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# A new process for making reservoir-type microcapsules using ink-jet technology and interfacial phase separation ☆

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**Abstract**

A new microencapsulation technique that utilizes interfacial mass transfer between two mutually soluble liquids has been developed. The technique is based on formation of a solid polymer film at the interface of a solution of a water-insoluble polymer and an aqueous solution, resulting from the mutual mass transfer of solvents (i.e., solvent exchange). Reservoir-type microcapsules were prepared by inducing this phenomenon to occur on the surface of an aqueous droplet. One method of implementation employed a dual microdispenser system that consisted of two ink-jet nozzles. The nozzles, producing droplets of a polymer solution and an aqueous drug solution, respectively, were aligned to allow collision of pairs of the droplets. The collision resulted in spreading of the polymer solution on the aqueous droplet and simultaneous solvent exchange, to form a polymeric membrane around the aqueous droplet. The formation of the polymer membrane depended largely on the favorable spreading of the polymer solution on the aqueous droplets and fast solvent exchange, and required judicious selection of the organic solvent. Simple and fast screening methods were developed for selection of a proper solvent. Ethyl acetate was chosen as one of the most desirable solvents through the screening procedures. Ethyl acetate and the dual microdispenser system were used to form microcapsules that were subsequently examined by microscopic methods to demonstrate their unique geometry.


*Keywords:* Microencapsulation; Solvent exchange; Solvent screening; Ink-jet nozzle; Dual microdispenser; Interfacial phase separation

## 1. Introduction

Microencapsulation is an attractive approach for protein formulation and delivery. Protein pharmaceuticals cannot be delivered orally and the need for infusion or frequent injection has consistently demanded the development of long-term delivery systems. However, many approaches to this end have suffered from the inactivation of encapsulated protein and the lack of control over the release kinetics [1,2]. Common inactivation sources of encapsulated proteins and representative stabilization strategies are summarized in Table 1. In an attempt to provide an alternative solution to these issues, a new microencapsulation method has been developed, which we call the ''interfacial phase separation.'' The name was

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Table 1
Common inactivation sources of encapsulated proteins and recent stabilization strategies [1]

| Inactivation source | Stabilization strategy |
|---|---|
| *Encapsulation procedure* | |
| Exposure to w/o interfaces | Reducing or avoiding denaturation at w/o interfaces |
| Mechanical stresses during preparation | Reducing mechanical stresses |
| Exposure to a hydrophobic organic solvent | Alternative solvents |
| *Protein release* | |
| Intermediate moisture level during hydration | Modifying moisture level |
| Acidification of the microenvironment | Counteracting acidification |
| Interaction between protein and polymer | Preventing adsorption |

coined to distinguish the method from other known techniques, such as solvent extraction and solvent evaporation methods.

### 1.1. The interfacial phase separation method

The interfacial phase separation method is a simple and mild technique to produce reservoir-type microcapsules that consist of a thin biodegradable polymer membrane covering a single hydrophilic core. It is based on the simple phenomenon of solid polymer film formation at the interface between an aqueous solution and a solution of a water-insoluble polymer upon contact of the two solutions (Fig. 1A). The main feature of this method is the production of reservoir-type microcapsules by causing the event to occur on the surface of an aqueous droplet (Fig. 1B).

The rationale behind the interfacial phase separation method is that the integrity of the encapsulated proteins can be preserved by the following strategies. First, sources of inactivation shown in Table 1 that arise during microencapsulation will be reduced when the stressful procedures are replaced with milder processes. The double emulsion–solvent evaporation/extraction method has widely been used for encapsulation of water-soluble drugs. One of the weaknesses of this method is that the large water/oil (w/o) interfacial area generated during the process is detrimental to the stability of the encapsulated drug, especially proteins and peptides [3,4]. The prolonged emulsification procedure may also subject the encapsulated protein to damagingly strong mechanical stresses [5,6]. In addition, most conventional microencapsulation processes produce a thorough mixture of a drug, a polymer, and an organic solvent in the form of a homogeneous solution, suspension, or emulsion, prior to breaking it up into microparticles. In this case, extensive exposure of proteins to hydrophobic environments such as polymers and organic solvents can cause denaturation of the encapsulated protein [1]. In the interfacial phase separation method, precursors of the microcapsules can be produced using low-impact droplet formation techniques such as ink-jet nozzles or ultrasonic atomizers. Microcapsules form as a result of collision of the two precursor droplets of the aqueous and the polymer solutions. This method does not involve emulsification, and the interfacial contact between the aqueous and the polymer solutions is limited to the surface of the aqueous droplet.

Second, reservoir-type microcapsules, i.e., mononuclear microcapsules generated by the interfacial phase separation method, will have advantages over multinuclear microspheres for the preservation of protein integrity during prolonged drug release. It has been noted that the stability of the encapsulated drugs is compromised by accumulation of the acidic degradation products of the encapsulating polymer in most PLGA microsphere systems [7]. In contrast, the polymer exists as a membrane in mononuclear microcapsules, and acidic degradation products will diffuse rapidly from the exterior due to the short diffusion distance. For this reason, drugs in mononuclear microcapsules will be less exposed to an acidic microenvironment than with monolithic microspheres or multinuclear microcapsules. Furthermore, the polymer/drug interface is limited to the polymer membrane covering the aqueous core and, thus, damage to protein drugs due to contact with polymer will be minimal in mononuclear microcapsules.

