International Journal of Pharmaceutics 363 (2008) 26–39

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

# Microencapsulation by solvent evaporation: State of the art for process engineering approaches

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ARTICLE INFO

*Article history:*
Received 29 March 2008
Received in revised form 15 July 2008
Accepted 18 July 2008
Available online 29 July 2008

*Keywords:*
Microencapsulation
Microsphere
Solvent evaporation
Solidification
Controlled release
Modeling

ABSTRACT

Microencapsulation by solvent evaporation technique is widely used in pharmaceutical industries. It facilitates a controlled release of a drug, which has many clinical benefits. Water insoluble polymers are used as encapsulation matrix using this technique. Biodegradable polymer PLGA (poly(lactic-co-glycolic acid)) is frequently used as encapsulation material. Different kinds of drugs have been successfully encapsulation: for example hydrophobic drugs such as cisplatin, lidocaine, naltrexone and progesterone; and hydrophilic drugs such as insulin, proteins, peptide and vaccine. The choice of encapsulation materials and the testing of the release of drug have been intensively investigated. However process-engineering aspects of this technique remain poorly reported. To succeed in the controlled manufacturing of microspheres, it is important to investigate the latter. This article reviews the current state of the art concerning this technique by focusing on the influence of the physical properties of materials and operating conditions on the microspheres obtained. Based on the existing results and authors' reflection, it gives rise to reasoning and suggested choices of materials and process conditions. A part of this paper is also dedicated to numerical models on the solvent evaporation and the solidification of microspheres. This review reveals also the surprising lack of knowledge on certain aspects, such as the mechanism of formation of pores in the microspheres and the experimental study on the solidification of microspheres.

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**Contents**



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doi:10.1016/j.ijpharm.2008.07.018

## 1. The techniques of microencapsulation and their applications

The technique of microencapsulation by solvent evaporation is widely applied in pharmaceutical industries to obtain the controlled release of drug. The obtained polymer microspheres with drug trapped inside can degrade and release the encapsulated drug slowly with a specific release profile. This controlled drug release has outstanding clinical benefits: reducing of dosing frequency, more convenience and acceptance for patients, and drug targeting to specific locations resulting in a higher efficiency (Berkland et al., 2002; Freiberg and Zhu, 2004).

There are different methods to use microencapsulation by solvent evaporation technique. The choice of the method that will give rise to an efficient drug encapsulation depends on the hydrophilicity or the hydrophobicity of drug.

For insoluble or poorly water-soluble drugs, the oil-in-water (o/w) method is frequently used. This method is the simplest and the other methods derive from this one. It consists of four major steps (Fig. 1): (1) dissolution of the hydrophobic drug in an organic solvent containing the polymer; (2) emulsification of this organic phase, called dispersed phase, in an aqueous phase called continuous phase; (3) extraction of the solvent from the dispersed phase by the continuous phase, accompanied by solvent evaporation, transforming droplets of dispersed phase into solid particles; and (4) recovery and drying of microspheres to eliminate the residual solvent.

Many types of poorly water-soluble drugs have been formulated into polymeric systems (Table 1). Some examples are given in Table 1, in which PLGA is poly(lactic-co-glycolic acid), PLA is poly(lactic acid) and PEG is poly(ethylene glycol).

The aforementioned method is not suitable for the encapsulation of high hydrophilic drugs. There are two main reasons: (1) the hydrophilic drug may not be dissolved in the organic solvent; (2) the drug will diffuse into the continuous phase during emulsion, leading to a great loss of drug. Four other alternative methods have been proposed and therefore make it possible to encapsulate the hydrophilic drugs.

1. The w/o/w double emulsion method: the aqueous solution of hydrophilic drug is emulsified with organic phase (w/o emulsion), this emulsion is then dispersed into a second aqueous solution forming a second emulsion (w/o/w double emulsion);
2. the o/w co-solvent method: when the drug is not soluble in the main organic solvent, a second solvent called co-solvent is necessary to dissolve the drug;
3. the o/w dispersion method: the drug is dispersed in form of solid powder in the solution of polymer and organic solvent;
4. the o/o non-aqueous solvent evaporation method: the aqueous phase is replaced by oil (such as mineral oil).

Table 2 presents the examples of hydrophilic drugs that have been encapsulated with the aforementioned methods. It shows that several methods are possible for the successful encpasulation of one hydrophilic drug. The optimal method is to be chosen after trials.

For the same drug, the drug encapsulation efficiency may vary depending on the method used (Herrmann and Bodmeier, 1998). The physical properties of obtained microspheres are strongly dependant on the nature of materials and also on the parameters during the manufacturing of microspheres (Izumikawa et al., 1991; O'Donnell and McGinity, 1997; André-Abrant et al., 2001). The main factors influencing the properties of the microspheres are summarized in Fig. 2.

## 2. Choice of materials

### 2.1. Dispersed phase

#### 2.1.1. Polymer

The biodegradability or biocompatibility is an essential property for the polymer used for pharmaceutical applications. 'Biodegradability' means that the components are degraded into harmless components which are either metabolized or excreted. 'Biocompatibility' means that the component should be physiologically tolerable and should not cause an adverse local or systemic response after administration.

Polymers and copolymers of lactic and glycolic acids are the most commonly used to develop drug delivery systems due to their safe and FDA (Food and Drug Administration) approved applications in humans (Chulia et al., 1994). They can ultimately degrade by hydrolysis of their constituents, which are usual metabolic products. Other biodegradable polymers such as bacterial stor-

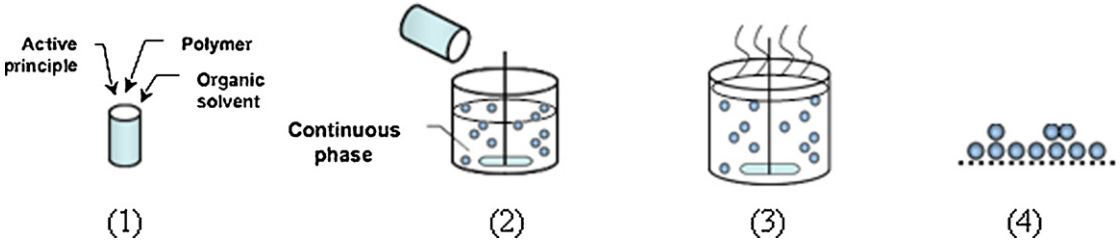


**Fig. 1.** Basic steps of microencapsulation by solvent evaporation.

**Table 1**
Examples of hydrophobic drugs encapsulated using solvent evaporation technique

| Name of drug | Polymer | References |
|---|---|---|
| Cisplatin, 5-fluorouracil (anticancer agents) | PLGA<br>PLGA | Verrijk et al. (1992), Boisdron-Celle et al. (1995) |
| Lidocaine (local anesthetics) | PLGA<br>PLA | Lalla and Sapna (1993), Chung et al. (2001) |
| Naltrexone, cyclazocine (narcotic antagonists) | PLA<br>PLA<br>PELA (PLA + PEG) | Yolles et al. (1975), Mason et al. (1976), Li et al. (1999) |
| Progesterone (hydrophobic steroids) | PLGA<br>PLA<br>PLA | Cowsar et al. (1985), Bums et al. (1993), Aso et al. (1994) |

**Table 2**
Examples of hydrophilic drugs encapsulated using solvent evaporation technique

| Name of drug | Method | References |
|---|---|---|
| Insulin | o/o<br>w/o/w<br>o/w dispersion | Mana et al. (2007)<br>Meinel et al. (2001), Singh et al. (2001)<br>Furtado et al. (2006) |
| Proteins | o/o<br>w/o/w | Viswanathan et al. (1999)<br>Li et al. (2000), Diwan and Park (2001), Dai et al. (2005) |
| Peptides | w/o/w<br>co-solvent<br>o/w dispersion<br>o/o | Herrmann and Bodmeier (1998), Reithmeier et al. (2001)<br>Herrmann and Bodmeier (1998), Luan et al. (2006)<br>Herrmann and Bodmeier (1998), Reithmeier et al. (2001)<br>Herrmann and Bodmeier (1998) |
| Vaccine | w/o/w | Little et al. (2005), Azevedo et al. (2006), Feng et al. (2006) |

age polyesters have been studied for pharmaceutical and medical applications (Amass et al., 1998). Poly-3-hydroxybutyrate and its copolymers with hydroxyvalerate are members of this biopolymer group. They are produced biosynthetically by bacteria from natural raw materials and indeed can be readily broken down by microorganisms under different conditions.

