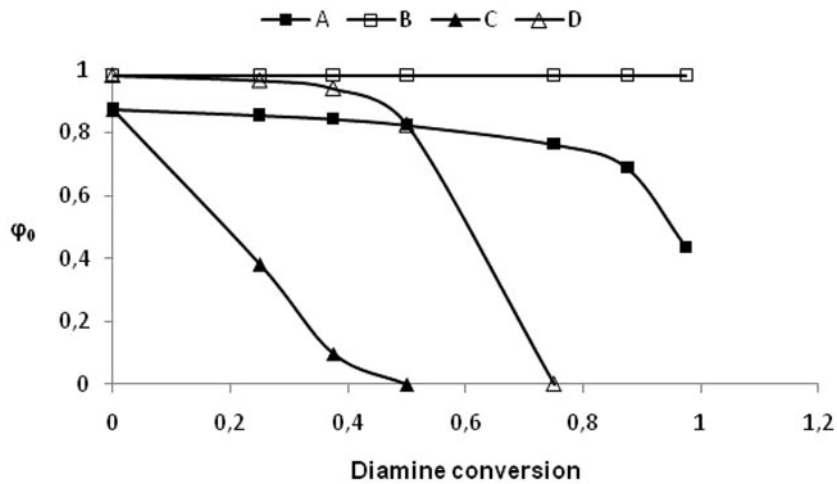



Figure 7. Evolution of the neutral fraction of diamine in function of the diamine conversion. Hexamethylenediamine concentration 0.4 M. (A and B) Reaction with diisocyanate, (C and D) reaction with diacid chloride and (B and D) aqueous phase buffered by 0.4 M NaOH.



### Monomer concentration ratio

In a classical polymerisation, the ratio of monomer bulk concentration has to be equal to 1 (aqueous monomer concentration to organic monomer concentration) in order to obtain a strict equivalence of functional groups and attain high molecular weight of polymer. In the case of interfacial polymerisation, the situation is more like a semi-batch reactor with the aqueous phase monomer supplied continuously by diffusion to the reaction zone. To achieve molar equivalence of the two monomers at the reaction zone, the ratio of monomer bulk concentration has to be superior to 1. Then, an excess of aqueous monomer promotes the formation of a polymer with high molecular weight distribution (Zydowicz et al., 2001; Wagh et al., 2009).

### Influence of the organic solvent

The selection of the solvent is critical and complex. It defines the:

- Solubility of organic soluble monomer in the organic phase,
- Solubility of the polymers, precipitation conditions and swelling,
- Partition coefficient of the aqueous soluble monomers between the two phases and
- Diffusion coefficient of the aqueous soluble monomers.

To avoid toxicity, low polar solvents are preferred but that would reduce solubility of the organic soluble monomers. This may limit the process in practice, especially when needed to solubilise the active ingredient in the organic phase. Data are not available to evaluate the impact of the solvent on the migration of the aqueous soluble monomer in the organic solvent and especially in the polymer membrane. The impact of the solvent on the partition coefficient is better defined (Morgan and Kwolek, 1959; Arshady, 1989). The more polar the solvent, the higher will be the partition coefficient, as seen in Table 5.

The partition coefficient strongly determines membrane formation. Using the model described earlier, the influence of the solvent selection on the membrane thickness can be demonstrated as shown in Figure 10.

The solvent may also impact the swelling of the polymer. Polymers that are more soluble in the solvent will produce a thicker and more porous membrane (Arshady, 1989). Faster precipitation of the polymer in low soluble solvents results in slower diffusion of the monomer through the membrane (Gaudin and Sintes-Zydowicz, 2012) (Figure 11). Moreover, if the solvent is polar, then there are some specific interactions with the water-soluble monomer affecting membrane formation (Odian, 2004). In many cases, a mix of solvents is used. As an example, chloroform/carbon tetrachloride would allow a high partition coefficient and limit interactions between the diamine and the solvent (Morgan and Kwolek, 1959).