To reduce the method to practice, it is necessary to produce a plurality of droplets of the aqueous and the polymer solutions and induce collisions between pairs of the droplets. In the present study, reservoir-type microcapsules were produced using a dual microdispenser system consisting of two ink-jet noz-

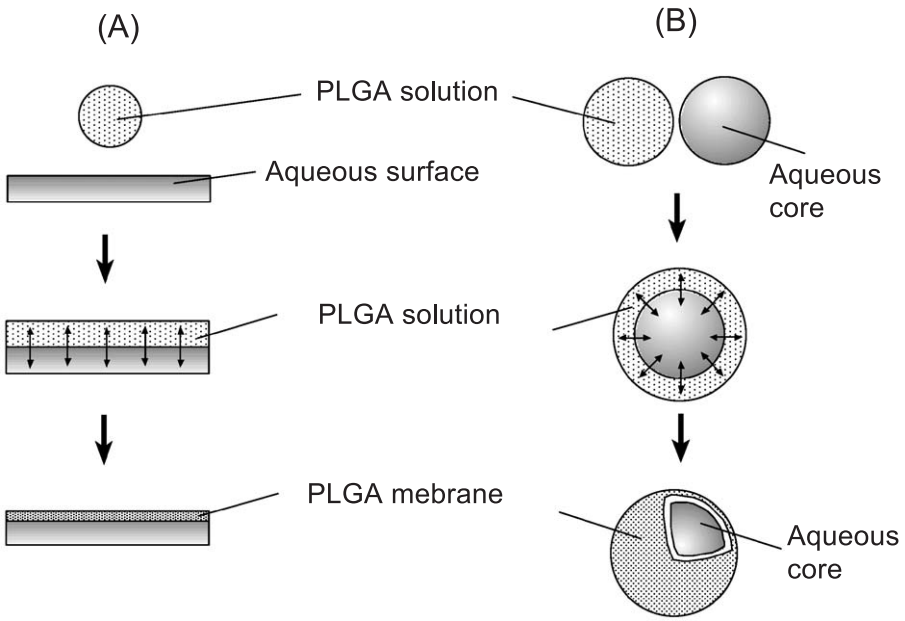


Fig. 1. Schematic description of the formation of a polymer membrane on an aqueous (A) film and (B) droplet through solvent exchange at the interface between the aqueous and the polymer solutions.

zles that delivered an aqueous solution and a polymer solution, respectively. The two nozzles, continuously producing two streams of liquid droplets, were aligned in a way that caused droplets from one stream to collide with droplets from the second stream. Following the collision between a pair of the droplets, the polymer droplet spread over the aqueous droplet to cover the surface of the aqueous droplet. Mass transfer between the two liquids (i.e., solvent exchange) resulted in the formation of a

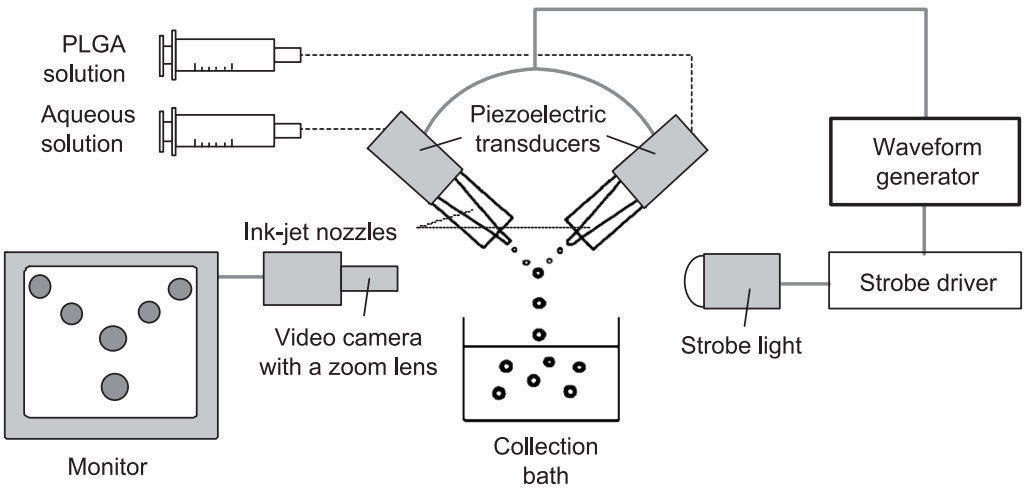


Fig. 2. Schematic description of the dual microdispenser system.

polymer membrane on the surface of the aqueous droplet. Thus, the formation of a polymer membrane on the aqueous surface required the droplet of the polymer solution to spontaneously spread on the aqueous droplet and to simultaneously phase-separate the polymer upon the contact with the aqueous surface. In a preliminary study, it was observed that the aforementioned behavior was mainly dictated by the organic solvent that was used to dissolve the polymer. For successful implementation of this method, therefore, judicious selection of a proper solvent was particularly important.

This paper describes a method of selection of an organic solvent which meets the above conditions and the preparation of microcapsules using selected solvents and the dual microdispenser system.

## 2. Materials and methods

### 2.1. Solvent selection

#### 2.1.1. Solvent selection according to polymer solvency

Poly(lactic acid-co-glycolic acid) (PLGA) (lactic acid/glycolic acid = 50:50, intrinsic viscosity = 0.58 dl/g, Birmingham Polymers) was used as the encapsulating polymer. Organic solvents having a Hilde-

