SOLVENT STABLE MICROCAPSULES FOR CONTROLLED RELEASE OF ACTIVES

Mario Ammendola

UNIVERSITAT ROVIRA i VIRGILI

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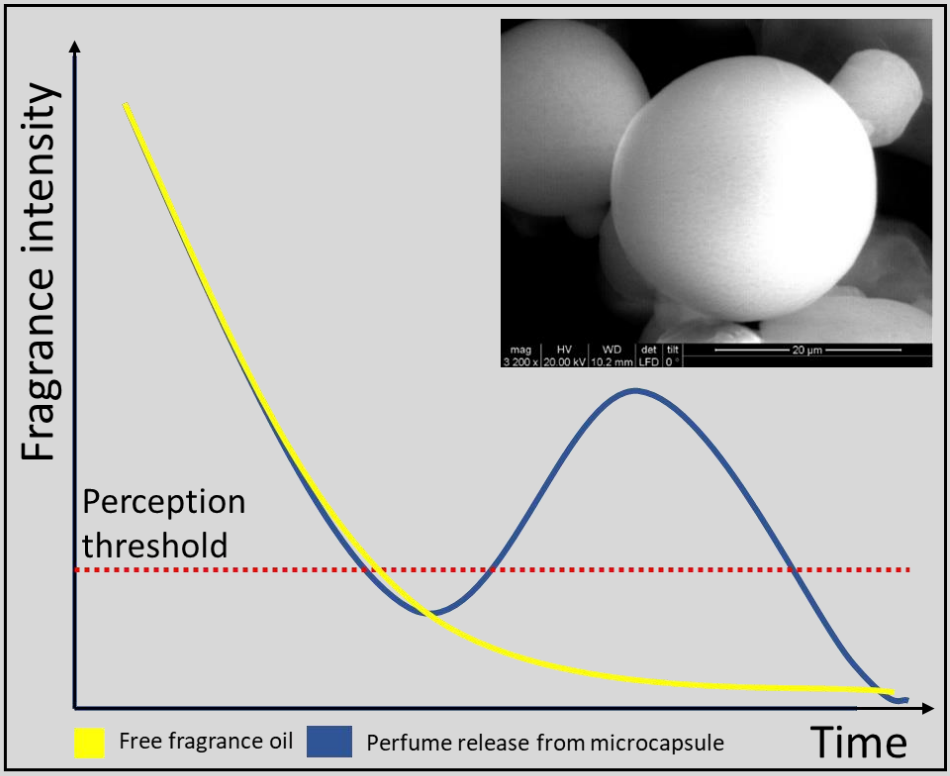

DOCTORAL THESIS
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Solvent stable microcapsules for controlled release of actives

by

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Doctoral Thesis

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Universitat Rovira i Virgili

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We state that the present study, entitled "Solvent stable microcapsules for controlled release of actives", presented by Mario Ammendola for the award of the degree of Doctor, has been carried out under our supervision at the Chemical Engineering Department at the University Rovira i Virgili, and that it fulfils all the requirements to be eligible for the Doctor European Mention.

Tarragona, November 2019

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Tarragona, October 2019

Supervisor of the doctoral thesis

Dr. Ricard Garcia-Valls

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Mario Ammendola

I have not failed. I've just found 10,000 ways that won't work.

Thomas Edison

Table of Contents

Summary

This thesis is focused on the production and characterization of polymeric microcapsules. Microcapsules are spherical particles with diameter between 1 μm and 1000 μm. They are constituted by a polymeric shell and a core material entrapped by the wall. The most common reasons for encapsulation are protection and control the release of the active. Microcapsules are applied in several fields, such as pharmaceutic, food, medicine, agriculture, cosmetics and textile, among others. Due to their multiple use, different microencapsulation techniques have been developed and the technology is in continuous progress due to big market impact of microcapsules.

In the present work, the main objective is the development of solvent stable microcapsules for controlled release of actives, to be included in consumer goods for personal and home care applications. The core material is a technical accord, called Sweet & Smart (S&S), that is a mix of fragrances with a high content of low logP perfume raw materials, that makes difficult its encapsulation. The encapsulation of S&S would make possible the enlargement of the palette of perfumes to be encapsulated and consequently a wider flexibility in the perfume formulations. The result is the possibility to provide different perfume characters, adducing commercial value to the consumer goods. Another important point of the work is sustainability of the system, because of modern societal trends aimed at finding more eco-friendly solutions.

Therefore, the first step of the work was the selection of the materials. Materials and encapsulation technique are not independent choice. We selected cellulose acetate (CA) as wall material and it was constant in all the work. CA meets our environmental considerations because it is a natural derived polymer and it has been found to be degradable; moreover, it passed the screening test that we performed.

The second step was the exploration of the encapsulation technique and the study of process parameters. We started with processes based on atomization technology. First by spray drying, because of its easiness and because it is an economic and industrially available process. Then, we developed an encapsulation process, the vapor induced phase separation (VIPS) by implementing the immersion precipitation technique (IPS). IPS is a technique in which the polymeric solution containing solvents, polymer and core material is atomized by passing through a nozzle and the phase inversion precipitation is induced by immersion in liquid non-solvent. In VIPS, the phase separation is induced by non-solvent vapor, allowing a better control of the precipitation rate of the encapsulation material. The third technique is a solvent evaporation using Pickering emulsifier. Pickering emulsifier are solid particles that stabilize an emulsion instead of surfactants. The interest in this technique is growing because of the better stability of the emulsions and the possibility to avoid adverse effects of surfactants.

The prepared microcapsules were characterized through different techniques: SEM, Optical Microscopy, TGA, GC/MS, among others. The morphology of microcapsules for industrial applications is a crucial point, because perfume materials are quite expansive. A core-shell structure allows to optimize the amount of perfume contained in the capsules and their release. Therefore, the activity of the capsules, that is defined as the weight percentage of active encapsulated, and the encapsulation efficiency, defined as the mass of encapsulated active compared to the mass of the active added to the initial formulation, take on a very important value.

Finally, the performance of the microcapsules was evaluated in standard industrial test, such as the laundry machine test, to assess their potential application in full product formulations.

Sommario

La tesi è focalizzata sulla produzione e caratterizzazione di microcapsule polimeriche. Le microcapsule sono particelle sferiche con diametro compreso tra 1 µm e 1000 µm. Sono costituite da un guscio polimerico e da un materiale intrappolato all'interno del muro. Le ragioni più comuni per l'incapsulamento sono la protezione e il controllo del rilascio dell'attivo. Le microcapsule vengono applicate in diversi campi, tra cui quello farmaceutico, alimentare, medico, agricolo, cosmetico e tessile. A causa del loro uso molteplice utilizzo, sono state sviluppate diverse tecniche di microincapsulazione e la tecnologia è in continuo progresso a causa del loro grande impatto sul mercato.

Nel presente lavoro, l'obiettivo principale è lo sviluppo di microcapsule stabili ai solventi per rilascio controllato di attivi, da includere nei beni di consumo per applicazioni quali la cura della persona e della casa. Il materiale di base è un accordo tecnico, chiamato Sweet & Smart (S&S), che è un mix di fragranze con un alto contenuto di profumazioni a basso logP, che ne rende difficile l'incapsulamento. L'incapsulamento di S&S renderebbe possibile l'ampliamento delle possibili profumazioni e una maggiore flessibilità nelle formulazioni dei profumi. Il risultato è l'aggiunta di valore commerciale ai beni di consumo. Un altro punto importante del lavoro è la sostenibilità del sistema, a causa delle moderne tendenze della società volte a trovare soluzioni più ecologiche.

Pertanto, il primo passo del lavoro è stata la selezione dei materiali. I materiali e la tecnica di incapsulamento non sono una scelta indipendente. Abbiamo selezionato acetato di cellulosa (CA) come materiale per le pareti della capsula, utilizzandolo costantemente durante tutto il lavoro. CA soddisfa le nostre considerazioni ambientali

poiché è un polimero di derivazione naturale ed è ritenuto degradabile; inoltre, ha superato i test di screening che abbiamo eseguito.

Il secondo passo è stato l'esplorazione della tecnica di incapsulamento e lo studio dei parametri di processo. Abbiamo iniziato con processi basati sulla tecnologia di atomizzazione. Innanzitutto mediante *Spray dryer*, per la sua semplicità e perché è un processo economico e disponibile a livello industriale. Dopodiché, abbiamo sviluppato un processo di incapsulamento, la separazione di fase indotta da vapore (VIPS) implementando la tecnica di precipitazione ad immersione (IPS). L'IPS è una tecnica in cui la soluzione polimerica contenente solventi, polimero e attivo viene atomizzata passando attraverso un ugello e l'inversione di fase è indotta tramite l'immersione in un liquido di non solvente. Nel VIPS, la separazione di fase è indotta da vapore di non solvente, consentendo un migliore controllo della velocità di precipitazione del materiale di incapsulamento. La terza tecnica è l'evaporazione con solvente mediante una *Pickering emulsion*. I *Pickering emulsifier* sono particelle solide che stabilizzano un'emulsione al posto dei tensioattivi. L'interesse per questa tecnica sta crescendo a causa della migliore stabilità delle emulsioni e della possibilità di evitare gli effetti negativi dei tensioattivi.

Le microcapsule preparate sono state caratterizzate attraverso diverse tecniche: SEM, Microscopia ottica, TGA, GC / MS, tra le altre. La morfologia delle microcapsule per applicazioni industriali è un punto cruciale, perché le fragranze utilizzate sono piuttosto cari. Una struttura *core-shell* consente di ottimizzare la quantità di profumo contenuta nelle capsule e il loro rilascio. Pertanto, l'attività delle capsule, definita come percentuale in peso di attivo incapsulato, e l'efficienza di incapsulamento, definita come la massa di attivo incapsulato rispetto alla massa dell'attivo aggiunta alla formulazione iniziale, assumono un valore molto importante .

Infine, le prestazioni delle microcapsule sono state valutate in test industriali standard, come il test della lavatrice, per valutare la loro potenziale applicazione nelle formulazioni complete del prodotto.

Resumen

Esta tesis se centra en la producción y caracterización de microcápsulas poliméricas. Las microcápsulas son partículas esféricas con un diámetro entre 1 µm y 1000 µm. Están constituidas por una carcasa polimérica y un material central atrapado por la pared. Las razones más comunes para la encapsulación son la protección y el control de la liberación del activo. Las microcápsulas se aplican en varios campos, como el farmacéutico, alimentario, médico, agrícolo, cosmético y textil, entre otros. Debido a su uso múltiple, se han desarrollado diferentes técnicas de microencapsulación y la tecnología está en progreso continuo debido al gran impacto de las microcápsulas en el mercado.

En el presente trabajo, el objetivo principal es el desarrollo de microcápsulas solventes estables para la liberación controlada de activos, que se incluirán en bienes de consumo para aplicaciones de cuidado personal y doméstico. El active es un acuerdo técnico, llamado Sweet & Smart (S&S), que es una mezcla de fragancias con un alto contenido de materias primas de perfume de bajo logP, que dificulta su encapsulación. La encapsulación de S&S permitiría la ampliación de la paleta de perfumes a encapsular y, en consecuencia, una mayor flexibilidad en las formulaciones de perfumes. El resultado es la posibilidad de proporcionar una diferente perfumación, aportando valor comercial a los bienes de consumo. Otro punto importante del trabajo es la sostenibilidad del sistema, debido a las tendencias sociales modernas y la necesidad de encontrar soluciones más ecológicas.

Por lo tanto, el primer paso del trabajo fue la selección de los materiales. Los materiales y la técnica de encapsulación no son una elección independiente. Seleccionamos acetato de celulosa (CA) como material de pared y fue constante en todo el trabajo. CA cumple con

nuestras consideraciones ambientales porque es un polímero derivado natural y se ha encontrado que es degradable; además, pasó la prueba de detección que realizamos.

El segundo paso fue la exploración de la técnica de encapsulación y el estudio de los parámetros del proceso. Comenzamos con procesos basados en tecnología de atomización. Primero por *Spary Dryer*, por su facilidad y porque es un proceso económico e industrialmente disponible. Luego, desarrollamos un proceso de encapsulación, la separación de fases inducida por vapor (VIPS) mediante la implementación de la técnica de precipitación por inmersión (IPS). IPS es una técnica en la cual la solución polimérica que contiene solventes, polímero y activo se atomiza al pasar a través de una boquilla y la precipitación de inversión de fase es inducida por inmersión en un líquido de no solvente. En VIPS, la separación de fases es inducida por vapor de no solvente, lo que permite un mejor control de la velocidad de precipitación del material de encapsulación. La tercera técnica es una evaporación de solvente usando *Pickering emulsifier*. Los *Pickering emulsifier* son partículas sólidas que estabilizan una emulsión en lugar de tensioactivos. El interés en esta técnica está creciendo debido a la mejor estabilidad de las emulsiones y la posibilidad de evitar los efectos adversos de los tensioactivos.

