Single-Pot Semicontinuous Bench Scale Apparatus To Produce Microparticles

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ABSTRACT: This work presents both the design of a novel process to produce microparticles with a shell—core structure and a bench scale apparatus purposely realized. The developed process was designed to respond to mandatory needs of process intensification. It involved the coupling of two emergent technologies: atomization assisted by ultrasonic energy and microwave heating. The former was used to atomize polymeric solutions; the latter was applied to stabilize the produced droplets by drying. Both operations were performed in the same vessel with the aim to have a single-pot process chamber and were carried out by a semicontinuous procedure. Basic design criteria and advantages of the ultrasonic—microwave coupled operations in the realized apparatus are presented and discussed. Results of testing and of operating runs to produce shell—core microparticles are also reported, emphasizing the main features of the produced particles.

INTRODUCTION

Many industrial applications involve the use of particles on micro- and nanoscale with a shell—core structure. This configuration allows encapsulation of special ingredients (drugs or other active molecules), for many purposes: to prolong release of pesticides and herbicides in the agriculture field; to enclose spices in the food industry; to incorporate essences, vitamins, and solar filters in the field of cosmetics; and to modify release of drugs from dosage systems in pharmaceutical manufacturing.[1,2]

Microencapsulation can be achieved by both physicochemical and mechanical processes, being the choice based on several criteria such as nature of materials (i.e., chemical properties of ingredients, solubility in aqueous polymeric solutions, and kind of polymers typically used as carriers) and final desired properties (particles size, structure, etc.).[3] In mechanical processes a crucial role is played by the droplets formation step, i.e., the atomization of liquid jet in fine droplets (spray). The vibration frequency is the key parameters in the liquid break up phenomenon,[4] even if other feed liquid properties, mainly surface tension and viscosity, affect threads formation and, in turn, droplet size.

Spray-drying offers several advantages when compared to other microencapsulation techniques fundamentally because it can be a mild "one-step" processing operation to move from a liquid feed into a powder product.[5] However, there are some disadvantages associated with the common nozzle systems used (rotary, pressure ,or two-fluid atomizers), such as lack of control of the mean droplet size, broad droplet distributions, and risk of clogging in the case of suspensions. Ultrasonic nozzles, although not routinely used in laboratory scale spray-drying equipment, allow these problems to be overcome by generating droplets with a relatively uniform size distribution, which, in turn, could lead to microspheres having more homogeneous size distributions.[6] Moreover, traditional atomizers use only a small fraction of the provided energy (centrifugal, pressure, or kinetic energy) to fragment the liquid; as most of it is transformed into the particles' kinetic energy, involving expensive plant configurations in the recovery operations. These disadvantages can be reduced using an ultrasound atomizer: drop velocity is 1—10% lower than in hydraulic or air-atomizing nozzles,[7] reducing fluid compression costs upstream[8] and drying chamber size downstream.[9] This would also offer availability of high amplitude/power units for large commercial operations; high efficiency of ultrasonic transducer (about 85%); ease of installation; and low maintenance costs, due to the absence of moving parts, such as rotors and gears.[10] Finally, the ultrasonic atomizers are subjected to a low mechanical stress that avoids the deactivation of bioactive substances.[7,10] In literature, as shown in a previous review,[11] many works demonstrate that better results are obtained by using ultrasonic atomization instead of the conventional one: in operative easiness avoiding the typical disadvantages of pneumatic nozzles (clogging, broad droplets distribution)[6,12] and also in money saving, keeping simplicity, efficiency, and reproducibility of the processes.[13,14]

In the chamber of a spray drier the produced fine droplets are dried by convective heating using air streams (modified atmosphere at given reduced pressure if heat sensitive materials are used) which promote simultaneous heat and mass transfers. The air streams that undergo all the necessary treatments such as dehumidification, filtration, and sterilization to be used for the heating must have the appropriate thermal conditions. Use of the microwave technology in heating applications can be seen as a powerful tool in the drying process. A peculiarity of microwave heating is the energy transfer:[15,16] microwave energy is directly delivered to materials through molecular interactions (loss mechanisms) with electromagnetic field via conversion of electromagnetic energy into thermal energy. The high heating rate represents the key feature of the microwave warm-up because it enables rapidly achieving in reduced times what would otherwise take a long time to be done with conventional heating.[15,17,18] Other advantages are volumetric and selective
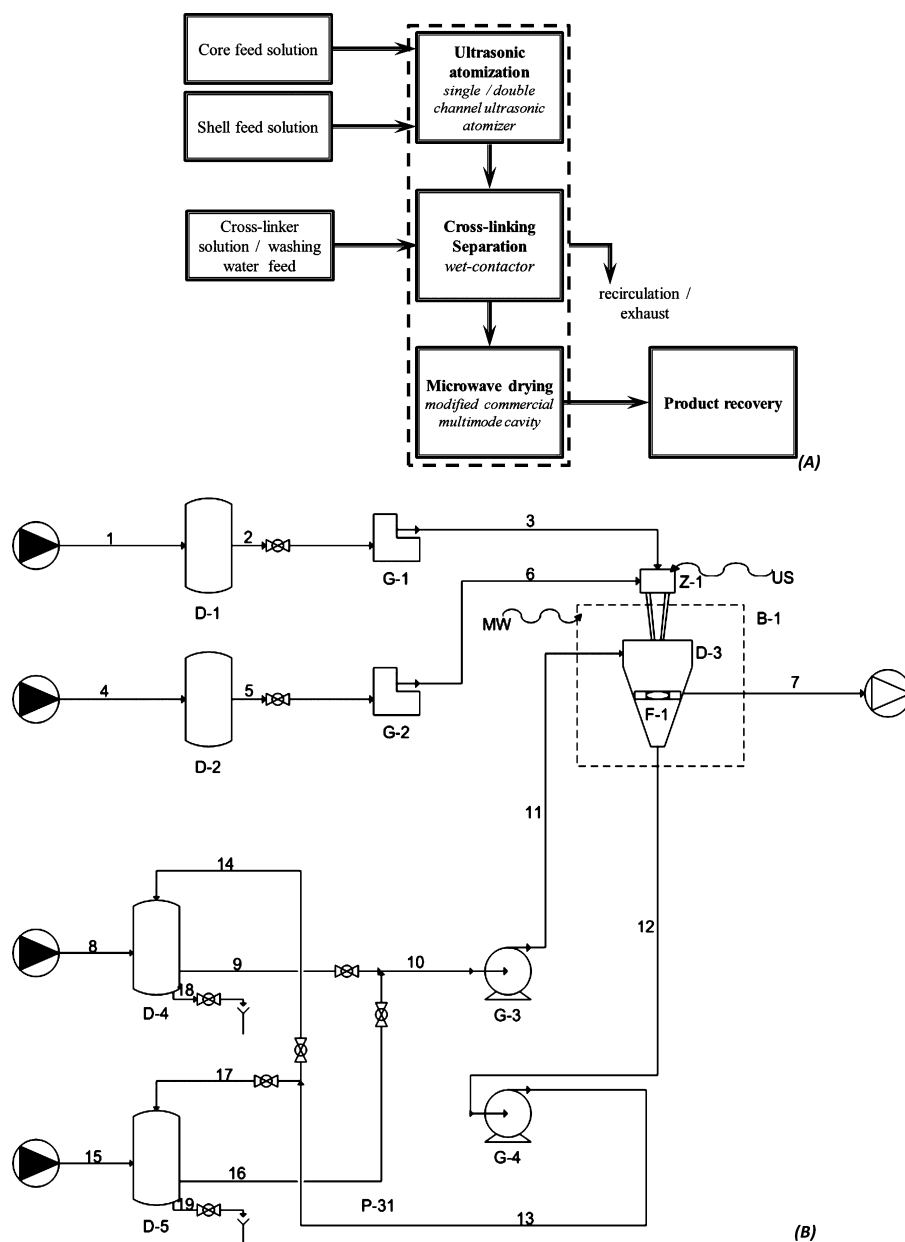
Figure 1. (A) Schematic diagram of the microparticles production. (B) Layout of the microencapsulation single-pot semicontinuous bench scale apparatus (Z-1, ultrasonic double channel atomizer; D-3, wet collector; B-1, microwave oven cavity; G-1/G-2, peristaltic pumps—core and shell feeding channels; G-3/G-4, centrifugal pumps—reticulation solution feeding and suspension recirculation; D-1/D-2, core and shell feeding tanks; D-4/D-5, reticulation solution tank, rinsewater tank; and F-1, filter; box with dashed line: MW cavity).

