European Journal of Pharmaceutics and Biopharmaceutics 80 (2012) 471–477

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Short review (expert opinion)

Intensifying the microencapsulation process: Ultrasonic atomization as an innovative approach

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ARTICLE INFO

Article history:
Received 21 April 2011
Accepted in revised form 13 January 2012
Available online 25 January 2012

Keywords:
Microencapsulation
Process intensification
Atomization assisted by ultrasonic energy
Microparticles production

ABSTRACT

In this review, new approaches to the microencapsulation processes, widely used in the manufacturing of pharmaceutical products, are discussed focusing the attention on the emerging ultrasonic atomization technique. Fundamentals and novel aspects are presented, and advantages of ultrasonic atomization in terms of intensification and low energy requests are emphasized.

1. Introduction

The need for reducing energy consumption, emissions, wastes and risks, and sustainability represents, nowadays, a mandatory rule in the new approaches to process operations [1–3]. This tendency is growing a current issue also in pharmaceutical field where the future of many dosage-system productions depends on the capacity of introducing innovation in the functionality profile of new formulations as much as of performing advancements in manufacturing even if, due to the high value-added of pharmaceutical products and their small scale of productions for a long time, the possibility to enhance or to optimize has been often considered as a venturesome investments [4]. An example of new approaches in pharmaceutical productions can be found in the development of single-pot apparatuses to mix, to granulate, and to dry powders simultaneously: one pot is used to manage different processes, achieving reduced costs and other advantages [5,6]. Moreover, use of microwave energy as alternative heat source is another step toward innovation in the manufacturing of pharmaceuticals [7].

Encapsulation process is an operation that, in the last decades, was subjected to continuous innovations because it represents a unique route to produce dosage systems able to guarantee the successfulness of pharmacological therapies. Many methods have been investigated with the aim to produce encapsulated drugs in micro-carriers overcoming serious problems associated with their low absorption and stability in physiological environments and to their release control. In particular, manufacturing of encapsulated molecules has been performed by various technologies involving different equipments, steps, materials, and energy request [8].

The investigation on uses of ultrasonic devices in atomization stage in encapsulation processes is the core of this review. Many literature papers are revised with the aim to emphasize the role of process parameters on particles properties and the features of customized apparatuses currently used. These latter are built/used to overcome the limitations typical of common equipments such as lack of versatility and high consumption of resources. On this point, the strategies of the process intensification, that is, development of process miniaturization, reduction in capital cost, improved inherent safety and energy efficiency, and often improved product quality, are also introduced [1,2,9]. Two brief sections provide a background useful when dealing with the themes above reported, that is, encapsulation techniques and concepts of process intensification.

2. Microencapsulation: steps and scale of production

Microencapsulation is a process by which solids, liquids, or even gases may be enclosed in microscopic particles through the formation of thin coatings of wall material around an active substance [10]. A multitude of compounds has been incorporated in microcapsules and microspheres by several different techniques, to stabilize them, to convert them into powders, to mask undesired taste, or to provide modified release properties [11].

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doi:10.1016/j.ejpb.2012.01.006

The preparation of encapsulated systems is achieved by both physical–chemical and mechanical processes [8,12,13] (Table 1). Choice of the process derives from the polymer nature, the desired particles size, and the chemical features of drug, especially drug solubility in the polymeric material [14]. However, most of the techniques of microencapsulation are based on modifications of three original methods: solvent extraction/evaporation, phase separation (coacervation), and spray drying. For each method, the fundamental steps to follow are: incorporation of bioactive compounds; droplets formation; solvent removal; microparticles harvest; and drying [15,16] (Fig. 1).

The droplet formation step determines size and size distribution of the resulting microspheres. The main procedures used for droplet formation in microspheres production are as follows: stirring, static mixing, extrusion (single pathway system, multichannel system, or membranes), and dripping (single droplet formation or jet excitation).

In stirring, increasing the mixing speed generally results in decreased microspheres mean size, as it produces smaller droplets by stronger shear forces and increased turbulence [17–20]. The extent of size reduction depends on the viscosity of both the disperse and the continuous phases [8,21–23], interfacial tension between the phases [8,21,22,24], their volume ratio [24,25], geometry and number of impellers, and size ratio of impeller and mixing vessel [26,27]. Static mixing consists in use of baffles or other flow obstacles installed in a tube. The baffle arrangement splits and recombines the fluid stream passing through the tube, creating turbulence and inducing back-mixing.