Las microcápsulas preparadas se caracterizaron mediante diferentes técnicas: SEM, microscopía óptica, TGA, GC / MS, entre otras. La morfología de las microcápsulas para aplicaciones industriales es un punto crucial, porque los materiales de perfume son bastante caros. Una estructura *core-shell* permite optimizar la cantidad de perfume contenido en las cápsulas y su liberación. Por lo tanto, la actividad de las cápsulas, que se define como el porcentaje en peso del activo encapsulado, y la eficiencia de encapsulación, definida como la

masa del activo encapsulado en comparación con la masa del activo agregado a la formulación inicial, adquieren un valor muy importante. .

Finalmente, se evaluó el rendimiento de las microcápsulas en una prueba industrial estándar, como el test de la lavadora, para evaluar su aplicación potencial en formulaciones completas de productos.

1. General introduction

This chapter is a general introduction of the theme of the work. An overview about microcapsules and microencapsulation technology will be presented, concerning the most common techniques to encapsulate and an introduction of the main industrial fields that are using this technology for different purpose. Then, the objectives and the scope of the work will be enounced.

1.1 Microcapsules

Encapsulation is described as a process of enclosing particles of solids or droplets of liquids or gasses in an inert shell, which in turn isolates and protects them from the external environment.[1] The encapsulation technology takes inspiration from nature, in which different cases exist, from macroscopic as well as microscopic scale. Egg or seed are examples of the first case, while a cell along its contents is the best example of the second one. Particles, spheres and capsules are the resultant products of the encapsulation process, which differentiate in morphology and internal structure.[2] Such capsules have a spherical or irregular shape. Two different components are identified in particles or capsules, namely shell and core. The core contains the active ingredient, also called internal phase, coated material, fill or payload. On the other hand, the shell is also known as wall material, membrane or carrier, and it covers or protects the core material. At present, there is not an universally accepted size range to classify the capsules; anyway, a generally accepted classification of the capsules could be[3]:

- Nanocapsules, with a diameter smaller than 1 μm.
- Microcapsules, with a diameter from 1 μm to 1000 μm.
- Macrocapsules, with a diameter larger than 1000 μm.

In this work, the focus is pointed on the second ones, so, from now on, we will always refer to microcapsules and microencapsulation. With the term microcapsule is defined a microparticle made by a polymeric wall containing a different material inside, the encapsulated material. Depending on their morphology, microcapsules can be classified as mononuclear, polynuclear and matrix types.[1] In figure I-1 some of the possible morphologies are represented.

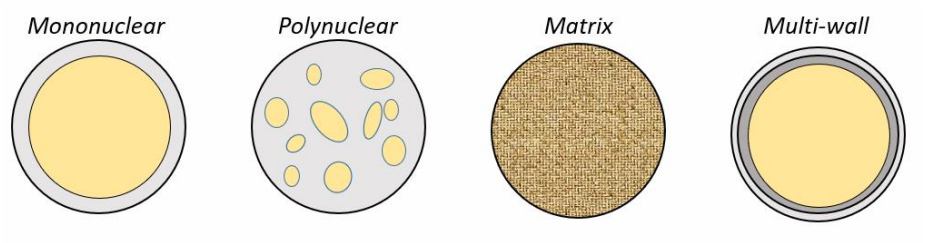

Figure I-1 Morphology of different types of microcapsules

Mononuclear (core-shell) microcapsules contain the core surrounded by the shell, while polynuclear capsules contain different cores enclosed within the shell. In matrix capsules the core is homogeneously distributed into the shell material. Moreover, capsules can also exhibit the core material enclosed within multiple shells, providing different chemical and physical properties. The morphology of the internal structure depends largely on the selected shell materials and the microencapsulation methods that are employed.[4]

The reasons for encapsulation are several, including[1,5,6]:

- Reduce the reactivity of the material that is being encapsulated
- Protect the encapsulated material against evaporation or loss into another medium
- Facilitate handling, application and storage of encapsulated material
- Promote controlled release
- Mask unpleasant taste and flavor
- Convert liquid drugs in a free-flowing powder
- Prevent incompatibility among the drugs
- Immobilize enzyme and microorganism
- Handle liquids as solids

1.2 Microencapsulation techniques

Several preparation technologies available for the encapsulation of core material have been reported. Depending on the materials or the product application, the most suitable method must be chosen. The particle size required, the physical and chemical properties of the core and the shell, the release mechanism intended, the production scale and the costs must be considered as well. However, the size, structure, and the shape of the microcapsules depend on the materials involved and on the process of production[7,8]. The selection of microencapsulation method and the encapsulating agent are interdependent. So, based on the encapsulating agent or method applied, the appropriate method or encapsulating agent is selected.[9] Generally, an ideal coating material should exhibit the following characteristics[10]:

- Good rheological properties at high concentration and easy work-ability during encapsulation
- Capable to disperse or emulsify the active material and stabilize the emulsion produced
- Nonreactivity with the active core materials both during processing and on prolonged storage
- The ability to seal and hold the active within its structure during processing or storage
- The ability to provide maximum protection to the active material against environmental conditions
- The ability to completely release the solvent or other materials used during the process of encapsulation.

In general, microencapsulation techniques are divided into two basic groups, namely chemical and physical, with the latter being further subdivided into physico-chemical and physico-mechanical techniques.[1]

The peculiarity of the chemical processes is the reactivity of the external wall material surrounding the encapsulated core material. On the other hand, physical methods are characterized by the use of different driving forces such as temperature or pressure, leading to the formation of the wall that coats the core material[11]. Some of the most common processes used for microencapsulation are summarized in table I-1, and a brief description of them is given below.

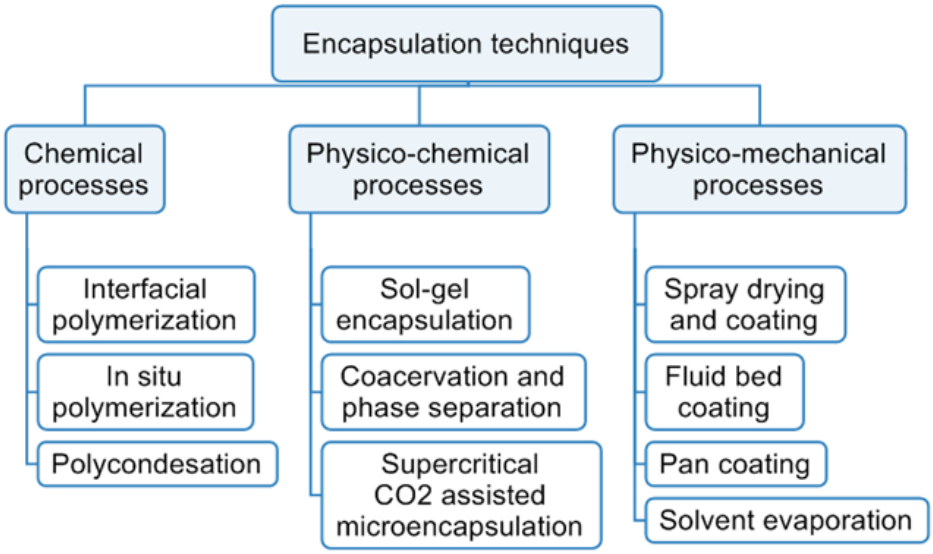

Table I-1 Scheme of the main common encapsulation techniques

1.2.1 Chemical and physico-chemical methods

1.2.1.1 Interfacial polymerization

Interfacial polymerization is a technique mainly developed toward the end of the 1960s, applied on microcapsules production by the mid-1970s. Since then, the encapsulation of core substances by this process has been widely used in several industries, including pharmaceutical, agriculture and cosmetic. The basis of this method is the Schotten Baumann reaction between an acid chloride and a compound containing an active hydrogen atom, such as an amine or

alcohol, polyesters, polyurea, polyurethane.[6]

In Interfacial polymerization, the capsule shell is formed on the surface of the droplet or of the particle by polymerization of the reactive monomers.[2] It is a two steps process; firstly, a stable micro-emulsion is formed and then a polycondensation reaction occurs at the interface of the emulsion, when the two immiscible phases are crosslinked. The main advantages of this technique are the easiness and the reliability of the process, the possibility to directly control the capsule mean size and the relatively low cost and capability of scale-up. In figure I-2 a scheme of how a capsule formation by interfacial polymerization occurs is represented.[12]

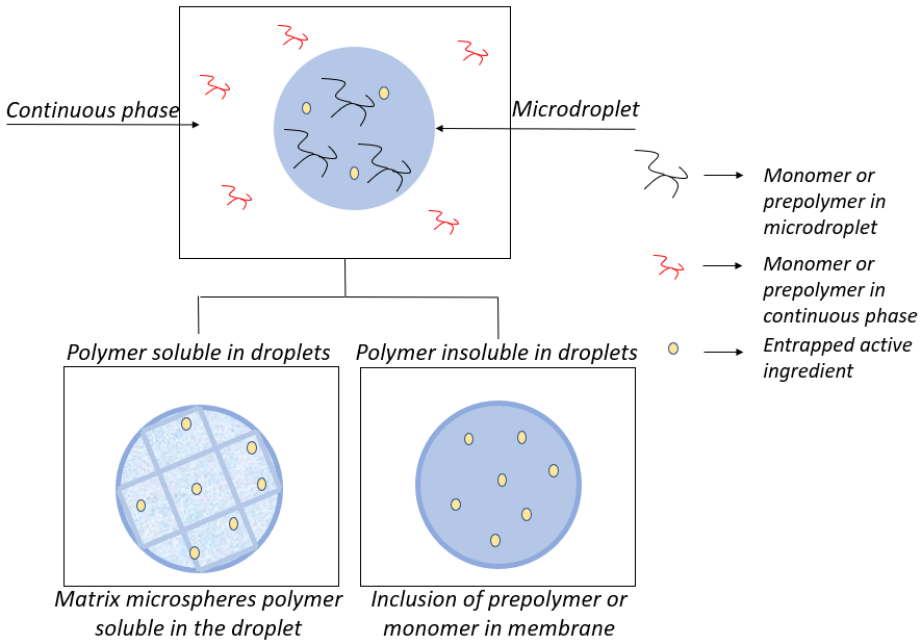

Figure I-2 Microcapsule formation by interfacial polymerization

Microcapsules or microspheres are formed depending on the solubility of the polymer and the crosslinking agent in the droplets. If they are soluble, microspheres are formed; otherwise, microcapsules are prepared.

1.2.1.2 Coacervation

Coacervation is a physicochemical process for microencapsulation and the most frequently used. It is also called phase separation. This was the first reported process to be adapted for the industrial production of microcapsules. It appeared in the 1950s by National Cash Register Company, USA, and was used to produce a two-component ink system for carbon less copy paper.[9] This technique is defined as a partial desolvation of a homogeneous polymer solution into a polymer-rich phase (coacervate) and the poor polymer phase (coacervation medium). The term originated from the Latin *acervus*, meaning heap.[1] Two different coacervations exist, namely simple and complex, according to the number of polymer types present. In the first case, a desolvation agent is added and it promote the phase separation, while complex coacervation involves complexation between two oppositely charged polymers. A generic scheme of a coacervation process is reported in figure I-3.

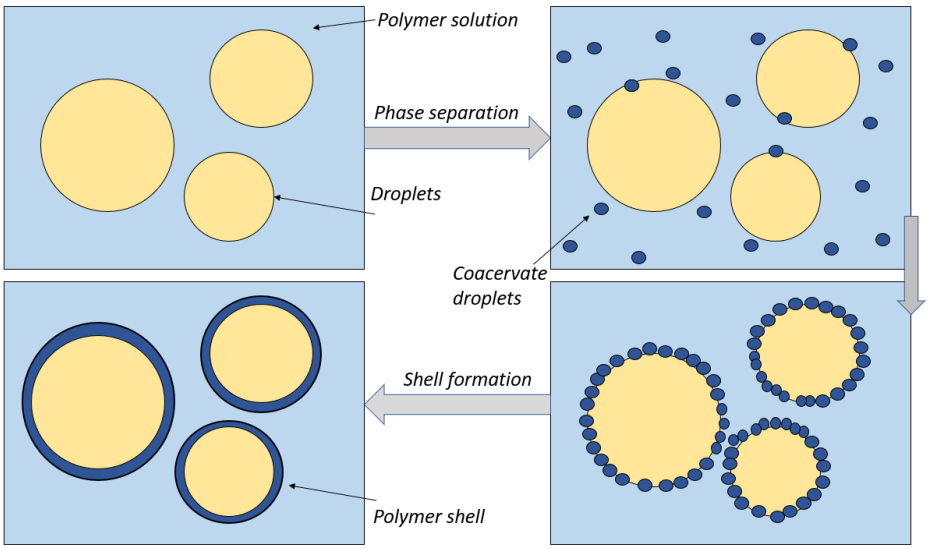

Figure I-3 Representation of a coacervation process

Generally, three basic steps are involved in complex coacervation:

- Formation of a three-immiscible chemical phase
- Deposition of the coating
- Solidification of the coating

In the first step the phase involved are a liquid manufacturing vehicle, the core material and the shell material. The core material is dispersed in a solution of the coating material and the coating material phase, an immiscible polymer in liquid state, is formed in several ways (changing temperature of polymer solution, addition of non-solvent, addition of salt and so on). The second step includes deposition of liquid polymer upon the core material. Finally, the prepared microcapsules are stabilized by cross-linking, desolvation or thermal treatment.[2]