heating (depending on dielectric properties, see the following), uniformity of heating and better moisture leveling in the drying operation, fast on and off switching, more compact equipment, clean environment at the point of use, and possible high power densities development in the processing area. All these features, thus, make microwave heating a powerful tool for process intensification.[19]

Relevant parameters in microwave heating are dielectric properties of the matter which express the energy coupling of a material with electromagnetic microwave field and, thus, the heating feasibility (dielectric behavior).[20−22]

Coupling of different novel technologies, including ultrasonic and microwave, has been experienced only in recent applications. Ultrasonic atomization was used to improve product quality/process yields in combination with supercritical antisolvent

(SAS) technique[23] to obtain micro- and nanoparticles, in combination with microwave assisted heating to regenerate adsorbents used for exhaust air purification[24] at reduced costs.

Ultrasonic (US) and microwave (MW) energy were thus proved to be efficient tools in energy saving, in process simplification, and in process miniaturizing, i.e., efficient tools toward processes intensification. However, to our knowledge, the coupling of both the technologies, ultrasound for the atomization and microwave for drying, was not explored up to now in the production of microparticles for pharmaceutical applications. In this work, microwave and ultrasonic technologies were combined to develop enhancements in production of pharmaceutics. The final goal of this research was to overcome some limitations which characterize many conventional preparation techniques: batch procedure often carried out in

different vessels for different process-steps, long times, and high energy request. In particular, in this paper the development of a novel process to produce microparticles with a shell—core structure is presented. The process was designed with the coupling of two emergent technologies: atomization assisted by ultrasonic energy and microwave heating. The first technique was used to atomize liquid polymeric solutions (ultrasonic nozzle features: double channel, 25 kHz); the microwave heating (in multimodal commercial chamber at 2.45 GHz) was applied to stabilize the produced droplets by drying. Microparticles were produced starting from fine droplets of a polymeric solution that, when in contact with a saline agent (bivalent cations), is able to form a cross-linked structure (reticulation) conferring to the droplets a rubbery-like consistence. All the processes (atomization, reticulation, drying) were performed in the same vessel with the final goal to have a single-pot process chamber. The overall particles manufacture was carried out by a semi-continuous procedure (a schematic process diagram is reported in Figure 1A). Components and layout of the realized bench-scale apparatus are also reported in detail as well as the working protocol and all techniques adopted to characterize the produced microstructures.

■ SEMICONTINUOUS BENCH SCALE APPARATUS CONSTRUCTION

In the following subsections, the components selected to build up the bench scale apparatus and the plant layout are presented. An overlook of the layout is reported in Figure 1B. The tuned working protocol is also described.

Component Features and Selection Criteria. The main part of the bench-scale apparatus is the atomization section. It was set up using a sonotrode in which a disc-shaped ceramic piezoelectric transducer receives high frequency electrical energy from the Broadband Ultrasonic Generator and converts the energy into vibratory mechanical motion at the same frequency. A 25 kHz Ultrasonic Nozzle (dual liquid feed probe Sono-Tek 025-00010, Sono-Tek corporation), with a conical atomizing surface shape, having a tip diameter of 11.684 mm and an orifice size of 1.016 mm and a microbore (internal diameter of 0.406 mm) installed, was selected as the atomizer device (see Figure 2). The dual liquid option was chosen since it is ideal for microencapsulation, as the two liquids are mixed right at the nozzle atomizing surface. The selection of the 25 kHz model first derives from the need to process fluids more viscous than water and then from the specifications about maximum flow rate, median drop diameter, and length of the tip that are 3.3 mL/s, 55 μm, and 55 mm respectively, using water as the testing material. In the case of the selected atomizer device (diameter of tip 11.684 mm; orifice 1.016 mm; microbore internal diameter 0.406 mm) a maximum flow rate of 0.3 mL/s is obtainable. The tip (Figure 2) of 55 mm is one of the longest available to allow the insertion of the nozzle in the microwave cavity at the center of a vessel in turn placed in the microwave cavity, acting as a wet collector to catch the fine produced droplets. The selection of the conical shape for the atomizing surface, among the many available options, has been based on the need to ensure a wide spray pattern distribution of the nebulized liquid.