The solubility of the polymer also has an impact on its final molecular weight distribution. High molecular weight with a distribution of long chains will be obtained when first oligomers are soluble because they will stay and grow in the solvent for long periods of time. In contrast, fast precipitation of oligomers due to low solubility will give low molecular weight of the polymer with a distribution of short chains.

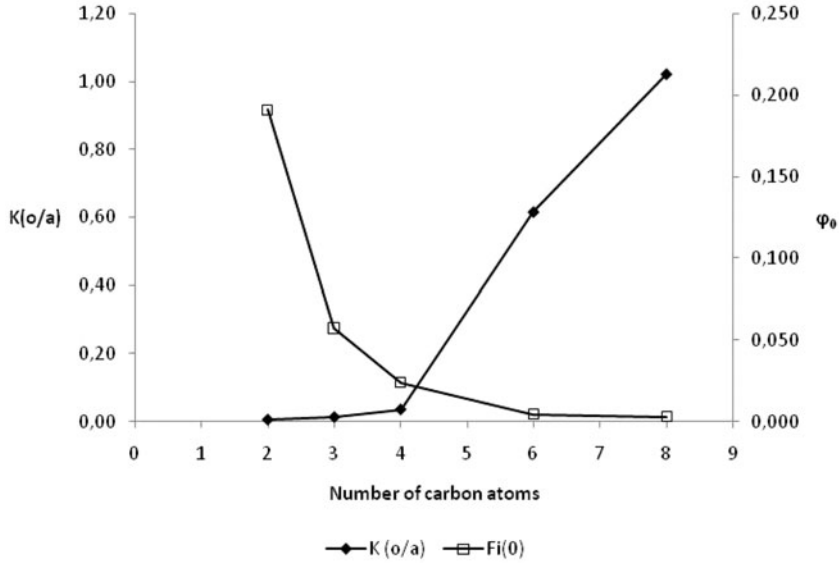



Figure 8. Influence of the carbon number of a linear diamine on the partition coefficient and the neutral fraction of diamine (organic solvent: chloroform; pH = 11).

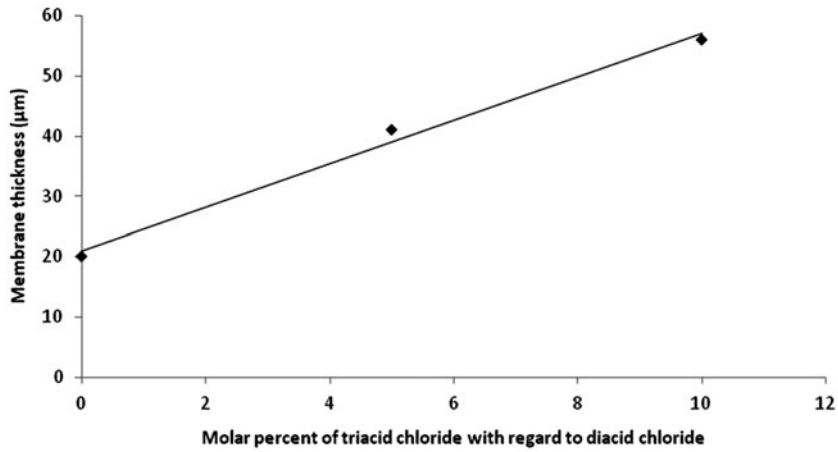



Figure 9. Membrane thickness versus di to triacid chloride concentration (Danicher et al., 1999).

Table 5. Organic solvent/water partition coefficient, hexamethylenediamine, pH = 12, $T = 25\,^{\circ}C$ (adapted from Morgan and Kowlek, 1959).

| Solvent | Formula | $K_{o/a}$ |
|---|---|---|
| Cyclohexane | $C_6H_{12}$ | 0.00549 |
| Xylene | $C_8H_{10}$ | 0.020 |
| Carbontetrachloride | $CCl_4$ | 0.0286 |
| Nitro-benzene | $C_6H_5NO_2$ | 0.0725 |
| Mix | $CHCl_3/CCl_4$ (30/70 v/v) | 0.1562 |
| Dichloromethane | $ClCH_2CH_2Cl$ | 0.1786 |
| Chloroform | $CHCl_3$ | 1.4286 |

## Influence of the temperature

Less data is available on the impact of temperature, most probably because many encapsulated actives are heat labile and microcapsules are produced at room temperature.