1.2.1.3 In situ polymerization

Another chemical microencapsulation process is the *in-situ* polymerization. This process is ideal for protecting hydrophobic materials and involves the deposition of a polymeric material at the solid/liquid interface.[13] A continuous solution and an immiscible core material are mixed forming a stable emulsion; then, the capsule shell formation happens due to a polymerization process of the specific monomers or pre-polymers added to the emulsion. A main point of this technique is that reagents are added to the core material, because the polymerization take occurs only in the continuous phase. This is what more differentiates this process from the interfacial polymerization. The most common example of this method is the condensation polymerization of melamine with formaldehyde to form cross-linked urea-formaldehyde (UF) or melamine-formaldehyde (MF) capsule shells.[14,15] In figure I-3 the shell forming process is represented. Firstly, the core material is dispersed into an aqueous phase containing a small fraction of emulsifier, which the addition of monomers or pre-polymers

of urea with formaldehyde (or melamine with formaldehyde) follows. The polycondensation reaction starts when the pH of the system is lowered, yielding crosslinked resin (UF or MF). When the molecular weight of the resin reaches high values, the resin itself becomes insoluble into the aqueous phase, precipitates out and deposits at the oil-water interface of the droplets. Finally, the resin hardens and the shell of the microcapsules is formed.[16]

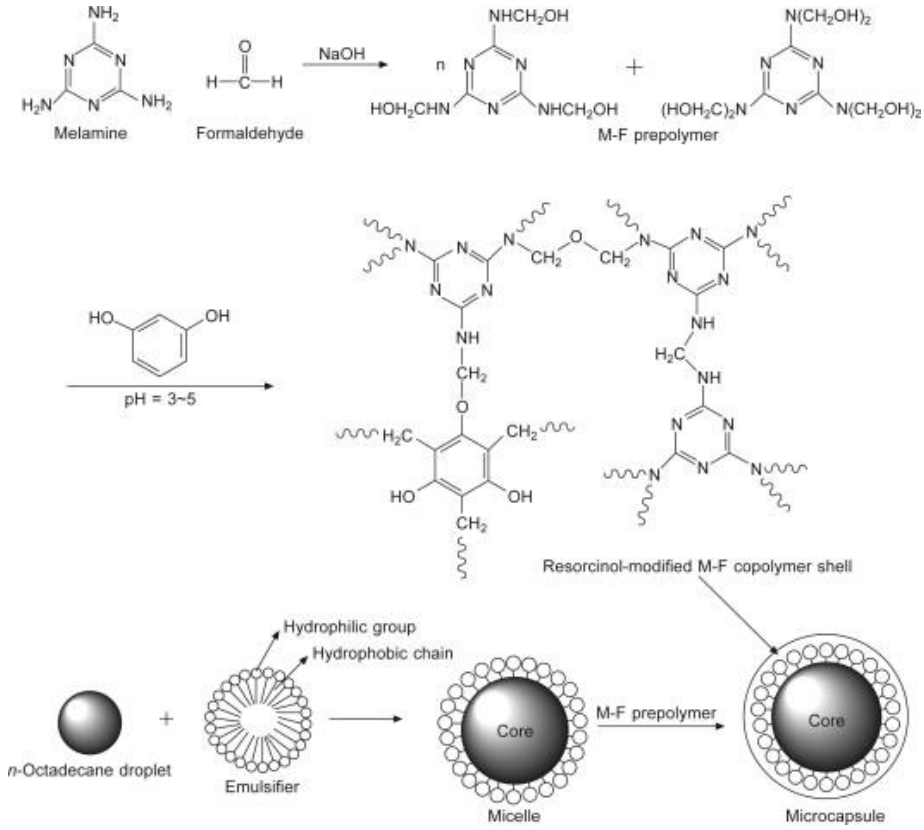

Figure I-4 Schematic formation of the n-octadecane microcapsules by in-situ polymerization[14]

1.2.1.4 Processes using supercritical fluids

Supercritical fluids, especially supercritical carbon dioxide ($scCO_2$), have aroused interest in developing new encapsulation techniques because of the opportunity to eliminate organic solvents or minimize their use. This technology has big advantages over the classical microencapsulation processes.[17] In the pressure-temperature diagram, supercritical fluids show both pressure and temperature higher than those of the critical point, that indicate the final point of the liquid-gas phase transition curve. CO_2 has relatively accessible critical conditions (31.1°C and 73.8 bar), as indicated in figure I-4. It allows to operate in very mild process conditions. Moreover, $scCO_2$ is non-toxic and non-flammable, abundant, colorless, odorless and relatively low cost. By varying the temperature and pressure, its properties changed and $scCO_2$ can act as solvent, antisolvent, solute or drying agent; consequently, several particles characteristics can be designed by adjusting the processing conditions.[18,19] The main disadvantage of this process are the high operation and equipment costs.

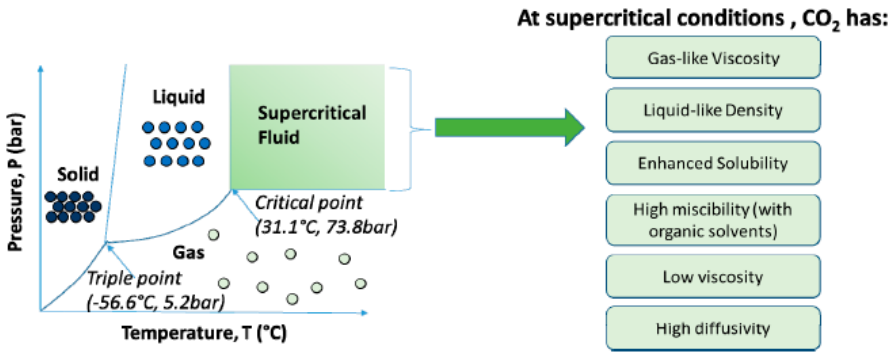

Figure I-5 Phase diagram of carbon dioxide and its properties at supercritical conditions[20]

1.2.2 Physico-mechanical methods

1.2.2.1 Spray drying

Microencapsulation by spray-drying is one of the most common methods used for microencapsulation, the most common used in food industry. This is due mainly to its effectiveness and price; spray drying production costs are lower than those associated with most other methods of encapsulation. It has been used since the late 1950s to provide flavor oils with protection against degradation/oxidation and to convert liquids in powders.[10] Spray drying of active agent is commonly achieved by emulsifying, dissolving or dispersing the core material in an aqueous solution of shell material, followed by atomization and spraying of the mixture into a hot chamber. In figure I-5 a schematic representation of the equipment is showed.

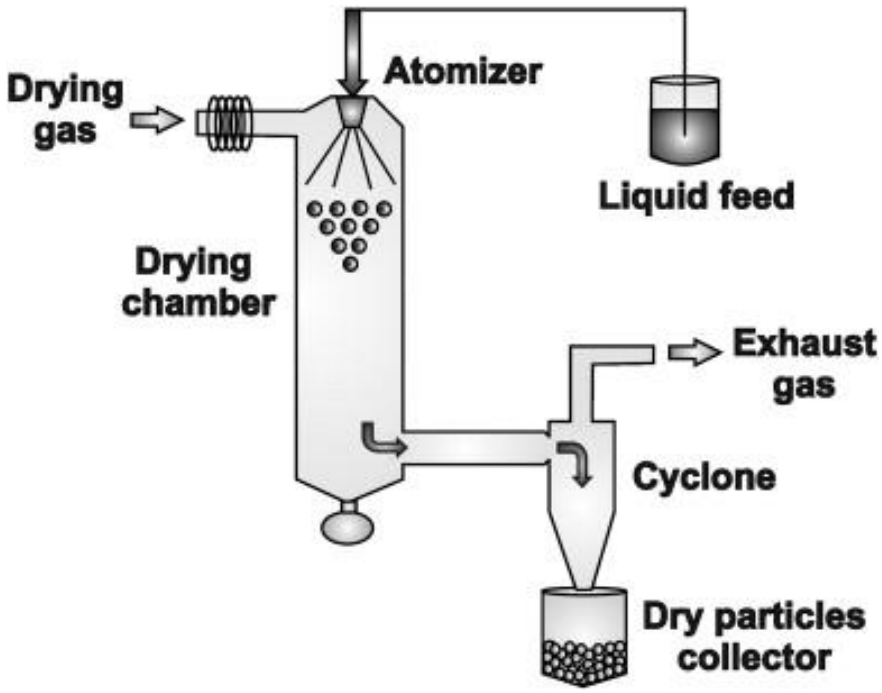

Figure I-6 Schematic representation of the spray drying process

In this process a film of shell material is formed around the droplet surface, retarding the evaporation of the larger active molecules, as long as the smaller water molecules are evaporated. It is also possible to spray-dry a feed solution containing organic solution like acetone or ethanol, but higher safety risks need to be considered. That is the reason because these organic solutions are used much less by industries.

The properties of the dried product depend on the physical and chemical properties of the feed and the dryer design, and the operation. Additional benefits of the spray drying technique include the ability to produce powders of a specific particle size and moisture content, irrespective of the dryer capacity. It is a continues and easy operation which is fully automatically controlled with a quick response time, and is also applicable to both heat sensitive and heat-resistant materials.[21] Besides the advantages presented, there are some disadvantages related to the spray drying technique. First, some low-boiling actives can be lost due to the relatively high temperature used during the process; another drawback is the limitation in the choice of the wall material, because a low viscosity at approximately high concentration is needed. In table I-2 some of the main advantages and disadvantages of this technique are listed.

Advantages	**Disadvantages**
Low operation cost	No uniform capsules
High quality of capsules in good yield	Limitation in the choice of wall material
Rapid solubility of capsules	Very fine powder (further processing)
Small size	Not suitable for heat-sensitive material
High stability of capsules	

Table I-2 Main advantages and disadvantages of the spray drying technique

1.2.2.2 Fluidized-Bed

Fluidized-bed coating was first developed by D.E. Wurster in the 1950s; hence, the term “Wurster process”.[22] Fluidized bed technology is a very efficient way to apply a uniform layer shell material onto solid particles. The capability of coating particles with basically any kind of shell material is one of the most interesting aspect of this technology.[23] Fluid-bed coaters have become more popular with the increasing of the demand of encapsulated materials in the global market. It is a three-step process. During the first one, the particles to be coated are fluidized in a coating chamber in which a hot atmosphere is promoted. The coating material is then sprayed thorough a nozzle onto the particles, inducing the film formation, to which wetting and drying stages follow. The rapid evaporation of the solvent or the mixtures is accomplished by the hot air in the chamber. This technology allows specific particle size distribution and low porosities to be designed into the product.[24] Other advantages of the fluidized bed are the smaller flow area and easiness of control. Moreover, it is a low-cost drying technology compared with others drying equipment, such as spray dryers.[25] Different types of fluid bed coaters are top spray, bottom spray and tangential spray, and their scheme is showed in figure I-7.

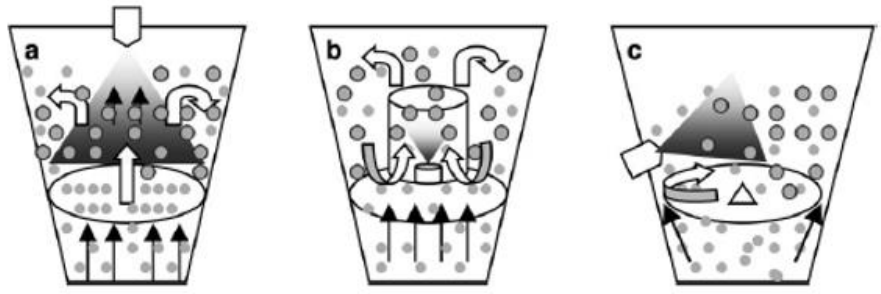

Figure I-7 Schematics of a fluid-bed coater. a) top spray; b) bottom spray; c) tangential spray

- In the top spray the coating material is sprayed downwards onto the fluid bed, coating the particles and encapsulated them. By opposing the flows of the coating materials and the particles, increased encapsulation efficiency and prevention of cluster formation is achieved. The top spray fluid-bed coaters allow higher yields of encapsulated particles then bottom and tangential sprays. However, in this configuration, is impossible to control the distance that the particles travel before contacting the substrate, so coating imperfections can occur due to premature droplet evaporation.[10]
- The bottom spray, also called Wurster's coater, is widely used for coating particles as small as 100 µm. It is characterized by a cylindrical nozzle and a perforated bottom plate. Both the particles and the coating materials flows move upwards, with a cyclic process that is repeated until the desired thickness and weight is obtained. In this configuration, the path of droplets concurrently toward the core particles is very short, making premature droplet evaporation almost absent.
- The tangential spray is composed by a rotating disc at the bottom of the coating chamber, with a gap between them, through which the particles move. The nozzle is placed above the disc and the coating material is released, covering the particles after a minimum travel distance, that allows a higher yield of encapsulated particles.

1.2.2.3 Pan coating

Pan coating is one of the oldest industrial procedures for forming small, coated particles or tablets; this method was developed in the 1880s. A scheme of a pan coater is reported in figure I-8. It is useful to obtain particles of a size between micrometers and a few millimeters.

