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Technological solutions for encapsulation

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Abstract:
Encapsulation offers broad scope of applications. It can be used to deliver almost everything from advanced drugs to unique consumer sensory experiences; it could be also employed as a protection system or a sensing material. This cutting-edge technology undergoes rapid growth in both academic and industrial conditions. Research in this matter is continuing to find a new application of microcapsules as well as to improve the methods of their fabrication. Therefore, in this review, we focus on the art of the encapsulation technology to provide the readers with a comprehensive and in-depth understanding of up-to-day development of microcapsule preparation methods. Our goal is to help identify the major encapsulation processes and by doing so maximize the potential value of ongoing research efforts.

Keywords: encapsulation technologies, microcapsules, polymerization reactions
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1 Introduction

According to science, encapsulation, developed roughly 65 years ago, is a major interdisciplinary research technology [1]. In general, capsules are circular cross-section shape particles with certain free volume inside, where a core material can be allocated. As shown in Figure 1, the core material can be also called an internal phase, a filler, a matrix or an active. Encapsulation may be as well explained in the frames of supramolecular chemistry as a process where a guest molecule is confined inside the cavity of a host and leads to the formation of a capsule. Capsules with a diameter size between 1 nm and 1,000 nm are named nanocapsules, while the capsules with a size rage 1–1,000 μm and above (> 1 mm) are called microcapsules and macrocapsules, respectively [2, 3].

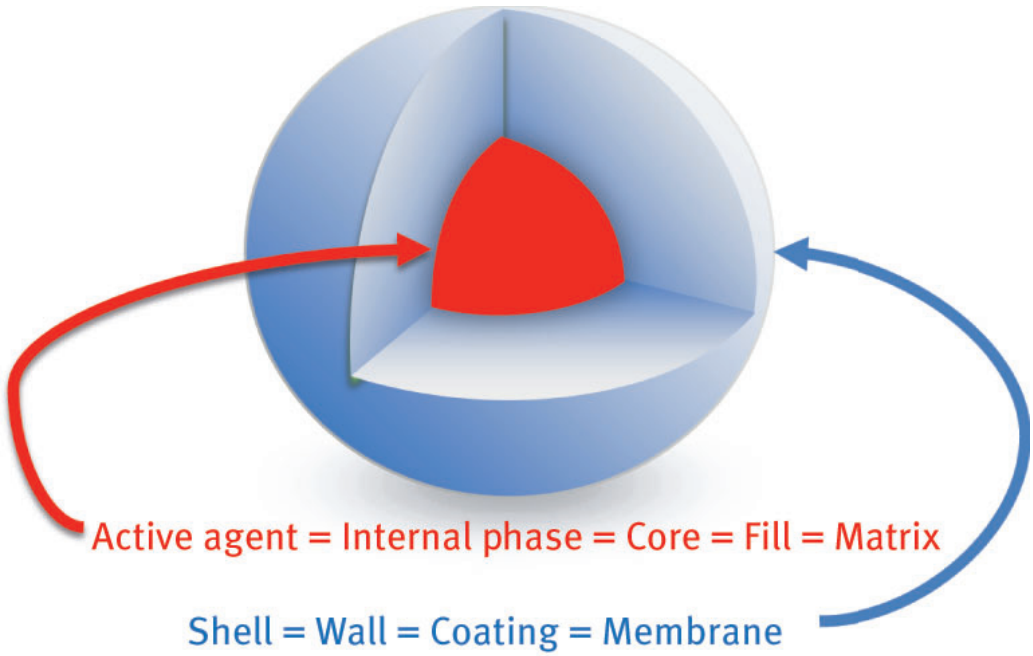

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Figure 1: Microcapsule.

Capsules can exhibit different morphologies depends on a material used for their fabrication, although also the preparation technique has a significant impact on their final outcome [4]. Depending on the structure of the capsules, they can be characterized as continuous core/shells, polycore capsules, continuous core capsules with more than one layer of shell material and the matrix type, where encapsulated agent is incorporated within the shell material. Representation of aforementioned structures of the capsules is shown in Figure 2[5]. Relying on the preparation method used, different morphologies are formed. Rough approximation of the capsule's size range obtained by each technique is presented in Table 1.

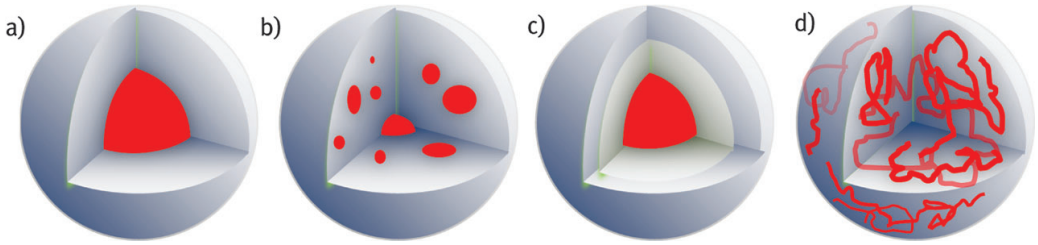
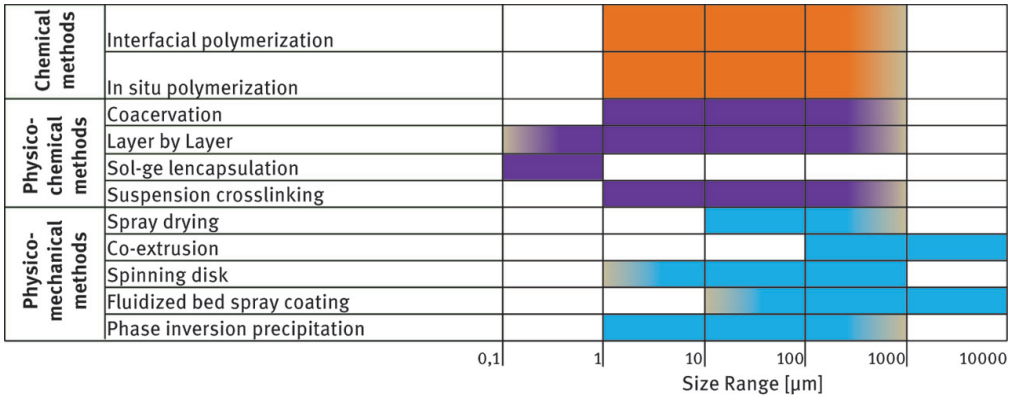


Figure 2: Microcapsules morphologies: (a) continuous core/shells, (b) polycore capsules, (c) continuous core capsules with more than one layer of shell material, and (d) the matrix type capsules.

Table 1: Capsules size range determined by the preparation technique



Encapsulation is a dynamic research field due to novel technologies, production paths and demand for innovative applications. Running a search on "encapsulation", over 80,000 records can be found up to date, by the use of Web of Science tool (Figure 3). Since 1953, when Green and Schleicher patented the first method for microcapsule preparation, different techniques for microcapsules fabrication have been developed.

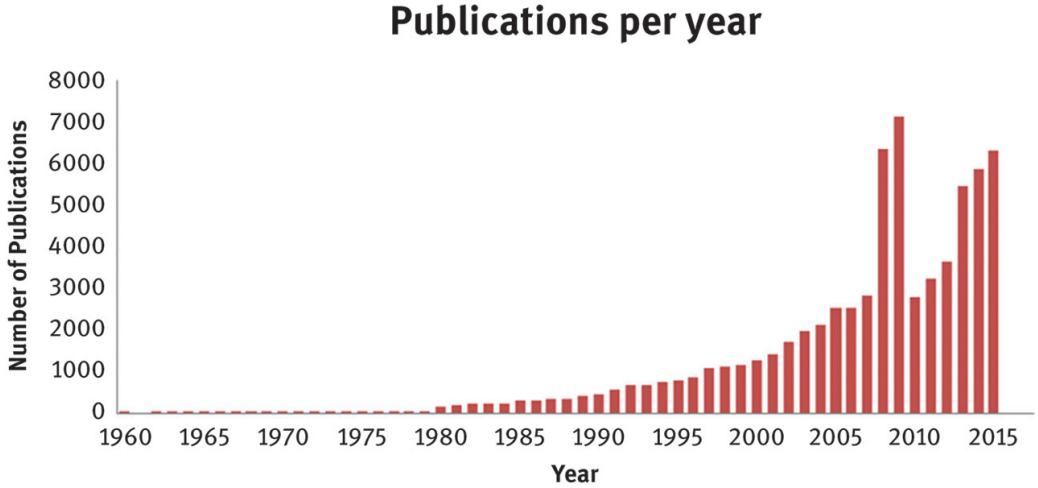


Figure 3: Publications per year on "encapsulation" (tool used: Web of Science, May 2016).

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This review does not pretend to cover the abundant published literature on the subject, but to be representative of the observed tendencies in capsule fabrication for consumer good products, medicine, food chemistry, agriculture, etc. The first part of this review is dedicated to describe chemical methods, such as interfacial polymerization and *in situ* polymerization (suspension, emulsion, dispersion polymerization), while the second one provides detailed information about physicochemical methods, such as coacervation, layer-by-layer (LbL) assembly, sol–gel encapsulation and suspension cross-linking. Finally, we will dedicate the third part to describe physicomechanical methods, such as spray-drying, co-extrusion and phase-inversion precipitation.

2 Chemical methods

Chemical methods involve sphere fabrication along with various polymerization reactions. This indicates that the starting materials in these cases are monomers or prepolymers. Further subdivision of these techniques along with a short description is detailed below [6].