After having identified the best features of the atomizing device, an appropriate liquid delivery system (pumping or feeding section) has been studied. First, a plastic tube, chemically compatible with the liquid to be sprayed, was selected. Similarly, a suitable secure tube insertion in the fitting was done not to have loose fittings causing degradation of the nozzle performance, also
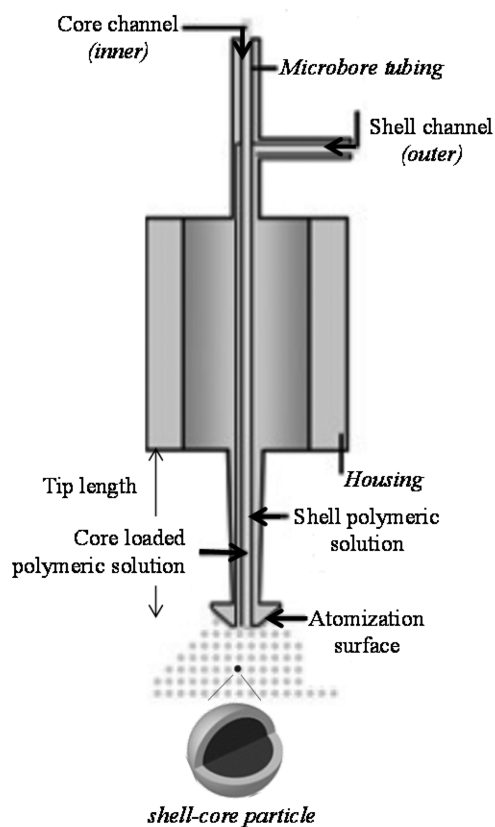

Figure 2. Sketch of the double channel ultrasonic nozzle atomizer (Z-1).

becoming quite hot for the absorption of the ultrasonic energy. Moreover, the selection of the best option depended on several factors, such as cost, precision required, needed flow rates, and required maintenance. Usually, there are six basic methods of liquid delivery that are routinely used with ultrasonic spray nozzles: gear pumps, piston pumps, syringe pumps, pressurized canisters, gravity systems, and peristaltic pumps. These latter were chosen (Verderflex OEM mod. Au EZ) for the advantages they offer: they are excellent with virtually any type of feed solution, the liquid is not in contact with motor parts, and tube changing and cleaning are flexible and quick. Finally, the feed circuits were completed by two independent pipelines, formed by silicon flexible tubes ended by a stretch of plastic, not flexible, tubing.

The stabilization section of the bench scale apparatus consists of a device named "wet collector" (Figure 3A), i.e., a sort of hydrocyclone, purposely realized to distribute the reticulation solution (or hardening solution) along the wall of its semiconical structure to ensure the contact with the atomized fine drops (outgoing from the atomizer which is placed, as above-reported, at the center of the wet collector); a filtering device, placed within the wet collector, where the final products (the cross-linked particles) are recovered; and a feeding and recirculation circuit of both the hardening solution and the washing water (posthardening). Details on the connection between the above described components are reported in next paragraph.

The wet collector was designed on the basis of literature suggestions on hydrocyclone sizing,[25] even if some adjustments were done to satisfy the needs of the novel plant. All characteristics of the wet collector are reported in Figure 3A–C). The fluids entrance in the wet collector (reticulation solution, rinsewater) is not tangential; unlike common hydro-
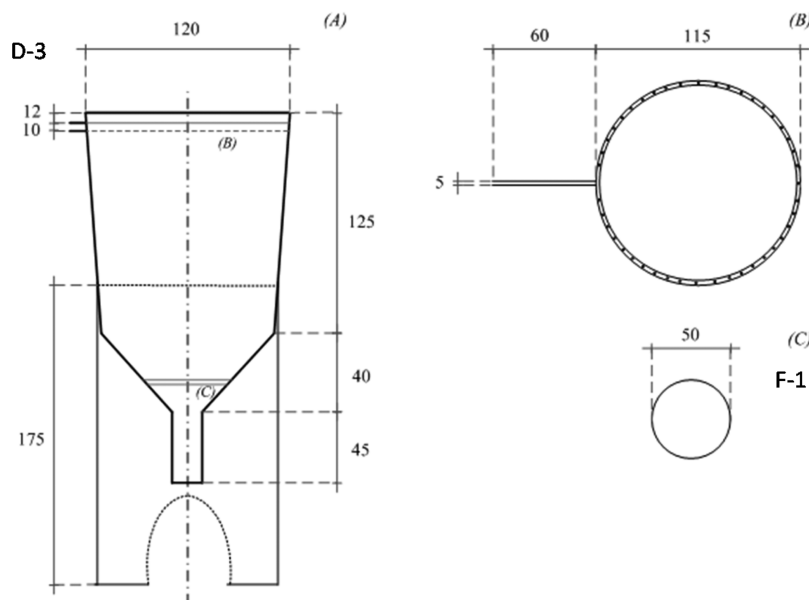
Figure 3. (A) Wet collector; (B) reticulating solution/rinsewater dispenser; (C) filter. Quotes are in millimeters.

cyclones, it is guaranteed by a dispenser (Figure 3 B) (pierced circular tube) mounted on the upper part of the wet contactor. The filtering device is a porous disc (Figure 3, (C)) with the following features: diameter =50 mm; thickness =5 mm; porosity grade =4 (pore size in the range 5−15 μm). Then, the choice of the two centrifugal pumps (DC15/5 Totton pumps) for the feeding and recirculation circuits of both the hardening solution and the washing water made done on the basis of two requirements: (i) the need to obtain a uniform distribution of the liquid solution in the wet collector to promote contact between reticulating agent and droplets, thus avoiding formation of undesired films, and (ii) the need to overcome pressure drops due to the filter presence. Finally, a commercial multimodal cavity (De Longhi Perfecto-Easy MW314) is dedicated to the set up of the first developed oven prototype containing the wet collector, to perform the "on line" last step, i.e., the microwave drying, of the microparticles production process. It is worth noting that the wet collector was designed on the basis of the geometric features of the multimodal cavity and was realized in Pyrex to be used in the microwave oven.