The substance used as coating is applied as solution or as an atomized spray to the core material in the coating pan. The core material has to be solid to be suitable for this technique. The following step is the solvent removal from the particles, usually accomplished by passing warm air in the coating pans over the coated materials or in drying oven.[26] Generally, for an effective coating, solid particles greater than 600 microns are considered essential. It is a process extensively employed for the preparation of controlled release beads, mostly in the pharmaceutical industry.[27]

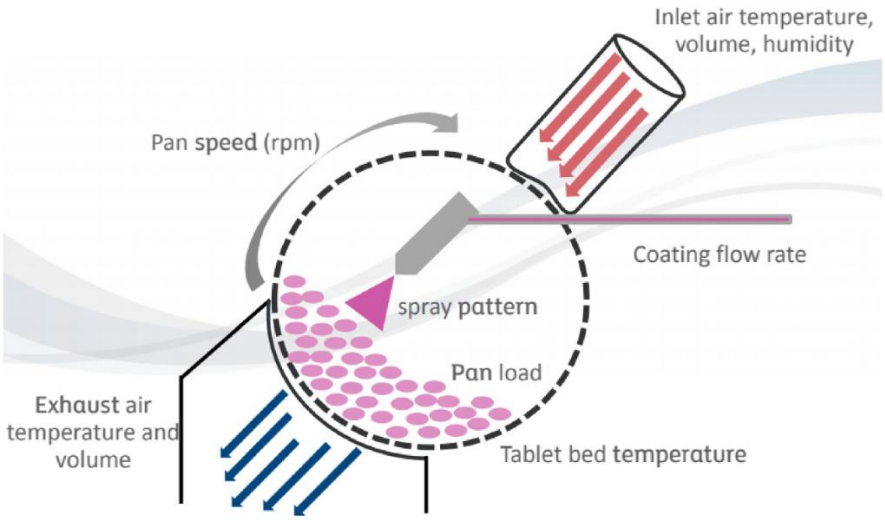

Figure I-8 Scheme of a perforated pan coater, main characteristics and some process parameters (Kerry Inc.2018)

1.3 Application fields of microencapsulation

Due to the different reasons aforementioned, microcapsules can perform multiple functions and thus, their applications are diverse. Microencapsulation technology is therefore widely used in several industries, especially in food and pharmaceutical ones. Moreover, it finds large applications in medicine, pharmaceutics, home and personal care, agriculture, cosmetics, textile, food, construction and waste water treatment, among others. In figure 8 the global microencapsulation

market share, by application, in 2018, is represented.

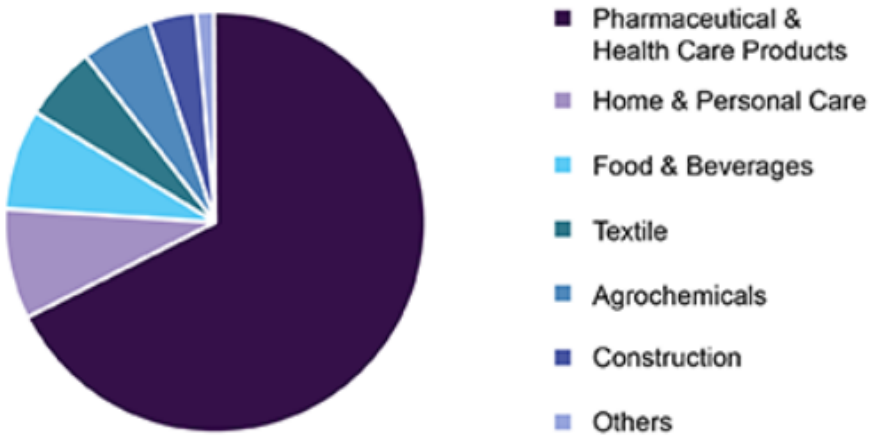

Figure I-9 Global microencapsulation market share, 2018 (Source: www.grandviewresearch.com).

Pharmaceutical products reached the highest market share in 2018. In this specific fields, the encapsulation technology is mainly applied to mask the bitter taste of the drugs and to reduce the gastric and/or other irritations caused by the drugs, apart from the controlled release of the core materials.[28] Recently, a great number of patents and publications was released. Hughes[29] provided a way to deliver an active drug to a posterior part of an eye of a mammal to treat or prevent a disease or condition affecting mammals. The method consists in delivering an effective amount of ester prodrug of the active drug such as tazarotene, prodrug of the tazarotenic acid. The prodrug is contained in biodegradable polymeric microparticles prepared using the o/w emulsion solvent evaporation methods. Janczyk *et al*[30] used an electronic tongue for the detection of bitter taste-masking microencapsulation of active pharmaceutical ingredients (APIs), namely ibuprofen and roxithromycin, non-steroidal anti-inflammatory and antibiotic drugs, respectively. The comparison between the chemical images obtained measuring pure API solutions and API encapsulated taste-masking additives shows significantly differences. Moreover, the

same character of change was found in both APIs. A large literature exists regarding microencapsulation of drugs for pharmaceutical industry. However, encapsulated drugs still have limitations in organ-specific drug delivery. Obtaining high reproducibility of microencapsulated drugs remain a challenge.[31]

Food industry is also one of the most interested in microencapsulation technology, accounted for ≈8% share of the overall revenue in 2018. Improving flavor, color and texture properties and extend the shelf-life of the products are the main reasons. Moreover, ingredients that have functional health benefits, such as antioxidants and probiotics, are of great interest.[32] However, most of these ingredients show low stability; since they are easily decomposed, they need a protection from the environmental factors. Microencapsulation is a way to solve this issue. In recent years, there has been a great deal of research aimed at producing microcapsules that meet the requirements of the food industry. Rocha *et al*[33] produced microcapsules of lycopene by spray drying. Lycopene is a carotenoid present in several fruits and vegetables, and it is widely used as red food colorant. However, due to the high number of double bonds, lycopene is easily decomposed by oxidation during the storage. The functionality of the capsules was analyzed by applying them to a cake. The results showed that the cake made with microcapsules was more pigmented that the standard one. Jiménez-Martín *et al*[34] prepared microcapsules of omega-3 fatty acid from fish oil from double and multilayered emulsion *via* spray drying. Impact of the microcapsules on frozen chicken nuggets were studied, investigating the effects of time of frozen storage on the oxidative stability and sensory properties of this product compared to that with bulk fish oil addition. Results of the study showed that the time of frozen storage had no effect on the sensory quality of chicken nuggets enriched with omega-3 fatty acids.

Microencapsulation of omega-3 fatty acids from fish oil could be used to enrich pre-fried frozen meat products with fish oil, improving the oxidative shelf-life and preserving the sensory quality characteristics of the products. In the study of Robert *et al*[35], pomegranate bioactive compounds (polyphenols and anthocyanins) were encapsulated with maltodextrin or soybean protein isolates by spray drying. Pomegranate polyphenols show prevention of cardiovascular disease and cancer, while the anthocyanin pigments have a well-known role in nutraceutical and health benefits given by natural oxidants, that confer them antimicrobial, anti-inflammatory and anti-carcinogenic properties. However, these molecules are unstable to different stimuli (pH, temperature, light) and the fresh juice has a short shelf life. Microencapsulation technologies is a way to address this issue, *via* the stabilization of polyphenol and anthocyanins for use in industrial purposes. The stability of the bioactive compounds microcapsules powders was studied, showing the protective effect of the shell material. Moreover, the stability in real-condition test, when the microcapsules were added to the yogurt, was analyzed, confirming that the pomegranate capsules studied could be used to design functional foods.

Another big share market is related to the cosmetics, home and personal care products. This is a multibillion-dollar market and has shown great expansion. A strategy to be successful in such a competitive sector is to differentiate the products. This purpose can be achieved by means of new and emerging technologies, such as microencapsulation.[36] Microencapsulation can promote cosmetic and personal care base products by introducing innovation, added new functional properties and, consequently, added value.[37] This technology offer an ideal and unique carrier system for active ingredients, allowing the controlled and targeted release, isolation and protection of the active

compounds, improved stability and efficacy, to mask undesirable odor and also the improvement of the tactile and visual appearance of a variety of cosmetics and personal care products.[4] Vitamin C has several biological and dermatological functions; it provides photo protection, it promotes collagen biosynthesis and causes melanin reduction. However, Vitamin C is highly unstable to air, light, oxygen and it easily decomposes into inactive compounds. Yang *et al*[38] show a method of encapsulating vitamin C in an inorganic layered material with high biocompatibility and skin affinity, so perfectly applicable as cosmetic ingredient. The ternary system described by the authors, exhibited an enhanced storage stability and a sustained releasing of Vitamin C into the skin through the *stratum corneum*, facilitating the penetration of the molecule. Caffeine has shown increasing interest from cosmetic application due to its biological activity. It is used as an active compound in anti-cellulite products, it has potential antioxidant properties, protecting cells against the UV radiation and slowing down the process of photoaging of the skin, it increases the microcirculation of blood in the skin and it also stimulates the growth of hair[39]. Cangueiro *et al*[40] prepared alginate microspheres by emulsification/internal gelation technique for the improvement of absorption of caffeine through an *in vitro* skin permeation model performed by Franz diffusion cell, to be applied as carriers for anticellulite treatment. Their study demonstrates that the encapsulation of caffeine by emulsification/internal gelation method can be an alternative for the delivery of this compound and it may be applied also for other drugs.

In the context of microencapsulation applied to the personal/home care industry, fragrances encapsulation assumes a big importance. Fragrances are small substances with scent. These aroma molecules add pleasant scent to human body, objects and living spaces, providing favorable effect also on our emotional perception[41].

Both natural and synthetic compounds are used to obtain these molecules. However, fragrances compounds are generally unstable due to their reactive functionalities, such as aldehyde, ketone, ester and lactone, liable to hydrolysis and oxidation. Since fragrances are considered vital in communicating product efficacy in terms of cleanliness, hygiene and freshness in that kind of consumer products[42], researchers have been working to develop technologies to include them in the most effective way. To capture the fragrance in its original form with minimum change and maximum retention and to mitigate its volatility, the most common method is the encapsulation approach. The shell of the capsule can act as a diffusion barrier and enhance the retention of pristine fragrance[43]. In addition to that, encapsulation of fragrances helps to protect them from uncontrolled interaction with the environment and to complete release the aroma when and where it is desired.[44]

In figure I-9 the schematic representation of the core material release through the polymer microcapsule shell is showed. The release of the fragrance at appropriate time and place is a very important characteristic of the encapsulation process, increasing the effectiveness and reducing the costs associated to the application.

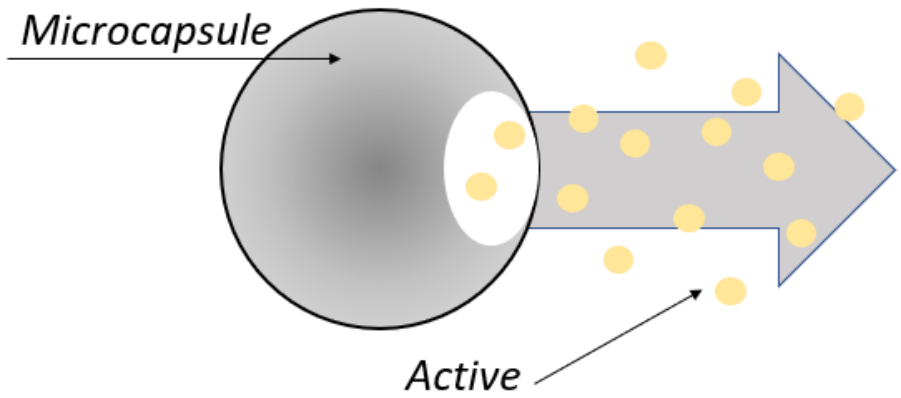

Figure I-10 Release of the active from the microcapsule

There are many factors affecting the release rates, including the solubility of the internal phase in the environment, the type of polymer shell employed, the molecular weight of the polymer coating, the particle size of the capsule and the interaction between the shell and core material.[13] In figure I-10 an example of the benefit of fragrance encapsulation as perceived by the consumers is represented.

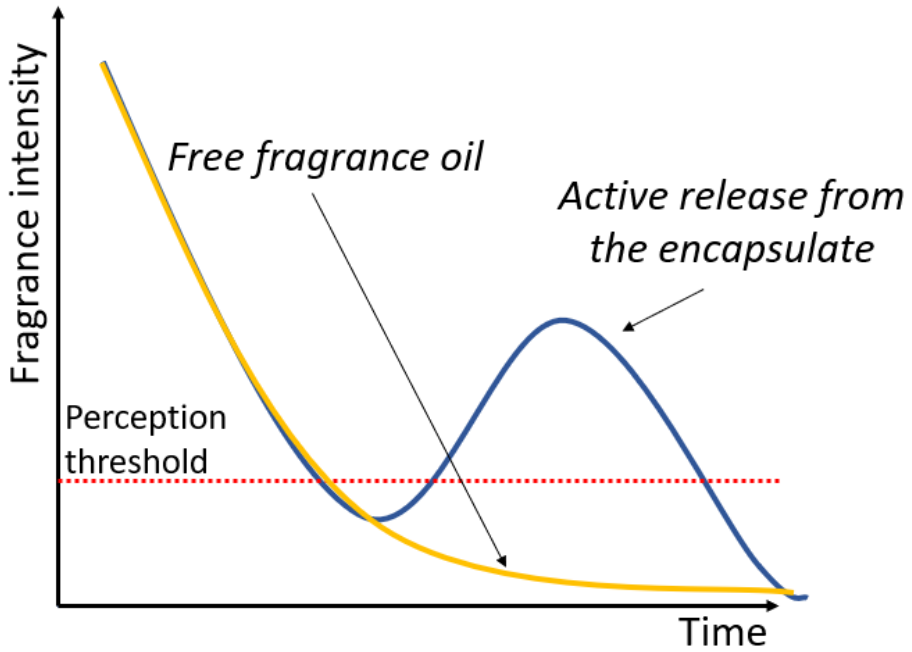

Figure I-11 Benefit of fragrances encapsulation for consumers perception

To understand the importance in the market of this technologies, some examples of fragranced products are following reported: air fresheners bath additives, candles, decorative cosmetics, deodorants, antiperspirants, perfumes, soaps, and hair-care, household, oral hygiene, personal-care, shaving, skin-care and laundry (detergents, softeners) products.[45]

1.4 Motivation of the thesis

As mentioned before, the interest in the microencapsulation technology is increasing during the last years due to the several benefits that it can bring. This technology is continuously developing, because of the need to produce capsules with excellent properties and by more simple methods. Recent published patents and publications in the area of microencapsulation suggest that both industrial and academic sectors are urging to explore this area, as represented in figure 11.