2.1 Interfacial polymerization

Generally, the interfacial polymerization employs two monomers to react at the interface of a droplet, which lead to the formation of a capsule, as shown in Figure 4[7, 8]. [9]. The first to report interfacial polymerization technology was an American polymer scientist – Dr. Morgan from Dupont Nemour Company – who together with his research group published a series of articles in 1959 [10–13]. A few years later, the technology has been expanded, and since 1960 this method has been widely employed for encapsulation; however, the first patent that describes the basic methodology of this process was filled-in by Beestman and co-inventors in 1983 [14]. Since then, the method has been improved significantly.

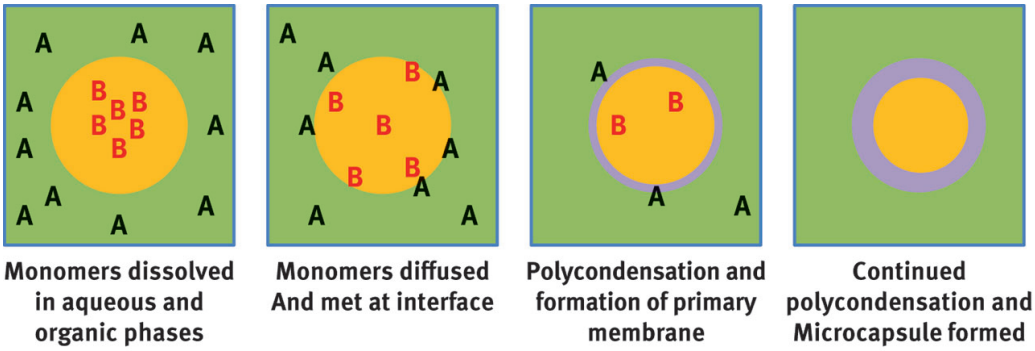

Figure 4: Graphical simplification of interfacial polymerization general procedure.

Interfacial polymerization's tunable conditions make it applicable to various camps, e. g. agrochemicals, self-healing, pharmaceutics and cosmetics. Mainly four groups of polymers have been considered by researchers utilizing this technique: polyamides, polyurethanes, polyureas and polyesters [15]. Interfacial polymerization can be classified as a relatively simple, flexible and low-cost methods; thus, it is a valid method for industrial capsule manufacturing. Nevertheless, it seems that the process is still not well understood, e. g. the effect of the temperature, catalyst, surfactant and active ingredient are not entirely clear [16, 17]. One of major advantages of the interfacial polymerization techniques is its controllable character. Capsule mean size and membrane thickness can be directly designed. For instance, an interesting method of emulsification by the use of micropore metal membranes was proposed by Richard Holdich and his group [18]. The authors were able to directly control the size and homogeneity of the produced droplets, which were the matrices for the capsule shells.

Tylkowski et al. [19] fabricated microcapsules based on a new liquid crystalline lightly cross-linked polyamide, in which the state of order can be triggered by means of external stimuli, such as temperature and light. Figure 5 shows the scanning electron microscope (SEM) image of microcapsules prepared by the authors with toluene as a filler, deposited on a millipore teflon filter and dried at room temperature. The microcapsules appear separated, well-formed and globe shaped but deflated. According to the authors, this evidence can be related to the entrapped toluene evaporation in the high-vacuum conditions (10×10^{-2} mbar) employed in sample preparation. Figure 5(b) shows the SEM image of one of the microcapsules after fracturing in liquid nitrogen, while Figure 5) shows the details of the fractured surface. The outer surface appears smooth and dense

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and few heterogeneity can be seen on the inner face. In the case of other polyamide capsules synthesized by the authors, one side of the shell appeared smooth, while the other one possessed a cellular structure [20]. An explanation for the dissymmetric structure of this kind of shell structure was proposed by Janssen and Nijenhuis [21, 22]: the wall of the capsules consists of a polymer formed by a polycondensation reaction at the oil/water interface; at or close to the organic side of the interface the reaction between monomers takes place and the polymer precipitates at the interface. This results in the production of a thin top layer of polymer, through which water and hydrophilic compounds (such as the diamine) can diffuse; as a consequence, the monomers proceed reacting under the formation of the sub-layer. The above-mentioned authors observed, in an oil-in-water dispersion, the appearance of little droplets which coalesce on the organic side of the membrane which is filling with water. This phenomenon is stopped by the polymer precipitation at their surface, which leads to the formation of a cellular inner structure; the longer the reaction time, the more heterogeneous is the inner surface of the membrane: for reaction times lower than 3 h, as in our case, the internal and external surfaces were found relatively homogeneous and smooth [23]. Incorporation of azobenzene photosensitive molecules into a capsule shell has also been performed by Marturano and co-workers [24]. The authors reported for the first time a straightforward route for the preparation of solid shell polymer nanocapsules with controlled UV-triggered release. A miniemulsion interfacial polymerization technique has been employed by the authors to prepare lightly cross-linked polyamide capsules with a hydrophobic liquid core. Based on the presented data, it can be concluded that an appropriate selection of surfactant type, its concentration and processing conditions allowed tailoring the size of the resulting nanocapsules. Podshivalov et al. [25] have studied an influence of agitation speed on the size of the capsules obtained by the interfacial polymerization process. The authors have utilized polyuthane–urea microcapsules containing galangal essential oil as a filler. The investigators performed the polymerization at the oil–water interface in oil–water emulsion. According to the authors, threshold value of agitation speed (4,000 rpm/min) was a decisive condition of the microcapsule size. Moreover, they reported that at higher agitation speed, the break-up of oil droplets strongly increases. As expected, higher agitation rate resulted in smaller size of microcapsules and with a narrower size distribution. A new type of poly(vinyl alcohol)(PVA)–polyurea composite microcapsules, containing isophorone diisocyanate as a core material, has also been successfully prepared via PVA-mediated interfacial polymerization in an oil-in-water emulsion by He and co-workers [26]. The authors reported a facile and versatile preparation protocol of robust microcapsules by using commercial and cost-effective raw materials. Prepared spherical microcapsules with a core content of ~80 wt% exhibited reliable service life and water resistance. Furthermore, the authors reported that investigated microcapsules possess enough mechanical stiffness for postprocessing. As stated in the publication, designed microcapsule shells were able to rupture when the crack approached, releasing the self-healing agent for crack healing. According to the authors, developed microcapsules exhibit remarkable performance for corrosion protection, and they could be used in structural materials with the ability to atomically heal cracks.

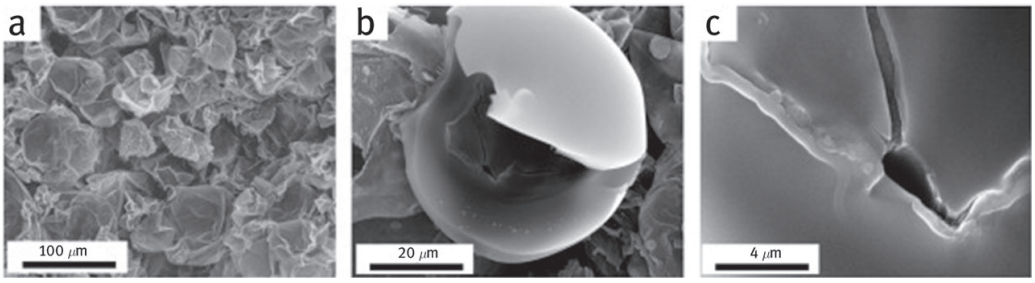

Figure 5: SEM micrographs of: (a) polyamide microcapsules containing toluene as a filler; (b) a single microcapsule after fracturing in liquid nitrogen; and (c) detail of the fractured surface. Wall thickness: 180 nm. Reprinted from European Polymer Journal, 45/5, Bartosz Tylkowski,Malgorzata Pregowska,Emilia Jamowska,Ricard Garcia-Valls,Marta Giamberini, Preparation of a new lightly cross-linked liquid crystalline polyamide by interfacial polymerization. Application to the obtainment of microcapsules with photo-triggered release, 1420-1432, Copyright (2009), with permission from Elsevier.

2.2 *In situ* polymerization

In situ polymerization is a broad concept that includes: (1) suspension polymerization, (2) emulsion polymerization and (3) dispersion polymerization. The literal translation of *in situ* means "in place," which in terms of polymer science means in reaction mixture. Both the chemical methods presented in this review – interfacial polymerization and *in situ* polymerization – include polymerization reactions; however, in case of the *in situ* polymerization monomer or prepolymer are present only in the single phase of the reaction mixture, whereas in the interfacial polymerization each of the liquid phases contains at least one reactive monomer [6]. A clear

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division among the terms "suspension," "emulsion," "dispersion," and "precipitation" as used in reference to heterogeneous polymerization systems was proposed by Arshady [27].

2.2.1 Suspension polymerization

The term suspension polymerization was very well-defined by Vivaldo-Lima and co-workers [28], who described it as a process in which monomer or monomers, relatively insoluble in water, is (are) dispersed as liquid droplets with steric stabilizer and vigorous stirring (which is maintained during polymerization) to produce polymer particles as a dispersed solid phase. Initiators soluble in the liquid monomer phase are employed in this polymerization process. In case when particle porosity is not required, the suspension polymerization is also known as pearl and bead polymerization. The main challenge in this technique is the formation of an as uniform as possible dispersion of monomer droplets in the aqueous phase with controlled coalescence of these droplets during the polymerization process. Based on the data collected by Vivaldo-Lima and co-workers, the microcapsule fabricated by this process typically have diameters in a range of 10 μm to 5 mm, which are strongly influenced by the following parameters: the interfacial tension, the degree of agitation and the design of the stirrer/reactor system govern the dispersion of monomer droplets. Moreover, the presence of suspending agents (e. g. stabilizers) hinders the coalescence of monomer droplets and the adhesion of partially polymerized particles during the course of polymerization, so that the solid beads may be obtained in the similar spherical form in which the monomer was previously dispersed in the water phase. Commercially available beads with a size above 10 μm can be easily separated from the suspension by filtration or/and sedimentation and then applied as a part of a final commercial products [29].