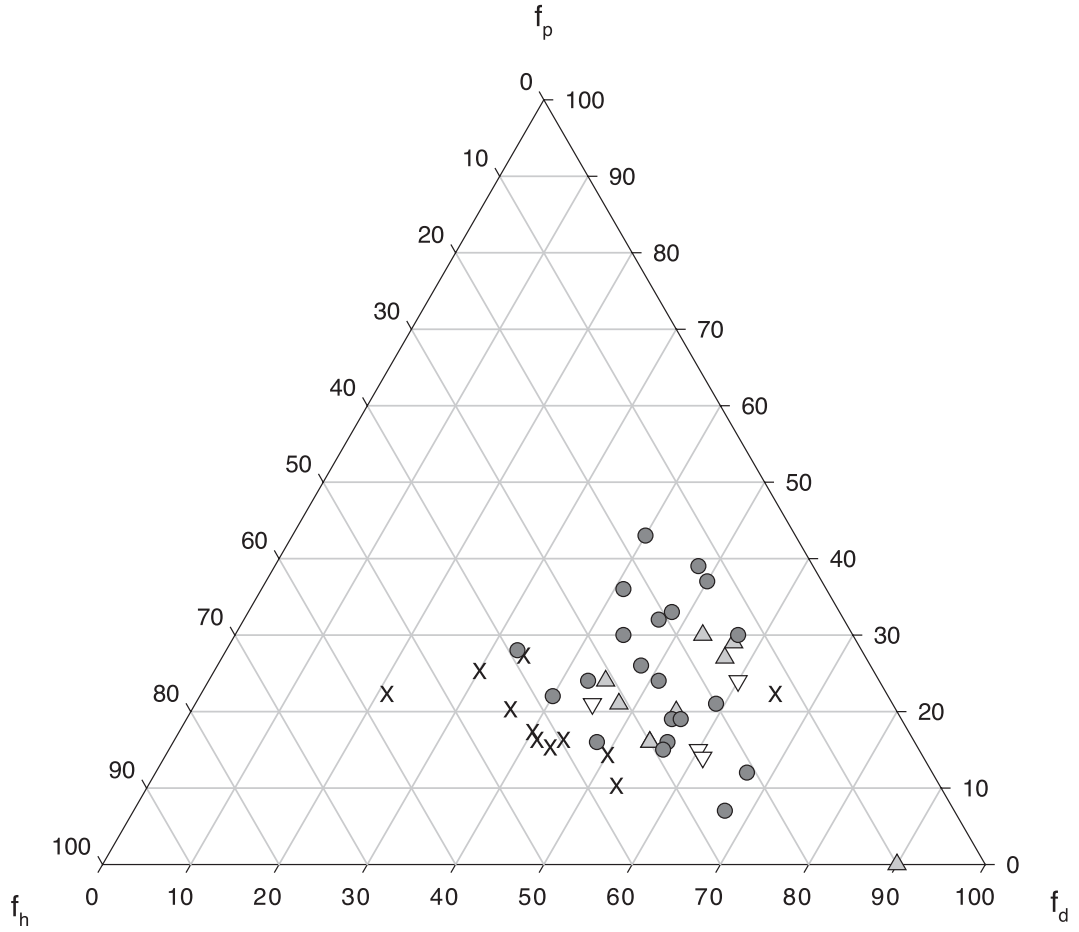


Fig. 3. Comparison of Hansen's solubility parameters for various solvents: contributions of dispersion forces ($f_d$), polar interactions ($f_p$), and hydrogen bonding ($f_h$). (●) Good solvent; (△) intermediately good solvent; (▽) intermediately poor solvent; and (×) poor solvent.

brand solubility parameter of 16–24 $MPa^{1/2}$ were screened for polymer solvency. Dried PLGA (125 mg) was added to glass vials containing 5 ml of the test organic solvent. The vials were agitated overnight at room temperature. Solubility of PLGA was judged by visual examination. Solvents were classified into four groups: good solvents that formed clear polymer solutions; intermediately good solvents that formed turbid polymer solutions upon heating; intermediately poor solvents that were marginally able to swell the polymer; and poor solvents in which the polymer remained intact. The results were summarized on a triangular graph developed by Teas [8], according to Hansen's solubility parameters [9] of the solvents.

### 2.1.2. Solvent selection according to spreading capability and membrane quality

A library of PLGA solutions (5%) was constructed using the good solvents selected above. A 10-μl droplet of each solution was placed on a layer of hydrogel containing 0.5% agarose and its spreading observed. The diameter of the polymer film that formed on the gel was measured 10 s after the

Table 2
Properties of the organic solvents relevant to the interfacial phase separation method

| | Organic solvent | Water solubility[a] (%w/w) | Surface tension[a] (dyn/cm) | Optical density[b] (620 nm) | Film diameter[b] (mm) |
|---|---|---|---|---|---|
| 1 | Acetone | ~ 100 | 22.7 | 0.1925 | 18.7 |
| 2 | *n*-Butyl amine | ~ 100 | 23.2 | 0.0165 | 20.7 |
| 3 | Tetrahydrofuran | ~ 100 | 26.4 | 0.0710 | 19.5 |
| 4 | Ethylene glycol methyl ether acetate | ~ 100 | 27.4 | 0.5555 | 28.0 |
| 5 | Acetic acid | ~ 100 | 27.4 | 0.9417 | 17.2 |
| 6 | Diethylene glycol monomethyl ether | ~ 100 | 28.5 | 1.2260 | 10.7 |
| 7 | Diethylene glycol dimethyl ether | ~ 100 | 29.5 | 0.4045 | 18.4 |
| 8 | Diethylene glycol monoethyl ether acetate | ~ 100 | 31.4 | 0.1324 | 22.7 |
| 9 | *N*,*N*-Dimethylacetamide | ~ 100 | 32.4 | 0.6845 | 15.9 |
| 10 | 1,4-Dioxane | ~ 100 | 32.8 | 0.4787 | 19.1 |
| 11 | Formic acid | ~ 100 | 37.6 | 0.1786 | 11.2 |
| 12 | *N*-Methylpyrrolidone | ~ 100 | 40.7 | 1.6581 | 12.1 |
| 13 | Dimethyl sulfoxide | ~ 100 | 43.0 | 0.2245 | 11.1 |
| 14 | Propylene oxide | 59.0 | 22.2 | 0.0757 | 13.6 |
| 15 | Acrolein | 21.3 | 23.1 | 0.0262 | 16.7 |
| 16 | Ethyl acetate | 8.0 | 23.8 | 0.0438 | 16.3 |
| 17 | Ethyl formate | 10.5 | 24.0 | 0.0241 | 13.4 |
| 18 | Methyl acetate | 24.4 | 24.1 | 0.0145 | 17.6 |
| 19 | Acrylonitrile | 7.0 | 27.3 | 0.0138 | 13.9 |
| 20 | Acetyl acetone | 16.0 | 31.2 | 0.0182 | 20.0 |
| 21 | 2-Ethoxyethyl acetate | 23.0 | 31.8 | 0.0324 | 21.3 |
| 22 | Furfural | 7.9 | 41.1 | 0.0205 | 13.5 |
| 23 | Methyl formate | 3.0 | 25.0 | 0.0227 | 10.6 |
| 24 | Chloroform | 0.8 | 26.5 | 0.0242 | 4.9 |
| 25 | Methylene chloride | 1.3 | 27.9 | 0.0146 | 5.8 |
| 26 | Nitroethane | 4.5 | 31.3 | 0.0200 | 7.9 |
| 27 | Benzyl alcohol | 3.5 | 39.0 | 0.0140 | 8.6 |
| 28 | Aniline | 3.4 | 42.9 | 0.0295 | 8.1 |

[a] Data obtained from [12].
[b] Experimental data.

placement of the droplet. In order to assess the quality of the polymer membrane, a 96-multi-well microplate containing 200 μl of agarose gel in each well was prepared. Five microliters of each PLGA solution was simultaneously applied into the wells. The turbidity of the film that resulted after 1 min was measured at 620 nm using a Tecan SPECTRAFluor Plus microplate reader.