Extrusion is another mechanism for droplet formation. It consists in feeding the drug/matrix dispersion through a single or a plurality of pathways (micro-mixers consisting of an array of fine channels or microporous membranes), directly into the continuous extraction phase.

Dripping method, obtained by liquid spurt excitation, is powerful in combining productivity and microsphere size control. It is based on the vibration of a liquid jet to obtain its disruption into droplets: a longitudinal oscillation imposed on a liquid stream causes periodic surface instabilities, which break up the liquid into a chain of uniform droplets [28].

When the liquid jet is disintegrated in fine droplets, an atomization process occurs. Vibration frequency is the key parameters in the liquid break up phenomenon [29]. Very small droplets can be produced by increasing the frequency even if liquid feed properties (mainly surface tension and viscosity) affect threads formation (in terms of thickness) and, in turn, droplet size.

New microencapsulation technologies are relentlessly devised and invented by academics and industrial researchers: in 2002, over 1000 patents were filed concerning various microencapsulation processes. Some of these new processes have very little industrial relevance because of the extremely high cost-in-use, difficult scale-up, and/or narrow applicability range. However, some of these processes stand out as being promising, sensible, and likely to be scaled up in the near future for the encapsulation of active ingredients [13,30]. Furthermore, the literature concerning microencapsulation processes generally focuses on methodologies of particles preparation, with the objectives of maximum possible loading and controlled release. Articles describe the influence of formulation parameters (physicochemical) such as nature and concentration of constituents, viscosity of the phases. Process parameters such as stirring rate, addition rate of the coacervation or polymerization agent, and temperature are also studied. Information obtained from this kind of study is undoubtedly very important for the design of microencapsulation systems, even if results obtained at laboratory scale cannot be extrapolated to a larger scale (pilot or industrial). When no specific methodologies are followed on the bench-scale for producing microcapsules (i.e., trial and error research approaches are adopted), there is a high risk of changes of the main characteristics of the capsules (size, structure, and content) produced at larger scales [8]. Today, a large number of microencapsulation processes are identified at different production scales (Table 2).

Table 1
Fundamental preparation methods of micro-encapsulated systems [11].

Physical/chemical processes	Mechanical processes
Phase separation or coacervation	Spray drying
Interfacial polymerization	Spray cooling
Reticulation in suspension	Fluid bed
Thermal gelatinization	Electrostatic laying
Solvent evaporation	

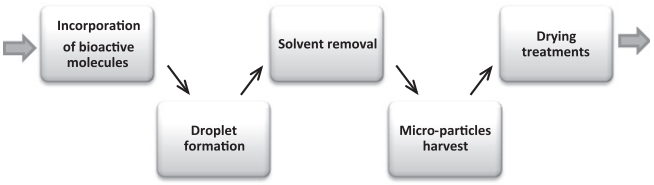

Fig. 1. Fundamental steps in microencapsulation process.

3. Process intensification

The current industrial scenery is founded on compromises based on the needs of the industrial processes developed to satisfy both the increasing market requirements and the mandatory rules in sustainable productions such as raw material/energy savings, respect of environmental constraints of industrial-scale processes [3]. In this frame, process intensification started as a new chemical engineering field in the past few years and is currently rapidly growing. It consists in looking for safer operating conditions, lower wastes and costs, higher productivity and developing of multifunctional devices [31]. It is difficult to refer to a unique and exact definition of the term process intensification; many literature papers agree on the following description [3,32]. Process intensification may be defined as a strategy that aims to achieve process miniaturization, reduction in capital cost, improved inherent safety and energy efficiency, and often improved product quality. Additional benefits of process intensification include simpler scale-up procedures and possibility to allow the replacement of batch processing by small continuous reactors, which frequently give more efficient overall operation [1,9]. The philosophy of process intensification has been traditionally characterized by four words: *smaller*, *cheaper*, *safer*, and *slicker* [33]. Wherever possible, aim of the intensification is to develop and use multi-functional modules for performing heat transfer, mass transfer, and separation duties (Fig. 2). Process intensification encompasses not only the development of novel, more compact equipments but also intensified methods of processing which may involve the use of ultrasonic and radiation energy sources [9].