Non-biodegradable polymers with good biocompatibility are also used as drug carriers, such as ethyl cellulose (degradable but no biodegradable) and polymethyl methacrylate (biocompatible but non-degradable). Ethyl cellulose can be administrated orally to protect the drug against gastro-intestinal tract (Fatome et al., 1987) or administrated intraduodenally for a prolonged intestinal absorption (Takishima et al., 2002). Polymethyl methacrylate micro spheres are extensively used as bone cement material in antibiotics releasing for bone infection (such as osteomyelitis) (Stallmann et al., 2006) and bone tumours (Mestiri et al., 1993). Surgical removal is required afterwards because the polymethyl methacrylate is not degradable. Polymethyl methacrylate is also used as model polymer for big-scale process optimization (up to the batch of 100 L) in the work of Maa and Hsu (1996), since it is found to have similar

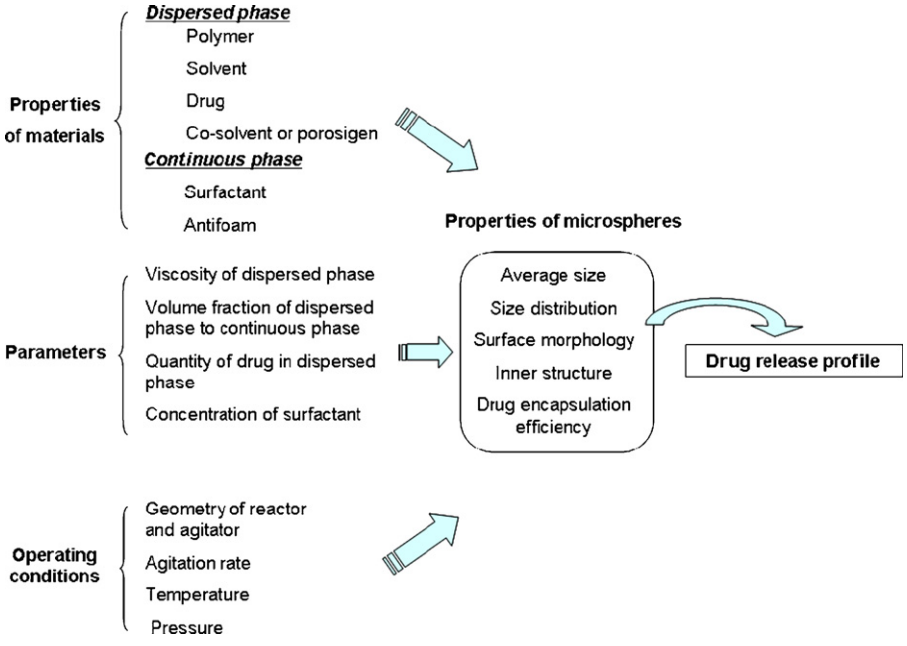


**Fig. 2.** Schema of the factors influencing the properties of microspheres.

**Table 3**
Polymers commonly used for microencapsulation using solvent evaporation technique

| Abbreviation | Complete name | Properties | References |
|---|---|---|---|
| PLGA, PLG | Poly(lactic-co-glycolic acid) or Poly(lactide-co-glycolide) | Good biodegradability and biocompatibility | Sah (1997), Witschi and Doelker (1998), Bahl and Sah (2000), Sah (2000) |
| PLA | Poly(lactic acid) or polylactide | Good biodegradability and biocompatibility, slow degradation rate compared to PLGA | Jalil and Nixon (1990), Freytag et al. (2000), Yang et al. (2000b), Chung et al. (2001) |
| PEG (used in co-polymer) | Poly(ethylene glycol) | Often synthesized with PLGA or with PLA to form a co-polymer with fast degradation rate | Huang et al. (1997), Li et al. (1999), Yang et al. (2000b) |
| PHB | Poly-3-hydroxybutyrate | Bacterial storage polyester; slower degradation rate than polylactic polymers | Amass et al. (1998) |
| PHB-HV | Poly-3-hydroxybutyrate with hydroxyvalerate | Bacterial storage polyester; slower degradation rate than polylactic polymers | Amass et al. (1998) |
| EC | Ethyl cellulose | Degradable, biocompatible, approved by FDA for pharmaceutical application; low cost | Fatome et al. (1987), Sa et al. (1996), Yang et al. (2000a), André-Abrant et al. (2001), Yamada et al. (2001), Takishima et al. (2002) |
| PMMA | Polymethyl methacrylate | Non-degradable but biocompatible, approved by FDA; bone cement material; low cost; alternative polymer for scale-up investigation | Mestiri et al. (1993), Elvira et al. (2004), Luan et al. (2006) |

behaviour with PLGA from the engineering point of view and it is much less expensive than PLGA.

The choice of polymer used as drug carrier depends also on the desired drug release rate, which is essentially determined by the polymer's physical properties. If one polymer cannot offer a satisfying drug release, a single polymer, called co-polymer, can be synthesized from two different polymers. The properties of the co-polymer are improved since it has two segments on the chain. In the work of Huang et al. (1997), a co-polymer (PEG/PLA) was synthesized from polyethylene glycol (PEG) and polylactic acid homopolymers (PLA) in order to increase the degradation rate. Hydrophilic PEG segments in the PLA copolymers enhances the diffusion of water or drug in the polymer carriers (Zhu et al., 1990). As a result, drug release is faster with PEG/PLA than with PLA.

Table 3 lists the polymers and copolymers usually used for microencapsulation by solvent evaporation and presents their main properties.

### 2.1.2. Solvent

For the technique of microencapsulation by solvent evaporation, a suitable solvent should meet the following criteria:

(1) being able to dissolve the chosen polymer;
(2) being poorly soluble in the continuous phase;
(3) having a high volatility and a low boiling point;
(4) having low toxicity.

The main solvents used in the literature and their properties are presented in Table 4.

Chloroform was frequently used before, but due to its toxicity and low vapour pressure, it is gradually replaced by methylene chloride.

Methylene chloride is the most common solvent for the encapsulation using solvent evaporation technique because of its high volatility, low boiling point and high immiscibility with water. Its high saturated vapour pressure compared to other solvents (at least two times higher) promises a high solvent evaporation rate, which shortens the duration of fabrication of microspheres. However this solvent is confirmed carcinogenic according to EPA (Environmental Protection Agency) data and the researchers are making great efforts to find less toxic replacements.

Ethyl acetate shows promising potential as a less toxic substitute of methylene chloride. But due to the partial miscibility of ethyl acetate in water (4.5 times higher than that of methylene chloride), microspheres cannot form if the dispersed phase is introduced directly into the continuous phase. The sudden extraction of a big quantity of ethyl acetate from the dispersed phase makes the polymer precipitate into fibre-like agglomerates (Freytag et al., 2000). To resolve this problem created by the miscibility of solvent with water, three methods can be used:

(1) the aqueous solution is pre-saturated with solvent (Bahl and Sah, 2000);
(2) the dispersed phase is first emulsified in a little quantity of aqueous solution; after the formation of drops this emulsion is poured into a large quantity of aqueous solution (Freytag et al., 2000);

**Table 4**
List of solvents commonly used for microencapsulation by solvent evaporation

| Name | Vapour pressure (mbar) at 20 °C; boiling point (°C); solubility in water (g/L) at 20 °C | Advantages disadvantages | References |
|---|---|---|---|
| Chloroform | 212; 61; 8 | Low solubility in water; higher toxicity than dichloromethane | Huang et al. (1997), Maia et al. (2004) |
| Dichloromethane (methylene chloride) | 453; 39.7; 20 | Dissolvation of most of the polymers; almost immiscible in water; high volatility and quite low boiling temperature; high toxicity | Herrmann and Bodmeier (1998), Li et al. (1999), Yang et al. (2000a), Yang et al. (2000b), Berchane et al. (2006) |
| Ethyl acetate | 100; 77; 90 | Low toxicity; partially soluble in water; very low vapour pressure | Herrmann and Bodmeier (1995), Sah (1997), Herrmann and Bodmeier (1998), Freytag et al. (2000) |
| Ethyl formate | 259; 54; 105 | Low toxicity; partially soluble in water | Sah (2000) |

(3) the dispersed phase is emulsified in a little quantity of aqueous solution, the solution is agitated and the solvent evaporates leading to solidification of microspheres (Sah, 1997).