A very interesting paper was published by Sánchez-Silva et al. [30] in which the authors compared a laboratory scale and a pilot plant conditions for suspension-like polymerization process for the microencapsulation of paraffin wax by polystyrene. The authors carried out both designed experiments in water using polyvinylpyrrolidone, as a suspension agent, and benzoyl peroxide, as an initiator. According to the researchers, the suspension-like polymerization is an easy and an efficient method for microcapsule production at both scales. However, the scientists strongly underline that the condition of the reaction requires high temperature (108 °C) and 6 hours to complete the reaction, not counting the time required for the maintenance of the experimental setup.

Another impressive example of suspension polymerization microencapsulation was reported by Supsakulchai, Nagai and Omi [31]. The scientists encapsulated inorganic materials, such as titanium dioxide (TiO_x), in polystyrene-based matrix. In a frame of the presented project, the authors first prepared an emulsion by glass membrane emulsification process, then they performed polymerization step and finally they recover capsules by centrifugation. To favor the TiO_2 dispersion stability in the oil phase, the authors applied two strategies. The first one was based on an addition of a co-monomer, 2-ethylhexyl acrylate, while the second one was created by adding the same co-monomer, however, in the presence of a cross-linking agent, such as a divinyl benzene. It should be mentioned that by using both the approaches the authors obtained uniform composite particles with the average diameters in a range 20–25 μm. The method used by the authors allows mass production in one batch, easy modification of the capsule walls, flexibility of monomer selection and cross-linked polymers applicable as advantages and undesirable sub-micron aggregates and the possibility of phase separation during the polymerization step as the process drawbacks.

2.2.2 Emulsion polymerization

Emulsion polymerization occurs when monomer is added dropwise to the solution of core material and surfactant (emulsion). Katampe et al. [32] have used this type of encapsulation technique to fabricate microcapsules by enwrapping an oily core material in an amine–formaldehyde condensation product formed by *in situ* polymerization. Their invention included a synthetic viscosity modifier (cross-linked polymer of acrylic acid) which was added to the aqueous phase of the oil-in-water emulsion. According to the investigators, this component allows the production of a more uniform, controlled, relatively small-size microcapsules. Bonetti et al. [33] optimized the semicontinuous emulsion polymerization protocol to synthesize poly(*n*-butylacrylate)@polystyrene nanocapsules. The authors developed a novel variation of the emulsion polymerization encapsulation, which includes two-step process. First, the core-forming monomer was emulsified in a continuous phase. Subsequently, the polymerization of the nanodroplets was initiated by 2,2-azobisisobutyronitrile and the second monomer was added (during a second step). The authors highlighted that by employing these biologically friendly solvent method (by using i. e. water), they got microcapsules with a size diameter in an order of 10^2 nm.

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2.2.3 Dispersion polymerization

Dispersion polymerization takes place when the monomer, initiator and dispersant are present in the same batch. Great influence in this process has a solvent, which needs to be sufficient for all aforementioned substrates but it does not dissolve a produced polymer; thus the polymer will precipitate in it [34]. Lee et al. [35] patented the microencapsulation of a pigment dispersed with a polymeric dispersant and a polymerization initiator in an aqueous solvent system. The innovation of the presented patent based on two or more additions of monomers led to the polymerization and subsequent thicker shell formation. According to the authors, two (or more)-step dispersion polymerization technique provides microcapsules with high amount of encapsulating polymers around the pigment, thus with improved mechanical properties in comparison to the one-step dispersion polymerization technique. Bourgeat-Lami and Jacques Lang [36] have employed dispersion polymerization to encapsulate silica beads with styrene in an aqueous ethanol medium using poly(*N*-vinyl pyrrolidone) as a stabilizer and 2,2-azobis (isobutyronitrile) as an initiator. To promote encapsulation on the surface of the beads, the authors treated the silica with 3-(trimethoxysilyl) propyl methacrylate, which was grafted onto its surface. Polymerization reaction was performed in a batch process, in the ethanol/water mixture. Silica beads that gave the most satisfactory results had 450 nm of diameter; nevertheless, even the synthesis that utilized those beads led to the creation of the composites that contained more than one silica bead per composite. Mostly, the composites contained up to four silica beads. Micrometer-sized silica-stabilized polystyrene latex particles and submicrometer-sized polystyrene−silica nanocomposite particles have been prepared by Schmid and co-workers [37]. The investigators used the dispersion polymerization of styrene in alcoholic media in the presence of a commercial 13 or 22 nm alcoholic silica sol as the sol stabilizing agent. The authors reported that micrometer-sized near-monodisperse silica-stabilized polystyrene latexes were obtained when the polymerization was initiated by a nonionic initiator (2,2-azobisisobutyronitrile), while submicrometer-sized polystyrene–silica nanocomposite particles were produced by using a cationic azo initiator. At the end of the process, the particles were transformed into core/shell microcapsules by a calcination as illustrated in Figure 6.

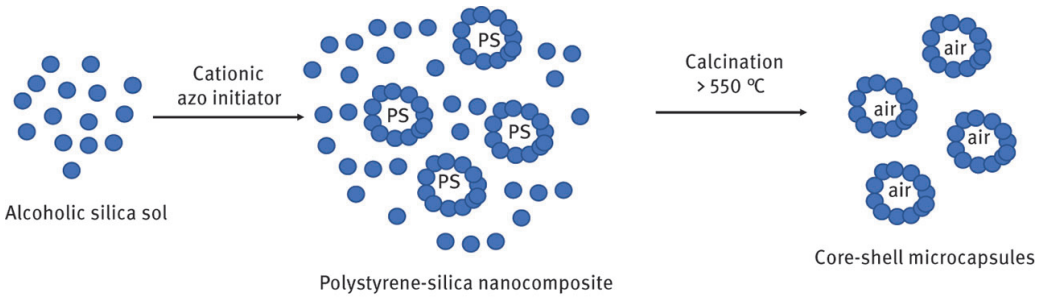

Figure 6: A schematic representation of submicrometer-sized polystyrene–silica nanocomposite particles production and their transformation into core/shell microcapsules by a calcinations.

3 Physicochemical methods

Physicochemical methods involve procedures where chemical interaction occurs along with various physical transformation to shape the capsules.

3.1 Coacervation

Coacervation is the first method concerning encapsulation technology protected by an international patent law. This pioneer method was developed and described by Green & Schleicher, from the National Cash Register Company, Dayton, USA, who in 1953 filled in a US Patent# 2730456 by a title: Manifold record material. The inventors encapsulated trichlorodiphenyl inside microscopic gelatin capsules by coacervate forces. Since then, the coacervation has been defined as a process in which "an active agent is distributed within the homogenous polymer solution, and by triggering coacervation colloidal polymer aggregates (coacerates) are formed on the outer surface of an active agent droplet." The process can be initiated by varying one or more of parameters of the system, such as temperature, pH or the composition of the reaction mixture (addition of water-miscible nonsolvent or salt). In case of the aforementioned patent, the coacervation was initiated by the addition of sodium sulfate salt.

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Coacervation techniques are divided into two subgroups, which differ in the mechanism of the phase separation:

- simple coacervation – occurs when a selected polymer for microcapsule preparation is salted out or desolvated.
- complex coacervation – is achieved by a complexation of two or more oppositely charged polyelectrolytes. The method is presented schematically in Figure 7. It is a four-step process: (A) dispersion of the core material in homogenous two-different-polymer solution, (B) initial agglomeration of polyelectrolytes after triggering the coacervation, (C) coacervation of polymer on the surface of the core and (D) wall hardening.

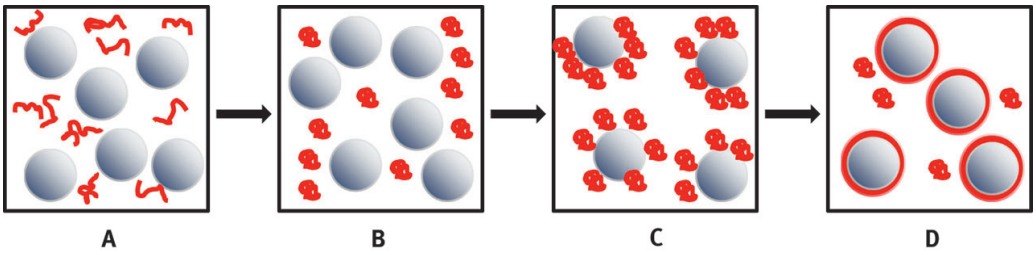

Figure 7: Schematic overview over the principal process steps in the capsules production by complex coacervation.