### 2.2. Preparation of microcapsules

The microdispenser system used to produce droplets of the aqueous and polymer solutions consisted of two ink-jet nozzles, shown in Fig. 2. Ethyl acetate was used as a polymer solvent, unless specified otherwise. A 2% PLGA solution and an aqueous solution containing 0.2% sodium alginate were fed through each nozzle at a controlled flow rate. For confocal microscopy, 0.2% FITC–dextran was added to the aqueous solution and 0.03% Nile Red was added to the PLGA–ethyl acetate solution. The two liquids were delivered using syringe pumps through ink-jet nozzles, the orifices of which were 60 μm in diameter (MicroFab Technologies). The liquid streams were perturbed by a frequency generator (Hewlett-Packard model 33120A), to produce a series of droplets of uniform size. The trajectories of the two jets were precisely controlled to ensure collisions between every pair of droplets. Collision of two droplets was observed using a video camera (LCL-903 HS, Watec America) under stroboscopic illumination (MicroFab Technologies). The microcapsules thereby formed were collected in a water bath to complete solidification of the polymer membrane.

For comparison, microcapsules were also produced using the double emulsion–solvent evaporation method described in the literature [10] with a slight modification. For confocal microscopy, 0.003% Nile Red was added to the PLGA solution in methylene chloride and 20% FITC–dextran solution was used as the aqueous solution.

### 2.3. Morphological characterization of microcapsules

#### 2.3.1. Light microscopy (LM)

Nascent microcapsules were observed by LM. A drop of the microcapsule suspension was placed on glass cover slips and the microcapsules were observed with a Nikon Labophot 2 microscope.

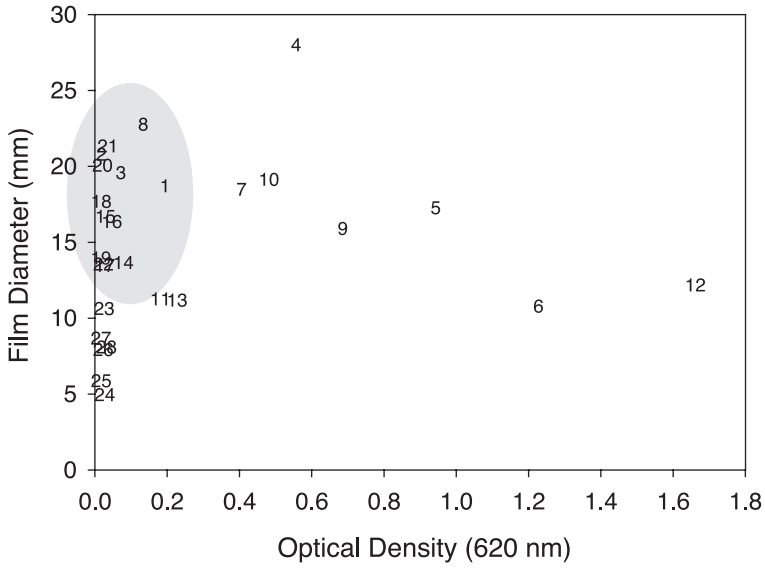


Fig. 4. Evaluation of organic solvents from their spreading over a hydrogel surface and subsequent formation of a polymer membrane. Preferable solvents lie in the shaded portion of the plot. Legends for solvents are indicated in Table 2.

Table 3
Parameters used for solvent screening

| Ethyl acetate ($CH_3COOC_2H_5$) | |
|---|---|
| Hildebrand solubility parameter [12] | 18.6 $MPa^{1/2}$ |
| Hansen multicomponent parameters [11] | $f_d$, $f_p$, $f_h$ = 56, 19, 25 |
| Solubility in water [12] | 8% w/w |
| Surface tension [12] | 23.8 dyn/cm |
| Optical density of the PLGA film (at 620 nm) | 0.0438 |
| Film diameter | 16.3 mm |

Ethyl acetate is used as an example.

### 2.3.2. Confocal laser scanning microscopy (CLSM)

The internal structure of the microcapsules was imaged using an MRC-1024 Laser Scanning Confocal Imaging System (Bio-Rad) equipped with a krypton/argon laser and a Nikon Diaphot 300 inverted microscope. Microcapsules produced by the above methods were centrifuged and washed with distilled water prior to observation. All confocal fluorescence pictures were taken with a 20× objective and excitation at 488 and 568 nm. Green and red fluorescence images were obtained from separate channels.