After using the aforementioned methods, the microspheres are manufactured successfully with ethyl acetate. However, the microspheres prepared by methylene chloride are spherical and more uniform, while the use of ethyl acetate results in particles which appear to be partly collapsed (Herrmann and Bodmeier, 1998). The drug encapsulation efficiency reduces significantly compared to the microspheres made by methylene chloride according to Herrmann and Bodmeier (1998). The author assumed that it is due to the high solubility of ethyl acetate in water, leading to the loss of drug. Based on this assumption, we make a further assumption that it is due to two main causes: (1) more drug is entrained into the continuous phase by the higher mass flux of solvent, which is driven by the diffusion from the dispersed phase into the continuous phase; (2) the big quantity of solvent present in the continuous phase increases the solubility of drug in the continuous phase, facilitating the diffusion of drug into the continuous phase.

Ethyl formate shows also interesting results. Sah (2000) has succeeded in manufacturing microspheres of PLGA with ethyl formate. He observed that the evaporation rate of ethyl formate in water was 2.1 times faster than that of methylene chloride although ethyl formate possesses a lower vapour pressure and a higher boiling point according to the authors. This phenomenon is explained by the fact that more molecules of ethyl formate are exposed to the air–liquid interface because of its higher water solubility. His work proved that water immiscibility of a solvent is not an absolute prerequisite for making an emulsion. More experiments have to be carried out to confirm the promising use of ethyl formate.

In summary, less toxic solvents have been tested and show a promising future. But there are not enough results to compare the quality of microspheres prepared by different solvents. Methylene chloride is still the most used solvent because it evaporates fast, shows high drug encapsulation efficiency and produces microspheres with spherical and more uniform form.

#### 2.1.3. Alternative components

In certain cases, other constituents are added in the dispersed phase such as co-solvent and porosity generator.

Co-solvent is used to dissolve the drug that is not totally soluble in the solvent in the dispersed phase (Reithmeier et al., 2001; Luan et al., 2006). Organic solvents miscible with water such as methanol and ethanol are the common choices.

Porosity generator, called also porosigen or porogen, is used to generate the pores inside the microspheres, which consequently increases the degradation rate of polymer and improves drug release rate. Organic solvents such as hexane, which do not dissolve poly(lactic acid) and poly(lactic-co-glycol acid) can be incorporated into microspheres to form pores (Spenlehauer et al., 1986). Incorporating Sephadex (cross-linked dextran gel) into insulin–PLA microspheres significantly increases microsphere porosity (Watts et al., 1990). Appropriate amount of *n*-heptane added in the ethylcellulose/dichloromethane emulsion for encapsulation of aspirin also increases the porosity. However, if an excess of *n*-heptane is introduced, microspheres with high porosity leads to a very low drug encapsulation efficiency (Yang et al., 2000a).

### 2.2. Continuous phase

#### 2.2.1. Surfactant

The surfactant, also called tensioactive agent, is frequently employed for the dispersion of one phase in another immiscible phase and for the stabilization of obtained emulsion. It reduces the surface tension of continuous phase, avoids the coalescence and agglomeration of drops and stabilizes the emulsion. A suitable surfactant should be able to give microspheres a regular size and a small size distribution, guaranteeing a more predictable and stable drug release.

Before choosing the type of surfactant and its concentration, it is important to know the polarity of the two immiscible phases, the desired size of microspheres and the demand on the sphericity of microspheres.

Surfactants for emulsions are amphiphilic. That means one part of the molecule has more affinity to polar solutes such as water (hydrophilic) and the other part has more affinity to non-polar solutes such as hydrocarbons (hydrophobic). When it is present in an emulsion, the surfactant covers the surface of drops with its hydrophobic part in the drop and its hydrophilic part in the water.

There are four different types of surfactant classified by the nature of the hydrophilic part of molecule: anionic, cationic, amphoteric and non-ionic.

The anionic surfactants release a negative charge in the aqueous solution. They have a relatively high HLB (hydrophile–lipophile balance) level because they are prone to be hydrophilic.
The cationic surfactants on the contrary release a positive charge in aqueous solution.
The amphoteric surfactants behave as anionic in alkali pH and as cationic in acid pH.
Non-ionic surfactants have no charge.

For the most used emulsion of methylene chloride/water, typical stabilizers include:

non-ionic: partially hydrolyzed PVA (polyvinyl alcohol) (André-Abrant et al., 2001), methylcellulose (Berchane et al., 2006), tween (Yang et al., 2000a) and span (Jalil and Nixon, 1990);
anionic: sodium dodecyl sulphate (SDS);
cationic: cetyltrimethyl ammonium bromide (CTAB).

Among these surfactants, partially hydrolyzed PVA is mostly used because it gives the smallest microspheres (Jeffery et al., 1991).

The increase of surfactant concentration reduces the size of microspheres (Jeffery et al., 1993; Sansdrap and Moës, 1993; Carrio et al., 1995; Yang et al., 2001). The addition of surfactant lowers the surface tension of the continuous phase and the diminution of the latter one decreases the particles size. However, due to the critical micelle concentration (CMC), the surface tension cannot decrease infinitively. When surfactant concentration reaches a certain level, the solution surface is completely loaded. Any further additions of surfactant will arrange as micelles and the surface tension of the aqueous phase will not decrease any more.

#### 2.2.2. Alternative components

Besides the surfactant, the antifoam is sometimes added into aqueous phase in the case of strong agitation because the foaming problem will disturb the formation of microspheres. When the stirring speed increases, more air is entrained and foam forms. So anti-foams of silicon and non-silicon constituents are used to increase the rate at which air bubbles are dissipated (Torres et al., 1998; Berchane et al., 2006).

Recent studies show that it is possible to prepare microspheres without surfactant by replacing it with an amphiphilic biodegradable polymer. The advantage is to avoid the potential harm of surfactant residual on the surface or inside the final microspheres. In the work of Carrio et al. (1995), PLA oligomers prepared by direct condensation of D,L-lactic acid have an amphiphilic surfactant-similar structure since the polymers are composed of a hydrophobic

polyester chain ended by a carboxylic acid group, which can be ionized to form hydrophilic carboxylate polar heads at neutral pH in water. PLA oligomers are used to manufacture surfactant-free progesterone-containing PLGA micro spheres. They are introduced via the dispersed phase and enter the structure of final microspheres. Microspheres of PLGA prepared with them exhibit shapes and sizes comparable to those prepared by hydrolyzed PVA. The usage of biodegradable amphiphilic polymers in manufacturing of microspheres shows big potential. Syntherization is a common approach to graft an amphiphilic segment on a biodegradable polymer (Bouillot et al., 1999; Van-Butsele et al., 2007; Zhou et al., 2008).

## 3. Parameters and operating conditions

After a review on existing works, the impact of parameters and operating conditions on the properties of microspheres is summarized in Table 5. It is found that the study of the impact on some properties of microspheres such as inner structure is missing in the literature. More work has appealed to fill this blank.

### 3.1. Viscosity of the dispersed phase

An empirical equation describes the impact of viscosity on the size (Calderbank, 1958):

$$d_{32} = A\left(\frac{\mu_d}{\mu_c}\right)^{0.25}, \quad (1)$$

where $d_{32}$ is the average diameter (Sauter's diameter) of microspheres, $\mu_d$ is the viscosity of the dispersed phase, $\mu_c$ the viscosity of the continuous phase and $A$ is a coefficient which depends on many other factors (see Section 3.3).