Layout Description. As above-reported, the layout of the realized apparatus is shown in the Figure 1B. Both the solutions, core and shell feed (line paths: 1−2−3 and 4−5−6), stocked in separate tanks (D-1 and D-2, respectively), are sent by the peristaltic pumps (G-1 and G-2) to the ultrasonic double channel atomizer (Z-1), placed at the geometric axis of the wet collector (D-3), which is in turn positioned inside the microwave oven cavity (B-1). The feed core line is directed to the inner channel of the double channel nozzle; the shell line is addressed to the outer ones. The two solutions come in contact only at the exit of the two channels, at the atomizer's tip, where they are nebulized and placed in contact to the hardening solution (line path: 8−9−10−11) . In the first operation stage, the filter (F-1) is not present to ensure a continuous recirculation of the hardening solution. The recirculation (line path: 12−13−14) is essential to renew the contact surface between droplets and hardening solution and, therefore, to avoid film formation: feeding (G-3) and recirculation (G-4) pumps are both switched on. The obtained drops come in contact with the hardening solution (a volume of 300 mL, with a volumetric flow rate of about 37 mL/s), which is

uniformly delivered by the dispenser. Drops become particles owing to the cross-linking with the hardening solution: the obtained suspension is continuously recycled to the storage tank, with the same volumetric flow rate of feed, i.e., 37 mL/s. Therefore, the hardening solution becomes increasingly concentrated in particles each time it is spread by the dispenser (even if it is kept diluted), until the end of the atomization process. At this point, while the suspension is stored in the hardening solution tank (D-4), the filter is placed within the wet collector. Therefore the suspension is fed back to wet collector, where all the liquid accumulates owing to the filter presence. The feeding pump (G-3) is switched off, while the recirculation pump (G-4) is switched on: at this stage, the volumetric flow rate in the recirculation line is of about 1 mL/s due to the filter pressure drops, with a consequent cross-linking time of about 5 min. The following washing step (line paths: 15−16−10−11 and 12−13−17) can be done in a manner similar to the previous hardening step, by closing the valve of the hardening fluid's vessel and opening the valve of the washing water's tank (D-5), respectively. Particles settled on the filter are "on-line" stabilized by microwave drying under given conditions. At last, they are recovered by scraping once it was extracted from the wet contactor (line path: 7). The purging of the D-4 and D-5 tanks are performed through discharges (line paths: 18 and 19).

It is worth to noting that the wet collector works as a single pot where all the different manufacturing steps are performed, i.e., feed atomization (droplets production chamber), droplets reticulation (particles production chamber), washing, and drying (particles stabilization chamber).

Semicontinuous Bench Scale Apparatus Exercise. The realized apparatus has been used for the encapsulation of a model molecule allowing the production of microparticles with the desired features (i.e., shell−core microstructures). Having this in mind, the adopted approach consisted of a comparison between shell−core and only core systems, i.e., matrix structures, in terms of loading and release of encapsulated active molecules. In the shell−core system preparation, the active molecules are put in a solution which is fed to the inner channel of the coaxial nozzle and is then atomized together with the external solution containing only the polymer, that surrounds the internal one

encapsulating it. The only core (matrix) system is instead obtained simply atomizing the internal solution, containing active molecules and polymer, in the inner channel leaving the external one empty. The shell−core system protects better the loaded active molecules, owing to the external coating, differently from the core only system where the active molecules are dispersed in the matrix, which makes their diffusion from the particle and the burst effects easier.

Finally, millimetric systems (beads), produced in the same conditions of microparticles but switching off the ultrasound generator, were compared to micrometric ones (microparticles) to investigate the effects due to the surface to volume ratio in the release studies.

■ MATERIALS

Medium molecular weight Manugel GHB sodium alginate (AL) (a list of abbreviations is reported in Table 1), purchased from

Table 1. Abbreviations List

acronym	description
AL	sodium alginate
CD	convective drying
GI	gastro-intestinal (tract)
MW	microwave energy drying
TOC	α-tocopherol
US	ultrasonic (energy)
USP	United States Pharmacopeia

FMC Biopolymer, was chosen as polymer. Sodium alginate was chosen for its capability to carry out a process in an aqueous environment (alginate needs cross-linking with aqueous ionic solutions) at room temperature and in the absence of organic solvents;[26] to undergo dissolution and biodegradation under normal physiological conditions; to have bioadhesive features, useful when formulating potential delivery vehicles for drugs to mucosal tissues, such as the gastro-intestinal (GI) tract;[27] and to be a natural additive used in many food applications.

α-Tocopherol (TOC) (the form of vitamin E which is preferentially absorbed and accumulated in humans) by Sigma Aldrich supplier was selected as the model molecule for its features of poor solubility in aqueous media (TOC solubility at 20 °C: 20.9 mg/L[28]) and thermo-sensibility typical of many drugs (TOC melting temperature: 4 °C (http://www.chemspider.com, TOC melting enthalpy: 50.6 kJ/mol—calculated by Chickos et al. method[29]). Other chemicals (all by Sigma Aldrich supplier) used in particles preparation were calcium chloride ($CaCl_2$) in water solution as cross-linker and Tween 80 as surfactant. As a cross-linking solution, calcium bivalent ions are mostly chosen in the alginate reticulation process in food, biopharmaceutical, and pharmaceutical applications, mainly due to the biocompatibility and rheological features of the produced gel. In particular, in this study, a cross-linking solution of $CaCl_2$ with a concentration and a flow rate of 8.9 g/L and 37 mL/min were used, respectively.

Moreover, solutions at different pH values, simulating the gastrointestinal or physiological conditions, were obtained using hydrochloric acid, sodium phosphate tribasic dodecahydrate, potassium dihydrogen phosphate, sodium and hydroxide.

■ METHODS

Process Parameters Tuning. Core and shell solution feeds have to be easily processed: too viscous solutions could lead to

the clogging of the nozzle channels. After having selected the best concentration for the two streams, the relevant flow rates of each of the inner (core) and outer (shell) streams are varied to control core diameter, shell thickness, and overall particle size.[30] Preliminary tests on the coaxial nozzle were performed in order to check the feasibility to obtain shell−core systems. A dripping test (i.e., keeping the ultrasounds switched off) was performed: both the inner (core) and the outer (shell) streams were highlighted using colored pigments to see the disposition of the internal drop with respect to the external shell. Different combinations of core/shell concentrations and flow rates of alginate solutions were tested on the basis of literature suggestions.[30,31] The best configuration resulted to be the one with a concentration of alginate in water of 1.5% w/w (solution viscosity 0.13 Pa s[32]) for both inner and outer solutions, able to satisfy the needs for better consistency, delayed migration of pigment, and, possibly, of model molecule, during the particles preparation, and spherical shape. Moreover, a good enwrapping of the internal drop in the external shell, as seen by pigments, was obtained for outer flow rates in the range 4−4.5 mL/min and for inner flow rates in the range 0.65−1.1 mL/min.