## 3. Results

### 3.1. Solvent selection

Sixty organic solvents with solubility parameters of 16–24 $MPa^{1/2}$ were tested to evaluate solubilization of PLGA. The results were summarized on a triangular graph using the method of Teas [8], as shown in Fig. 3. As described by Teas, the so-called fractional parameters were calculated as:

$$f_1 = 100\delta_i/(\delta_d + \delta_p + \delta_h) \quad \text{where } i = \text{d, p, or h.} \tag{1}$$

In Eq. (1), $\delta_d$, $\delta_p$, and $\delta_h$ are Hansen's multicomponent solubility parameters and represent the contributions from dispersion forces, polar interactions, and hydrogen bonding, respectively. The values of the solubility parameter and Hansen's multicompo-

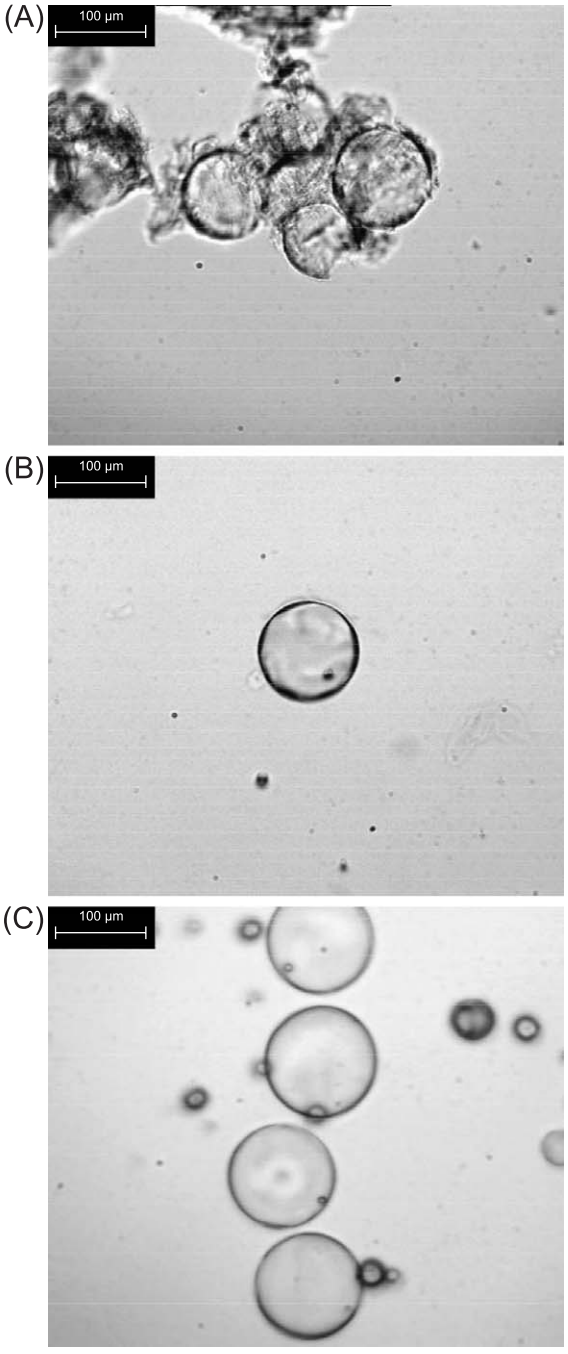


Fig. 5. Light microscopic images of microcapsules produced using (A) acetic acid, (B) methyl acetate, and (C) ethyl acetate. Bars: 100 μm.

nent solubility parameters for each solvent were obtained from the literature [11]. In the triangular graph shown in Fig. 3, good solvents for PLGA were localized in a region of relatively low $f_p$ and $f_h$ but of high $f_d$.

Good solvents for PLGA were further refined by their spreading capability and the quality of the membranes that they formed. Solutions of polymer in different solvents were placed on a layer of hydrogel. The polymer films that were thereby formed were evaluated with respect to their diameters and their optical densities, as shown in Table 2. The diameter of the film reflected the degree of spreading of each solvent and the turbidity was used to evaluate the quality of the polymer membrane. Solvents which formed membranes of relatively large diameters were preferable since this implied that a droplet of the polymer solution would spread easily over an aqueous droplet in the encapsulation process. Polymer membranes that displayed relatively low optical densities were preferred since the high turbidity meant formation of a rough and discontinuous precipitate that would not be able to control the drug release. Desirable solvents were then identified, as indicated in Fig. 4. The screening parameters for ethyl acetate, which were used in the most subsequent studies, are listed in Table 3.

### 3.2. Formation of microcapsules by the-interfacial phase separation method

In order to validate the above criteria as the selection guides to appropriate solvents, four solvents were selected from candidates and noncandidates, and used to produce microcapsules: ethyl acetate and methyl acetate from candidates; benzyl alcohol that generated a membrane of small diameter; and acetic acid from which the membrane made displayed a high optical density. Use of benzyl alcohol did not produce microcapsules. When the microcapsules were prepared using acetic acid as the solvent for the polymer, the surfaces of the microcapsules were covered by rough and seemingly discontinuous polymer precipitates (Fig. 5A). Microcapsules prepared using methyl acetate and ethyl acetate were transparent (Fig. 5B and C), indicating that the surrounding polymer layer was only a thin membrane. The internal structure of the microcapsules was examined using confocal microscopy and compared with that of microcapsules produced by the double emulsion–solvent evaporation method. The PLGA phase appeared red due to the presence of Nile Red and the aqueous phase appeared green due to the presence of FITC–dextran. Fig. 6 clearly shows that the microcapsules produced by the interfacial phase separation method consisted of a

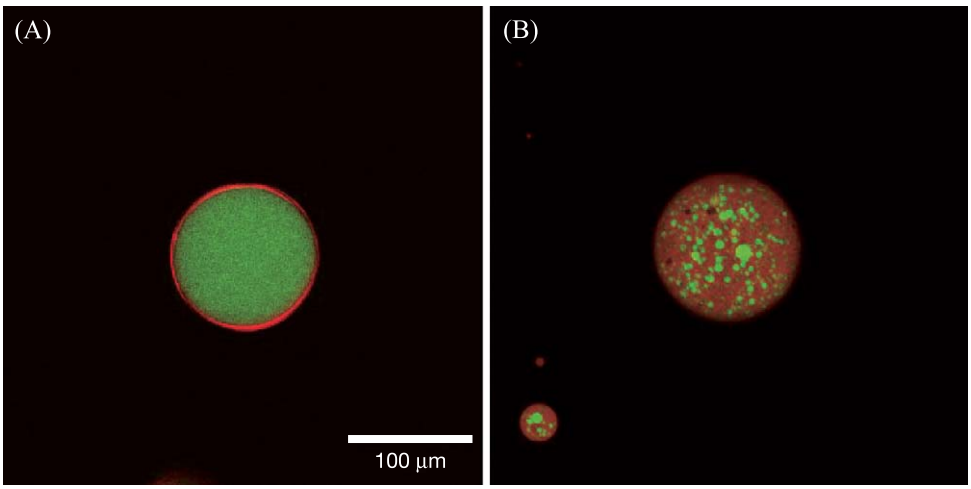


Fig. 6. Confocal laser scanning microscopic images of microspheres produced by (A) the interfacial phase separation method and (B) the double emulsion–solvent evaporation method.

single droplet of the aqueous phase and a polymer membrane that surrounds it. In contrast, the microsphere produced by the double emulsion method consisted of multiple droplets of the aqueous solution dispersed throughout the polymer matrix.