In the literature, it is very common to vary the viscosity of the dispersed phase. Instead, the viscosity of the continuous phase is rarely modified. That is because the viscosity of the continuous phase is very close to that of water. Even though adding addictives can significantly increase the viscosity of continuous phase, it is complicated to recover the microspheres from a viscous liquid.

Increasing polymer concentration or the molecular weight of polymer increases the viscosity of dispersed phase (André-Abrant et al., 2001). The size increases exponentially with viscosity. Increasing viscosity improves also the drug encapsulation efficiency.

In the work of Yang et al. (2000a), a higher polymer (ethyl cellulose) concentration results in a higher drug (aspirin) encapsulation efficiency. This result is confirmed by the work of André-Abrant et al. (2001) in which ethyl benzoate is capsulated by ethyl cellulose. The microspheres have a smoother surface. However the larger size and smooth surface caused by a higher concentration reduce the release of aspirin.

The higher molecular weight of the polymer increases the encapsulation efficiency of drug. This was observed when ethyl benzoate (the drug) is encapsulated in ethyl cellulose (the polymer) prepared using the o/w dispersion technique (André-Abrant et al., 2001). It is confirmed by the work of Herrmann and Bodmeier (1998) for encapsulation of somatostatin using the o/w dispersion method using poly(lactic-co-glycol acid), methylene chloride and hydrolyzed polyvinyl alcohol aqueous solution. Witschi and Doelker (1998) also found that in microspheres prepared using the w/o/w method the drug encapsulation efficiency tended to increase with increasing the molecular weight of polymer.

From the aforementioned studies it appears that increasing the viscosity of the dispersed phase increases the size of microspheres and drug encapsulation efficiency. Even though the type of solvent is also responsible of the viscosity of the dispersed phase, changing solvent to vary the viscosity is rarely taken into account in the production and this is rarely pointed out in the literature. This is because the type of solvent is basically chosen in such a manner that it provides a high evaporation rate and an optimal manufacturing of microspheres.

**Table 5**
Impact of parameters and operating conditions on the properties of microspheres

| | Factors | Reference | Impact on properties of microspheres | | |
|---|---|---|---|---|---|
| | | | Size | Surface morphology | Encapsulation of drug |
| Increase of the following parameters | Viscosity of the dispersed phase | Yang et al. (2000a), André-Abrant et al. (2001) | Bigger diameter | Smoother surface | Increase of efficiency; slower drug release |
| | Volume fraction of dispersed phase to continuous phase | Jeffery et al. (1991), Jeffery et al. (1993), Jeyanthi et al. (1997), André-Abrant et al. (2001) | Decrease in diameter or no influence | | Increase of efficiency |
| | Quantity of drug in the dispersed phase | Witschi and Doelker (1998) | | More porous and irregular shape | Low efficiency when the quantity of drug is too high due to the formation of big pores |
| | Concentration of surfactant | Jeffery et al. (1993), Sansdrap and Moës (1993), Carrio et al. (1995), Yang et al. (2001) | Smaller diameter | | |
| | Concentration of porosigen | Yang et al. (2000a) | Smaller diameter | Coarser surface with larger pores | No impact |
| Operating conditions | Increase of agitation rate | Gabor et al. (1999), André-Abrant et al. (2001), Yang et al. (2001), Mateovic et al. (2002) | Smaller diameter; small size distribution | | |
| | Increase of temperature | Witschi and Doelker (1998), Freitas et al. (2004) | Bigger diameter | Coarser surface | Decrease of efficiency |
| | Reduced pressure compared with atmospheric pressure | Izumikawa et al. (1991), Li et al. (1995b), Chung et al. (2001) | Smaller diameter or no influence | Smoother surface | Increase or decrease of encapsulation efficiency of drug (different observations by different authors); slower drug release |

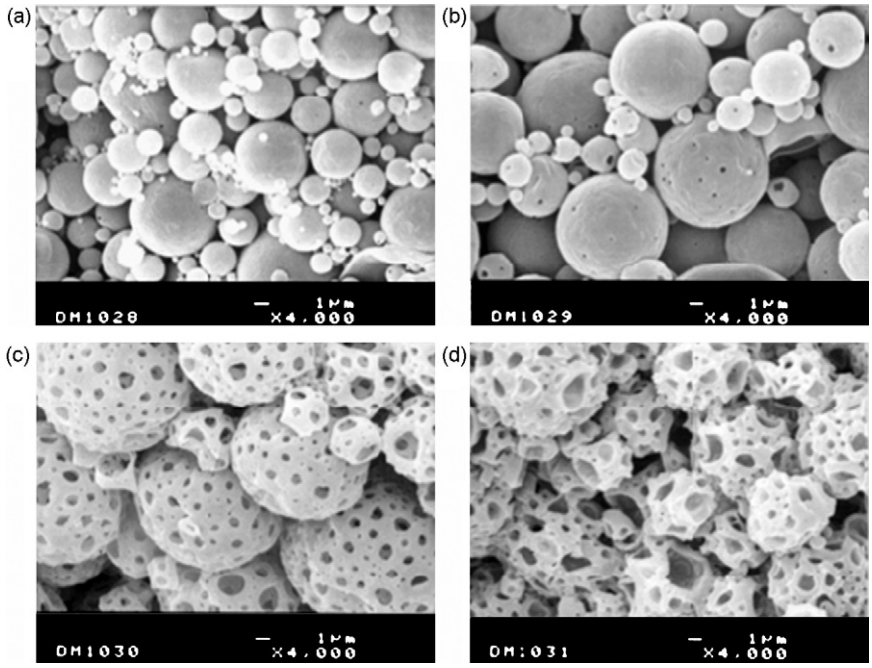


**Fig. 3.** Electron microscope photographs of Resomer RG504 (chemical name: DL-PLGA 50:50) microparticles prepared by the w/o/w solvent evaporation with increasing nominal drug loadings from 0 (a) to 1 (b), 5 (c) and 10 (d) (%, w/w) (Witschi and Doelker, 1998).

### 3.2. Quantity of active material (drug) in the dispersed phase

It has been observed that increasing the quantity of drug improves the encapsulation efficiency (André-Abrant et al., 2001). The authors assume that the loss of drug into the continuous phase is constant while other operating conditions do not change. Therefore, by increasing the total quantity of drug, the percentage of drug encapsulated is increased.

However, when too much drug is loaded, the encapsulation efficiency of drug will decrease. This may be explained by three reasons:

The quantity of drug loaded in the solvent is limited. During the solidification of microspheres, the quantity of solvent in the dispersed phase decreases. The drug has a tendency to be expelled from the dispersed phase.

Microspheres with high drug loading are more porous and have a more irregular shape (Witschi and Doelker, 1998) (Fig. 3). The over-porous surface is responsible for the loss of drug.

Too much drug loading increases the risk of drug leakage due to the limited space inside the microsphere and the shrinkage of the microsphere during its solidification. A simple model can explain it.

Let us assume that the drug (solid or in aqueous solution) is homogeneously dispersed inside the microsphere. The drug forms spherical drops and the distance between each drop is equal. Assuming that the drug loading is $N_d$ (%, v/v) in the dispersed phase and that one drop of diameter $D_d$ in a cubic space of length $L$, $N_d$ can take the following form:

$$N_d = \frac{(\pi/6)D_d^3}{L^3} \quad (2)$$

According to Fig. 4, the distance between two drops is $L_{drop} = L - D_d$ and can be expressed as a function of $N_d$ and $D_d$ from Eq. (2):

$$L_{drop} = D_d \left[ \left( \frac{\pi}{6N_d} \right)^{1/3} - 1 \right] \quad (3)$$

Eq. (3) is plotted in Fig. 5 where the distance between drops $L_{drop}$ decreases with decreasing size of the drop and the increasing drug loading.