To fine chemical and pharmaceutical industries, process intensification may offer a substantial shortening of the time-to-market, for instance by developing a continuous laboratory-scale process, which could be directly used as the scale of the manufacturing process. One must not forget that 1 g/s means about 30 tons/year in the continuous operation, which is a quite reasonable capacity for many pharmaceuticals. In such a case, the process development takes place only once, without any scale-up via pilot plant to industrial scale [33].

In this work, ultrasonic atomization techniques are the matter of discussion. Ultrasonic atomizers can be seen as tools for process

Table 2
Microencapsulation processes and their applicability.

Method name	Particle size, μm	Production scale	Process reproducibility	Time for preparation	Operation skill required
Air suspension	35–5000	Pilot scale	Moderate	High	High
Coacervation and phase separation	2–5000	Lab scale	Good	Less	Less
Multiorifice centrifugal	1–5000	Pilot scale	Moderate	High	High
Pan coating	600–5000	Pilot scale	Moderate	High	High
Solvent evaporation	5–5000	Lab scale	Good	Less	Less
Spray drying and spray congealing	600	Pilot scale	Moderate	High	High

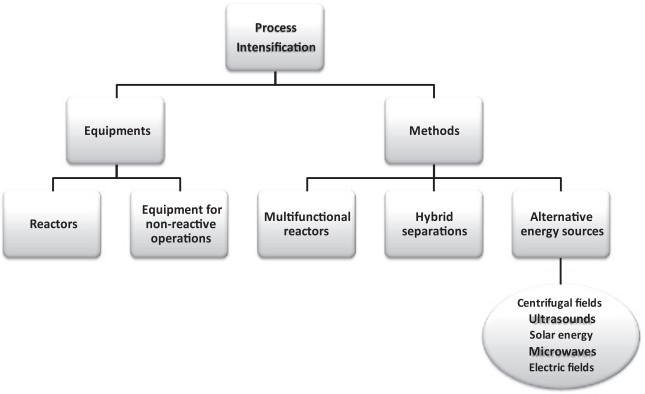

Fig. 2. Process intensification toolbox [33].

intensification since they require much less energy to produce droplets with respect to conventional atomization devices (pressure nozzle, centrifugal atomizer) because they operate involving low velocities. This feature responds to the need to reduce the energy request in manufacturing processes. In scientific and technical literatures, estimation data [34–36] of required energy involved in atomization processes of a given liquid flow rate are reported. The use of two fluid nozzles (atomization of a liquid assisted by a compressed gas) requires a volumetric power supply of about 41 MJm^{-3}, whereas centrifugal atomizer (in which the droplet was obtained because of the fast rotation of the feed) and pressure nozzle (in which the droplet was created by passing the pressurized feed into an orifice) require 33 MJm^{-3} and 12 MJm^{-3}, respectively (energy requirements: two fluids > centrifugal atomizer > pressure nozzle). The use of ultrasonic atomizer (droplets are achieved by spreading liquids onto a surface that is vibrated at ultrasonic frequencies), under defined conditions of volumetric flow rate, can further reduce the energy request around of 10 MJm^{-3}.

Moreover, low velocities in spray processes, in many cases, can address toward miniaturization of process chambers [37], reducing maintenance costs [38], and minimize denaturation risks due to thermal/mechanical stress of [39] sensible materials such as pharmaceuticals.

4. Microencapsulation processes based on ultrasonic atomization

4.1. Principles of ultrasonic atomization and advantages

Ultrasonic atomization is accomplished by several means: by focusing high-frequency ultrasonic energy on the surface of a liquid in a bowl shaped transducer (0.4–10.0 MHz), by ultrasonically vibrating a surface over which the liquid flows (18–100 kHz), or by feeding the fluid into the active zone of a whistle (8–30 kHz). Small droplets of a uniform size may be formed by feeding the fluid at a controlled rate through a small orifice in the tip of a horn vibrating ultrasonically in a longitudinal mode (Fig. 3) [40]. Vibration energy causes formation of liquid threads and then of droplets. Many literature references report studies that explain the liquid disintegration mechanism during ultrasonic atomization [41,42]. Cavitation and capillary wave mechanisms are the two rival theories that have been developed [28]. Cavitation phenomena occur at both high-energy intensity and frequency and are generated by the ultrasound wave as it passes through the liquid medium. Like any sound, the wave is transmitted as a series of compression and rarefaction cycles affecting the liquid molecules, thus generating voids (or cavities). These latter continue to grow in size until they become unstable, and then they violently collapse releasing energy to the liquid phase.