## 4. Discussion

A new microencapsulation technique that produces reservoir-type microcapsules based on collision of two microdrops of component solutions has been developed. Here, the microdroplets are generated using a dual microdispenser system. Upon collision, a polymer membrane forms around an aqueous droplet via spontaneous spreading of a polymer solution over an aqueous surface and nearly instantaneous mass transfer between the two liquids. According to the foregoing results, the physical properties of the organic solvent used to dissolve the polymer play a central role in determining the outcome of the encapsulation process. The organic solvent is required to meet the following criteria. It should dissolve the polymer, readily spread on the aqueous surface, and be miscible with water to a certain degree, thus allowing fast phase separation of the polymer.

One method predicting the solubility of a solute in a solvent is to compare their solubility parameters [13]. The solubility parameter reflects the cohesive force, which is the sum of attractive and repulsive intermolecular forces in a material [11]. In general, a good solvent for a solute such as a polymer has a solubility parameter close to that of the solute: a rule which is often called as ''like dissolves like'' [13]. The solubility parameter of PLGA (LA to GA = 58:42) is 16.8–18.7 $MPa^{1/2}$ [14]. However, upon screening 60 organic solvents having solubility parameters of 16–24 $MPa^{1/2}$, only half were found to produce clear PLGA solutions, while the rest were shown to be poor solvents or marginally able to swell PLGA. In order to gain insight into this disparity, use was made of multicomponent solubility parameters proposed by Hansen [9] and the graphic analysis method developed by Teas [8]. According to Hansen, the multicomponent parameter reflects contributions from three components that reflect dispersion forces, polar interactions, and hydrogen bonding. Teas developed an empirical method of analysis to predict the solubility of polymers in organic solvents used in the paint industry, using Hansen's solubility parameters. To apply the method of Teas, the fractional parameters of each solvent were calculated from Eq. (1) and were displayed on a triangular plot. Solvents which produced clear solutions of PLGA could be grouped in a reasonably well-defined area ('area of solubility') of the plot. Solvents lying outside of the area of solubility were found to be mostly poor or nonsolvents for PLGA. It is apparent that solvents such as alcohols that have relatively high values of $f_h$ are nonsolvents for PLGA, even though their solubility parameters are fairly close to that of PLGA. These results clearly indicate that what determines the solubility of the polymer in a given solvent is not only the closeness of the values of their solubility parameters but also the nature of the internal cohesive forces existing in each material. For example, when the polar interactions or hydrogen bonding make the major contribution to the solubility parameter of a solvent, the solvent is unable to dissolve a hydrophobic polymer such as PLGA. The results of this paper make it clear that this triangular graph can be used as a future reference for selection of the solvents meeting the first requirement of the newly developed encapsulation process.

Once solvents that are capable of dissolving the polymer have been identified, the polymer solution is then evaluated with respect to its capabilities of encapsulating the aqueous core and precipitating a polymer membrane. Whether the solvent (O) droplet encapsulates an aqueous (W) droplet of an equal size or vice versa depends on the surface tensions of these two liquids against air, $\gamma_O$ and $\gamma_W$, respectively, and the interfacial tension between them, $\gamma_{OW}$. For the solvent droplet to spontaneously spread over the aqueous droplet, the spreading coefficient $S_{OW} = \gamma_W - \gamma_O - \gamma_{OW} > 0$ [15], as shown in Fig. 7A. For the aqueous droplet to spontaneously spread over the polymer–solvent droplet, the spreading coefficient $S_{WO} = \gamma_O - \gamma_W - \gamma_{WO} > 0$, as shown in Fig. 7B. For relatively favorable spreading of the solvent droplet over the aqueous droplet, $\gamma_O$ and $\gamma_{OW}$ should be as low as possible. Given that the interfacial tension occurs when the molecules are exposed to the interaction forces dissimilar to those experienced in each bulk phase [13], it is possible to establish an approximate relationship

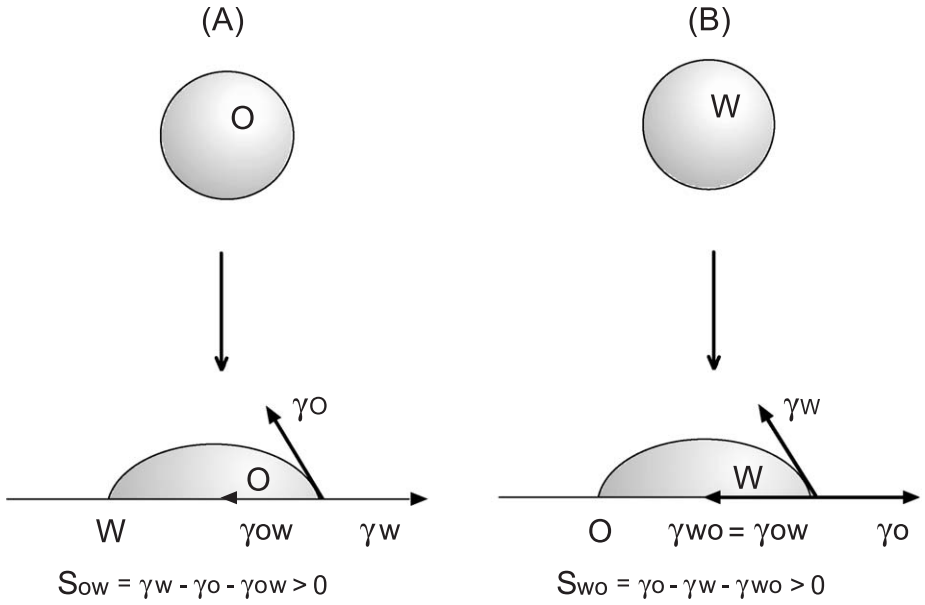


Fig. 7. Spreading behavior of a droplet over a surface depending on the spreading coefficient: (A) spreading of a polymer–solvent droplet over an aqueous surface and (B) spreading of an aqueous droplet over a polymer–solvent surface.