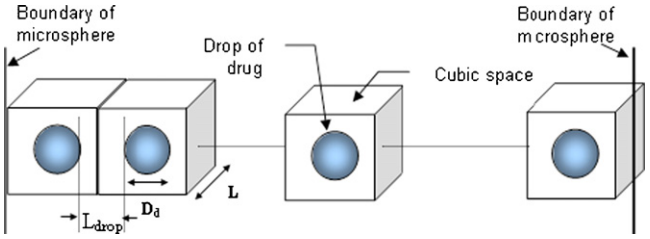


**Fig. 4.** Schema of model for distance calculation between drops of drug.

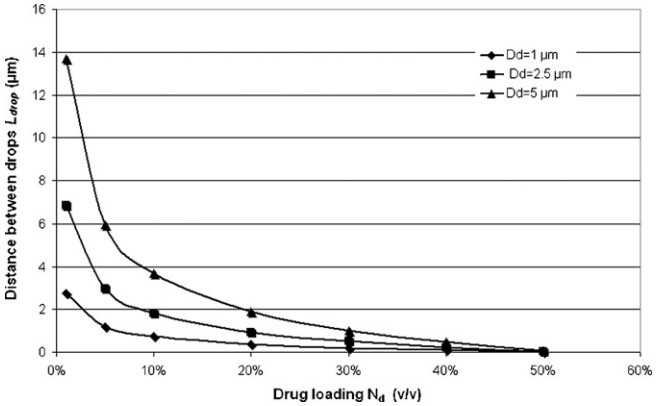


**Fig. 5.** Distance between drops of drug at different drug loading while the diameter of drop is 1 μm, 2.5 μm and 5 μm, calculated from Eq. (3).

It is better to increase the size of the drop to have a big distance between drops, avoiding the coalescence. However, the size of drop should remain reasonable as drops that are too big have less stability inside the microsphere, increasing the risk of drug leakage.

Obviously there is a limit for the quantity of drug (about 50% in Fig. 5). Moreover, during the solidification of microsphere, the microsphere shrinks because of the removal of the solvent. Since the volume of drug remains the same, the volume percentage of the drug becomes much more important than its initial value $N_d$. In order to assure an efficient drug encapsulation, the drug loading should respect the limit calculated for the solidified microsphere.

### 3.3. Agitation, geometries and size prediction

Agitation is one of the most important parameter for controlling the size of microspheres after the physico-chemical properties of materials. Many other factors linked to agitation have also an impact on the size of microspheres, such as: the geometry of the reactor, the number of impellers and their position and the ratio of impeller's diameter compared to the reactor's diameter (Maa and Hsu, 1996).

There is a great number of correlations that predict the size and distribution of the size of the drops in an emulsion of two immiscible liquids (Haas, 1987; Kumar et al., 1993; Maa and Hsu, 1996). The correlations take into account two aspects:

(1) The physical properties of materials, such as the density of continuous phase and the interfacial tension.
(2) The factors linked to agitation.

The most basic and the most employed correlation is based on the theory of Kolmogoroff (Hinze, 1955), it is expressed as:

$$\frac{d_{max}}{D} = c_1 \left( \frac{\rho_c N^2 D^3}{\sigma} \right)^{-3/5} \quad (4)$$

In Eq. (4), $d_{max}$ is the biggest drop size which can exist under turbulence, $D$ is the diameter of the agitator (m), $\rho_c$ is the density of continuous phase (kg/m$^3$), $N$ is the agitation rate (turns/s), $\sigma$ is the interfacial tension between the dispersed phase and the continuous phase (N/m) and $c_1$ is a constant. The value of the constant $c_1$ is experimentally determined and its value is affected by the factors linked to the agitation conditions as explained previously.

The average size such as Sauter's diameter $d_{32}$ can be estimated since it is proportional to the maximum diameter of drop $d_{max}$ (Hinze, 1955).

$$d_{32} = c_2 d_{max}, \quad (5)$$

where $c_2$ is a constant.

From Eqs. (4) and (5), it is clear that increasing the agitation rate decreases the average size of microspheres, as it is confirmed in the literature (Gabor et al., 1999; André-Abrant et al., 2001; Yang et al., 2001; Mateovic et al., 2002).

Other terms can be introduced into Eq. (5) to include the influence of other factors such as the volume fraction of the dispersed phase to the continuous phase $\Phi$ and their viscosity ratio (Calderbank, 1958; Chatzi et al., 1991; Davies, 1992).

$$\frac{d_{32}}{D} = c_3(1 + c_4\Phi) \left( \frac{\rho_c N^2 D^3}{\sigma} \right)^{-3/5} \quad (6)$$

$$\frac{d_{32}}{D} = c_5\Phi \left( \frac{\rho_c N^2 D^3}{\sigma} \right)^{-3/5} \left( \frac{\mu_d}{\mu_c} \right)^{0.25} \quad (7)$$

In Eqs. (6) and (7), $c_3$, $c_4$ and $c_5$ are constants. The value of $c_5\Phi((\rho_c N^2 D^3)/\sigma)^{-3/5}D$ is equal to that of the coefficient $A$ mentioned in Eq. (1).

In spite of empirical correlations, the influence of $\Phi$ on the size of microspheres is not quite clear. Instead of observing an increase in the diameter of the microspheres with the increase in volume percentage, there are many contrary observations in the literature. It is reported that an increase in the volume of the dispersed phase decreases the size of microspheres (Jeffery et al., 1991, 1993; Jeyanthi et al., 1997; André-Abrant et al., 2001) while in some other studies, no great influence was observed (Sansdrap and Moës, 1993; Gabor et al., 1999).

### 3.4. Pressure and temperature

#### 3.4.1. Disadvantage of elevating the temperature

The solvent evaporation rate can be accelerated either by increasing the temperature of the continuous phase (Li, 1994; Miyazaki et al., 2006) or by reducing the pressure in the reactor (Izumikawa et al., 1991; Chung et al., 2001, 2002; Meng et al., 2004). However, there are several drawbacks in the case of elevated temperature: the recovered total mass decreases; the size distribution shifts toward the larger size; the drug encapsulation efficiency decreases and the morphology becomes coarser (Freitas et al., 2004). Moreover, the temperature should not be too high so as not to disnature the drug and not to reach the boiling point of solvent. Therefore, applying a reduced pressure seems to be a better choice. This part of the review is dedicated to the impact of reducing pressure. Unfortunately few studies have been achieved on this aspect.

#### 3.4.2. Influence of the pressure on the process duration

In the work of Meng et al. (2004), bovine hemoglobin loaded PELA (poly(D,L-lactic acid)-co-poly(ethylene glycol)) microspheres were prepared by w/o/w emulsion method under atmospheric pressure and under reduced pressure (30 kPa). The solidification time was shortened from 240 min to 40 min by applying a reduced pressure. Similar observations have been reported in the work of Yang et al. (2000a) and Chung et al. (2001).

#### 3.4.3. Influence of the pressure on the drug encapsulation efficiency

Reduced pressure can improve the drug encapsulation efficiency in most cases. In the work of Izumikawa et al. (1991), progesterone-loaded poly(L-lactide) microspheres prepared using the o/w solvent evaporation technique were studied. They found that drug encapsulation efficiency was greater for microspheres that have been prepared using solvent evaporation at a reduced pressure (the RP method) at 200 mmHg than for those prepared using solvent evaporation at atmospheric pressure (the AP method) at 760 mmHg. The longer duration of the evaporation process using the AP method may have been the cause of larger drug loss. This argument is supported by the results in the work of Meng et al. (2004): the bovine hemoglobin encapsulation efficiency increases with the decrease of solidification time. However, others studies have contradictory results. The encapsulation efficiency of lidocaine (Chung et al., 2001) or albumin (Chung et al., 2002) in PLA microspheres prepared under a reduced pressure is lower than those prepared at atmospheric pressure. The authors explain that these contradictory results are due to the different droplet formation methods and the size of microspheres. Chung et al. (2001, 2002) used the o/w emulsification process to form PLA microspheres instead of the mechanical stirred method reported in the work of Izumikawa et al. (1991). The microspheres are about or less than 1 μm compared

with about 50 μm for the microspheres in the study of Izumikawa et al. (1991).