In preliminary tests, the atomization process and the drying process alone were tested, giving results similar to the one presented in the present paper. After these preliminary tests, the design and building of the single-pot apparatus was carried out. The process parameters to be used in the stabilization step were tuned in a previous study of sensitivity analysis. In particular, optimum values of microwave power and treatment time were set to avoid too high temperatures that could degrade the thermo-sensible α-tocopherol and to have microparticles well dried. A fictitious power level of 245 W, deriving from a duty cycle of 700 W in the multimodal cavity (De Longhi Perfecto-Easy MW314) with the magnetron switched on for 1/3 of the total operation time, was chosen; a process time within 30 min of irradiation (i.e., 10 min of effective irradiation) was proven to be effective. Moreover these irradiation conditions did not produce burns and material thermal degradation.

Microparticles Production. Particles production follows the working scheme described in the previous section Layout Description. Concentration of both the feeding solutions of alginate are of 1.5% (w/w), as defined by the preliminary tests described in the section Process Parameters Tuning. In particular, the core feeding solution is composed of alginate at 1.5% (w/w), α-tocopherol at 1% (w/w), and Tween 80 at 0.5% (w/w). The surfactant Tween 80 is introduced in the core feeding to reduce interfacial tension and consequently particles dimensions; moreover, a Tween 80 concentration of 0.5% (w/w) is required to obtain a stable emulsion of the water insoluble α-tocopherol with the water-soluble solution of alginate. This latter constituted the loaded feed solution and was prepared in a separate vessel. Specific flow rate values, concentrations, and all the other parameters defined for the apparatus exercise are summarized in Table 2; particle production runs were performed in triplicate.

To compare microwave drying (MW) with convective dehydration (CD) process, aiming at observing kinetic rates and possible changes in the release properties, several lots of wet particles, just produced in the apparatus, were introduced in a tray-oven with air at T = 45 °C.[33] This operative condition was suggested from literature where TOC stability was ascertained.[33]

Microparticles Characterization. All the measurements performed on produced microparticles were performed at minimum in triplicate.

Table 2. Parameters Selected for Particles Production

parameters	core feeding	shell feeding
flow rate, mL/min	1.1	4.2
alginate, % w/w	1.5	1.5
α-tocopherol, % w/w	1	-
Tween 80, % w/w	0.5	-
atomization/dripping time, min	2	
cross-linking time, min	5	
drying treatment	microwave (P = 245 W)/Convective (T = 45 °C)	

Image Analysis. Size control of particles (before and after drying) was performed by image analysis using optical microscope (Leica DM LP, equipped by the DFC 280 digital camera) pictures. It was carried out using the public domain software ImageJ 1.40g (Wayne Rasband, National Institutes of Health, USA; the software is freely available at http://rsb.info.nih.gov/ij/). Several snapshots for each obtained sample were image-analyzed in order to measure the size of no less than 100 of the particles. The process was manually carried out to avoid the potential errors in automated routines, because of the low brightness/contrast differences of the photos. The size was expressed in terms of mean value and standard deviation.

Dielectric Properties. To emphasize suitability and feasibility of microwave drying treatment, measurements of dielectric properties were performed. In particular, dielectric spectroscopy (i.e., measurements of the dielectric constant, which expresses how much energy from an external electric field is stored in a material, and of the loss factor account for the energy loss dissipative mechanisms in the material, as a function of the frequency) of fresh microparticles was performed using the open-ended coaxial line method (suitable measure fixture because the samples under investigation showed high dissipative features) by a network analyzer (Agilent Technologies, ES 8753) equipped with an open-end coaxial probe (Agilent Technologies, 85070D). Air, distilled water, and a short circuit block were used as standards in the calibration procedure. Investigated materials were subjected to dielectric spectroscopy in the frequency range 200 MHz−6 GHz; then values of the dielectric properties at 2.45 GHz (that is the working frequency of the used multimode microwave cavity) were extracted from the spectra.

Moisture and Temperature Measurements. Moisture measurements of both fresh and dried produced particles were carried out by a thermobalance (Ohaus MB45) to determine initial and residual amounts of aqueous solvent.

Temperature measurements, during microwave drying of particles, of both multimodal cavity environment and sample (particles) were done using optical fibers sensors (FISO FOT-L, Fort Optical Fibers, data being gathered by the FISO UMI-8 conditioner). An infrared pyrometer (Simpson mod. IR-10) was also used to confirm particles' surface temperature.

Differential Scanning Calorimetry. DSC scans of pure alginate, pure $CaCl_2$, a physical mixture of alginate and $CaCl_2$, alginate cross-linked particles obtained by atomization and then dried by convective drying (CD), and alginate cross-linked particles obtained by atomization and then dried in a microwave cavity (MW) were performed using a differential scanning calorimeter Mettler Toledo DSC-822 (Mettler, Switzerland). Samples were weighed and heated from 25 to 300 °C at a heating rate of 10 °C/min under a nitrogen flow rate of 50 mL/min, as suggested in the literature.[34]

Loading and Release Tests. Tests to assay loading and release of α-tocopherol from the produced particles (dried both convectively and by microwave heating) were carried out. To test the enteric nature of the particles, about 200 mg of these latter were put in 75 mL of an acid solution, 0.1 N hydrochloric acid (pH 1), simulating the pH in the stomach; after a time of 120 min, 0.2 M tribasic sodium phosphate was added to reach pH 6.8, simulating the pH in the intestine, according to United States Pharmacopeia (USP) suggestions. The temperature was kept at 37 °C at accurately controlled stirring conditions to avoid sampling errors due to the insolubility of the released TOC (to keep the dissolution bulk homogeneous). For both tests, samples of 1 mL were taken, using a syringe with a 0.22 μm filter to avoid the withdraw of particles, at given times, mixed with 9 mL of ethanol and centrifuged for 5 min at 6000 rpm (Remi, R-8C XS Bench Top Centrifuge) to extract α-tocopherol (which is not soluble in water). α-Tocopherol's presence was then detected by UV−vis spectrometer (Lambda 25 by Perkin-Elmer) recording the full absorption spectra in a wavelength range from 200 to 400 nm and identifying the peak height closest to 290 nm, in order to avoid incorrect measurements due to a shift in λ_{max}. The adopted procedure of spectra fitting instead of the simple reading of the absorbance at a given wavelength has been proved, in a previous work,[35] to be much more effective and in principle advantageous to be used to eliminate the interferences due to polymers or other substances.