During the last decades, several different research groups have improved the complex coacervation method. Dardelle and co-workers [38] have modified it to produce capsules with improved barrier properties for encapsulated material. First, the authors mixed selected polymers with various types of solid particles (kaolin, silica, Fe_2O_3). Then, they introduced a core material to the particle/polymer complexes, and the obtained hybrid coacervate sol gained a desired viscosity that allowed the aggregates to deposit on the core material to form the capsule shell. In other respects, Kumar et al. [39] patented a novel coacervation process in which the core material/polymer complexes were exposed to one or more coacervation agents in at least two distinctive stages. In this way, the inventors were able to produce capsules with a consistent particle size using easily scalable process. Baker and Ninomiya [40] developed a complex coacervation method, in which to achieve high core-content capsules and avoid unwanted agglomeration, the authors introduced two additional steps. First, they mixed a core material with a coacervation adjuvant (such as an ionizable colloid, an ionic surfactant, or an ionizable long-chain organic compound) prior to emulsification process, and then, after gelation step, the authors introduced a water-soluble wax that initiated hardening of produced capsule walls. Based on numerous published articles and reviews [41–44], it could be summarized that the coacervation processes during the last years became a widely used encapsulation method, due to their simplicity, low cost and reproducibility. Moreover, these methods can be easily scaled-up to fabricate microcapsule at the industrial setup. Nevertheless, these techniques need a constant attention and an adjustment of operating conditions (such as stirring, viscosity, pH and temperature). Besides, by using these methods, unwanted capsule agglomeration has been commonly observed.

3.2 Layer by layer

LbL assembly method was for the first time reported by Caruso & Crusco and Möhwald in 1998 [45]. The method was based on the self-assembling of oppositely charged polyelectrolytes on the outer surface of colloidal particles. The inventors prepared hollow silica and silica–polymer spheres with diameters between 720 and 1,000 nm by consecutively assembling silica nanoparticles and polymer onto colloids and subsequently removing the templated colloid either by calcination or by decomposition upon exposure to solvents. Scanning and transmission electron microscopy images reported by the authors demonstrated that the wall thickness of the hollow spheres can be readily controlled by varying the number of nanoparticle–polymer deposition cycles. Moreover, the authors stated that the capsule size and shape can be determined by the morphology of the templating colloid. The LbL technique can offer capsules with a broad permeability coefficient spectrum that can be tailored depending on the desired application, which includes biosensor, catalyst, agriculture, drug carrier, etc. Active targeting of nanoscale drug carriers can improve tumor-specific delivery; however, cellular heterogeneity both within and among tumor sites is a fundamental barrier to their success. Promising studies in this field have been carried out by Dreaden and co-workers [46], who described a tumor microenvironment-responsive LbL polymer drug carrier that actively targets tumors based on two independent mechanisms: (1) pH-dependent cellular uptake at hypoxic tumor pH and (2) hyaluronan-directed targeting of cell-surface CD44

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receptor – well-characterized biomarker for breast and ovarian cancer stem cells. Hypoxic pH-induced structural reorganization of hyaluronan–LbL nanoparticles was a direct result of the nature of the LbL electrostatic complex and led to targeted cellular delivery *in vitro* and *in vivo*, with effective tumor penetration and uptake.

As illustrated in Figure 8, the nanoscale drug carriers selectively bound CD44 and diminished cancer cell migration *in vitro* while co-localizing with the CD44 receptor *in vivo*. Because these LbL nanoparticle systems are simple, provide means of modular design and can provide enhanced blood half-life and enhanced tumor targeting, hyaluronan–LbL nanoparticles are promising candidates for targeted drug delivery to solid tumors for number of significant cancer types. The ability to target multiple tumor cell populations without the use of additional drug carrier may circumvent resistance from selective pressure while improving safety and treatment outcomes from actively targeted nanomedicines.

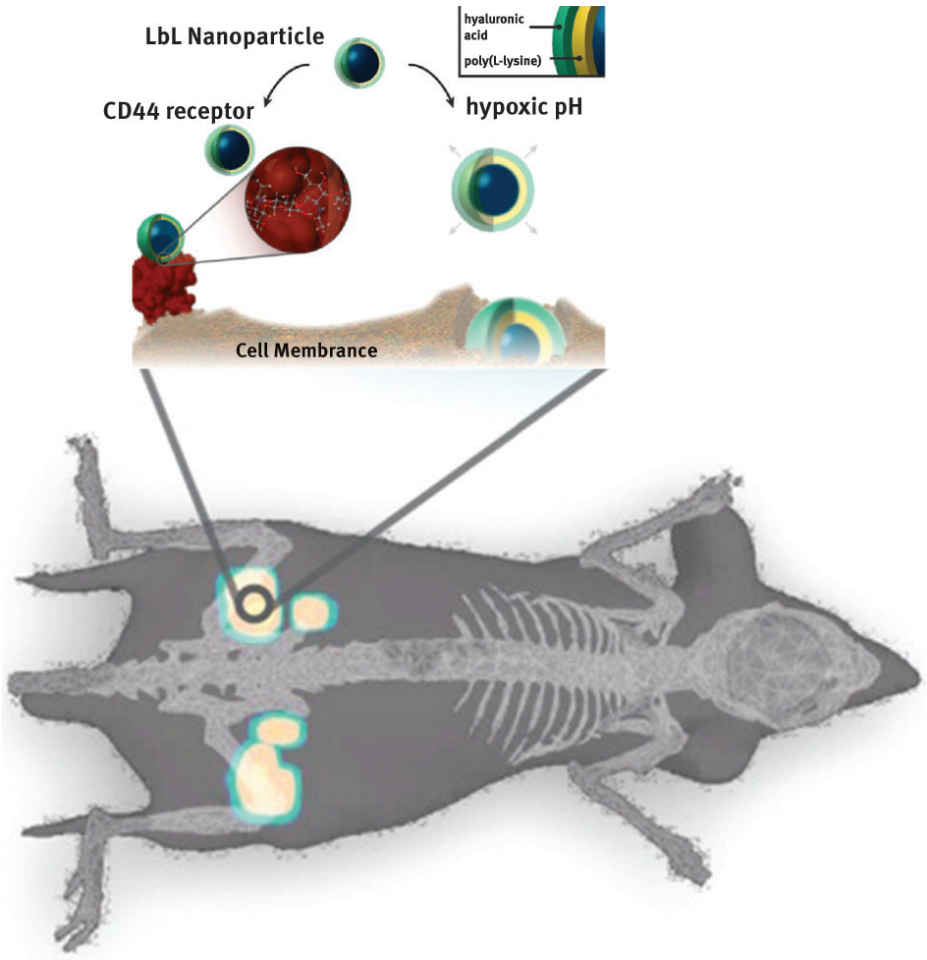

Figure 8: Schematic illustration of bimodal tumor targeted delivery.

Tao, Li and Möhwald [47] reported that LbL capsules containing an azo dye in their shell permitted photochemical control of the permeability of the capsule wall. In this investigation, the microcapsule shell was built by an azo dye – Congo red (CR) – and different polymers, including poly(styrenesulfonate, sodium salt) (PSS), poly-(allylamine hydrochloride) (PAH) and poly(diallyldimethylammonium chloride) (PDDA).

Figure 9 illustrates the general protocol which have been used for the LbL self-assembly of PDDA/CR onto the (PSS/PAH)3/PSS shells templated on melamine formaldehyde (MF) latex particles. In order to analyze morphology change of the microcapsule shell before and after irradiation caused by trans-cis photo-isomerization of azobenzene moieties incorporated in the capsule shell, the authors employed scanning force microscopy (SFM). Furthermore, the optical changes of the capsules were verified by using confocal laser scanning microscopy and SFM. All results generated by the authors provide useful insights into the photochemical reaction mechanisms on the self-assembled PDDA/CR composite capsules and release of encapsulated material. This kind of capsule with photo-controlled permeability could be of particular interest for applications in drug delivery, photocatalysis, optical materials and related medical areas such as photodynamic therapy or skin care. The concept of photosensitive microcapsules has also been studied by Bédard and co-workers [48] who constructed the microcapsules containing azobenzene moieties through LbL self-assembly of sodium salt of azobenzene, poly(vinylsulfonate) and PAH; however, contrary to Möhwald and co-workers, they investigated how *trans-cis* isomerization of the azo moieties influences the permeability changes of the shell and on encapsulation of the

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active material instead of its release during light irradiation. According to the authors, incorporation of azobenzene groups can cause shrinking of the microcapsule wall, increase their permeability and as a consequence encapsulate required materials. More recent examples using stimuli-responsive capsules based on azobenzene moieties in the capsule wall are deeply contemplated in [49].

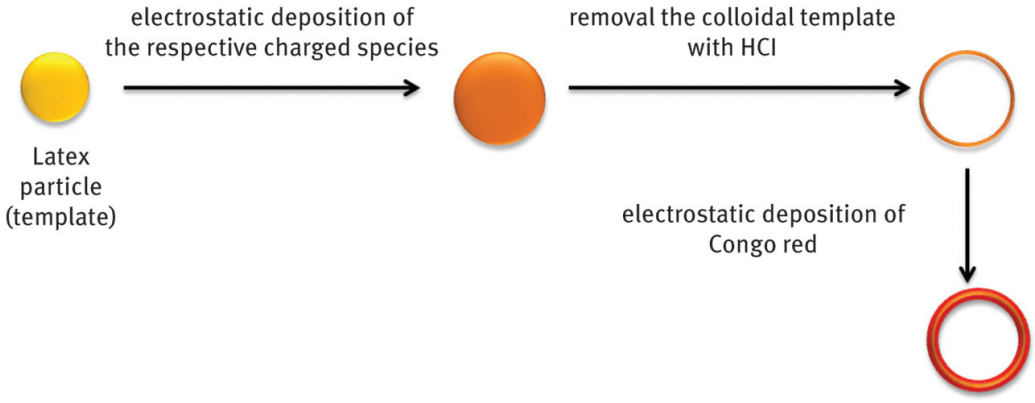

Figure 9: General procedure for the fabrication of hollow LbL self-assembly capsules composed of PDDA/CR onto the (PSS/PAH)3/PSS shells templated on the MF latex particles.