*3.4.4. Influence of the pressure on the surface of the microspheres*

The surface morphology of the microspheres examined by scanning electron microscopy indicates a porous and rough surface for the microspheres made using the AP method (Izumikawa et al., 1991). Conversely, the microspheres made using the RP method have an apparent smooth surface (Fig. 6). The authors think that this is related to the crystallinity of microspheres. They explain that the solvent removal under reduced pressure is too fast for polymer to crystallize. Therefore, the microspheres produced by AP method have crystalline polymer matrices and those produced with the RP method have amorphous polymer matrices. The microspheres of crystalline polymer matrices have rough surfaces with large surface areas whereas those of amorphous polymer matrices have smooth surface with smaller surface areas. Because of their porous surface the drug release rate of microspheres prepared at atmospheric pressure is much greater. The choice of the optimal pressure depends on the desired drug release rate.

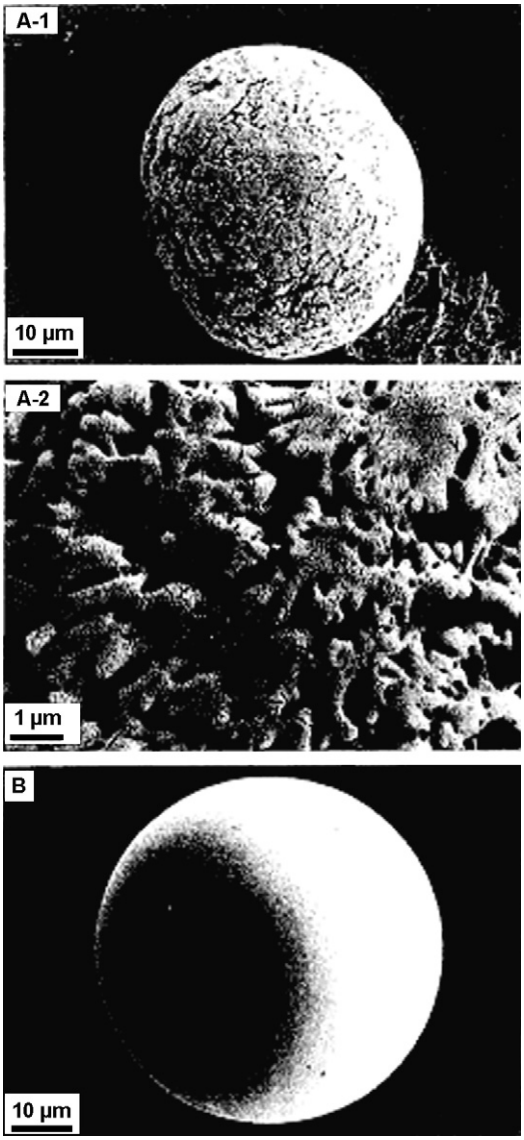


**Fig. 6.** Scanning electron micrography of progesterone-loaded (10%) poly(L-lactide) micro spheres (Izumikawa et al., 1991): prepared at atmospheric pressure (A-1 and A-2); prepared at reduced pressure (B). (reproduced with permission).

*3.4.5. Influence of the pressure on the size of the microspheres*

The microspheres prepared under different pressure have a similar size according to Meng et al. (2004). This result is not in agreement with the results of Chung et al. (2001, 2002), in which the microspheres prepared under reduced pressure have a smaller size than those prepared under atmospheric pressure. The influence of pressure on the size of the microspheres is not clear because of the insufficient studies. One possible explanation for the decrease of size might be interpreted by the Laplace equation, expressed as:

$$\mathrm{d}P = \frac{2\gamma}{r}, \tag{8}$$

where d$P$ is the pressure difference between outside part and inside part of liquid film of the droplet, $\gamma$ is the interfacial tension of liquids in the emulsion system, and $r$ is the radius of the spherical droplet (Atkins et al., 1998). $\gamma$ can be assumed constant since its value is weekly affected by the polymer concentration. Its value varies less than 8% when concentration of polymer is 10 times higher (Chung et al., 2001) or does not vary in function of the concentration (Maa and Hsu, 1996). Chung et al. (2001) explain that, from a qualitative point of view, d$P$ is expected to be greater under reduced pressure than at atmospheric pressure. According to Eq. (8), an increase of d$P$ leads to a decrease of $r$.

*3.4.6. Choice of the pressure and temperature*

Since reduced pressure increases the evaporation rate, it should be as low as possible. But once the pressure is lower than the saturated vapour pressure of the solvent at a given temperature, the solvent begins to boil. The formation of bubbles can destroy the drops of dispersed phase, so the reduced pressure needs to be kept higher than the saturated vapour pressure of the solvent at a given temperature. The same analysis can be done for the temperature that is to be kept below the boiling point at a reduced pressure.

There is no suggestion in the literature on how to choose the optimal pressure and temperature for a successful and rapid manufacturing of microspheres. However, values of pressure and temperature can be firstly estimated using the relationship between the saturated vapour pressure of solvent $P_{vap}$ and the temperature $T$, which is defined by the Clausius–Clapeyron equation:

$$P_{vap} = e^{-H_{vap}/RT+b}, \tag{9}$$

where $H_{vap}$ is the enthalpy of vaporization, $R$ is the gas constant and $b$ is a constant. The methylene chloride is taken as an example in Fig. 7. The pressure and temperature need absolutely to be kept from the zone that leads to the solvent boiling (the right side of the curve in Fig. 7. Higher temperature is possible in condition that the pressure is raised high enough, but this solution does not have many interests because of the high energy consuming. Keeping the temperature at the room temperature and reducing the pressure seems to be more promising.

## 4. Modelling

### 4.1. Solvent evaporation

Mathematical models have been built to analyze the solvent evaporation under atmospheric pressure in an open vessel (Li, 1994; Li et al., 1995a,b; Wang and Schwendeman, 1999). As shown in Fig. 8, there are two main mass flows: (1) the solvent diffuses from drops of the dispersed phase to the continuous phase (solvent diffusion rate $F_1$); (2) the solvent diffuses into the continuous phase

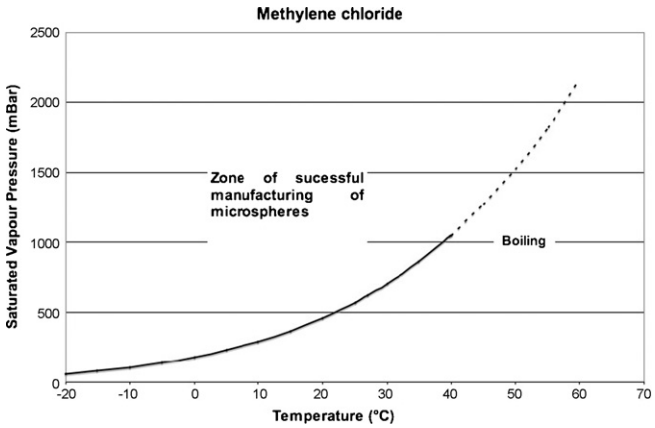


**Fig. 7.** Saturated vapour pressure of methylene chloride as a function of temperature (data from Chemical Engineer's Handbook 5th Edition).

and evaporates into the air (solvent evaporation rate $F_2$). Accompanied by the solvent evaporation, the drops of the dispersed phase become rich in polymer due to solvent removal and they begin to solidify.

Based on the literature review, the solvent evaporation process experiences three stages because of the interaction between the two mass flows. The profiles of solvent evaporation rate, the solvent concentration in the continuous phase and the mass change of solvent at different stages are shown in Fig. 9.

*Stage A:* At the beginning, when the dispersed phase is rich in solvent, the solvent diffusion rate $F_1$ into the continuous phase is greater than the solvent evaporation rate $F_2$. So the continuous phase becomes rapidly saturated with solvent. Consequently the concentration of solvent inside the continuous phase $C_s$ reaches the solubility (maximum concentration). This stage is very short with duration of several seconds. Therefore, it can be neglected.
*Stage B:* The quantity of solvent evaporated is compensated with solvent diffused into the continuous phase and $C_s$ remains constant. The duration of this stage depends on the initial quantities of the dispersed phase and of the continuous phase.
*Stage C:* The diffusivity of solvent in the dispersed phase decreases with an increase in polymer concentration (Guerrier et al., 1998; Vrentas and Vrentas, 1998; Kim and Lee, 2000; Doumenc and Guerrier, 2001; Hsu and Lin, 2005). $F_1$ becomes smaller than $F_2$ so $C_s$ begins to decrease. The moment that occurs the transition between stage B and stage C is the critical time $t_c$.

