New Microencapsulation Technique Using an Ultrasonic Atomizer Based on the Solvent Exchange Method

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INTRODUCTION

Microencapsulation is one of the most popular methods to produce controlled release parenteral dosage forms. For water-soluble drugs, the double emulsion-solvent evaporation/extraction methods have been widely used. One of the weaknesses of this method is that the large water/oil (w/o) interfacial area generated during the process can be detrimental to the stability of the encapsulated drugs, especially proteins and peptides.[1] In an attempt to alleviate this problem, we have developed a new microencapsulation method which we call the solvent exchange method. The solvent exchange method utilizes interfacial mass-transfer between two mutually soluble liquids to produce reservoir-type microcapsules. When a solution of a water-insoluble polymer is in contact with an aqueous solution, a solid polymer film forms at the interface between the two liquids as a result of the mutual transfer of solvents (i.e. solvent exchange). A reservoir-type microcapsule can be made by inducing this phenomenon to occur on the surface of an aqueous drop. Previously, we employed a dual microdispenser system to deliver this idea and successfully produced reservoir-type microcapsules.[2] In the dual microdispenser system, two ink-jet nozzles, where one produces aqueous drops and the other drops of a polymer solution, were aligned to collide pairs of microdrops emerging from each nozzle. Spreading of a drop of the polymer solution on the surface of an aqueous drop generated a continuous interface between the two liquids, and was immediately followed by interfacial solvent exchange to result in polymeric membrane covering the aqueous drop. In the present study, the solvent exchange method was implemented using a coaxial ultrasonic atomizer. The objectives of this study are to demonstrate that a large number of reservoir-type microcapsules can easily be produced in a short time by the ultrasonic atomizer, and to understand the encapsulation mechanism.

EXPERIMENTAL

Preparation of Microcapsules using the Solvent Exchange Method and the Ultrasonic Atomizer(s). Figure 1 describes a coaxial ultrasonic atomizer producing microcapsules. A solution of 2% poly(lactic-co-glycolic acid) (PLGA) in ethyl acetate (EA) and an aqueous solution containing 0.2% sodium alginate were separately fed into an ultrasonic atomizer through coaxial cables. Two separate single atomizers can be used instead of a coaxial atomizer. The two solutions were delivered using syringe pumps at controlled flow rates. For confocal microscopy, fluorescein isothiocyanate (FITC)-dextran and nile red were added to the aqueous solution and the PLGA solution respectively. Upon the onset of the vibration of the atomizer(s), both liquids were fragmented into microdrops, which became reservoir-type microcapsules. They were collected in a water bath containing 0.15 M calcium chloride and 0.5% polyvinyl alcohol (PVA) for stabilization of the microcapsules through formation of calcium-alginate gel. After an hour in the collection bath, the microcapsules were isolated by centrifugation, washed with distilled water, and then imaged using a confocal microscope or a bright-field microscope.

Preparation of Microspheres using the Double Emulsion-Solvent Evaporation Method. 50 μl of aqueous solution containing FITC-dextran was poured into 1 ml of 33% PLGA solution in methylene chloride (MC) labeled with nile red. The mixture was homogenized for 1 min using a vortex mixer. The resulting w/o emulsion was poured under magnetic stirring into 2 ml of 1% PVA solution saturated with MC to form a w/o/w emulsion. The double emulsion was poured into 200 ml of 0.1% PVA, and continuously stirred for 12 hours until most of MC evaporated, leaving solid microspheres. The microspheres were collected by centrifuge, washed with distilled water, and imaged using a confocal microscope.

Confocal Laser Scanning Microscopy (CLSM). The location of the PLGA solution and the encapsulated solution in the microcapsules was examined using MRC-1024 Laser Scanning Confocal Imaging System (Bio-Rad) equipped with a krypton/argon laser and a Nikon Diaphot 300 inverted microscope. All confocal fluorescence pictures were taken with a 20x objective and excitation at 488 nm and 568 nm

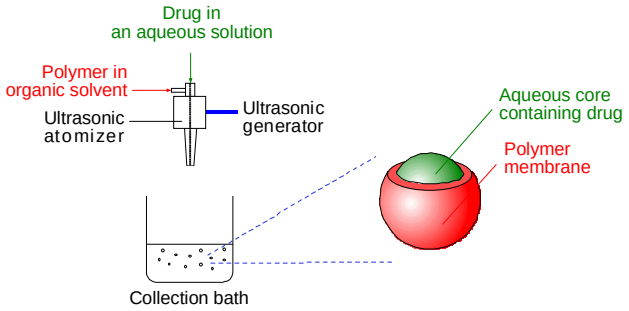

Figure 1. Schematic description of the microencapsulation system using a coaxial ultrasonic atomizer.