The capillary wave hypothesis is based on the so-called Taylor instability, that is, the atomization occurs when unstable oscillations split the peaks of surface capillary waves (capillary waves are composed by crests or peaks and troughs) away from the liquid bulk. Since the drops are produced from peaks, their sizes are proportional to the wavelength.

Use of ultrasounds in industrial processes has two main requirements: a liquid medium (even if in some applications, as, for example, in food industries, the liquid phase may be only 5% of the medium) and a source of high-energy vibrations, that is, ultrasound. The process parameters influencing ultrasonic liquid processing are *energy* and *intensity* (energy is defined as the energy

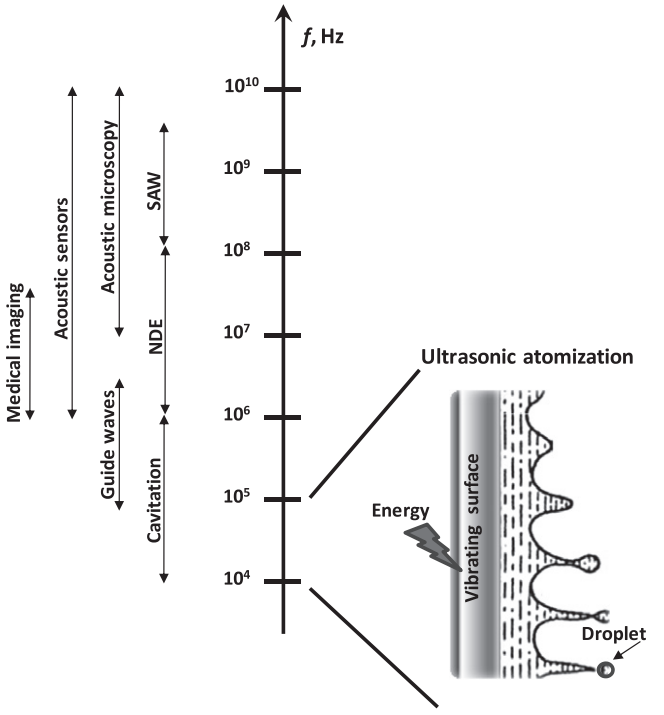

Fig. 3. Ultrasonic frequency ranges, kind of applications, and ultrasonic atomization mechanism sketch.

input per volume treated, whereas intensity is the actual power output per surface area of the sonotrode), *pressure, temperature,* and *viscosity*. Ultrasonic processing (or sonoprocessing) may lead to significant improvements in product quality, process enhancement, and cost reduction on a commercial scale, for several reasons, such as [38]:

i. availability of high amplitude/power units for large commercial operations;
ii. high efficiency of ultrasonic transducer (about 85%), with reduction in internal heating (absence of expensive cooling systems);
iii. ease to install and/or retrofit systems;
iv. competitive energy costs;
v. low maintenance costs, due to the absence of moving parts (the only part requiring replacement is the sonotrode, which is in direct contact with medium).

Globally, the use of ultrasonic devices appears to drive to flexible and robust processes.

Ultrasonic spray technology has been employed in industrial and research applications related to the electronics and biomedical areas, mainly for surface coating and liquid dispensing [42,43]. Popularity of the ultrasonic atomizer in such areas is mainly attributed to its ability to produce drops of small size and low inertia. Among ultrasonic atomization's advantages, velocity of drops produced from an ultrasonic atomizer is 1–10% larger than that of a hydraulic or air-atomizing nozzle. Mechanical stress caused by vibration is lower, avoiding deactivation of bioactive substances. Moreover, ultrasonic atomizer operates at low energy levels [41,39].