Apparatus Power Consumption. The apparatus power consumption was detected by a power consumption meter (Avidsen 103755, Avidsen Srl), reading both the instantaneous consumption in Watts (which also allows the detection and time of maximum consumption) and the total energy consumption in Joules.

RESULTS AND DISCUSSION

Image analysis for size measurements of both shell−core and matrix particles, done on both fresh and dried products, showed a narrow size distribution. Shell−core and matrix microparticles have an initial average size of respectively 78 and 76 μm; after microwave drying their size is reduced, by volumetric shrinkage of 85% to 40 μm, as highlighted in Table 3.

Table 3. Mean Size and Standard Deviation for Both Shell−Core and Matrix Microparticles, Shell−Core Beads, Fresh and Dried (via Microwave Heating); Volumetric Shrinkage Percentages for the Dried Ones

produced systems	mean size ± SD, μm	volumetric shrinkage, %
shell−core microparticles—*fresh*	78 ± 20	-
matrix microparticles—*fresh*	75 ± 20	-
shell−core beads—*fresh*	3860 ± 100	-
shell−core microparticles—*dried*	41 ± 12	86
matrix microparticles—*dried*	40 ± 11	85
shell−core beads—*dried*	1292 ± 99	96

Morphology observations revealed that fresh particles assume a light pendant shape because of the impact onto the wet wall of the collector. This shape is kept due to the fast cross-linking reaction[36] and is furthermore roughly preserved in dried particles.

To evaluate the feasibility and the convenience of stabilization by microwave drying, dielectric properties of fresh microparticles

were compared with those of water (Figure 4), that is, the microparticles most abundant component, and exhibits dis-
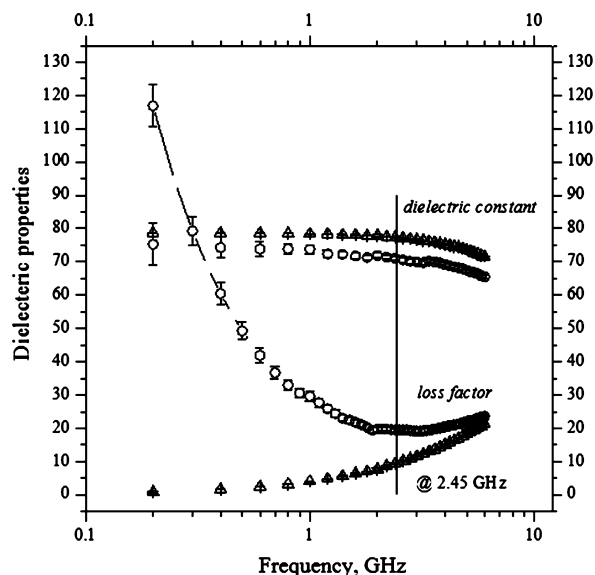

Figure 4. Dielectric properties (dielectric constant and loss factor) of fresh microparticles (hollow circles) and distilled water (hollow triangles).

sipative features (high dielectric properties). Indeed, water is composed of natural dipoles which can be easily polarized under an external electric field application. Interactions between materials and electromagnetic energy depend on the ability of the electric field to polarize the charges of the material and on the difficulty of the polarized structures to follow the rapid changes of the oscillating electric field. This latter phenomenon causes intermolecular frictions and thus heat generation (dielectric dissipative mechanisms) inside the matter.

In presence of an external electric field, different kinds of polarization mechanisms are possible: the electronic polarization, due to modification of the electrons positions around the nucleus; the atomic polarization, caused by positional shifts of the nucleus resulting from a nonuniform distribution of charges within the molecule; the orientation polarization (dipoles rotation), caused by the reorientation of the permanent dipoles under the influence of the electric field; and finally, the spatial charge polarization, observed in materials containing free electrons confined on the surface (Maxwell–Wagner effect).[15,20] Depending on frequency, one or two mechanisms can dominate over the others. In particular, the dipole rotation is the dominant polarization mechanism in irradiated materials rich in water, in the microwave electromagnetic spectrum region.

Therefore, taking into account that the loss factor expresses the loss energy dissipative mechanisms in the materials at the most used frequency of 2.45 GHz for the industrial drying (as well as in commercial microwave ovens), a loss factor higher than water's loss factor confirms that they can be easily heated by microwave. The loss factor increase is due to the residual ionic hardening solution, which also involves the decrease of the dielectric constant. In effect, decrease of the energy-storage ability is due to subtractions of water dipoles, because solvation effects occur (fewer dipoles can be polarized); whereas higher loss factor values are due to the enhancement of ionic dissipative mechanism.[20,37]

The expected feasibility of microwave drying was also confirmed by moisture measurements: from an initial content of about 95%, microwave drying assures a reduction to 3% in about 25 min, acceptable to avoid the impairment of the product stability. Moreover, during drying, the sample does not reach high or critical values of temperature, owing to the selected irradiation condition (the duty cycle function that assures keeping the magnetron—the microwave source—switched on for 20 s in a minute chosen as periodic time interval). In particular, the temperature monitoring showed that microparticle temperature decreased with time passing from 88 to 48 °C in about 25 min; meanwhile, the detected environmental temperatures inside the microwave cavity were assayed in the range of 35−42 °C.