between the interfacial tension and mutual solubilities of the two materials involved. Examples listed in Table 4 show that the interfacial tension between water and an organic solvent ($\gamma_{OW}$) is inversely proportional to the water solubility with a few exceptions. The exceptions with *n*-butyl alcohol and heptanoic acid are most likely due to the presence of functional groups capable of hydrogen bonding with water. For the solvents with significant solubilities in water, which will be preferably used in the interfacial phase separation method (see below), $\gamma_{OW}$ is negligible compared to the surface tension of water or not even definable. Therefore, the primary requirement for the spontaneous spreading in this particular system is that the solvent have a low $\gamma_O$. On the other hand, the phase separation of the polymer film is a result of mass transfer between the organic solvent and water, leading to a decrease in the solubility of the polymer in the solvent. In order to cause virtually instantaneous phase separation of the polymer membrane, the solvent used to dissolve the polymer should be soluble in water to a certain degree.

Table 4
Water solubility and interfacial tension against water of various liquids

| Solvent | Solubility in water (mg/kg)[a] | Interfacial tension between water and an organic solvent (dyn/cm)[b] |
|---|---|---|
| Ethyl acetate | 80 000 | 6.8 |
| *n*-butyl alcohol | 63 200 | 1.8 |
| Benzaldehyde | 6500 | 15.5 |
| Heptanoic acid | 3000 | 7.0 |
| Nitrobenzene | 2000 | 25.2 |
| Benzene | 1790 | 35.0 |
| Carbon tetrachloride | 793.4 | 45.0 |
| *n*-Heptane | 2.2 | 50.2 |

[a] From Ref. [12].
[b] From Ref. [16].

In the present study, a simple screening method was used that simulates the spreading of the polymer–solvent droplet over the aqueous droplet and the subsequent formation of a polymer membrane. Here dilute agarose gel was used in lieu of aqueous droplets to focus on how a polymer–solvent droplet that is placed on the aqueous gel spread to form a polymer membrane. The agarose gel provides an immobile aqueous platform that allows easy evaluation of the quality of the polymer membranes. In order to justify the replacement of the aqueous solution with an agarose gel, it was confirmed that the polymer solutions resulted in the polymer pre-

cipitate having similar tendencies in turbidity on the alginate solution as on the agarose gel. However, the diameter of the spread membrane on the aqueous solution was not easy to measure, since parts of some PLGA solutions tended to sink to the bottom of the aqueous solution. On the other hand, the agarose gel allowed comparison of the spreading capability of the polymer solutions without interference due to gravity.

Using the agarose hydrogel system, a relatively large film diameter was interpreted as high spreading capability of the polymer solution. Fig. 8A shows that for water-miscible solvents the film diameter can indeed be related to the surface tension $\gamma_O$ of the solvent, and that solvents having relatively low $\gamma_O$ tend to spread favorably over the aqueous gel. Once spreading occurred, a polymer membrane formed eventually by solvent exchange and/or evaporation from all tested solvents. However, the rate of the phase separation was much higher in solvents having a higher solubility in water. The water solubility of each solvent also contributed to the quality of the polymer membrane. When the solubility of the solvent in water is as high as ~100%, the polymer membrane is opaque and visibly discontinuous. That is, the discontinuous polymer precipitate does not allow transmission of light. For this reason, the turbidity of the membrane was employed as an indicator of the continuity of the membrane, which is essential for controlling the drug release. When the optical density of the polymer membrane was plotted versus the water solubility, a correlation was readily apparent (Fig. 8B): Solvents having low to medium solubility in water (0–60% w/w) resulted in transparent and dense membrane, whereas water-miscible solvents ( ~ 100% w/w) produced opaque and discontinuous membranes. Therefore, even though relatively high water solubility is preferred for the fast solvent exchange, too high water solubility may not be desirable because a discontinuous membrane results. Thus, both extremes of water solubility should be avoided, as low solubilities result in low rates of phase separation and high solubilities result in low membrane quality. Combination of the second (large membrane diameter) and third requirements (low optical density) leaves us a couple of candidate solvents indicated in Fig. 4.