4.2. Apparatuses based on ultrasonic atomization

The ultrasonic atomization can overcome some disadvantages typical of traditional atomizers. Rotary, pressure or two-fluid atomizers use only a part of their operating energy (centrifugal, pressure, or kinetic energy) to shatter the liquid, while most of this energy is transformed into kinetic energy of the particles. As a consequence, some problems can arise, such as a partial separation of the components in mixtures, or presence of defects on the microparticles surface. Equipments dimension and cost increase when speed of the atomized particles increases [44]. Unlike conventional atomizing nozzles that rely on pressure and high-velocity motion to shear a fluid into small drops, ultrasonic atomizers use only low ultrasonic vibrational energy for atomization [45]. Moreover, association of ultrasound to spray drying is a powerful tool. In fact, spray drying is, in principle, a continuous process, giving a good reproducibility and potential for scale-up. Spray drying is widely used in pharmaceutical and biochemical fields and in food industry due to large availability of equipments and easiness of industrialization. It is also a mild "one-step" processing operation to move from a liquid feed into a powder product [46]. Disadvantages typical of a spray dryer using a pneumatic nozzle to generate aerosol are: lack of control over the mean droplet size, broad droplet distributions, and risk of clogging in the case of suspensions. They can be overcome by employing ultrasonic energy to obtain the generation of droplets with a relatively uniform size distribution [47]. Moreover, the spray congealing method assisted by ultrasounds easily yielded spherical microparticles with a good encapsulation efficiency and size distribution [48,49]. Therefore, ultrasonic atomization could be proposed as a robust and an innovative single-step procedure with scale-up potential to successfully prepare microparticles [50].

The review focuses, in the following, on applications of ultrasonic atomization processes reported in a selection of papers on microencapsulation appeared in the more recent scientific literature. In particular, encapsulation of proteins, nutritive substances, and drugs in polymeric structures are presented concentrating the attention on the benefits that ultrasonic apparatuses show in terms of both of innovation of spray devices and of features improvement of produced particles.

Bovine Serum Albumin (BSA) microspheres were prepared by an ultrasonic atomizer fitted to a spray dryer [47]. An atomizer with an air stream carrier was chosen in order to prevent a possible clogging. Used parameters for atomizer were: flow rate 0.1–1 l/h, mean droplet diameter 20 μm, passage 1.0 mm, working frequency 100 kHz. An emulsion of an aqueous solution of BSA into an organic polymer solution (Poly(D,L-lactide-co-glycolide)), PLG, in dichloromethane) was slowly fed to the atomizer using a peristaltic pump. The microspheres obtained were then lyophilized and stored under desiccation. The impact of a number of process and formulation parameters on particles properties was evaluated. Regardless of the technological parameters, spherical particles with a more or less smooth surface structure were obtained. The mean particle diameter of all batches was found to be about 10 μm. However, a decrease in polymer concentration led to smaller particles. In fact, at a constant atomizing energy, a larger amount of organic solvent in the feed reduced the forces of attraction between polymer chains, helping the formation of smaller droplets. Important features of the ultrasonic system are that the polymer molecular weight was not influenced by ultrasonic oscillations as well as the amount of BSA is not denatured and, therefore, available from the particles. So this microencapsulation process gave particle yields and encapsulation efficiencies in the same range as conventional spray drying, but without the disadvantages of clogging or broad droplets distribution typical of pneumatic nozzles. Moreover, a relatively lower initial protein burst release was observed in microparticles produced by ultrasonic atomization, confirming the advantages of this technique on the conventional one.

A similar process with similar materials was developed by Freitas and co-workers: a spray-drying technique was associated with ultrasonic atomizer, using reduced pressure rather than hot air drying [37]. Also, in this case, the great advantage of the ultrasonic nozzle is that the velocity of the ejected microdroplets is one to two orders of magnitude smaller than in pressurized nozzles, so that the drying chamber can be of shorter dimensions. Moreover, reduced pressure as driving force for solvent evaporation from microdroplets obviates the need for large quantities of sterile hot air and makes this method well suitable for aseptic microsphere preparation. A protein/polymer emulsion (BSA solution in a system done by a mixture of polylactic acid, PLA, and poly(lactic-co-glycolic acid), PLGA, in a solvent) was fed, by means of a syringe pump, to a 100 kHz ultrasonic spray-head. Yields above 80% by far exceed values usually obtained in conventional spray-drying equipment for microsphere batches: owing to the narrow-angled spray-cone of the ultrasonic spray-head and the lack of significant air movement in the dryer, only a very small fraction of microspheres actually came into contact with the vessel. Product yield decreased when the relative atomization power was increased from 30% to 90%. It seems that the increased oscillation amplitude impaired the spreading of fluid on the atomization tip of the spray-head. However, atomization power did not have significant influence on particle size. Reproducibility of the particle size distribution for repeated production was highly satisfactory: the mean diameter averaged 18.25 ± 1.05 μm. Larger particle sizes for more concentrated polymer solutions are reported for both conventional as well as ultrasonic spray drying, which has to be attributed to the increased viscosity of the more concentrated solution. Therefore, also in this case, the higher yield and the reduced dimensions of drops, and then of particles, guarantee the production of a good system with money saving.