Furthermore, DSC results endorse the purpose to combine microwave with ultrasounds. DSC scans of pure sodium alginate (Figure 5A) showed first a typical endothermic peak to be attributed to the evaporation of water and then an exothermic behavior starting at around 200 °C, with its maximum at about 250 °C, highlighting the polymer decomposition.[38,39] $CaCl_2$ has two endothermic peaks at about 145 and 170 °C (all values coincide with literature data[34]). The physical mixture of pure
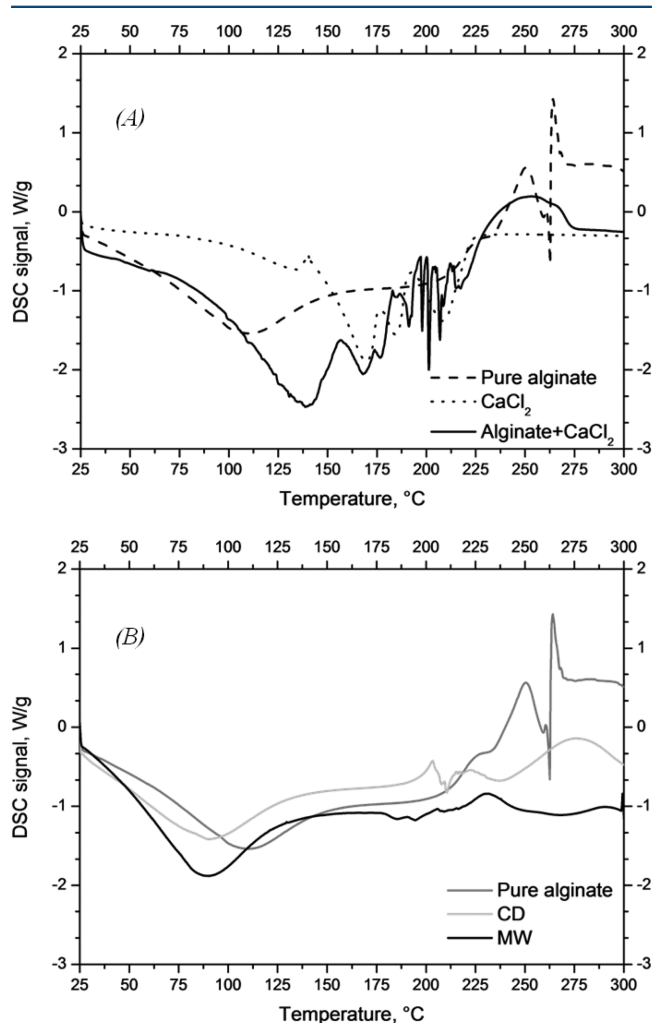

Figure 5. DSC scans of pure alginate, $CaCl_2$ powder, and physical mix of alginate and $CaCl_2$ (A). DSC scans of pure alginate and particles of cross-linked alginate obtained by atomization and then dried by convective drying (CD) or by microwave drying (MW) (B).
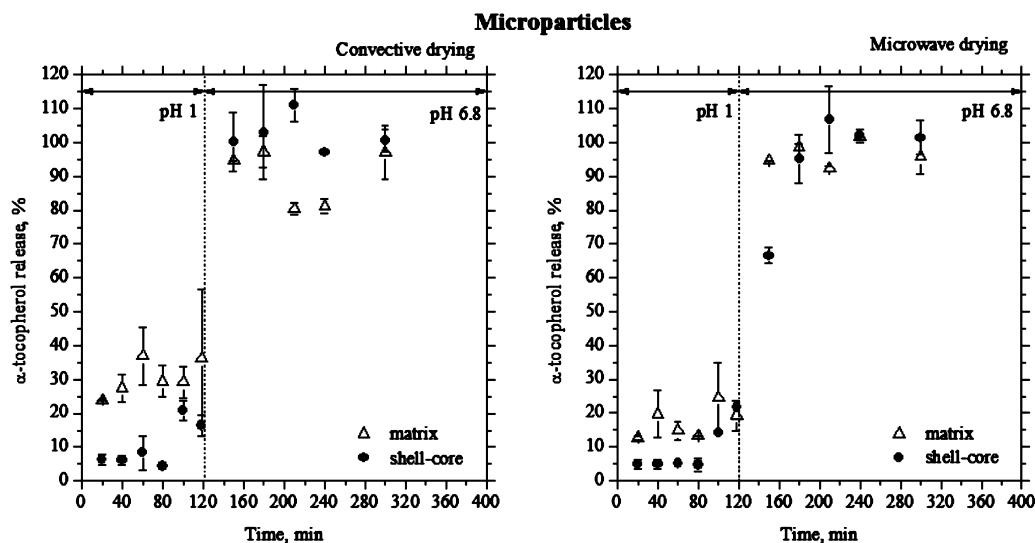
Microparticles

Figure 6. α-Tocopherol released (amount of TOC released and measured/theoretical loaded amount of TOC) from dried alginate microparticles (on the left after convective drying; on the right after microwave assisted drying).
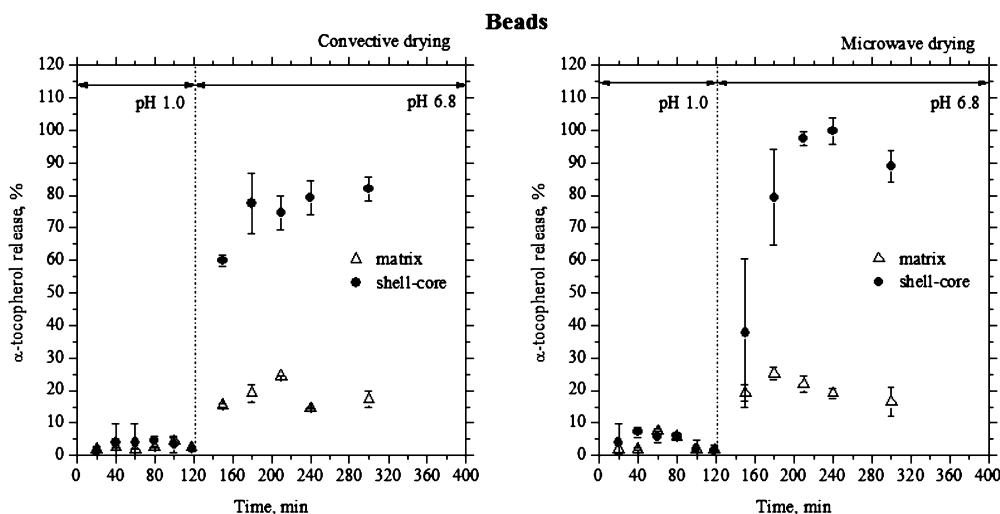
Beads

Figure 7. α-Tocopherol released (amount of TOC released and measured/theoretical loaded amount of TOC) from dried alginate beads (on the left after convective drying; on the right after microwave assisted drying).

alginate and $CaCl_2$ (solid line in Figure 5A) showed a combination of peaks typical of the two powders, underlining the absence of physical interaction between the two powders. Scans of atomized and dried particles (both via convective—CD—and microwave—MW—drying), as seen in Figure 5B, are similar to the scan of pure alginate, with jagged features typical of $CaCl_2$. However, the endothermic peak for the particles is at a lower temperature (about 85 °C) than for pure alginate, due to the evaporation of absorbed water, perhaps for the smaller water content in the dried forms. Moreover, the MW dried samples show a more pronounced endothermic peak than the sample convectively dried (the only parameter that differentiates the two samples is the kind of drying), maybe because microwaves cause a faster reorganization of the structure which traps the residual water.