Very interesting approaches have been performed by Hammond and Zhiyong [50] who designed nanosized capsules that exhibit a multifunctionality. The authors used (1) gold nanoparticles as core materials – which act as imaging and drug revisers and (2) therapeutic agents – which are allocated within 2 nm sized LbL capsule wall.

LbL assembly is an extremely valuable, economic and versatile technique for capsule formation. Final material properties can be easily tailored through the thoughtful selection of the active agent, coating material and assembly conditions. LbL as much as it is beneficial has one current limitation which is the standard manual, where numerous time-consuming centrifugation and resuspension are needed to perform the layering steps. Björnmalm et al. [51] overcome this problem introducing a novel fully flow-based technique using tangential flow filtration, which can make the process scalable, controllable and automatable production.

3.3 Sol–gel encapsulation

Sol–gel encapsulation is an abbreviation for "solution-gelling." The term stands for the process where sol is added to the precursor solution, and by alternating physicochemical factors the material is gelled and hardened into the shape of the capsules [52]. Broadly speaking, sol–gel processes can be divided into six steps: hydrolysis, condensation, gelation, ageing, drying and densification [53]. Sol–gel encapsulation techniques have been widely used [53–56]; however, in this review, we focus on the capsules prepared by the use of organosilanes which are extensively studied nowadays due to their surface functionalities and processing conditions (pH, gelation time, etc.). Organosilanes are also compatible with various biomolecules, such as drugs, proteins, antibodies, enzymes, nucleic acids, prokaryotic and eukaryotic cells, which makes silica and its derivatives a suitable capsule material for bioapplications. The most studied sol–gel methods for encapsulation of biological materials, which have been reported in literature, are hydrolysis and condensation of alkoxides, such as tetramethyl orthosilicate or tetraethyl orthosilicate [57–59]. The conventional routes can lead to decrease or total inhibition of the activity of entrapped biomolecules, due to the formation of an alcohol as a byproduct. Bhatia et al. [60] developed an aqueous sol–gel process in which sodium silicate was used as a precursor and the gelation phase was performed at neutral pH and room temperature. By applying the designed methodology, the authors were able to preserve the activities of encapsulated enzymes: high horseradish peroxidase and glucose-6-phosphate at values of specific activity upon immobilization 73 % and 36 %, respectively, after encapsulation. Moreover, the authors reported that encapsulated enzymes exhibited a pH-dependent behavior that is different from that of free enzymes. According to the authors, the silica matrixes offer a number of advantages over conventional organic polymers as immobilization platforms for biosensors owing to their superior mechanical strength, chemical inertness, hydrophilic nature and, above all, optical transparency.

Mikosch and Kuehne [61] have established experimentally optimized conditions of colloid and sol–gel coassembly for directly printed colloidal crystals. The authors used mixtures of 50 vol % of colloids to 50 vol % of 1,2-bis(triethoxysilyl)ethane (BTES) as the sol–gel precursor which led to the best results, with an efficient encapsulation of colloidal crystals with BTES. According to the authors, the developed method is easily scalable and could be adopted for inkjet printing of colloids, as well as for convective assembly (Figure 10).

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Figure 10: Artistic representation of the drop-casting and coassembly process. Reprinted with permission from (61). Copyright (2016) American Chemical Society.

The optimized conditions for co-assembly will facilitate the production of inkjet-printable photonic crystals that will ultimately lead to self-assembled laser resonators and filters, which can be precisely positioned and patterned into desired structures.

3.4 Suspension cross-linking

Microcapsule formation by this technique involves dispersion of an aqueous solution of the polymer-containing core material in an immiscible organic solvent (suspension/dispersion medium) in the form of small droplets. The suspension medium contains a suitable stabilizer to maintain the individuality of the droplet/microcapsules. The droplets are subsequently hardened by covalent cross-linking and are directly converted to the corresponding microcapsules. The cross-linking process is accomplished either thermally (at >500 C) or using a cross-linking agent (formaldehyde, terephthaloyl chloride, etc.). Suspension cross-linking is a versatile method and can be adopted for microencapsulation of soluble, insoluble, liquid or solid materials and to produce both micro- and nanocapsules [62]. Suspension polymerization reactions generally produce particles with a broad or bimodal size distribution. Bead particles, which are the intended product from a suspension polymerization, with diameters in the range of 10 μm–5 mm, are usually accompanied with unintended smaller particles [63]. Many aspects of suspension polymerizations have been reviewed in the literature [27–29, 64, 65]. The history of suspension cross-linking process originates from the pioneering work in three independent areas of applied polymer research in the late 1960s, which are very well-described in a review published by Arshady [66]. In 1969, Rhodes and co-workers [67] and Pasqualini et al. [68] reported the use of suspension cross-linking for the preparation of albumin microspheres for diagnostic investigations. At about the same period, Khanna and Speiser [69] fabricated epoxy resin microcapsules by cross-linking (curing) of the molten polymer in silicone oil. In 1971, work on the improvement of hydrophilic polymer supports for chromatography led to the development of suspension cross-linking procedures for the preparation of cross-linked procedures for the preparation of cross-linked agarose microspheres by Porath and co-workers [70] and cross-linked cellulose beads by Chimbo and Brown [71]. Suspension cross-linking procedure have been widely used for the preparation of polysaccharide-based polymer supports for chromatography and biomedical applications. Suspension cross-linking has also been the method of choice for the production radiolabeled albumin microspheres as diagnostic imaging reagents. The main challenge of suspension process is the tendency during polymerization for the viscous and adhesive droplets and pearls to agglomerate or to stick to each other, which leads to serious trouble from heat build-up and the formation of large polymer masses [72]. The control of size and size distribution of particles can be achieved by adjusting the reaction parameters, such as stirring speed, reaction temperature, composition and type of reactor system. In general, vigorous stirring, higher temperatures, higher catalyst concentrations and faster polymerization result in finer granules of product. However, too much agitation also may be harmful and may give beads deformed or containing holes because of stirring in of gas. If very effective suspending agents are used in corresponding amounts, quite fine granules result even at low rates of stirring. Addition of suspending agents or suspension stabilizers to the aqueous phase can prevent the agglomeration and sticking together during polymerization and can make the process dependable. Among good suspending agents are found water-soluble high polymers (the so-called protective colloids) such as PVA, polyvinylpyrroli-

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done, polyacrylic acid or natural gums [63]. Regulation of the encapsulated material release is still a challenging task for science nowadays. There have been many studies analyzing this matter, e. g. Dini et al. [73] published the preparation method of chitosan microspheres loaded with a drug hydroquinone. They have proved that the release of the drug was correlated with the degree of cross-linking. Therefore, by adjustment of the cross-linking agent used in the preparation step, in this case glutaraldehyde, control over drug release is possible.

4 Physicomechanical methods

Physical methods do not involve any polymerization reactions considering that the starting materials in these cases are polymers, thus broadly speaking only the formation of shape occur. Few examples of these techniques are listed below.

4.1 Spray-drying

Drying is the oldest known method for removing a liquid from wet bulk materials. Already in the older Stone Age, people have dried food to store it for a long time. In the seventeenth and eighteenth centuries, various substances were usually dried by hot air or smoke. In the nineteenth century, the drying by vacuum or by spraying was developed. A century later, the drum dryer and vacuum-freeze dryer were invented [74].

Spray-drying is a process where liquid phase (emulsion, suspension or solution) is forced to form droplets by an atomizer or a spray nozzle. In the advanced developed part of the devise, droplets are dried by the hot air and solidified capsules are created and collected. A schematic representation of this technology is shown in Figure 11.

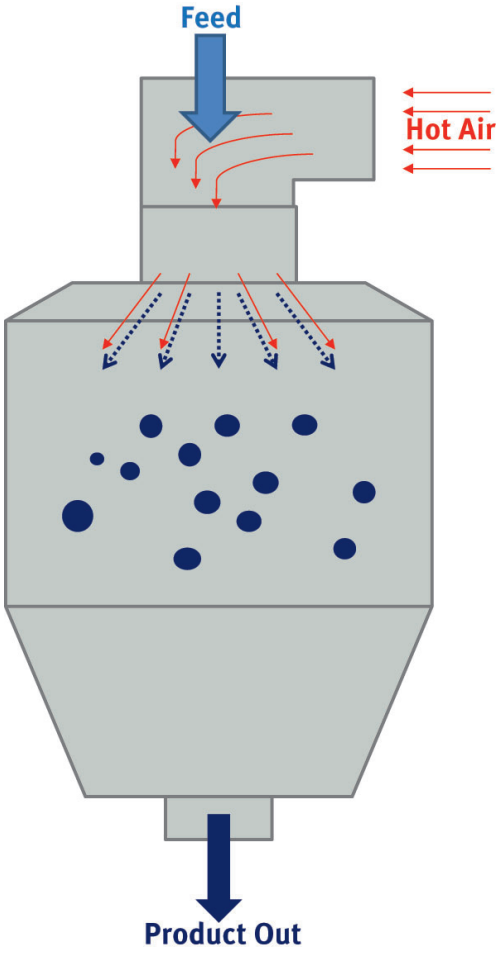

Figure 11: Schematic representation of basic spray-drying procedure.