Attempts toward a lower investment were done by Luz et al. who proposed the use of a simple and low-cost ultrasonic spray dryer system, in place of expensive commercially available equipments, to produce microparticles [51]. The equipment consisted of an ultrasonic atomizer, a tubular bendable furnace with two heating zones, as drying chamber, a micro-pored cellulose membrane supported on a sintered plate filter to collect particles, a vacuum pump to separate the dried material from air, and a filter flask located inside a vessel containing cold water to hold the condensed vapor. As a result, 60% of the atomized feed (dextrin aqueous solution) was collected over the membrane in a form of dried powder, thus the ultrasound spray drying system was considered efficient. The microparticles were spherically shaped, with a diameter ranging from 0.2 to 2.6 μm, confirming simplicity and efficiency of the coupling between ultrasonic atomization and spray drying.

Ultrasonic atomization was an useful tool also in the encapsulation of darbepoetin alfa, a synthetic form of glycoprotein hormone that controls red blood cell production, through spray freeze-drying and spray drying processes at a pilot scale [52]. A suspension of solid protein particles in polymer solution was atomized to form nascent microspheres in each process. In spray freeze-drying, the atomized spray was frozen in liquid nitrogen, followed by extraction of the polymer solvent in cold ethanol for hours to days. In spray drying, the polymer solvent was removed by evaporation; spray dried microspheres were further dried using carbon dioxide gas. The ultrasonic nozzles used for both processes produced droplets of comparable median diameter, about 60 μm or less, depending on the polymer kind, atomization power, and feed flow rate. Encapsulation efficiencies were very high, near 100%. The robustness of the ultrasound assisted process was demonstrated by the excellent reproducibility of physical and chemical characteristics of microspheres as well as of in vivo release kinetics.

Pulmonary delivery has also been a subject of interest for ultrasonic atomization process. In fact, it appears that although there is an optimal physical size of particles for nasal delivery, smaller particles, which are more easily obtained by ultrasonic atomization, are more efficient to transport drugs through the nasal mucosa. Particle size distribution measurements are critical during the development of nasal drug delivery systems and a suitable particle size will most likely be less than 20 μm. Small particles suitable for nasal delivery have been created via a number of other routes, but it has to be noted that ultrasonic atomization requires neither elevated temperatures nor phase separation inducing agents; therefore, it is an easily scaled and commercially viable particle production method giving micron and submicron monodispersed particles [53].

Biodegradable poly(D,L-lactide-coglycolide) (PLGA) microspheres containing polyethylenimine (PEI) condensed plasmid DNA (pDNA), suitable for nasal delivery, were prepared using a 40 kHz ultrasonic atomization system [54]. The production method was easily scalable to produce large quantities of microspheres. Moreover, microencapsulation of pDNA via ultrasonic atomization yielded microspheres with the majority of pDNA entrapped within the core and with very little surface localized pDNA, compared with the multiple emulsion method, that instead is a batch operation thus making large scale production difficult and expensive [55,15]. In conventional methods, encapsulation efficiencies will decrease due to a diffusion loss of the encapsulated compounds through the high surface porosity [56]. However, this phenomenon was not observed in the ultrasonic atomization method. This can be best explained considering that fast atomization rate can reduce the probability of loss for encapsulated compounds during the process when compared to the conventional methods [57,58].

There are also pressure and ultrasonic nozzles that are designed for 3-fluids (gas/liquid/liquid) and 2-fluids (liquid/liquid), respectively. When these nozzles are used for microencapsulation applications, inlet and wall material flow in separate channels and do not mix until they meet at the tip of the nozzle. Use of these nozzles eliminates the need for emulsion preparation prior to drying [29]. A coaxial ultrasonic atomizer is employed to produce a smooth coaxial jet comprising an annular shell (liquid flowing in the outer nozzle) and core material (liquid flowing in the inner nozzle), which is acoustically excited to break up into uniform core–shell droplets [59]. As the atomizer vibrates at an ultrasonic frequency, both liquids form a double layered film on the surface of the atomizer tip and are simultaneously fragmented into a large number of drops (Fig. 4). Collision occurs among drops in proximity, which is followed by a drop coalescence [39]. Fish oil was encapsulated in microcapsules: three nozzle types, a pressure nozzle with 1 liquid channel, a pressure nozzle with 2 liquid channels, and an ultrasonic atomizer with 2 liquid channels, were compared for their suitability to encapsulate fish oil in whey protein isolate [29]. Microcapsules produced by the 2-channel ultrasonic nozzle were observed to be more uniform in size and shape if compared to pressure nozzles. The ultrasonic nozzle showed a significantly narrower particle size distribution than the other nozzles. This study demonstrated that new ultrasonic nozzle designs can be a benefit for microencapsulation applications.