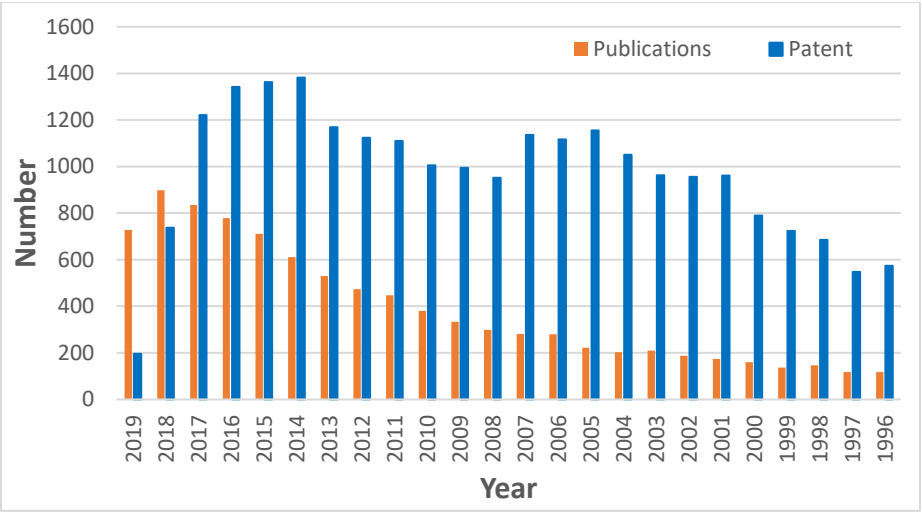

Figure I-12 Number of patents and papers published in recent years. Patent containing the word "microencapsulation" in the title, abstract, objective of invention or concepts (Source: ORBIT). Papers containing the word "microencapsulation" in the title, abstract or keywords of the document (Source: Web of Science). The 2019 is counted only through September 2019.

This work, in collaboration between the URV and the P&G company, reflects both purposes of bringing scientific knowledge about the aforementioned topic and providing the basis for a concrete technological research applicable to consumer goods. Several personal care, beauty care and home care products on the market already implement the microencapsulation technology, differentiating them from their competitors. In this context it is important to develop novel processes, or optimize existing ones, to microencapsulate active

principles with interest for these industries, thus contributing for innovative and high added value products creation, in response to human needs and desires.[36]

1.5 Objectives

The main objective of this thesis is the development of solvent stable microcapsules for controlled release of actives, to be included in consumer goods for personal and home care applications. The encapsulation necessity might be due to reasons like retarding the evaporation rate, improve the deposition, avoiding excessive draining into the laundry waters among others, depending on the specific application in the product. The main challenge of the work is the complex chemistry of the active material to be encapsulated.

A technical accord with a high content of logP perfume raw materials (PRMs) has been chosen, called Sweet & Smart (S&S). The reason for this choice is the enlargement of the palette of perfumes that would be possible to encapsulate as results of the success of the project and consequently a wider flexibility in the PRMs formulations and the possibility to provide different perfume characters, adducing commercial value to the consumer goods. This is a very valuable attribute, since nowadays the consumer's enjoyment for several consumer goods, such as personal care products, laundry detergents and fabric softeners, is enhanced using fragrance chemicals.[46]

The second key point of the work is the sustainability of the system. Modern societal trends are pushing the industrial directives and the focus of the research to more eco-friendly solutions. Moreover, during the last year, following the requests from the European Commission, European Chemicals Agency (ECHA) has started to prepare restriction proposals for intentionally added microplastic particles to consumer or professional use products of any kind.

According to the last considerations, the objectives of the work can be resumes as follow:

1. Selection of materials:
    a. that could accomplish the upcoming European regulation, promoting, therefore, the preparation of a sustainable system by using natural or natural derived materials;
    b. that are capable to interface the selected active (S&S) and full product formulation, such as heavy-duty liquid (HDL) and/or liquid fabric enhances (LFE);
2. Exploration of the microencapsulation technique and study of the process parameters:
    a. application of existing and common encapsulation techniques evaluating their feasibility when applied to the selected materials;
    b. development of new encapsulation technique, designing it based on the properties of the compounds utilized;
3. Preparation of the microcapsules and characterization. It includes the morphologic analysis and the study of the performance, in terms of activity, encapsulation efficiency and understanding of the factors influencing the encapsulation of each perfume component;
4. Assessment of the potential application of the prepared capsules in full product formulations.

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2. Selection of materials

In this chapter the materials utilized during the work are introduced. The reasons behind the choice of materials following the main scope of the project are stated; the, their properties and main applications are presented. After that, the tests carried out for the selection of the appropriate materials are described and shown.

2.1 Introduction

The selection of the materials for an encapsulation process is a crucial point. In fact, depending on the encapsulating agent, the encapsulation method that can be most adapted to the properties of the material is subsequently chosen. Moreover, the properties and stability of the final product depend on the interaction between the materials used as shell and core. For this reason, before proceeding with the encapsulation process, some considerations and some tests were necessary to define which was the suitable material to use as a polymer shell of the capsules. According to what already described in Chapter I, the main objectives of this thesis were to encapsulate an active created with specific properties (high percentage of low logP components) and to find a solution that was environmental-friendly.

The partition coefficient (P) is the ratio of concentration of a solute between two solvents at equilibrium, specifically for un-ionized solutes; it is therefore the measure of the difference in solubility of the compound in the two phases. Commonly, the two phases are water and 1-octanol[1]. During this work we will always refer to this case when we talk about partition coefficient. The logarithm of the ratio is thus logP. It can be expressed as follow:

$$\log P_{\mathrm{oct/wat}} = \log\left(\frac{[\mathrm{solute}]^{\text{un-ionized}}_{\text{octanol}}}{[\mathrm{solute}]^{\text{un-ionized}}_{\text{water}}}\right) \qquad \text{(II-1)}$$

2.2 Materials

The objectives of the thesis announced in the previous paragraph, become preliminary conditions for this work, which can be summarized as follows:

- The core material was fixed, and it was a technical accord called Sweet&Smart composed by a mix of 15 different fragrances;
- The shell material selection was made between polymers that were natural or naturally derived, or in any case that presented biodegradability properties.

Following the last indication, the polymeric material that has been chosen is the cellulose acetate (CA). The reasons that led to this choice are explained in the next paragraph. Moreover, titanium dioxide nanoparticles have been employed by preparing an organic/inorganic hybrid composite. The Sweet&Smart will be introduced later in this chapter and its components and properties will be listed.

2.2.1 Cellulose acetate

Cellulose acetate is the most widely used acetate ester of cellulose.[2] In a world where environmental protection is becoming increasingly important, cellulose acetate is playing an increasingly important role since it is a green polymer and that it derives from acetyl substitution of cellulose, which is the most abundant organic polymer on Earth[3,4]; it is an important structural component of the primary cell wall of green plants and many forms of algae, some species of bacteria secrete it in forms of biofilms and cotton and wood have a cellulose content of 90% and 40/50%, respectively.[5,6] CA was synthesized for the first time in 1865 by Schützenberger, who made it by heating cellulose in a sealed glass tube with acetic anhydride.[7] The first patent appeared in 1894 by Cross and Bevan to replace collodion and nitrocellulose for a hardly inflammable cellulose[8]. In the early 1900s it began to be used for textile and plastic applications, as well as for filter tow for cigarettes and for photographic film production.

Cellulose acetate can be composed of green lignocellulose[9] which is treated by acetylation process or by esterification of acetic acid and anhydride.[10,11] It has many advantages, such as good film forming property[12], high selectivity[13], good biocompatibility[14] and easy processing. As a plus, it is a low cost polymer, easy to handle, with unproblematic availability[15] and, as mentioned, it is environment friendly.[16,17] Nowadays it is widely used in filtration[18], adsorption of metal ions[19], water treatment[20], reverse-osmosis[21], textile fibers[22] and so on. World consumption of cellulose acetate is mainly in four different markets: filter tow for cigarettes, textile fibers, polarizer protection film in liquid crystal displays (LCD) and coatings, plastics and membranes. In figure II-1 the world consumption of cellulose acetate flakes is presented.

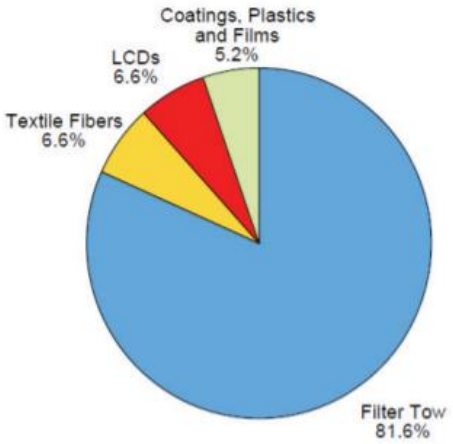


Figure II-1 World consumption of cellulose acetate flake (Source: CEH Marketing Research Report of Cellulose Acetate Flake, September 2016)

The chemical structure of CA is represented in Figure II-2.

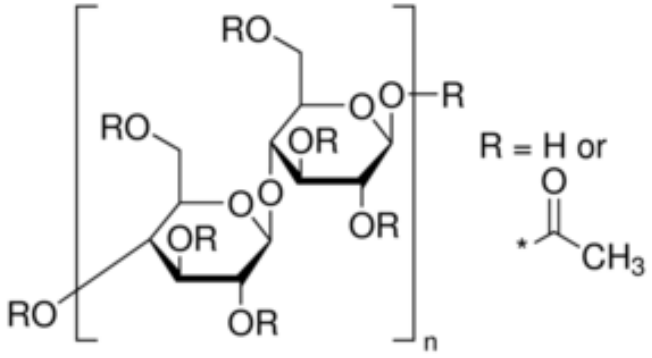


Figure II-2 Molecular structure of cellulose acetate

The mechanism of production of cellulose acetate starting from cellulose is shown in Figure II-3. First, the cellulose is reacted with acetic acid and acetic anhydride in the presence of sulfuric acid. A partial and controlled hydrolysis takes place to remove the sulfate and a sufficient number of acetate groups to obtain the desired product.

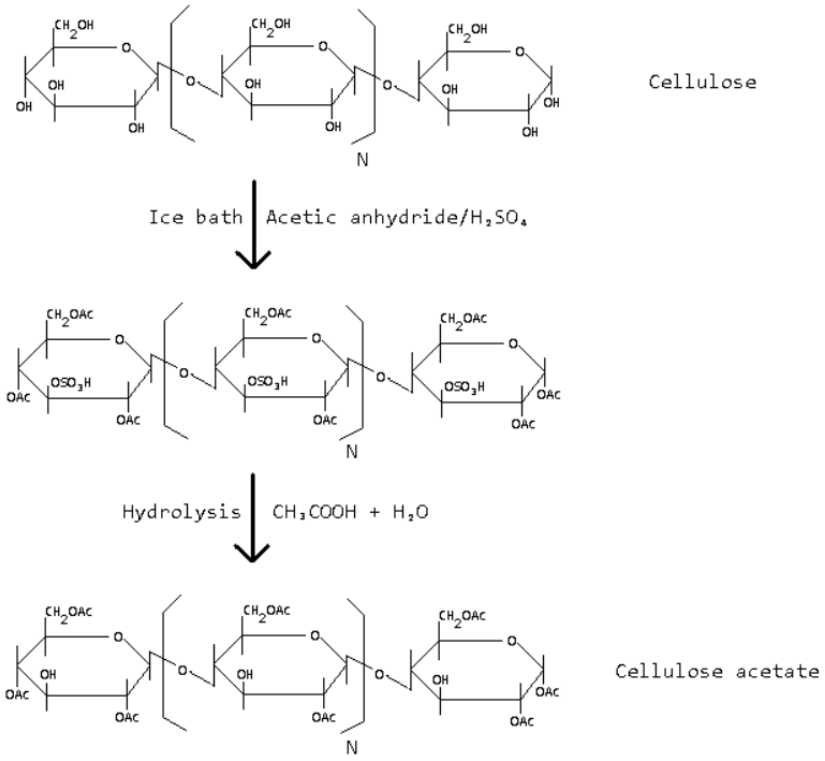


Figure II-3 Cellulose acetate preparation from cellulose

Depending on the way it is processed, different degree of substitution (DS) can be obtained. The DS of a polymer is the average number of substituent groups attached per base unit (in the case of condensation polymers) or per monomeric unit (in the case of addition polymers). The term has been mainly used in cellulose chemistry where each anhydroglucose (β-glucopyranose) unit has three reactive (hydroxyl) groups; degrees of substitution may therefore range from zero (cellulose itself) to three (fully substituted cellulose). Regarding CA, DS is the average number of acetyl groups attached per anhydroglucose.[23] The solubility of CA lies in the DS: CA with DS of 2-2.5 is soluble in some organic solvents, such as acetone, dioxane and methyl acetate and higher acetylated types are soluble in dichloromethane.[24] In addition, CA may also become water-soluble with a moderately low degree of substitution (0.4–0.9)[25], even if, at present, it is difficult to prepare such water-soluble cellulose acetate (WSCA) samples directly. The most commercialized cellulose acetate in the market are fully substituted cellulose triacetate (CTA) and partially substituted cellulose diacetate (CDA, DS=2,5). From now on, we will refer to cellulose acetate as cellulose diacetate, as we always utilized the partially substituted one.