Release properties of both microparticles and beads loaded by α-tocopherol were studied through release tests based on the USP enteric method. Several lots of both matrix and shell—core systems, as micro- and macro-particles, were stabilized adopting convective (conventional treatment at 45 °C, 220 min) and

microwave drying (novel treatment, at pulsed irradiation in about 25 min) and then subjected to the two stages release tests (at pH 1 and pH 6.8 environments for 120 and 280 min, respectively) at 37 °C and under controlled stirring. All the achieved release profiles are reported in Figures 6 and 7.

Both the kinds of microparticles (Figure 6) showed an encapsulation yield (amount of TOC released and measured/theoretical loaded amount of TOC) of around 100% (which means that the drug loadings were around 33% in the matrix systems and around 11.5% in the shell—core systems—see Table 2) and globally good enteric release properties, because α-tocopherol is completely released only at pH 6.8. However, it is important to note that shell—core microparticles show a better gastroresistance compared to the matrix ones, owing to the smaller amount of α-tocopherol released at acid pH for both types of drying treatments. This confirm the presence and the functional role of the shell structure. Also, microwave treatments cause a little delay in active molecules release, especially for shell—core microparticles (Figure 6 on the right), demonstrating the microwave drying usefulness in the controlled drug release:

microwave can affect, by a sort of curing, the polymeric structures. This can be explained on the basis of literature considerations about the use of microwave technology to modify the state of molecular interaction between the alginate chains with the aim to delay the release of small molecule drugs.[40] Wong et al. observed that the wavenumber of the hydroxyl and carbonyl FTIR peaks of microwave treated, blank alginate beads were lower than those of the untreated ones. This indicated that microwave irradiation increased the level of polymer−polymer interaction by hydroxyl and carbonyl moieties, which was expected to delay the drug release from the alginate beads. Moreover, the intensity of carboxyl and carboxylate peaks of alginate increased with harsher irradiation conditions, suggesting a reduction of interaction between Ca^{2+} ions and alginate and a consequent effect of drug release enhancement.[40] The first phenomenon can be used to explain the delayed release of α-tocopherol after particles irradiation by microwave. Moreover, microwave effects on drug release features of cross-linked alginate were proved to be a function of the alginate conformation.[41]

Even the macro shell−core structures (features in Table 3) display once again better release properties (and loading capacity) then the matrix systems (Figure 7). In effect, the shell−core configuration allows the α-tocopherol deactivation instead observed for matrix beads to be avoided: for these systems only the 20% of the theoretical load was released, and as no α-tocopherol was detected in the harvesting solution, the remaining 80% should undergo thermal degradation during the drying phase. Therefore, shell−core systems ensure a protective barrier against the heat, whose degradation effect on α-tocopherol, similar to that observed for matrix systems, was stated in the literature.[33] Moreover, also for macroparticles, microwave drying (Figure 7, right) gives better release properties: increased loading and delayed release.

It is worth noting that burst effects are influenced by the particle size, as can be seen comparing Figure 6 to Figure 7. This likely depends on the significant variation in the surface to volume ratio of the produced particles (microstructures and beads).

The power consumption of the apparatus is essentially due to particles drying, as shown in Figure 8, regardless of type (the difference in energy consumption between microwave and convective drying is only of some Joules whereas shorter drying times are required by microwave heating), with a percentage on the total consumed energy of about 95% (SD ± 2.1%): most of the consumed energy depends on particles properties, which
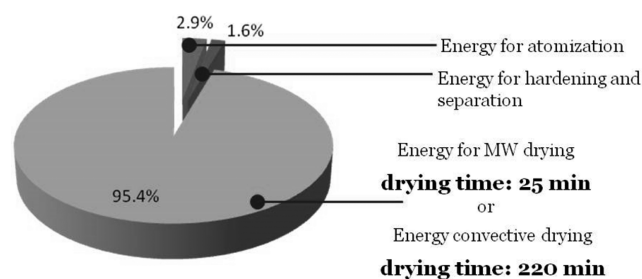

Figure 8. Power consumption in the different process stages: atomization (2.9%, SD ± 0.32%), hardening and separation (1.6% SD ± 0.12%), and drying (95.4% SD ± 2.1%). These percentages are defined as the ratio between the specific energies (Joule)/(g of fresh product) of a single section (for example, atomization section) to the sum of the three sections.

have an initial moisture of 95% (SD ± 1.0%), rather than on the apparatus' features.

Previous studies of the same research group[36] demonstrated that a laboratory ultrasonic atomizer, working at the highest flow rate allowed by the laboratory system used, requires a very low volumetric power supply, comparable with the lowest value realized on the plant scale using conventional techniques.[36] Since the lab scale usually requires a specific energy higher than the plant scale, the ultrasonic assisted atomization is confirmed to be a very promising technique in the intensification of the industrial processes.

CONCLUSIONS

In this paper the realization of a single-pot bench scale apparatus to produce microparticles by coupling ultrasonic and microwave techniques was presented together with details about components and criteria for their selection. A working protocol and parameters tuning procedure were also described.

Microparticles characterization showed that using the designed and realized apparatus makes it possible to obtain microsystems with a shell core structure encapsulating a functional molecule. Shell−core particles, in both micro- and macro-systems, resulted in better release and loading features for the production of oral pharmaceutical formulations. For the two kinds of produced microparticles (matrix and shell−core), the yield of encapsulation was found to be around 100%. Moreover, the particles had enteric release properties because α-tocopherol was completely released only at pH 6.8. However, shell−core microparticles showed a better gastroresistance if compared to the matrix ones. Finally, microwave treatments caused, especially for shell−core microparticles, a little delay in α-tocopherol release: this effect could be explored for the formulation of oral dosage forms requiring delayed drug delivery kinetics.

As a summary, the coupling of microwave and ultrasonic technologies can meet the process intensification requirements through the improvement of energy transfer rate (faster process times), the reduction of process chambers volume (lower particles inertia in atomizing, single-pot process realization), and the enhancement of the product quality (microparticles produced with tailored features).

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Notes
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