It is know that the diffusion coefficient D and the reaction rate K increase with temperature according to the Arrhenius law. In the case of polyamide formation, an increase of the temperature promotes the diffusion of the diamine through the primary membrane and therefore the formation of the membrane. An increase of the reaction rate has a little impact on the membrane formation because the growth of the membrane is mainly controlled by the diffusion of the diamine. Gaudin and Sintes-Zydowicz (2012) showed that temperature could have a quite strong effect on the partition coefficient. The partition coefficient $K_{o/a}$ of the diol used for the formation of polyurea–urethane nanocapsules increases when the temperature increases because hydrophilic interactions between the alcohol and water decrease. They observed an increase of diisocyanate monomer conversion when the temperature increases (Figure 11). The reason is that the amount of diol, which can diffuse in the organic phase and react with the diisocyanate increases.

Jin and Su (2009) also observed that temperature has an impact on the partition coefficient of diamine for the production of polyamide. They have seen, by infrared spectroscopy, that the quantity of pendant acid chlorides in the film is lower when the reaction temperature is higher. This means that more diamine monomers will transport through the organic/membrane interface and react with the triacid chloride monomers. The higher diamine/triacid chloride ratio results in lower content of pendant acid chlorides in the film produced.

An increase of the temperature promotes the transfer of the aqueous monomer in the organic phase by increasing its diffusion coefficient and its partition coefficient. Therefore, the formation of the membrane is accelerated. Using a temperature higher than room temperature is useful, but most of the time, higher temperatures are avoided because of sensitivity of encapsulated actives.

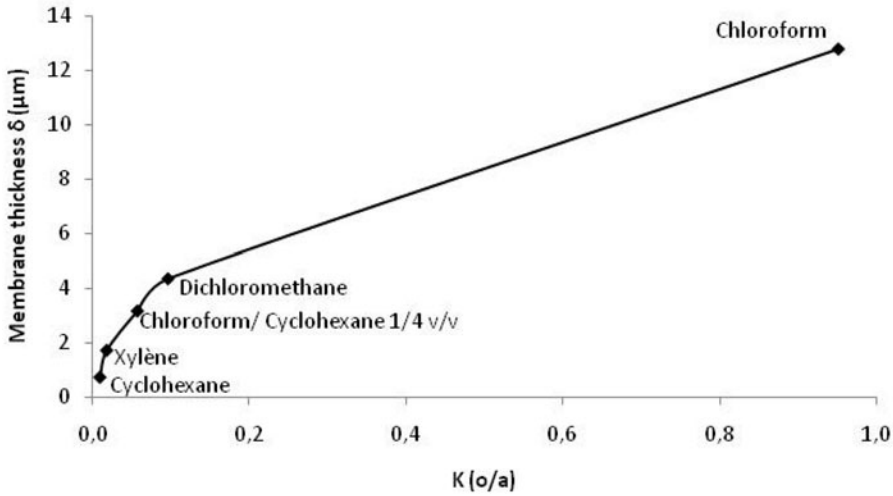



Figure 10. Influence of partition coefficient on the membrane thickness. Hexamethylenediamine, pH 12, $T = 25\,^{\circ}C$ (adapted from Poncelet et al., 1990).