Some properties limit the usefulness of CA, such as its low dimensional stability at high temperatures and humidity, its limited compatibility with other synthetic polymers and the need for high processing temperatures.[26] Apart from chemical modification (e.g., polymer blends, introduction of functional groups), preparing organic/inorganic hybrid composites is an alternative path to overcome these limitations. Example of inorganic compounds, such as zirconium[27], titanium[28], aluminium[29] and silica oxides[30], are reported in literature.

The biodegradability of CA has been subject of attention for many years and numerous studies have been conducted to assess it. Currently, CA is generally recognized as a biodegradable polymer within the scientific community.[31–34] Two mechanism were recognized: biological and photo degradation. Biological degradation occurs due to deacetylation by chemical hydrolysis and acetylesterases, allowing the degradation of studies of the cellulose backbone.[35] CA was also found with limited utility due to its degradation.[36] Besides biological degradation, photo degradation is an important alternative for decomposing CA materials in the environment. Although CA polymer alone has limited photo degradation in sunlight, many consumer products have additives that allow enhanced photo degradation. Titanium dioxide is commonly added to enhance the whiteness of CA materials and is a photo oxidation catalyst that causes degradation in sunlight.[32] Cellulose acetate/TiO_2 composite is a highly versatile material. It is applied as a ultrafiltration membrane[37], enzyme immobilization support material[38] and in electrochemical sensors[39], among others.

In our case, we have preliminarily proposed the use of composite hybrid capsules CA/TiO_2 with the aim of obtaining two advantages:

- hinder the flow of the liquid inside the capsule towards the outside by placing the nanoparticles
- increase the biodegradability of the final product by introducing a photocatalyst; in fact, TiO_2 nanoparticles (NPs) are of great importance for enhancing photocatalytic activity by facilitating access to reactive sites on the surface of the photocatalyst.[40]

2.2.2 Titanium dioxide

Titanium dioxide, also known as titanium (IV) oxide or titania, is the naturally occurring of titanium, chemical formula TiO_2. Its molecular structure is shown in figure II-4.

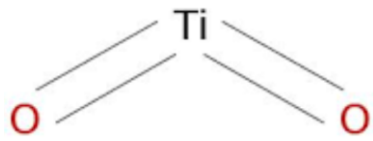


Figure II-4 Molecular structure of TiO_2

Titanium dioxide is the most widely used white pigment because of its brightness and very high refractive index, in which it is surpassed only by a few other materials. Commercial TiO_2 pigments are manufactured in two morphological crystalline forms (anatase or rutile). TiO_2 is a low cost and efficient photocatalyst[40,41], widely used in several fields, such as electrochemistry[42], hydrogen sensors[43], detoxification processes[44], dye-sensitized solar cells and so on.[45–47]

The photoactivity of TiO_2 has been extensively studied.[48–50] In particular, the photocatalyst activity of TiO_2 applied in CA is reported in several studies.[51,52] It is always assessed the effectiveness of TiO_2, enhancing the polymer photo degradation. In Figure II-5, degradation catalyzed by titanium dioxide can be identified, both in film or fibers.

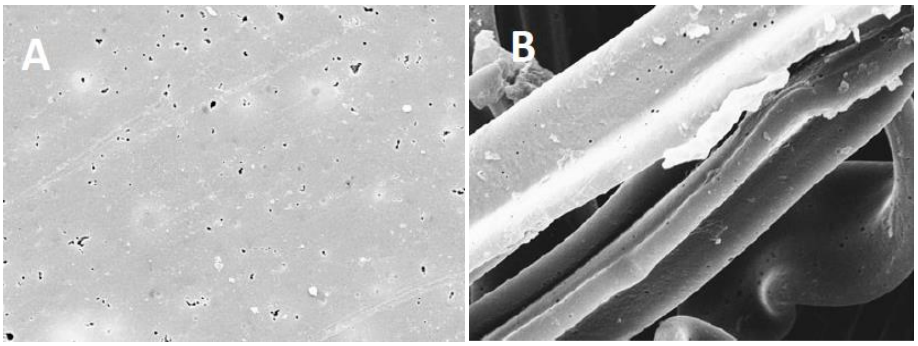


Figure II-5 Microscopy picture[40]: a) holes in a CA/TiO2 film; b) fibers irradiated in a weathereometer

A very important aspect about TiO_2 NPs is their toxicology. Previously, TiO_2 NPs were reported to be inactive substances.[53,54] Recently, it was demonstrated that they have different toxicity level depending on their properties, which greatly vary from the normal-sized TiO_2.[55] Many studies, by now, focus the attention on the negative effects that these nanoparticles cause to the human body, acting on different organs.[56–59] Generally, these disturbance are inversely correlated with the particle size and directly correlated with the administration dose.[60] In 2010, after investigations, the International Agency for Research on Cancer (IARC), classified titanium dioxide as “possibly carcinogenic to humans by means of inhalation (category 2B)”.

2.2.3 Sweet&Smart

The technical accord S&S is a mix of different fragrances and it was created specifically for this project.

2.2.4 Solvents

Two solvents have been selected and used during this work. The selection process was the same as for the materials; different solvents have been used in the first screening test and those that gave the best performances were used for encapsulation processes. Obviously, even for solvents it was decided not to use compounds that could be toxic or that could have caused problems in applications for body-care or for home-care.

Acetone and acetic acid were the solvents chosen for our work. Their properties are presented in Table II-2 and II-3:

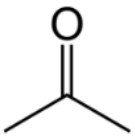
	Acetone
Molecular structure	
Chemical formula	C_3H_6O
Molecular weight	58.08 $g \cdot mol^{-1}$
Boiling point	56.05 °C
Melting point	-94.7 °C

Table II-2 Physicochemical properties of acetone

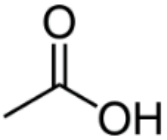
	Acetic acid
Molecular structure	
Chemical formula	$C_2H_4O_2$
Molecular weight	60.052 $g \cdot mol^{-1}$
Boiling point	118 to 119 °C
Melting point	16 to 17 °C

Table II-3 Physicochemical properties of acetic acid

2.3 Experimental section

As stated in Chapter I, the choice of the encapsulation process depends on the materials used. For this reason, before proceeding with the preparation of capsules, it is appropriate to conduct some tests to study the adequacy of the selected compounds. These tests were conducted by preparing membranes. Although some parameters are not the same if considering membranes or capsule (e.g., the surface

area changes considerably), this was the quickest way to obtain indicative information necessary for selecting the material to be used as the capsule shell.

Membranes were prepared *via* phase inversion by immersion precipitation. This is a process whereby a polymer is transformed in a controlled manner from a liquid to a solid state.[61] During preparation, polymer in liquid phase solidifies and the solid matrix is formed. By controlling the initial stage of phase transition the membrane morphology can be controlled and it is possible to prepare porous as well as non-porous membranes. The concept of phase inversion covers a range of different techniques, but most of the phase inversion membranes are prepared by immersion precipitation process. In that specific technique a polymer solution (polymer and solvent) is cast on a suitable support and immersed in a coagulation bath containing a non-solvent and the precipitation occurs because of the exchange of solvent and non-solvent. The solvent diffuses into the coagulation bath, whereas the non-solvent will diffuse into the cast film. After a certain time, the exchange of solvent and non-solvent proceeds until the solution becomes thermodynamically unstable and de-mixing takes place.[62] The obtained membrane structure depends on combination of mass transfer and phase separation.[63]

In order not to widen the discussion on this preliminary part too much, only the procedure for the system subsequently chosen will be described.

2.3.1 Materials

Cellulose acetate (Mn ≈30.000 $gmol^{-1}$), TiO_2 NPs (in anatase form) and Acetone were purchased from Sigma Aldrich. Glacial acetic acid was purchased from Scharlau. S&S technical accord and Neptune

Fair HDL were prepared and supplied by P&G. All the compounds were used as received without any further purification.

2.3.2 Membrane preparation

A certain amount of TiO_2 NPs was added in 30:70 (wt.%) acetic acid/acetone mixture and sonicated for 15 minutes. Then the cellulose acetate (10% by weight) was added and the solution was stirred for 24h. The resulting solution was cast on a glass with use of a casting knife of particular thickness and immediately immersed into the coagulation bath (water). Membrane precipitates in seconds. Prepared flat sheet membrane was taken out from the water and left overnight to dry on air. Membrane with different TiO_2 content were prepared, from 0% to 25% in weight respect to the polymeric phase. A scheme of the membrane formation process is represented in Figure II-7.

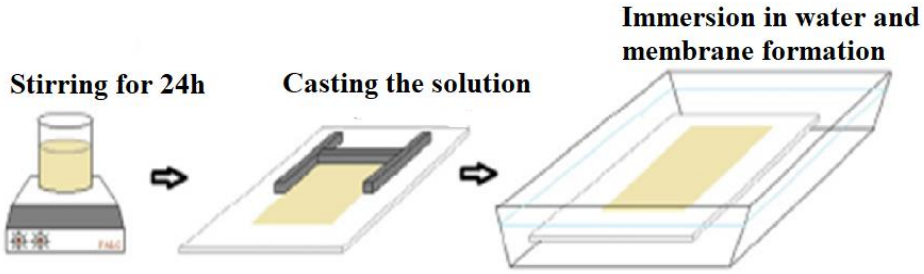


Figure II-7 Membrane formation process[64]

2.3.3 Methods and characterization techniques

Membranes morphology was investigated by means of Environmental Scanning Electron Microscopy (ESEM) FEI Quanta 600 apparatus. To obtain membranes cross-section micrographs without modifying their structure, they were immersed into liquid nitrogen and fractured.

Transmission Electron Microscopy (TEM) was used to determine the morphology and the size of the nanoparticles[65]. TEM images were obtained by JEOL 1011.

To verify the chemical stability of membrane in the presence of the phases that the capsules will interface in a real application, pieces of 2 cm^2 membranes were immersed in the S&S and in Neptune Fair for 10 days. After that time, they were taken out and dried with filter paper. The procedure was repeated 3 times for each membrane. The amount of absorbed liquid was calculated based on change in mass before and after immersion according to Eq. (II-2):

$$Weight\ gain\ (Wg) = \frac{(w_2 - w_1)}{w_1} 100\% \qquad \text{(II-2)}$$

where w_1 and w_2 refer to membrane weight before and after the test.

To understand the suitability of our system in conditions such as those found in real applications, for which our capsules will be prepared, a membrane permeability test has been developed. The polymeric wall of the capsules will have to interface on one side an active like the perfume described above, and on the other side a liquid with a heterogeneous chemical composition. Once again, the Neptune Fair was chosen for this test. The experiments were carried out in a double-compartment cell, called feed and stripping cell, connected by a circular window supporting the membrane. Feed and stripping solutions were placed in the compartments and stirred during experiments. The volume for feed and stripping solutions was always 200 ml.[66] In both cells, there was always the same base liquid (Neptune, Neptune diluted with water); in the feed cell 1% in weight of S&S was added. A picture of the apparatus is shown in Figure II-8. During the test, a lid closes the compartments at the top.