This method has been widely used since the nineteenth century in the industry due to its simplicity, flexibility and consistent particle size distribution and the system can be fully automated [75]. Nevertheless, spray-

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drying operation presents several drawbacks such as low thermal efficiencies, nozzle clogging and high maintenance costs. Moreover, product loss has been commonly observed, due to the agglomeration of capsules and material sticking to the internal chamber walls. Also, it is highly unlikely to obtain capsules of smaller size than 100 μm [76–78]. Therefore, the process calls for various optimizations. Maury et al. [79] studied the effects of spray-drying parameters on the material yield at laboratory scale spray-dryer. According to the authors a cyclone with the narrow outlet duct is more convenient at laboratory scale spray-dryer. Whereas the T_{inlet}/T_{outlet} was pointed out to be the most important operatory condition to optimize the product yield. This parameter cannot be too high because in other case the inside walls of the spray-dryer reaches the temperature higher than the sticky point of the material. The authors measured that when the parameter exceeds by approximately >10 °C, a product loss is observed. Biswas et al. [80] demonstrated that the morphology of spray-dried nanostructured microcapsules can simply be tuned by controlling the drying temperature, as illustrated in Figure 12.

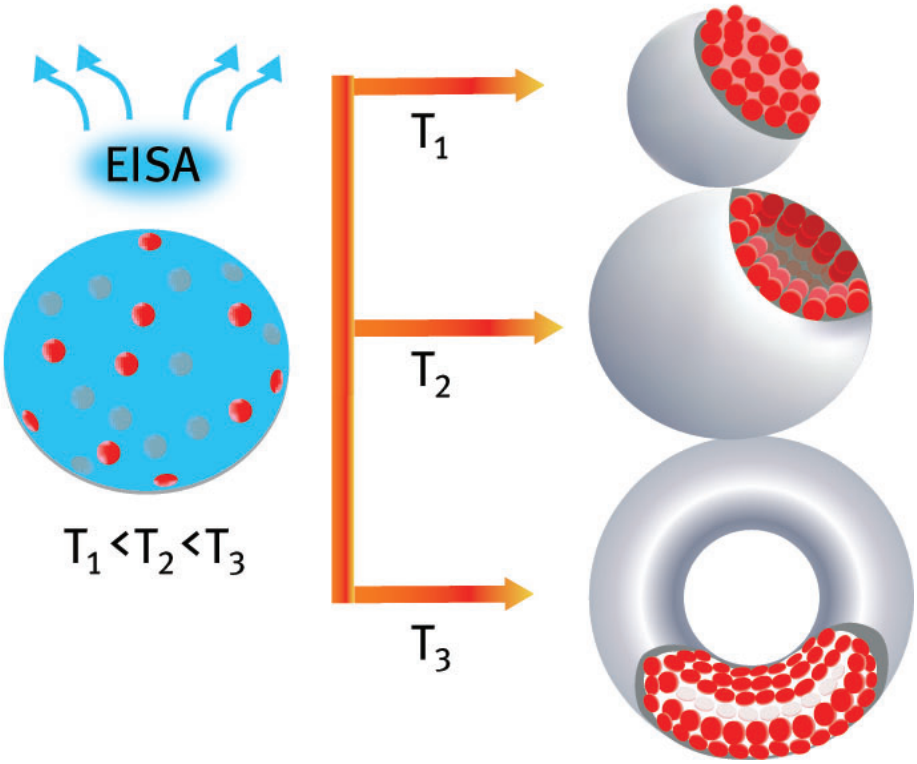

Figure 12: Graphical representation of spray-dried capsule's morphologies obtained with different drying temperatures. Reprinted (adapted) with permission from (80). Copyright (2016) American Chemical Society.

At lower temperature, the nanoparticles are assembled compactly forming spherical granules. In such a case, the size distribution of the granules gets narrowed down with respect to that of the initial droplets. Increase in temperature leads to the formation of larger hollow capsules with nanoparticles packed as a thinner shell. This is because of the preferential motion of the nanoparticles in droplet under a temperature gradient. At still higher temperature, subsequent buckling of the shell leads to the formation of toroidal granules. Polydispersity in granular size increases with temperature. Evolution of capsule shape corroborates with the Surface Evolver computer model, based on buckling of the elastic shell taking into consideration the rate of drying. Statistically averaged local volume fraction of the packed nanoparticles in the capsules remains nearly temperature independent, even though the external morphology changes significantly from sphere to toroid. Scattering experiments indeed differentiate between the two apparent structural correlations that can lead to larger capsule size at higher temperatures. The authors established that increase in capsule size with temperature and consequent buckling are due to the existence of an internal hollow core and not because of the formation of nonconsolidated fractal-like aggregates.

The aim of the research studies performed by Drusch and co-workers [81] was to identify principal parameters determining the oxidative stability of microencapsulated fish oil. The authors prepared the capsules by spray-drying using different types of *n*-octenylsuccinate-derivatized starch, gum Arabic, sugar beet pectin, sodium caseinate and/or glucose syrup. They identified two principal components to classify the different microcapsules accounting for up to 79 % of the variance as shown in Figure 13. The principal components were

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determined by physicochemical parameters reflecting the emulsifying ability of the encapsulant and the drying behavior of the parent emulsion. Microcapsules, which were identified by principal component analysis to be significantly different, exhibited a low stability upon storage, showing that the principal components and, thus, the underlying physicochemical parameters analyzed in the present study are correlated with core material stability. Bertolini and co-workers [82] have investigated the stability of monoterpenes encapsulated in gum Arabic by spray-drying. The authors used the following core materials: citral, linalool, β-myrcene, limonene and β-pinene at concentrations of 10, 20 and 30 % with respect to the wall material. The authors observed that the chemical functionality, associated with the solubility and diffusion through the forming matrix, determines the degree of retention in the production of capsules by spray-drying, in the case of monoterpenes encapsulated in gum Arabic. The order obtained was hydrocarbon > aldehyde > alcohol for monoterpenes with similar molecular weights. Hydrocarbons with the same molecular weight ($C_{10}H_{16}$) and similar solubilities presented different yields in the drying process. According to the authors, these differences were associated with the molecular structures of the monoterpene isomers. The observed order was bicyclic > monocyclic > acyclic, demonstrating the contribution of steric factors to retention in addition to the ability to undergo polarization.

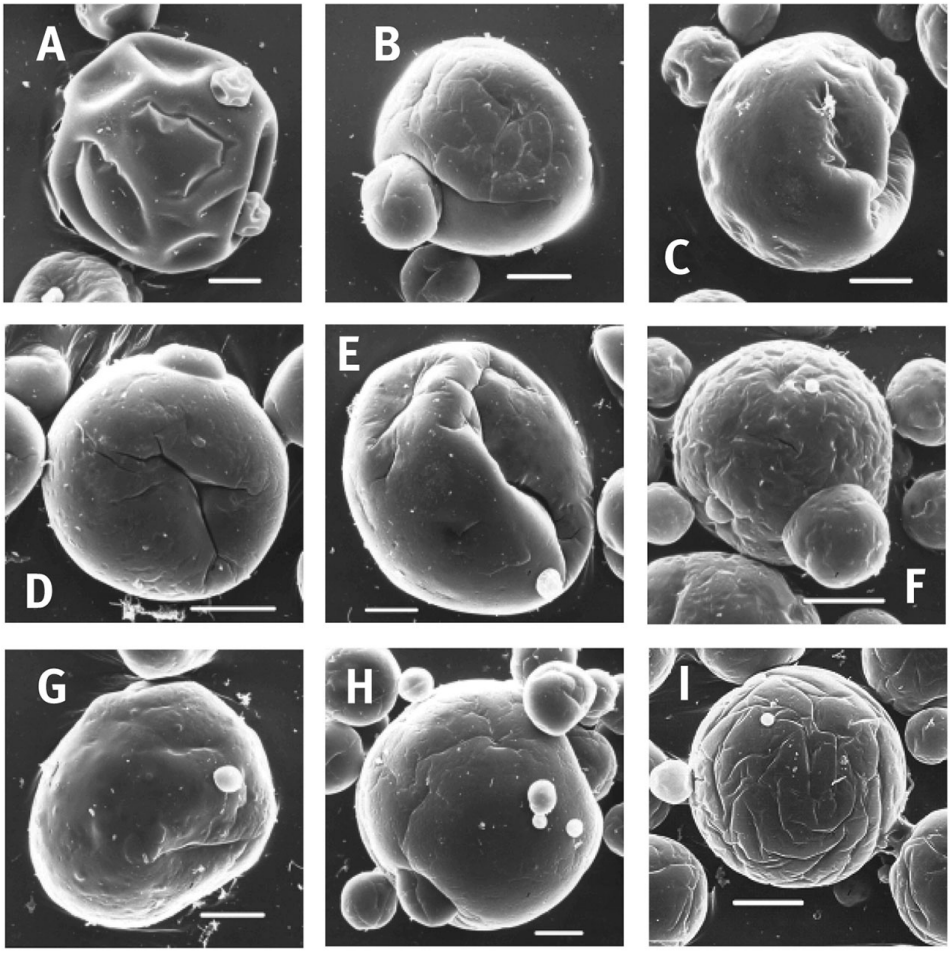

Figure 13: Scanning electron micrographs of microencapsulated fish oil spray-dried at 180/70 °C (A, nOSA-starch type 1; B, nOSA-starch type 1/glucose syrup; C, nOSA-starch type 2; D, nOSA-starch type 2/glucose syrup; E, nOSA-starch type 1/gum Arabic; F, gum Arabic; G, sugar beet pectin; H, caseinate/glucose syrup, 1/4; I, caseinate/glucose syrup, 1/19). White bar = 10 μm. Reprinted (adapted) with permission from (81). Copyright (2007) American Chemical Society.