Park and Yeo presented a microencapsulation method using a coaxial ultrasonic atomizer based on interfacial solvent exchange [60]. In this system, PLGA solution in ethyl acetate, as external phase, and an aqueous solution containing optional solutes, as core phase, was separately fed into an ultrasonic coaxial atomizer. Microcapsules were collected in a water bath containing PVA as stabilizer and then were centrifuged and washed. When microparticles are collected in the water bath, it is important to efficiently disturb the water surface, otherwise films of polymer may accumulate on the surface, forming a solid layer that obstructs the entrance of the microcapsules into the bath. Generally, simple magnetic stirring can easily break the stability of the water surface, but also vibration of the bath, provided by an ultrasonic bath or by sonication probes, can be useful. Alternatively, the polymer solvent can be first removed by evaporation combining the solvent exchange method with spray drying. After the feed atomization into the drying chamber, where a stream of warm gas is introduced to evaporate solvent and to solidify microcapsules, separation of particles and gas can be performed in a cyclone attached to the drying chamber. The polymer solvent can be also removed by direct freeze-drying, when the active ingredient is sensitive to high temperature [39]. The ratio of flow rates of the two solutions (Q_{pol}/Q_{aq})

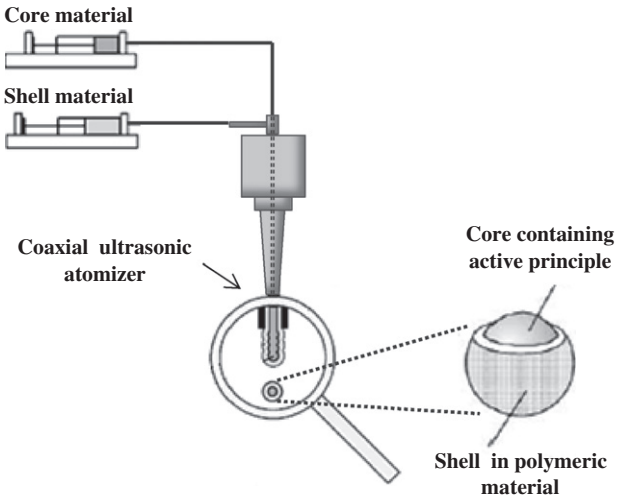

Fig. 4. Principles of coaxial ultrasonic atomization.

plays a significant role in determining the probability of collision between micro-drops of the two liquids. When Q_{pol} is larger than Q_{aq}, the aqueous drops can easily find the polymer partner, a thicker membrane is produced, and the coalescence between aqueous drops is avoided. Moreover, the aqueous drops, having a surface tension larger than polymer's drops, resist deformation and are encapsulated within the polymer drops. Both extremes of flow rates should be avoided, in fact, if flow rates are too low, the population density of the micro-drops is not high enough to collide with other drops. On the other hand, if flow rates are high, the size distribution tends to shift to a higher value. At last, it is preferable to use a large volume of collection bath to make a sink condition around the solvent exchange area. Besides discussions about the influence of formulation and process parameters on product quality, it is worth noting that ultrasonic atomization is characterized by only a brief exposition of the encapsulated materials, such as proteins, to the mild ultrasonic vibration. Moreover, the energy applied to the ultrasonic atomization is less than a few watts, which is far below a damaging level. Therefore, ultrasonic atomization is advantageous to process various protein formulations under mild conditions, avoiding denaturation.