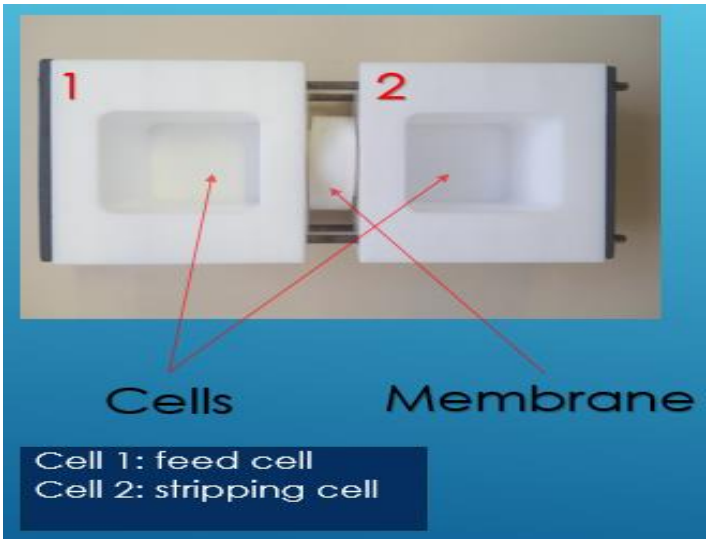


Figure II-8 Apparatus for the permeability test

The diffusion along the membrane was evaluated by analyzing, through Liquid-Liquid Extraction Gas Chromatography/Mass Spectrometry (LLE-GC/MS), samples taken from the stripping cell at different timing. The LLE was carried out according to literature.[67] Permeability was calculated as in Eq. (II-3)[68]

$$P = \frac{-dC}{C}\frac{1}{dt}\frac{V}{A} \qquad \text{(II-3)}$$

or in its integrated form

$$-ln\frac{C}{C_0} = \frac{A}{V}Pt \qquad \text{(II-4)}$$

where P is the permeability in cm min^{-1}, C are molar concentrations, A is the membrane area, V is the feed solution volume, and t is time in minutes.

The resulting capsules morphology is controlled by the balance of the interfacial tensions for the three phases involved in the capsules

formation and relates to the wetting conditions within the system.[69] The morphology of droplets of three immiscible liquids was derived and explained in terms of spreading coefficients by Torza and Mazon.[70] Then, this theory was expanded to encompass solid polymers[71]. Briefly, if droplets of immiscible liquids (phase 1 and 3) are brought in contact with a third mutually immiscible liquid (phase 2), the final equilibrium morphology can be deduced by determining the various interfacial tensions between the phases (γ_{12}, γ_{23} and γ_{13}). The spreading coefficient S_i for each phase can be defined as:

$$S_i = \gamma_{jk} - (\gamma_{ij} + \gamma_{ik}) \quad \text{(II-5)}$$

and designating phase 1 to be that for which $\gamma_{12} > \gamma_{23}$, then $S_1 < 0$. Then, there are only three possible combination of S_i, that is,

$$S_1 < 0,\ S_2 < 0,\ S_3 > 0; \quad \text{(II-6)}$$

$$S_1 < 0,\ S_2 < 0,\ S_3 < 0; \quad \text{(II-7)}$$

$$S_1 < 0,\ S_2 > 0,\ S_3 < 0. \quad \text{(II-8)}$$

When the condition in Eq. (II-6) are satisfied, the particles adopt a core/shell morphology (figure II-9.A) with phase 1 appearing as the core within a shell of phase 3. When Eq. (II-7) is satisfied, “acorn”-shaped particles are formed (II-9.B), and when Eq. (II-8) is satisfied, two separate droplets are preserved (II-9.C).

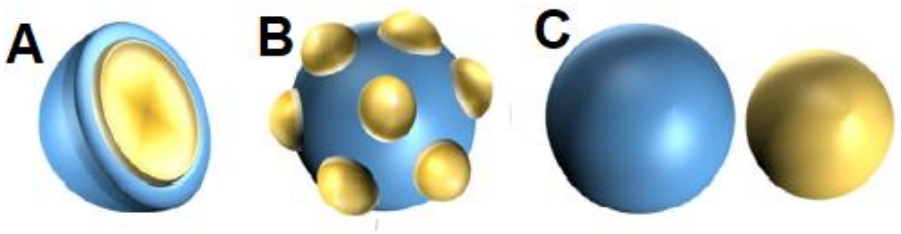


Figure II-9 Possible final microcapsule morphologies (post solvent-evaporation) dependent on spreading coefficients of the different phases: a) core/shell; b) acorn; c) dissociated[69]

To determine the interfacial tensions, also the surface tensions are required. Surface tension of the cellulose acetate (γ_p) was taken as 37mN m^{-1} from the literature.[72] Dynamic surface tensions (DST) of water and S&S were calculated using a Kruss BP50 Bubble Pressure Tensiometer. DST is measured using the internal pressure of a bubble at an immersed capillary for a surface age of 1000ms.

Interfacial tensions between the polymer and the liquids were calculated from the mean contact angle using Young's equation:

$$\gamma_{sv} = \gamma_{sl} - \gamma_{lv} cos\theta \qquad \text{(II-9)}$$

where l, s and v refer to liquid, solid and vapor phases, respectively.

Dynamic interfacial tension between water and S&S was calculated by means of a Drop-Volume (DV) Tensiometer (Lauda TVT1) at room temperature, based on two repetitions of 9 independently formed drops.

2.3.4 Results and discussion

CA membranes and CA/TiO_2 membranes were prepared *via* phase inversion by immersion precipitation technique. In Table II-4, the composition of the prepared membranes is shown. The wt.% of CA is respect to the solution, while the wt.% of TiO_2 is respect to the CA.

Sample	CA [wt.%]	TiO_2 [wt.%]
1	10	0
2	10	5
3	10	10
4	10	15
5	10	20
6	10	25

Table II-4 Composition of the prepared membranes

In Figure II-10 the ESEM pictures of the cross section of the membranes are presented, in order of increasing concentration of TiO_2. Sample 1 in Fig. II-10.A, not containing TiO_2, appears like an homogenous layer, while when increasing the TiO_2 concentration, it is possible to notice the particles embedded in the polymeric matrix. In Fig II-10.E and F, agglomerates of particles are visible, due to a big concentration of titanium in the initial solution. Thanks to the micrographs at bigger magnification, it is possible to notice that the morphology of the membranes changes considerably depending on the concentration of nanoparticles; in particular, porosity is increasing with the increasing concentration of TiO_2.

In figure II-11.A, sample 1 appears as a dense structure, while in the next two pictures, referring to samlpe 4 and 6 (TiO_2 concentration 15% and 25%) it is clearly visible the porosity generated during the membrane formation process. This is in accord with the literature[15,64], where TiO_2 concentration of 20/25% in CA system resulted in greater formation of macrovoids and more porous structures. Morphology is affected by the time required to complete the demixing process associated to the phase inversion. Slow demixing results in dense membrane, whereas fast demixing causes pores in membrane.[17]

Demixing acceleration during solidification of casting solution is reported to be directly proportional to thermodynamic instabilities.[73]

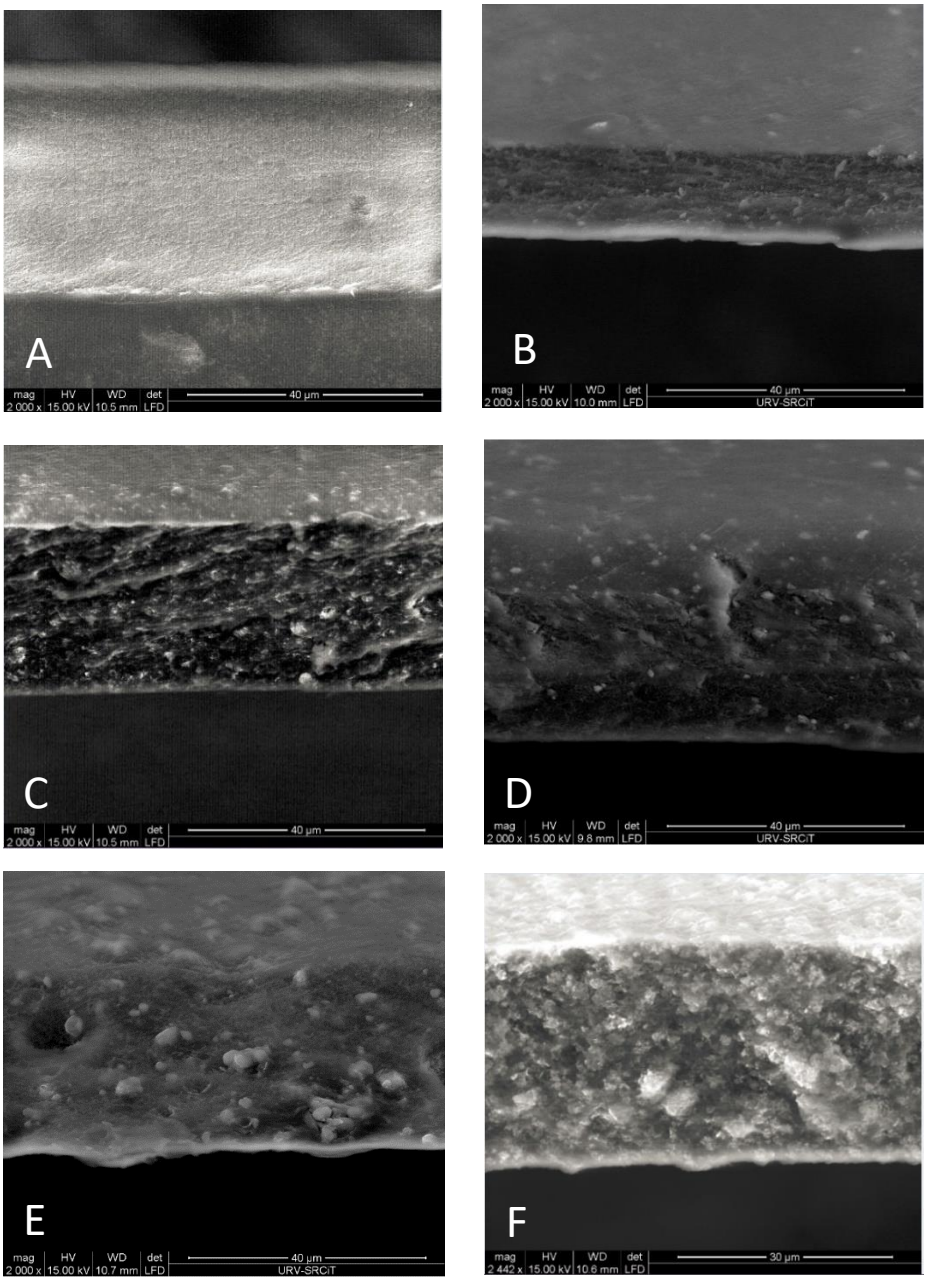


Figure II-10 ESEM micrographs of the membranes. a) sample 1; b) sample 2; c) sample 3; d) sample 4; e) sample 5; f) sample 6

In our case, high concentration of TiO_2 nanoparticles blended with CA, increased the thermodynamic instability in the casting membrane, accelerated the solvent-nonsolvent exchange when dipping the membrane in water. Hence, addition of 15% or more TiO_2 nanoparticles, caused generation of porosity in the membrane.[74] Another important aspect is the non-homogeneous dispersion of the nanoparticles during sonication. The agglomerates probably were not homogeneously dispersed, leading to incomplete bonding and porosity generation when CA was added to the TiO_2 dispersion.

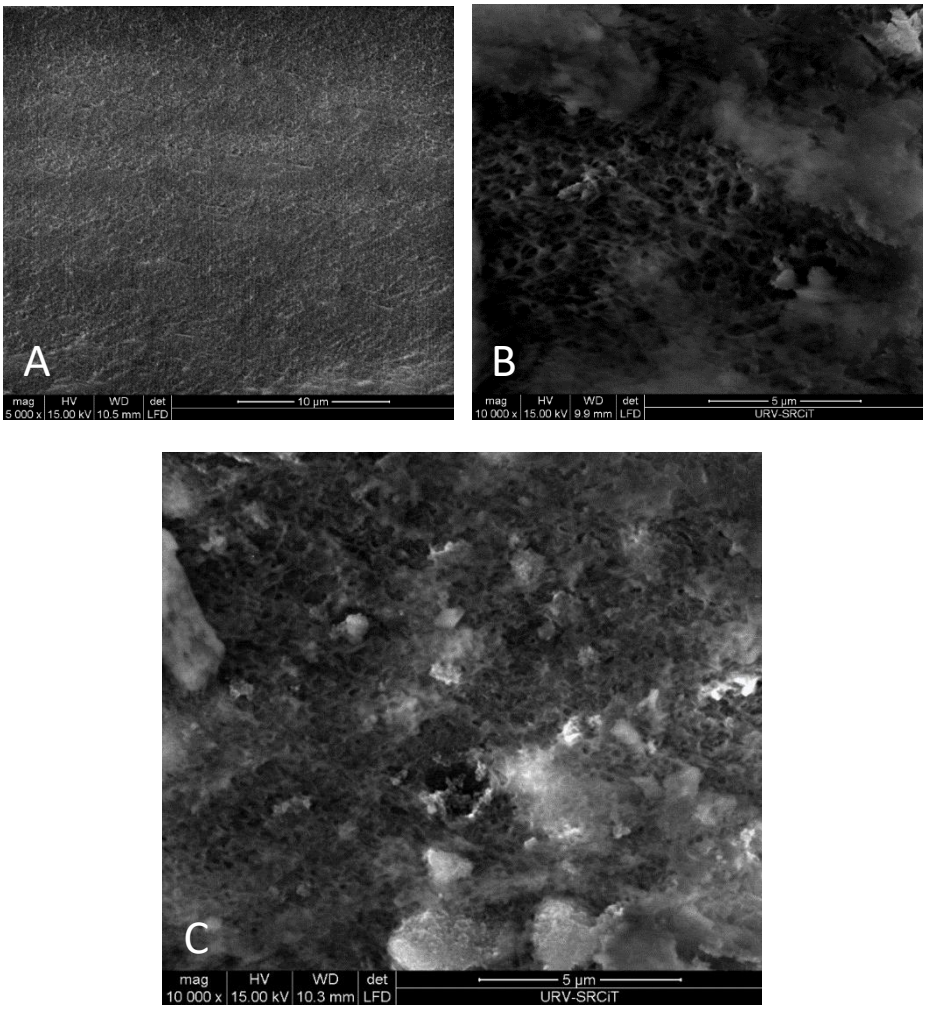


Figure II-11 ESEM magnification of sample 1 (a), sample 4 (b) and sample 5 (c)

Figure II-12 shows physical appearance of TiO_2 nanoparticles in anatase phase. As it is observed the particles are within 10-25 nm nanometer size with hexagonal shape, with the tendency to form agglomerates.