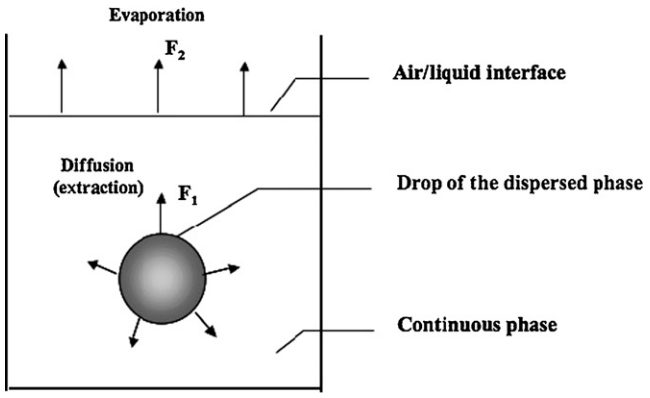


**Fig. 8.** Schema of solvent diffusion and evaporation steps.

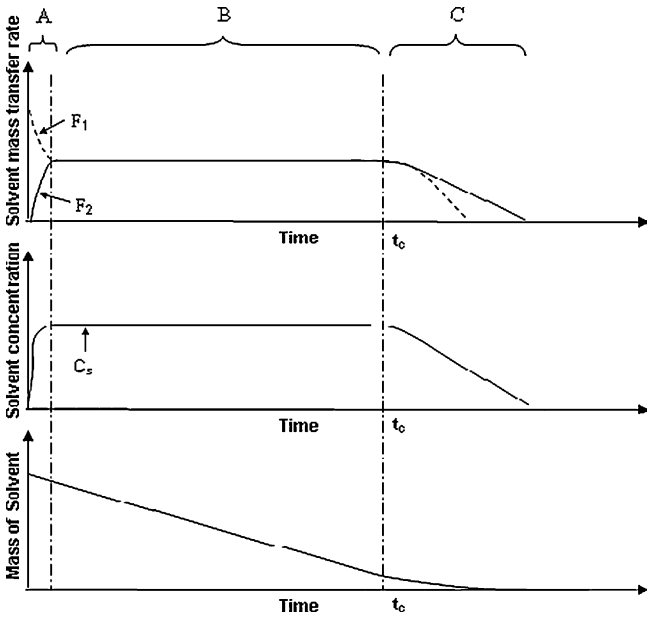


**Fig. 9.** Evolution of the solvent mass transfer rate, the solvent concentration in the continuous phase and mass of solvent with time.

Since the duration of stage A is so small that it does not have effect on the solvent evaporation profile, the evolution of mass of solvent under atmospheric pressure can be divided into two parts (Li, 1994; Li et al., 1995a). First the mass of solvent decreases linearly and then exponentially after the critical time $t_c$ (profile of mass of solvent in Fig. 9).

Assuming that the concentration of solvent is zero above the surface of the continuous phase, the solvent evaporation can be described by the following equation, which is based on Fick's law:

$$\frac{dM}{dt} = -AKC_s, \tag{10}$$

where $M$ is the total mass of solvent in the reactor (kg), A is the surface area of air-water interface ($m^2$), $t$ is the time (s), $K$ is the evaporation constant (m/s) and $C_s$ is the concentration of solvent in the continuous phase ($kg/m^3$). During stage B, $C_s$ is equal to the solubility of solvent in the continuous phase $C_{sol}$. So the first part of the solvent evaporation profile is linear.

During state C, $C_s$ decreases and if $V$ is the volume of the continuous phase, d$M$ can be approximated by:

$$dM = V dC_s, \tag{11}$$

where d$C_s$ is the infinitesimal variation of solvent in the continuous phase. So the resolution of Eqs. (10) and (11) gives rise to:

$$C_s = C_{sol} e^{-(A/V)K(t-t_c)}, \tag{12}$$

Thus $C_s$ decreases exponentially.

According to the film theory for mass transfer between two phases (Backhurst et al., 1974), the evaporation constant $K$ is defined as:

$$K = \frac{D_c}{\delta} \tag{13}$$

where $D_c$ is the diffusivity of organic solvent in the continuous phase ($m^2/s$) and $\delta$ is the thickness of diffusion boundary layer on the liquid side (m).

$\delta$ can be calculated as following (Cussler, 1984):

$$\delta \propto D^{-5/4} V^{1/4} \omega^{-3/4} \nu^{5/12} D_c^{1/3} \tag{14}$$

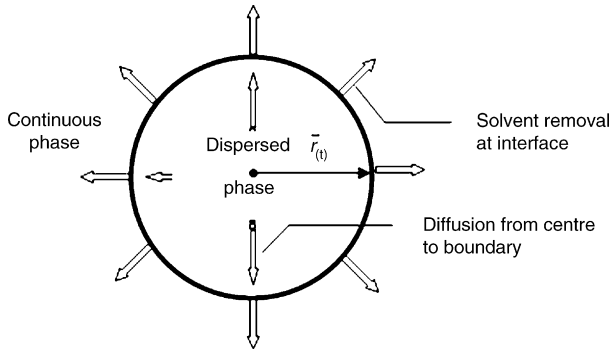


**Fig. 10.** Schema of mass transfer model in one single drop of polymer and solvent: $\bar{r}_{(t)}$ is the average radius of drop that decreases with time.

where $D$ is the diameter of impeller (m), $V$ is the volume of the continuous phase ($m^3$), $\omega$ is the rotation speed of the impeller ($s^{-1}$)and $\upsilon$ is the kinematic viscosity of the continuous phase ($m^2/s$).

Based on this theory, $\delta$ is only linked with operating conditions. This is confirmed by the work of Li et al. (1995a), in which $K$ is independent of the solvent concentration. However in the work of Wang and Schwendeman (1999), the authors find that $K$ is dependent of the solvent concentration, defined by the following relationship:

$$K = -\frac{V}{A}\frac{\mathrm{d}\ \ln C_s}{\mathrm{d}t}, \tag{15}$$

Because very little work has been carried out on the modelling of solvent evaporation, there is a large uncertainty on the value of $K$ and on the parameters that influence this value.

This model predicts only the pure solvent evaporation profile. It is valid when the mass transfer coefficient between the organic solvent and the continuous phase is higher than the mass transfer coefficient at the air-water interface. The model concerns only the mass transfer at the air–liquid interface and gives no information on the manufacturing of microspheres, such as the influence of the solidification of microspheres on the solvent evaporation profile if the polymer is added into the organic solvent. Therefore, more detailed model, which focuses on the solidification of the microspheres, is necessary.

### 4.2. Solidification of microsphere

During the solidification of the drop of the dispersed phase into solid microsphere, two mass transfers take place: the solvent diffusion inside drop and the solvent diffusion at the boundary of the dispersed phase into the continuous phase (Fig. 10).

Few microscopic models exist for microsphere solidification. The articles concerning numerical investigations on liquid droplet drying by spray drying can be good references. In both cases, there is liquid diffusion inside the drop and convection at the boundary of the drop. In the case of spray drying, the temperature of air around the drop is extremely high and there is a phase change of water at the surface of drop. Contrary to the spray drying, there is only diffusion of solvent from the dispersed phase to the continuous phase during microsphere solidification. Therefore, the heat conduction and temperature gradient inside the drop is not necessary to be taken into account.

The model is normally composed of the following equations:

(1) Fick's equation describing the diffusion inside the drop.
(2) Equations for the boundary conditions.
(3) Equation of calculation of shrinkage of drop, the value of diameter at each moment is needed in the previous equations.

#### 4.2.1. Diffusion inside the drop

The drop is assumed to be perfectly spherical and the concentrations of polymer and solvent are assumed to be homogeneous in the beginning. The volume fraction of solvent at the surface of drop is assumed to be always in equilibrium with the concentration of solvent in the continuous phase.

The diffusion inside the drop follows Fick's law. It can be expressed by diffusion equation (Shabde et al., 2005; Sloth et al., 2006):

$$\frac{\partial w_s}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D_s \frac{\partial w_s}{\partial r}\right) \tag{16}$$

where $w_s$ is the mass fraction of solvent; $r$ the radial coordinate (the distance of the point to the centre of drop) and $D_s$ the diffusivity of solvent in the dispersed phase.