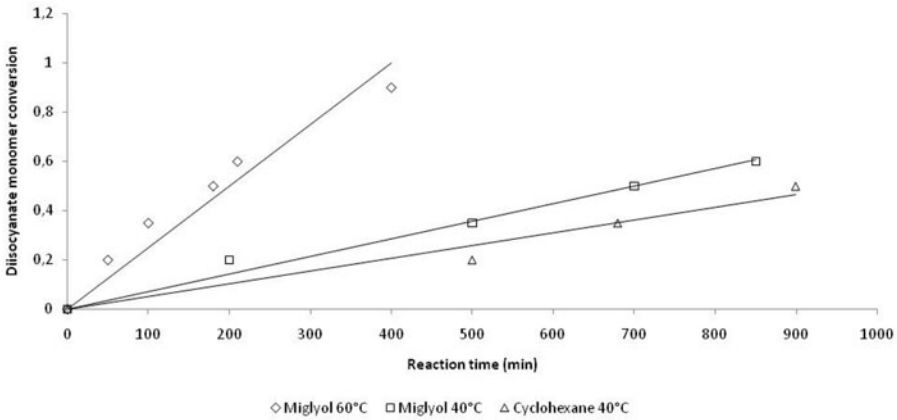



Figure 11. Diisocyanate monomer conversion degree in function of time for different solvents and temperatures (from Gaudin and Sintes-Zydowicz, 2012).



## Control of microcapsule size

Size and size dispersion of the microcapsules are mainly defined by the dispersion process (Poncelet et al., 1990). It will then depend on the emulsification device (turbine reactor, static mixer and homogeniser) and the energy applied to the system (rotational speed and pressure). The simplest model assumes breakage of the dispersed phase by eddies formed by turbulence (Kolmogorov theory):

$$\frac{d}{L} = KWe^{-0.6} \tag{10}$$

and

$$We = \frac{\rho u^2 L}{\sigma} \tag{11}$$

where $d$ is mean droplet diameter, $L$ is characteristic length (generally the impeller diameter) and $K$ is a constant depending on the dispersion design, We is the Weber number with $\rho$ as the density of dispersed phase, $u$ the linear speed (generally the turbine tip velocity) and $\sigma$ the interfacial tension between the dispersed and continuous phase. This correlation is valid for non-coalescing dispersions, with the dispersed phase having low viscosity and volume fraction (Berchane et al., 2006).

From Equations (10) and (11), it could be concluded that droplets, and consequently microcapsule size, decrease asymptotically with the impeller speed. This is in agreement with the observations of Alexandridou and Kiparissides (1994), i.e. a shift of droplet size distribution to smaller diameters when the stirring rate increases until a critical value of stirring rate is reached. This evolution of microcapsule size with stirring rate is also observed with microcapsules prepared by *in situ* and interfacial polymerisation for self-healing applications (Brown et al., 2002, 2003; Yuan et al., 2007; Yang et al., 2008) and also with the formation of poly(lactide-co-glycolide) microspheres prepared by an oil-in-water emulsion solvent extraction technique (Berchane et al., 2006; Shorty et al., 2012). Berchane et al. (2006) have measured mean microsphere diameters at different Weber number and obtained the value of the constant $K = 0.65$ from a least squares fit to the experimental data. They demonstrated that the correlation provides a close fit to the experimental mean diameters.

Reducing the interfacial tension by addition of surfactant also reduces the size of the resulting microcapsules but could also affect the transfer of the diamine, and especially the partition coefficient (Koishi et al., 1969). However, some authors did not observe significant change to the microcapsule diameter when a surfactant was added but the size distribution became narrower and sharper (Koishi et al., 1969; Zhang et al., 1995). The team of Zhang explained that the surfactant molecules adsorbed on the droplet surfaces prevent the droplet from coalescing, therefore more uniform microcapsules can be obtained.

### Impact of stirring on membrane formation

As discussed earlier, the stirring rate modifies microcapsule size but can it lead to a modification of the membrane formed. Assuming that the limiting process is the transfer of the