Under this investigation, the products encapsulated in gum Arabic showed a reduction in content during the shelf-life study at controlled temperature. There was little variation in the content during the first 20 days, but after this there was an accentuated and variable loss for the majority of the monoterpenes studied. The observed order of retention was β-pinene > citral > limonene > β-myrcene > linalool.

A novel route for fast, scalable and continuous assembly of highly monodispersed core–shell microencapsulates was presented by Liu et al. [83], who used Eudragit RS (a co-polymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups) as the main shell component and silica as the core component. Because the core–shell architecture could be formed directly by evaporation-induced self-assembly during the single-step spray-drying process, no prolonged chemical reactions or organic solvents were needed. The investigators demonstrated that the microcapsule wall thickness can be easily tuned

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by adjusting the ratio of the materials in the precursors. The resultant microencapsulates were shown to encapsulate almost 100 % of the active component (in this case, a water-soluble compound, rhodamine B), while the release rates could be directly correlated to the microstructures. This study provides a new scope for practical synthesis of hybrid nanocomposites and functional heterostructures, including core–shell structures with distinct controlled release properties for each section.

4.2 Co-extrusion

Co-extrusion was first patented in 1957 and in future was developed by the group that originally patented the technique [84]. It is a process where dual fluid stream is pumped through the nozzle. One of the liquids contains core material and the other wall material. Droplet is formed by the vibrations applied at the exit of the concentric tubes. Then, the droplet undergoes solidification by chemical cross-linking, cooling or solvent evaporation [85]. A schematic representation of co-extrusion is shown in Figure 14.

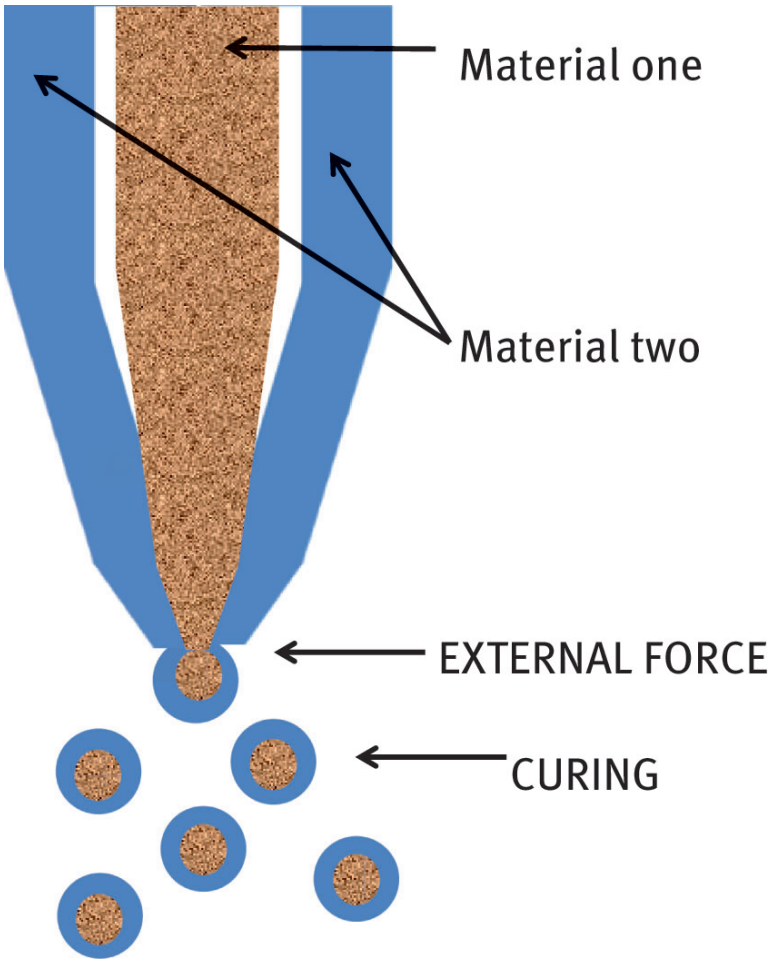

Figure 14: Schematic of a co-extrusion process.

Depending on the device, a monocentric or concentric nozzle system is used, which produces different types of microcapsules, respectively, by extrusion and co-extrusion. The concentric system presents internal and external nozzles that allow the production of reservoir-type microcapsules [86]. Extrusion microencapsulation has been used almost exclusively for the encapsulation of volatile and unstable flavors in glassy carbohydrate matrices. The main advantage of this process is the very long shelf-life imparted to normally oxidation-prone flavor compounds, such as citrus oils, because atmospheric gases diffuse very slowly through the hydrophilic glassy matrix, thus providing an almost impermeable barrier against oxygen. Shelf-lives of up to 5 years have been reported for extruded flavor oils, compared to typically 1 year for spray-dried flavors and a few months for un-encapsulated citrus oils [87]. Very recently, Pasukamonset et al. [88] published very interesting results concerning the microencapsulation of phenolic extracts of *Clitoria ternatea* (CT) petal flower extract through the extrusion method of alginate with calcium chloride ($CaCl_2$). The authors reported that the encapsulation efficiency varied in the range from 74 ± 1 % to 85± 1 % depending on the percentage of CT (5–20 %), alginate

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(1–2 %) and $CaCl_2$ (1.5–5 %). The results showed that the optimized condition of CT-loaded alginate beads (CT beads) was as follows: 10 % CT, 1.5 % alginate and 3 % $CaCl_2$ (w/v). Under this condition, the maximal antioxidant capacity of 11.7 ± 0.1 mg gallic acid equivalent/g_{beads} and the encapsulation efficiency of 84.8 ± 0.4 % were obtained. Moreover, the provided results demonstrated that the prepared microcapsules possessed smooth surface shape with a particle size distribution of 985 ± 0.5 μm. Without any doubts, this report provides a novel food-grade encapsulation formulation to improve the stability as well as the biological activity of plant polyphenols. Recently, Shinde et al. [89] evaluated the co-extrusion using alginate and apple skin polyphenols to protect *Lactobacillus acidophilus* in a milk beverage at 4 °C. The authors decided to employ probiotic bacteria and polyphenols for microcapsule preparation due to their great demand in food products. Lactic acid bacteria have been used to ferment or culture foods for at least 4,000 years. The bacteria have been used in particular in fermented milk products from all over the world, including yoghurt, cheese, butter, buttermilk, kefir and koumiss. Probiotics are defined as "live micro-organisms which, when, administered in adequate amounts, confer a health benefit on the host" [89] and polyphenols possess antioxidant capacity, anti-inflammatory and anticarcinogenic properties, as well as protective effects against a variety of chronic diseases [90–93]. The results published by Shinde et al. [89] indicated that the co-extrusion technology was efficient to protect probiotics after 50 days of storage, due to very low decrease on cell viability. Very recently, Silva et al. [94] reported exciting results concerning encapsulation of *Lactobacillus paracasei* BGP-1 probiotic dispersed into sunflower oil or coconut fat by using the co-extrusion process. Under this study, the authors used alginate or alginate-shellac blend as capsule shell materials and fluidized bed or lyophilization as post-treatment processes to dry the capsules. By using the co-extrusion method, Silva et al. [94] have been able to prepare capsules with a diameter between 0.71 and 0.86 mm, which encourage their application in solid foods, such as cereal bars, dark chocolate and mixed nuts. The authors reported that after 60 days of storage at 25 °C, the viability of probiotic loaded into capsules dried by fluidized bed was up to 6 log CFU/g, corresponding to 90 % of the initial probiotic population. In addition, the formulation produced with alginate-shellac and coconut fat was the most effective at improving probiotic survival in simulated gastrointestinal fluids, mainly by reducing the porosity of microcapsules, in which 7.5 log CFU/g of probiotics (95 %) survived at the end of the assay. Thus, according to the authors, immobilization of probiotics in coconut fat co-extruded with alginate-shellac blend followed by fluidized-bed drying is a promising technology to protect and extend the viability of probiotics in functional foods.

Wang et al. [95] investigated a co-extrusion as a feasible approach of a canola oil encapsulation with alginate and alginate–high methoxyl pectin. The authors have also studied how conditions of co-extrusion affect capsule characteristics, core oil stability and retained phenolic content. They discovered that flow rates of core and shell are the critical parameters to create stable spherical oil beads. The authors demonstrated that the shell wall composition is responsible for the bead size, core oil stability and retained phenolic content. He and co-workers [96] have used a minifluicid device to fabricate calcium alginate capsules by extrusion (Figure 15).