RESULTS

Reservoir-type microcapsules were produced using ultrasonic atomizers. Figure 2 shows CLSM images of the microcapsules produced by the solvent exchange method and those by the double emulsion-solvent evaporation method. Figure 2 makes it clear that the microcapsule produced by the solvent exchange method was composed of a single drop of the aqueous phase surrounded by a polymer membrane. By contrast, the microspheres produced by the double emulsion method consisted of multiple drops of the aqueous solution embedded within the polymer matrix.

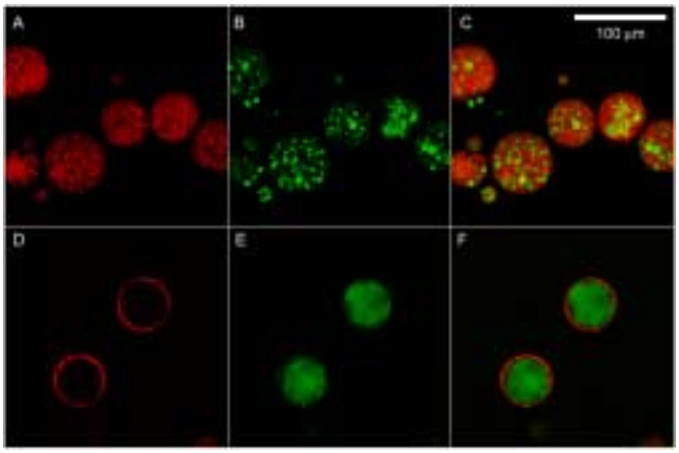

Figure 2. CLSM images of microspheres produced by a double emulsion-solvent evaporation method (A, B, and C) and by the solvent exchange method (D, E, and F). Panels A and D: The PLGA phase appears red due to the presence of Nile red. Panels B and E: The aqueous phase appears green due to the presence of FITC-dextran. Panels C and F: Images of the PLGA and the aqueous phase were overlapped.

Microcapsules could also be produced using a pair of ultrasonic atomizers which delivered the two liquids separately. Two ultrasonic atomizers were aligned to cause collision between the groups of microdrops generated from each atomizer. The microscopic image shown in Figure 3 indicates that the microcapsules produced by the separate atomizers are identical to those by the coaxial atomizer.

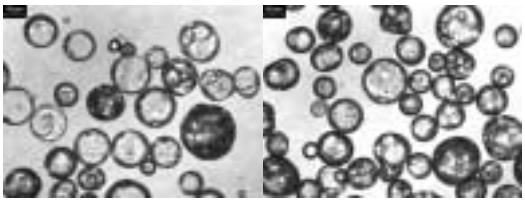

Figure 3. Bright-field microscopic images of reservoir-type microcapsules produced by two separate atomizers. Scale bar = 50 μm.

DISCUSSION

In the present study, ultrasonic atomizer(s) were employed as a means to implement the solvent exchange method. The ultrasonic atomizer is a device that atomizes liquid by vibrating at ultrasonic frequency.[3] The atomizer consists of three sections: front horn, the atomizing section; rear horn, through which liquid enters into the atomizer; a middle section consisting of piezoelectric transducers. Vibration energy provided by the piezoelectric transducers allows the liquid delivered to the atomizing surface to overcome the surface tension and spread on the surface forming a liquid film. The liquid film absorbs the underlying vibration energy and collapses into plurality of microdrops.

A coaxial nozzle consisting of an inner and outer nozzle was built to deliver the PLGA solution and the aqueous solution separately. The two liquids broke up into microdrops by the ultrasonic vibration. Microscopic examination showed that the particles collected in the water bath were reservoir-type microcapsules consisting of a single aqueous core surrounded by a polymer membrane. It is clear that here the contact between the aqueous and the polymer solutions is limited to the surface of the aqueous drop. Unlike the double emulsion-solvent evaporation method which generates a large w/o interfacial area, the solvent exchange method exposes only the drugs on the surface of a single aqueous drop to the w/o interface.

The fact that microcapsules also formed when the two liquids were delivered through separate atomizers indicates that the microcapsules are products of coalescence among multiple drops. The coaxial atomizer is especially advantageous for this purpose, since it can effectively concentrate the drops in a limited space, and thus the collision among the drops is most likely.

CONCLUSIONS

A new microencapsulation technique based on the solvent exchange method was used to produce reservoir-type microcapsules. The solvent exchange method utilizes interfacial mass-transfer between two mutually soluble liquids. A coaxial ultrasonic atomizer provided conditions that generate the interface specifically on the surface of aqueous drops. The microencapsulation is a result of random collision among multiple drops of polymer and aqueous solution. From the mild nature of the encapsulation process and the unique geometry of the microcapsules, it is expected that this method provides several advantages over conventional methods, especially in encapsulation of proteins or peptides.

ACKNOWLEDGEMENTS

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