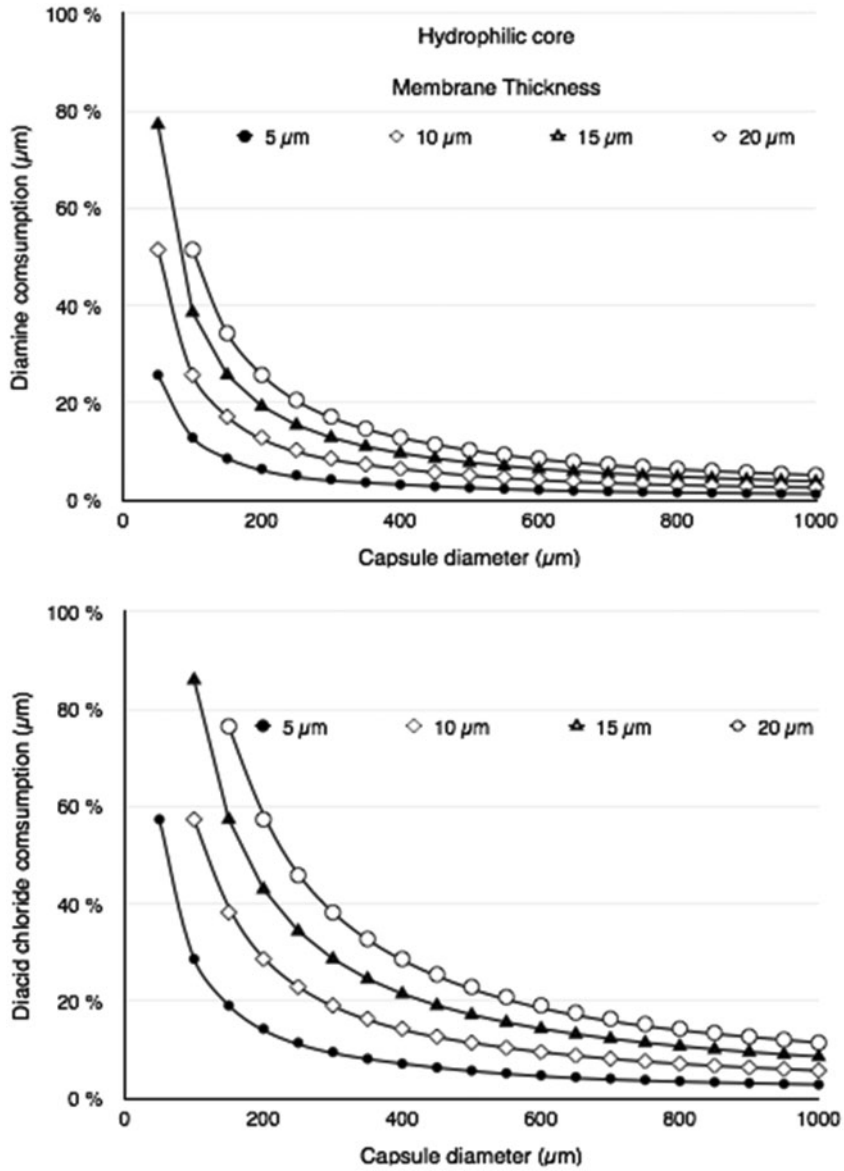



Figure 12. Consumption of the monomer inside the droplets during production of the nylon 6,6 membrane ([DA] = 400 mol/m$^3$; [DC] = 718 mol/m$^3$, dispersed versus continuous phase volume ratio = 1/4).



hydrophilic monomer through the membrane, the stirring rate may not have a significant impact on membrane formation. The emulsion droplets are formed in turbulent flow conditions, leading to a fast transfer at liquid interfaces in regard to diffusion through the membrane. Nevertheless, in the case of aqueous core polyphtalamide microcapsules, Koishi et al. (1969) showed that the apparent partition coefficient of diamines increases slightly with the stirring rate. It seems that the transfer rate of diamine from aqueous to organic phase is increased with stirring rate.

According to Salaün et al. (2011), the stirring rate can also have an influence on the final membrane composition. Indeed, an increase of stirring rate promotes the formation of urethane linkages in the production of aqueous core poly (urethane–urea) microcapsules.

### Impact of size on monomer consumption

Obviously, forming the membrane decreases the concentration of monomers and consequently decreases the membrane formation speed. In some cases, the concentration of monomers is so low that reaction is stopped. Figure 12 simulates the formation of a polyamide membrane, either with a hydrophilic or hydrophobic core. From this example, a few conclusions may be drawn:

- The volume of continuous phase is generally four or more times larger than the dispersed phase. At similar concentrations, the monomer in the core is then consumed faster. Increasing the concentration inside the dispersed phase is generally limited by the solubility of the monomer.
- The smaller the dispersed phase droplets, the greater is the importance of the consumption of monomers for a given membrane thickness. For capsules >100 μm, the consumption is limited. The membrane thickness is relatively independent of the size (Poncelet and Neufeld, 1989) and limited by the transfer process through the membrane.
- While producing small capsules (<100 μm), the consumption is important. The membrane formation is also limited by decrease of monomer concentration. The smaller the capsules, the thinner will be the membrane.