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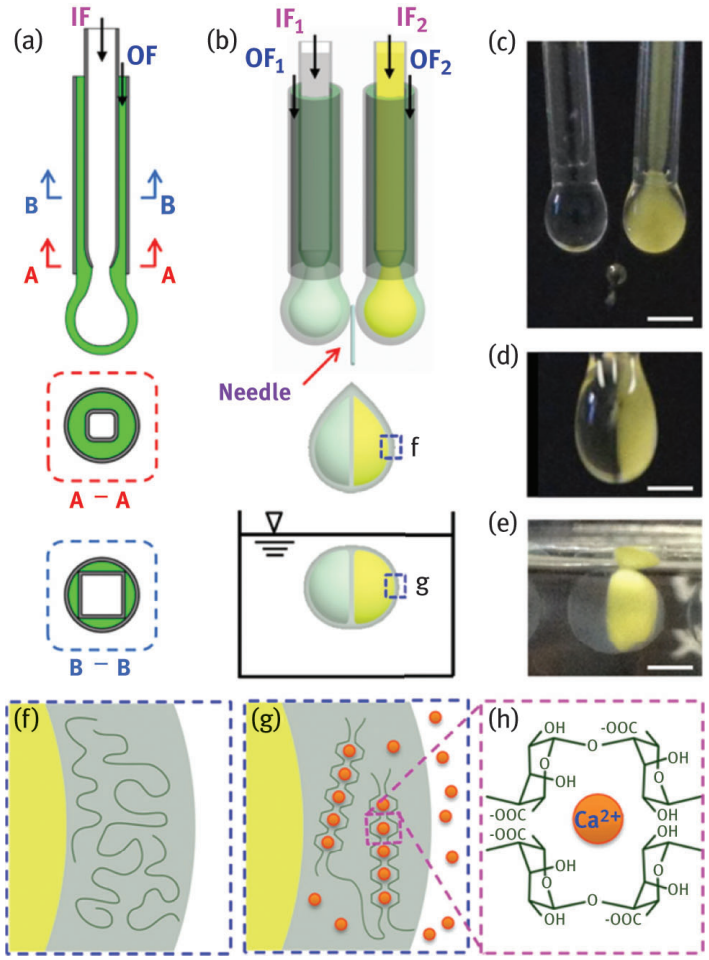

Figure 15: Coextrusion minifluidic devices for fabrication of dual-compartmental Ca–Alg capsules. (a) Schematic illustration of the coextrusion minifluidic device for fabricating water-in-water (W/W) droplets. (b) Schematic illustration showing the combination of two coextrusion minifluidic devices for fabricating the dual-compartmental Ca–Alg capsules. (c–e) Digital photos showing the generation of two different W/W droplets at the outlets of the devices (c), the coalescence of the two W/W droplets triggered by the stainless steel needle (d), and the formation of dual-compartmental Ca–Alg capsules in the $Ca(NO_3)_2$ solution (e). Folic acid (yellow color) is added in the core compartment of one W/W droplets for labeling. The scale bars are 2.5 mm. (f–h) Schematic illustrations showing the cross-linking mechanism of alginate in the shell solution (f) by cross-linking with Ca^{2+} from the $Ca(NO_3)_2$ solution (g) via formation of egg-box structures (h). Reprinted (adapted) with permission from (96). Copyright (2016) American Chemical Society.

The authors reported that this novel approach offers an impressive control level over the volume and number of multiple compartments by adjusting flow rates and numbers of orifices of the device. Dual-compartmental capsules obtained by the authors contained one-half shell with a constant release rate and the other half shell with a temperature-dependent release rate. Therefore, the authors fabricated capsules with different permeability rates, which makes them a huge potential for various advanced applications as a multifunctional material. Nevertheless, the size of the capsules needs to be decreased, because now it is situated in the mm range, and it is an insuperable obstacle for many application.

4.3 Fluidized-bed spray coating

Originally developed as a pharmaceutical technique, fluidized-bed coating is now increasingly being applied in the food industry to fine-tune the effect of functional ingredients and additives. The main benefits of such miniature packages, called microcapsules, include increased shelf-life, taste masking, ease of handling, controlled release and improved esthetics, taste and color. Fluidized-bed coating increasingly supplies the food industry with a wide variety of encapsulated versions of food ingredients and additives. Compared to pharmaceutical fluidized-bed coating, food industry fluidized-bed coating is more obliged to cut production costs and, therefore, should adopt a somewhat different approach to this rather expensive technology. Solid particles are suspended in a temperature and humidity-controlled chamber of high-velocity air where the coating material is atomized [1, 24]. Though fluidized-bed drying offers a lot of advantages, freeze and spray-drying are

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preferred drying techniques for probiotic microencapsulation. Compared to lyophilization, fluidized-bed drying is more cost effective. Due to an optimal heat and mass transport as well as equal temperature distribution, drying and granulation processes in a fluidized-bed dryer can be carried out at lower temperatures compared to spray-drying which results in higher survival rates of encapsulated bacteria [25]. Further, granulation and coating procedures can be combined within one fluidized-bed drying process. At least, the coating material determines the protection and targeted release properties. Due to their numerous advantages, the fluidized-bed technology has gained significant importance in the last century in many industrial processes. Fluidized beds are particularly advantageous due to the simple solid handling through the fluid-like behavior, intensive solids mixing and the resulting uniform temperature distribution, large exchange surface between solid and gas and high heat transfer value between solid and gas. In most cases, the heat required for the drying process in fluidized beds is provided by means of a preheated fluidizing gas. Moreover, additional thermal energy can be inserted to the process either by immersed heating elements, e. g. steam-heated tubes, or by heating of the fluidization chamber wall. Due to the contact of particles with heated surfaces, additional heat transfer is available leading to process intensification, i. e. higher drying rates due to increased heat transfer area. Lower gas inlet temperature is requested, which is preferable for heat-sensitive products. However, limited number of tubes, influence on flow field and fouling are subject to the limitations of the process intensification by contact heating [74].

4.4 Phase-inversion precipitation

Phase-inversion precipitation method comprises mass transfer and phase separation processes which occur when polymeric solution in the form of droplet get in contact with a nonsolvent and the polymer precipitates. Phase-inversion or immersion precipitation is usually isothermal, ternary system. This technique includes involvement of three components: solvent, nonsolvent and polymer. Process begins by dissolving polymer in its solvent and molding it into a wanted shape, for example film or droplet. Then, the solution is immersed in the nonsolvent bath, which will activate the exchange between molecules of solvent and nonsolvent. Transfer between the solvents will inevitably force precipitation of the polymer, resulting in the final porous structure of the obtained membrane [97].

Bogdanowicz and co-workers [98] prepared photoresponsive microcapsules, based on poly(α–methylstilbenesebacoate-co-α-methylstilbeneisophthalate) (P4), containing different core materials, by using a phase-inversion precipitation process. The authors made the hypothesis that phototriggered release from such microcapsules occurs as a consequence of E–Z photoisomerization of α-methylstilbene moieties in the polymer backbone, which forms a microcapsule shell during UV irradiation. Photoresponsive microcapsules were prepared using P4. P4 is a novel nematic liquid-crystalline polymer of our synthesis with a glass transition of 45 °C and clearing point of 238 °C. This polymer possesses an amorphous structure and a reasonably low glass transition value, thanks to the incorporation of isophthaloyl moieties in the polymer backbone. Before preparing and characterizing microcapsules, we performed an exhaustive characterization of a membrane based on the P4 polymer obtained by using conditions as similar as possible to microcapsule preparation. In this way, we tried to simulate the morphology and the behavior of the microcapsule shell under UV irradiation. In order to establish whether microcapsule shell morphology and behavior could be altered as a consequence of photoirradiation, a complete characterization of a flat membrane based on P4 polymer was first carried out by the investigators. By employing Environmental Scanning Electron Microscope studies, the author demonstrated that P4 membrane and microcapsules containing chloroform as filler possessed very similar asymmetric cross-sectional morphologies. The presence of vanillin in chloroform during phase-inversion precipitation process had an influence on the cross-sectional structure of microcapsules containing this perfume. The authors observed that the outer surface morphologies of all prepared microcapsules appeared like a dense film. Based on atomic force microscope investigations, the authors investigated that the P4 film morphology changed drastically as a consequence of its exposure to UV irradiation at 365 nm (i. e. its surface became much smoother and surface roughness was decreased ca. 24 %). This reasonably induced about a 21 % decrease of the water contact angle value. Release experiments, performed by the investigators, showed that vanillin release from microcapsules in water at room temperature was strongly influenced by UV irradiation: in the absence of irradiation, release was negligible, while, when microcapsules were submitted to continuous irradiation with UV light for 35 min, vanillin was quickly released after an induction time of about 20 min. Panisello et al. [99], by use of phase-inversion precipitation, were able to control polysulfone microcapsule morphology through the adjustment of the composition of the precipitation bath. The aforementioned bath was composed of pure water, which is a nonsolvent for a polysulfone, or of a mixture of water and polysulfone solvent. The results obtained by them show that high concentration of a solvent in the nonsolvent bath favors sponge-like structures. Pena et al. [100] investigated polysulfone microcapsules made by the phase-immersion precipitation method. Based on the generated results, the authors proposed a treatment to avoid the presence

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of the solvent (DMF) in the prepared capsules, and also to increase the amount of the encapsulated material, in this case vanillin. The treatment consists immersing the capsules in a saturated vanillin aqueous solution for 4 days. By following this procedure, the author demonstrated that the DMF can be totally removed from the core of the microcapsule increasing the amount of encapsulated vanillin to around 100 %.

5 General conclusions

A survey of the main encapsulation processes is presented. As well seen in this review, through the years, this field of science has done tremendous progress [101]. To provide a good understanding of the up-to-day development of microcapsule preparation methods and polymer structures used as capsule shell materials, information collected from the literature has been summarized in this work. We have highlighted the processes that have been utilized not only in the academic setup, but as well at the industrial scale. Versatility of the techniques available so far offers enormous resources of possible advanced applications. Nevertheless, to further promote the practical application of capsules, improved and automatable setup units as well as cheap polymers for microcapsule walls must be developed. In addition, developing delivery systems which is controlled release process of encapsulated cargo substances still remains an interesting but challenging task.

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