Another example of use of multiple concentric nozzles to produce core–shell microparticles was proposed by Berkland et al. [59]. The goal of this work was to fabricate uniform double-walled microspheres comprising PCPH (Poly[(1,6-bis-carboxyphenoxy) hexane]) cores and PLG (Poly(D,L-lactide-co-glycolide)) shells designated PLG(PCPH), as well as PLG cores and PCPH shells designated PCPH(PLG). Therefore, a dual polymer jet was formed, pumping the two different polymer solutions (PLG or PCPH in methylene chloride) in the coaxial nozzles. An additional coaxial nozzle supplied a carrier stream, containing surfactant, which surrounded the emerging dual polymer jet aiding the break up of the jet and avoiding the drops tendency to recombine. The relative flow rates were varied in order to control core diameter, shell thickness, and overall particle size. Variation of the formulation parameters allowed complete encapsulation by the shell phase. The combination of coaxial nozzle with ultrasonic system allows the production of microspheres having a shell thickness from less than 2 μm to 10s of microns, keeping the complete core encapsulation.

Coaxial ultrasonic atomization was also used for the encapsulation of indomethacin, a non-steroidal anti-inflammatory drug, in PLGA [61]. Liquid feed in the inner tube consisted of a PLGA solution in dichloromethane containing indomethacin, and liquid feed through the coaxial outer tube consisted of only PLGA solution in dichloromethane. The PLGA within the outer layer deposited as a partial coating on the droplets containing the drug. The shell-core microparticles were collected in a surfactant-containing solution bath, under mixing to allow complete solvent evaporation. Results showed that the presence of a second liquid layer increases the encapsulation efficiency of drug, preventing drug loss during the solvent evaporation. Obviously, the smaller droplets size, deriving from the use of the ultrasonic atomizer, allows a larger surface exposed to the evaporation, reducing the time of particles production. Moreover, all the formulations consisted of a mixture of three different internal morphologies, that is, solid structure, one or more smooth and spherical particles within a hollow shell, and only hollow shell. In particular, hollow particles, having a smaller aerodynamic diameter, will have a great benefit for the pulmonary delivery, showing once again the usefulness of ultrasonic technology in several fields of the drug targeting.

An interesting apparatus of microencapsulation using ultrasonic atomization was proposed by Pilon and Berberoglu [62]. A tubular housing was coupled to a source of gas flow, such as a fan or a pressurized tank, to have laminar flow. The ultrasonic atomizer, which can also have a coaxial configuration, was mounted in the tubular housing, perpendicular to the gas flow. The capsules obtained were carried to an UV or to both UV and IR curing sections. Then, the cured microcapsules were collected in a collection chamber using either electrostatic attraction or an air filter. The microcapsules transport in the flow could be assisted by applying the same electric charge to the droplets and the walls of the housing channel to prevent both droplet coalescence and deposition on the walls of the flow channel. The apparatus showed some advantages on conventional encapsulation technologies. First of all, the elimination of collection and hardening baths reduces time and costs because filtering, washing, and drying steps become unnecessary. Another advantage of eliminating the collection bath is avoiding that some droplets, especially the small ones, once hitting the surface of a liquid can spread on the surface and loses their core–shell structure or their spherical shape. The use of a gas flow amplifies the capillary waves resulting from the ultrasonic vibrations, achieving tighter droplet diameter distribution and less consumption of ultrasonic power, thus preventing the degradation of some materials, such as cells and bacteria. A special treatment of the capsule surface can be also obtained by selecting the gas flowing in the housing channel. Moreover, use of an UV chamber in the apparatus allows either polymerization of shell material, as monomer, or polymer hardening by solvent evaporation, around a water-soluble core, when water/oil emulsion is atomized. Therefore, thanks to the combination of alternative source of energy, such as ultrasound and UV, high pressures and temperatures are not needed anymore.

5. Conclusions

The examined papers on microencapsulation assisted by ultrasonic energy confirmed the interest in continuing investigations on the encapsulation process owing to the number of possible ways to perform the production of microsystems and to the large number of parameters influencing each process. Different approaches are followed the target always being to produce microparticles with desired dimension and size distribution, according to their specific applications.

The use of ultrasonic devices in many researches emphasizes the new approaches in terms of energy optimization in pharmaceutical manufacturing. Ultrasound applications have a long history in industrial and medical fields mainly related in power uses (cleaning), electronics and biomedicals (diagnostics). Nowadays, the expansion of interest in spray sonoprocessing is, undoubtedly, the result of the need to move toward intensified preparing methods. In fact, despite the large amount of experimental work done, further researches devoted both to the design and to the optimization of single-pot ultrasonic assisted processes to produce microparticles under controlled conditions could offer a new step of innovation.

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