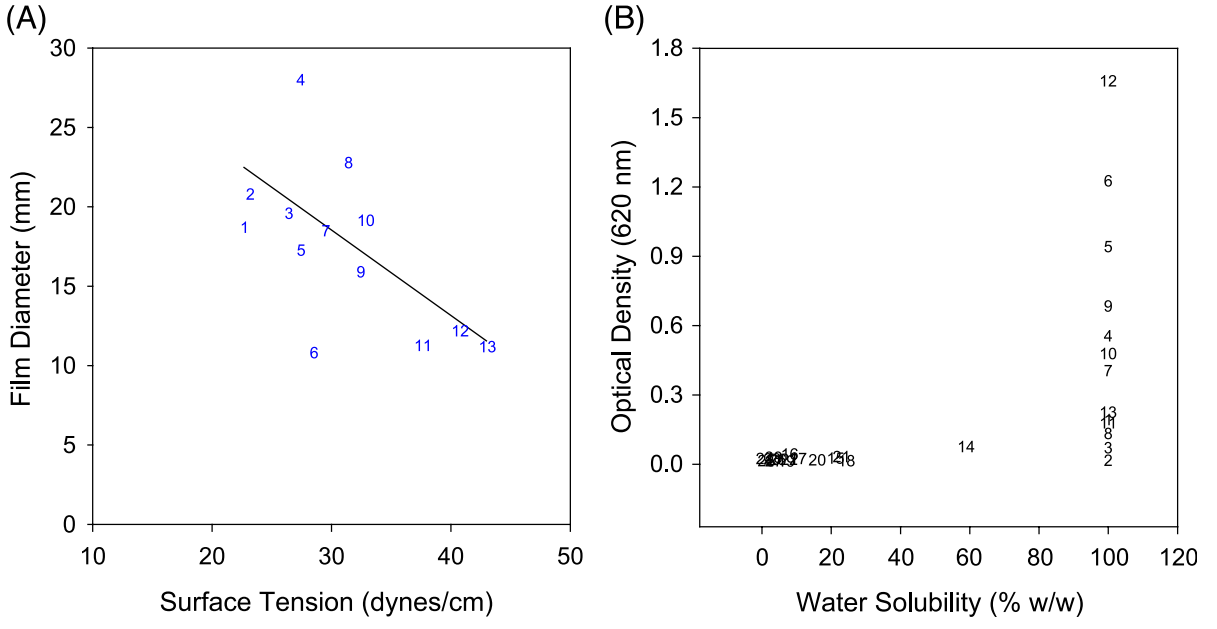


Fig. 8. (A) Film diameter as a function of the surface tension of the solvent–air interface, a measure of the degree of spreading of a polymer–solvent droplet on a hydrogel surface, and (B) optical density as a function of the solubility of the solvent in water, a measure of membrane quality. Legends for solvents are indicated in Table 2.

In support of the above criteria as the selection guides, it was observed that benzyl alcohol, which was rejected because of the small membrane diameter, did not produce microcapsules. When acetic acid was used for the solvent, the discontinuity of the polymer precipitates covering the spherical core was noticeable (Fig. 5A). These results confirm that the optical density is a legitimate criterion for the quality of the membrane. On the other hand, both ethyl acetate and methyl acetate produced desirable microcapsules having a seemingly continuous membrane. These observations confirm that the three criteria described thus far are valid guides for selection of appropriate solvents.

Among the candidate solvents, ethyl acetate was used in foregoing studies because of its safety. Relatively hydrophilic organic solvents such as ethyl acetate have been used with increasing popularity as an alternative to toxic methylene chloride [17–20]. However, the relatively high solubility of ethyl acetate in water has often made it difficult to produce dense and regular microspheres using the conventional emulsion method because of the relatively fast extraction of the solvent into the continuous phase [17]. Therefore, it has sometimes been necessary to dope the continuous phase with additional ethyl acetate in order to delay diffusion of the solvent out of the discontinuous phase [21]. For this reason, the morphology of microspheres prepared by the emulsion method has been found to be far more dependent on the phase ratio (the volume ratio of the organic phase to the aqueous phase) when ethyl acetate is used as a substitute for methylene chloride [17]. The hydrophilicity of methyl ethyl ketone, another alternative solvent, has caused the same problem [22]. In contrast, utilizing relatively hydrophilic organic solvents is a major feature of the interfacial phase separation method. The relatively high surface tension of the aqueous solution will ensure the aqueous droplet sustains the spherical shape while being encapsulated by the polymer–solvent droplet. Thus, unlike the emulsion method, the formation of a w/o emulsion is not a requirement for capsule formation. Elimination of such a condition allows more flexibility in the selection of organic solvents, which is in turn beneficial from the standpoints of toxicological and environmental safety.

One of the advantages expected of this new approach is that the encapsulated drug will survive the fabrication process as well as the release period and maintain its stability throughout the lifetime of the product. It is believed that the ink-jet method used for droplet formation in this approach subjects the encapsulated drugs to reduced mechanical stress, compared to the conventional emulsification method. It is possible to compare a priori the magnitude of the stresses that the fluids experience in this new method and traditional techniques such as the double emulsion–solvent extraction/evaporation method. A flow-induced stress of the order of or exceeding $\sigma/R$ must be applied (i) to form a droplet of radius $R$ from an ink-jet nozzle of radius $R_t \sim R$ or (ii) to deform and break a droplet of radius $R$ in a suspension in an agitated tank [23]. Here, $\sigma$ is the surface tension of the interface between the aqueous core liquid and air, i.e., about 70 dyn/cm. In the double emulsion method, $\sigma$ is the interfacial tension of the interface between the aqueous core liquid and the solvent–polymer solution, i.e., about 35 dyn/cm. The radius of the aqueous mononuclear cores produced with the current method is about 50 μm. By contrast, the average radii of the aqueous droplets that are dispersed in each multinuclear capsule in the double emulsion method for producing microcapsules are about 1–2 μm. Therefore, the double emulsion method subjects the aqueous droplets containing the stress-sensitive molecules to flow induced stresses that are more than 10 times as large as the new ink-jet-based method. In the current method, the liquid also experiences stresses in the ink-jet nozzle before emerging into the ambient air. The shear stress that the fluid experiences is largest at the wall of the nozzle and is of the order of $\mu U/R_t$, where $\mu$ is the viscosity and $U$ the average velocity of the fluid in the nozzle [23]. If the average velocity for the ink-jet method is taken to be 3 m/s and the nozzle radius to be 30 μm, the shear stress experienced by the fluid before it emerges from the nozzle is of the order of $10^3$ dyn/cm$^2$ while the flow induced stress that is imparted to the jet after it emerges from the nozzle to break it into droplets is of the order of $10^4$ dyn/cm$^2$. By contrast, the flow-induced stress that is imparted to the fluid in the double emulsion method is of the order of $10^5$ dyn/cm$^2$. It is also noteworthy in the ink-jet method that fluid is subjected to these forces

for just tens of microseconds. By contrast, the emulsion is subjected to forces in an agitated tank for minutes. Therefore, the ink-jet method is indeed gentler from the standpoint of subjecting the fluid to stresses.

## 5. Conclusion

A new microencapsulation technique called the interfacial phase separation method was developed. Solvent screening methods were developed and shown to be valid tools for selection of appropriate solvents. The production of reservoir-type microcapsules using one selected solvent was demonstrated using a dual microdispenser system employing ink-jet nozzles.

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