### Impact of size on microcapsule properties

According to Berchane et al. (2006), a good estimate of the average microcapsule size prior to microcapsule preparation is important for the pharmaceutical industry where microcapsules of specified mean diameter and size distribution are desirable. In particular, the known size distribution is suitable for design of controlled release drug delivery. Indeed, many studies have demonstrated that a reduction of size increases the release of active ingredient by diffusion (Berchane et al., 2010; Shorty et al., 2012). Smaller microcapsules had a higher surface to volume ratio

and thus a higher diffusion rate of active ingredient compared to larger microcapsules. The release rate from microcapsules is then size dependent.

The microcapsule size also has an impact on release of the active by rupture of the microcapsules. In the case of self healing applications, the rupture of microcapsules is the mechanical trigger of the healing process and without it, no healing occurs. Different authors observed that the rupture of the membrane of microcapsules is more difficult when the microcapsule size decreases (Brown et al., 2002; Keller and Sottos, 2006; Yuan et al., 2007; Yang et al., 2008). Keller and Sottos (2006) observed that during dry compression, smaller microcapsules are more resilient to failure than their larger counterparts. Yang et al. (2008) also made the same observation with microcapsules fabricated via interfacial polymerisation of polyurethane. Brown et al. (2002) observed that virgin fracture toughness increases significantly with decreased microcapsule diameter. Thus, the self-healed microcapsules with the highest diameter exhibited the greatest healing efficiency.

In bioreactor and biotechnological applications, the rupture of microcapsules must also to be controlled. Poncelet et al. (1989) observed an increase in breakage of polyamide membrane microcapsules with the diameter in a shear field. They explain that it can be due to a lowering of internal pressure and a reduction of membrane resistance with size.

## Concluding summary and remarks

A survey of the main parameters controlling membrane formation by interfacial polymerisation is presented. Selection of the monomers and the chemistry, impact of the concentration and the pH and consideration of the physical processes controlling membrane formation were analyzed. Despite the complexity of the process, known trends and understanding of the role of process parameters have been proposed to facilitate the process design.

Several questions have been raised and an attempt has been made to provide at least some hypothesis toward possible solutions. For example, it can be asked why industry works more with polyureas than polyamides? Despite a fast polyamide reaction, polyurea membranes are thicker and denser. Moreover, polyureas form internal cross-links leading to a more resistant membrane, while in the case of polyamides, tri-functional amines must be added to achieve similar results.

In this contribution, information collected from the literature has been summarised. This provides a good understanding of how the membrane is formed and some approaches for future developments. We are however conscious of real limitations in the understanding of the processes. Two hypotheses have been proposed to explain the porosity of the membrane without actually a clear determination of the main process leading to this porosity.

In fact, industry is concerned about meeting certain specifications such as mechanical resistance or degrees of permeability and membrane thickness. However, finding correlations between such properties and production parameters are quite complex and often specific to each application. Little data exist to guide formulators in this regard. This often leads to contradictions in results between different experiments done by different authors.

A second problem is that most scientific studies have been conducted in ideal and simple situations. Industry on the other hand is not using simple monomers, but often multi-functional oligomers. Little is known about the effect of temperature or addition of catalyst to the formulation, while one may expect a real impact both on membrane formation kinetics and also on the final properties of the microcapsules. In addition, the impact of the surfactant and even the active ingredient on the polymerisation process is not clearly understood.

We are conscious of the fact that making general rules about such a complex process, based on different chemistries, is quite risky. However, this study permits a re-evaluation of some assumptions and provides a basis to plan future research to answer several questions. We felt that a better understanding of the interfacial polymerisation process can start through this communication, hopefully providing a basis for other authors to propose other explanations or understanding of this important industrial process operation within the broad field of encapsulation.

## Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the article.

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