Because of drop shrinkage the drop has a moving boundary problem, a coordinate transformation can simplify the calculation (Li et al., 1995a; Sloth et al., 2006). The normalized position variable $\xi$, is defined as:

$$\xi = \frac{r}{\bar{r}(t)} \tag{17}$$

where $\bar{r}(t)$ is the radius of drop.

For the convenience of modelling, some authors (Li, 1994; Li et al., 1995a,b) transformed the diffusion equation in mass flux to volume flux.

$$\frac{\partial \phi_s}{\partial t} = -\nabla(\phi_s \upsilon_p + J_s) \tag{18}$$

where $\phi_s$ represents the volume fraction of solvent; $J_s$ the volume flux of solvent relative to polymer velocity and $\upsilon_p$ the velocity of the polymer.

The volume flux $J_s$ is calculated in the new coordination as:

$$J_s = \frac{1}{\bar{r}(t)}\frac{D_s}{RT}\nabla_\xi \mu \tag{19}$$

where $\mu$ is the chemical potential, $R$ is the gas constant and $T$ is the temperature.

The diffusivity of solvent in the dispersed phase $D_s$ in Eqs. (16) and (19) is strongly dependant on the concentration of polymer in the dispersed phase. This dependence is intensively investigated in the domain of film casting or polymer films drying. Based on the free volume diffusion model developed by Vrentas and Duda (1977a,b), the correlation can be written as (Kim and Lee, 2000; Kobuchi and Arai, 2002):

$$D_s = D_o(1-\phi_p)^2(1-2\chi\phi_p) \tag{20}$$

where $D_o$ is the solvent self-diffusivity, $\phi_p$ is the volume fraction of polymer and $\chi$ is the Flory–Huggins coefficient. It quantifies the mutual affinity between polymer and solvent.

$D_s$ can be also calculated as an exponential type (Reuvers and Smolders, 1987):

$$D_s = r_1 10^{-(r_2 + r_3\phi_p)} \tag{21}$$

where $r_1$, $r_2$ and $r_3$ are constants depending on the system.

#### 4.2.2. Boundary conditions

Similar boundary conditions are frequently used in the models of the droplet solidification by spray drying (Shabde et al., 2005; Sloth et al., 2006) and in the model of the solidification of the microsphere (Li et al., 1995a): There is no mass flux in the centre of the drop. At the boundary of the drop, there is the mass transfer of solvent (or water) accompanied by the decrease of the size of the drop.

In the centre of drop, it is expressed either in mass fraction or volume flux:

$$\frac{\partial w_s(t, \xi = 0)}{\partial t} = 0 \tag{22}$$

or

$$J_s(t, \xi = 0) = 0 \tag{23}$$

At the boundary, the condition may be written as (Sloth et al., 2006)

$$D_s \frac{\partial \omega_s(t, \xi = 1)}{\partial r} = (1 - \omega_s(t, \xi = 1)) \frac{d\bar{r}(t)}{dt} \tag{24}$$

In the case of microspheres made using solvent evaporation (Li et al., 1995a), the volume flux can be expressed similar to the heat transfer of forced convective flow around a spherical particle (Bird et al., 1960) at the boundary of the drop. By using the modified Frossling empirical equation for spherical particles suspended in an agitated vessel (Scherwood et al., 1975), the volume flux of solvent $J_s$ is expressed as:

$$J_s(t, \xi = 1) = \frac{\rho_{cp} D_s}{\bar{r}(t)} (2.0 + 0.60 Re^{1/2} Sc^{1/3}) \tag{25}$$

where $\rho_{cp}$ is the relative density of the continuous phase (compared to water), *Re* is the Reynolds number of the continuous phase and *Sc* is the Schmidt number of the continuous phase.

*4.2.3. Size evolution of drop*

The size change of the drop is calculated directly from the mass loss of solvent (and co-solvent). In drop solidification (Li et al., 1995a), in droplet drying by spray drying (Sloth et al., 2006) and in film drying (Guerrier et al., 1998), it is expressed as:

$$\frac{d\bar{r}(t)}{dt} = -J_s(t, \xi = 1) \tag{26}$$

Based on Eq. (26), the size of drop is supposed to decrease continuously accompanied by the solvent evaporation. This assumption is challenged by another approach based on the formation of crust, with a receding crust-bulk interface (Nesic, 1989). The comparison between two approaches is schematized in Fig. 11. The size decreases at the beginning accompanied by the solvent removal. A layer of crust forms at the surface, and the size change is slowed down and even stopped (Fig. 11A). The crust layer thickens and the crust bulk increases inside the drop until total solidification.

Experimental investigation, especially on the size evolution of drop during microsphere solidification is necessary to validate these hypotheses. Unfortunately there is a lack of such studies in the literature.

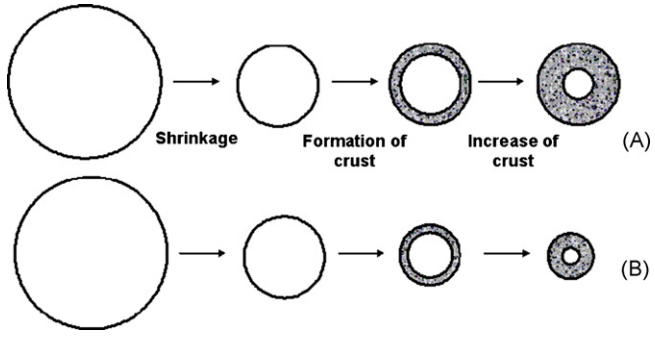


**Fig. 11.** Two approaches for evolution of drop size during solidification: (A) formation of crust and size decrease stopped; (B) formation of crust accompanied by continuous size decrease.

*4.2.4. Numerical results*

In the literature concerning the solidification of microspheres, to our knowledge a concrete model is built only by Li (1994) and Li et al. (1995a). This model is capable of predicting:

(1) the solvent residual in the microspheres;
(2) the numerical prediction of drop size;
(3) the gradient of the polymer and the solvent concentration in different area inside the drop which is critical for the final structure of solid microspheres.

The solvent residual in the microspheres is experimentally validated. Despite the interesting and promising study, the numerical results of drop size and concentration gradient were not compared with experimental results. Actually, scarce experimental results on this aspect are found in the literature. This reveals the big technical difficulties of experimental investigations at the scale of single drop.

## 5. Conclusion

The controlled release of drug in pharmaceutical applications can be achieved by the microencapsulation by solvent evaporation technique. The properties of materials and the process engineering aspects strongly influence the properties of microspheres and the resultant controlled release rate.

PLGA polymer is frequently used because of its biodegradable property. Methylene chloride is the most widely used solvent thanks to its high volatility and capacity to dissolve most polymers. Due to its carcinogenic nature, efforts are being made to replace it and substitutes such as ethyl acetate and ethyl formate give promising results.

After the choice of materials, the microspheres with the desired properties (size, surface morphology and drug release rate) are obtained by varying the operating conditions. The increase of viscosity of the dispersed phase and the quantity of drug improve the drug encapsulation efficiency. Reduced pressure has proved to accelerate the solvent evaporation and to improve the drug encapsulation efficiency in most cases. The microspheres made under reduced pressure have smoother surface, reducing the drug release rate. Contradictory results appear in the literature. They concern the influence of the quantity of the dispersed phase and the influence of the pressure on the sizes of microspheres and highlight the specificity of each experimental work.

Modeling approaches can perform a deeper analysis on the process. A model is proposed by the authors to explain the origin of drug leakage due to the limited distance between drops of drug in one microsphere. Empirical equations summarize the influence of agitation, viscosity and quantity on the size of microspheres. There are very few numerical models dedicated to the complex physical phenomena involved during the solidification of microspheres. Insufficient experimental investigations make it even more difficult to validate the models.

Future work will consist in carrying out appropriate experiments focusing on the microspheres to validate numerical models. Properties of microspheres such as their inner structure, the size and distribution of pores inside the micro spheres have to be deeply investigated.

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