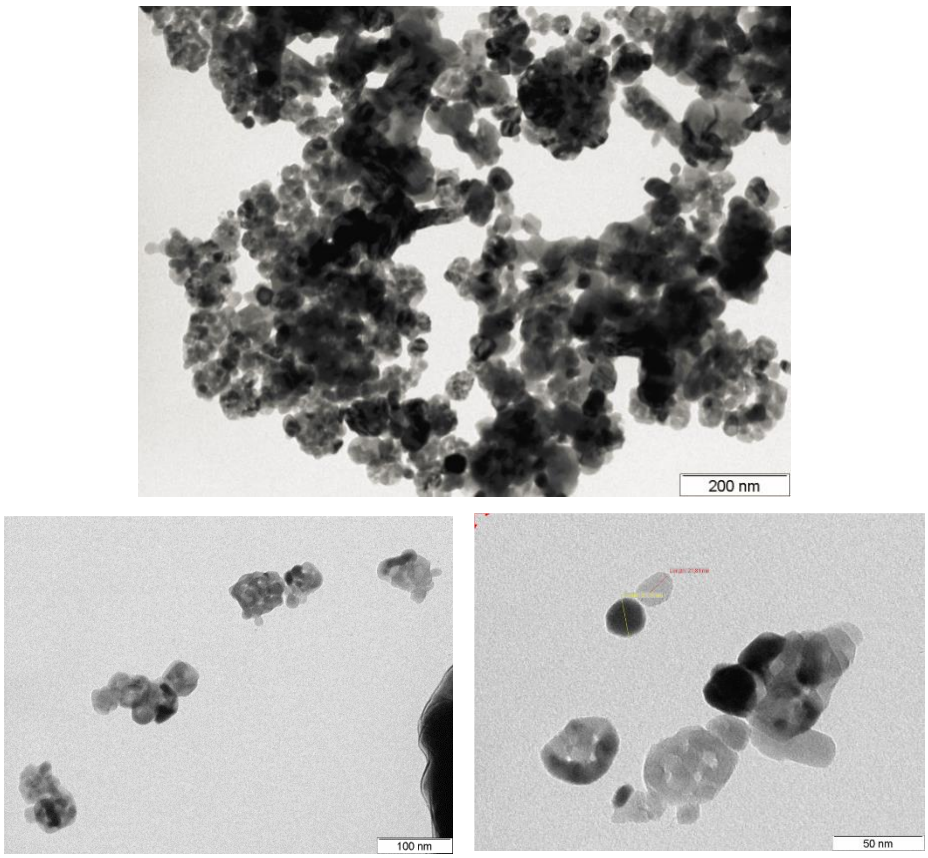


Figure II-12 TEM pictures of TiO_2 nanoparticles in anatase phase

The weight gain of the membranes after 10 days of immersion in S&S and Neptune Fair is represented in Figure II-13. The membrane without TiO_2 and those with a low concentration of nanoparticles (up to 10%), show a decidedly low swelling in both the solutions in which they were immersed, particularly in S&S. The other membranes, consisting of a higher percentage of titanium (from 15% to 25%), present a different behavior and a very high swelling. This is due to the morphology shown above; the high porosity that these membranes present explains the

high weight gain compared to those with a low concentration of TiO_2, whose dense structure leads to a much lower swelling.

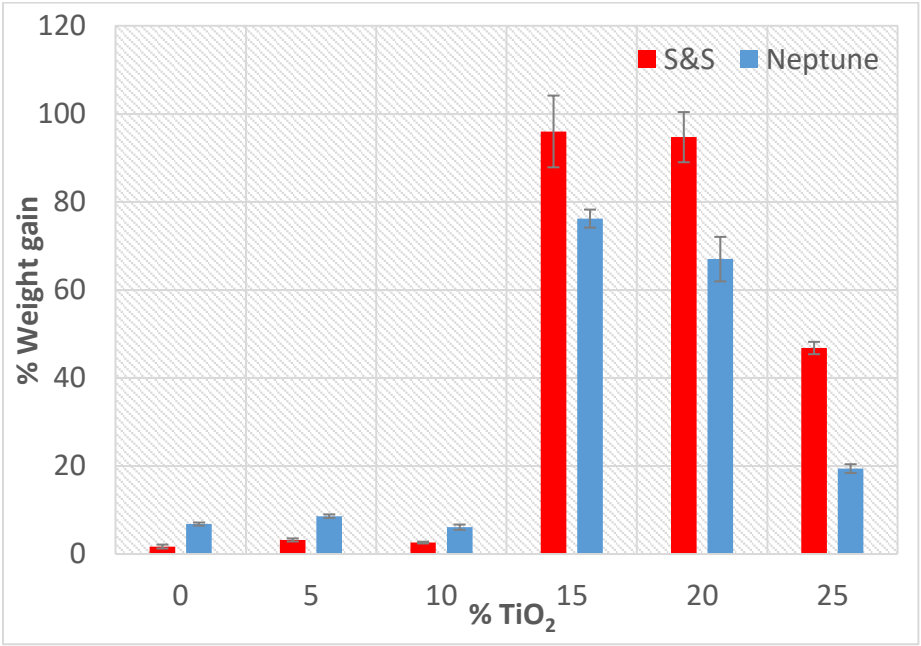


Figure II-13 Immersion test results for CA/TiO_2 membranes

Following these results, our attention focused on the first 3 samples, from 0 to 10% of TiO_2 concentration. The values of weight gain related to these samples are shown in Table II-5. The results of the immersion in S&S are very low; even if the values referring to the immersion in Neptune are slightly higher, we decided to consider acceptable a swelling up to the 10% of the initial weight. Hence, sample 1, 2 and 3 resulted promising for the microcapsules production.

Sample	%TiO_2	%WG in S&S	%WG in Neptune
1	0	1.7 ± 0.9	6.8 ± 0.7
2	5	3.2 ± 0.7	8.4 ± 0.8
3	10	2.6 ± 0.4	6.1 ± 1.2

Table II-5 Data of immersion test

The diffusion of S&S along the membrane was evaluated through the permeability test. Following the indication of the immersion test, sample 1,2 and 3 were used to perform this test. In every case, collected data indicate that in the stripping compartment the perfume was not present or at least it was under the detection limit. In fact, sometimes a very low peak in correspondence of PRMs retention time was found, but since it was under the limit of quantification (LOQ), it was impossible to determine the relative concentration. The LOQ is defined as the lowest amount of an individual analyte which can be quantitatively determined with suitable precision and accuracy.[75] As example, a GC spectrum is reported in figure II-14.

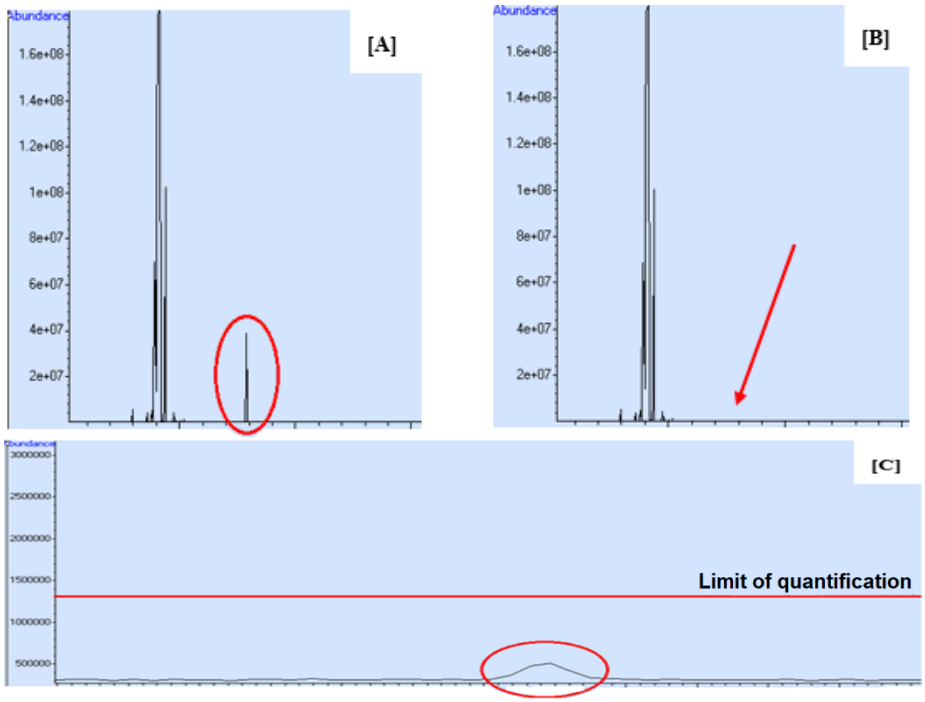


Figure II-14 Example of GC/MS result for the CA/TiO2 membranes. a) in the feed cell the peak related to a specific PRM b) at the same retention time, in the stripping cell that peak is not visible; c) zoomed image of [B] in which it is quite clear that the peak is under the limit of quantification

In figure II-14.A, the resulting peak of a PRM is clearly visible and it is related to the feed cell; figure II-14.B, referring to the stripping

cell, does not show any peak at the same retention time. Enlarging this area, a very small peak is visible (figure II-14.C). Anyway, it is too low to calculate the concentration of the PRM. This result was repeated for all the tests carried out on the 3 membranes, meaning that the systems were promising to act as barrier against the S&S; the CA and CA/TiO_2 membranes are capable to block the diffusion of the perfume from one side to the other one.

The permeability values of the membranes are reported in Table II-6. They were found to be very similar, considering the experimental error associated to all the procedure. It means that the presence of the nanoparticles is not influencing the diffusion properties of the membranes.

Sample	%TiO_2	Permeability [cm/min]
1	0	0.81
2	5	0.75
3	10	0.86

Table II-6 Permeability of CA/TiO_2 membranes

The similar morphology, together with the comparable properties highlighted through the immersion and permeability tests, led us to finish our research on the CA/TiO_2 blend, focusing only on the system composed exclusively of cellulose acetate. The literature of recent years that highlights the damaging effects of titanium nanoparticles[76] and their potential exclusion from home-care and fabric-care applications over the next few years has been a further motivation to abandon the initial idea of using nanoparticles as a catalyst to improve the biodegradability of CA.

The interfacial tensions and contact angles measured are resumed in Table II-7. The predicted morphology for our system, according to the measurements, is a core-shell structure.

θ_{pw} [°]	θ_{op} [°]	γ_{op} [mN/m]	γ_{pw} [mN/m]	γ_{ow} [mN/m]	S_1	S_2	S_3	Predicted morphology
59	0	8.4	0.3	11.3	-19	-3.1	2.6	Core-shell

Table II-7 Interfacial tensions contact angle and spreading coefficient calculated according to Eq. (II-5/7)

It should be noted that the interfacial tension between the polymer and the other two phases is measured using a membrane and calculating the contact angle with the liquids. It is therefore an indicative value. Furthermore, in the calculations carried out to calculate the spreading coefficient, we have noticed that when the contact angle changes, even by a few degrees, the predicted morphology would change, returning to case illustrated in figure II-8.C (dissociated). Although it is not mentioned in literature, we are probably in a thermodynamic border-line situation.

2.4 Conclusions

The selection of materials was carried out in the first part of the work, based on the scope of the project. Environmental considerations and screening test were the base of the choice. Immersion and permeability test indicated cellulose acetate as a promising material to encapsulate S&S and form stable microcapsules. Titanium dioxide has been investigated as a blend for CA, for its photocatalytic activity to enhance the biodegradability of the polymer and for the idea that the nanoparticles could have represented a further obstacle to the path of the liquid from the inside to the outside of the capsule. After not finding advantages in the use of the blend CA/TiO_2, rather than the membranes

prepared exclusively with CA and considering the possible health risks attributable to the use of nanoparticles, we have chosen to end our work with TiO_2. Thermodynamic measurements of interfacial tension allowed us to calculate the spreading coefficient, which is a parameter that allows us to predict the structure of the capsules starting from the phases involved in their preparation. The predicted morphology is of core/shell, which reflects the purpose of the thesis and the applications for which the capsules will be prepared. However, there are some approximations on the methodologies and a change of the predicted morphology is associated to the minimum change of some measurements.

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3. Preparation and characterization of capsules *via* Spray Drying technique

In this chapter an introduction of the spray drying technique is provided, including the main applications related to the microcapsules technology focusing on those that use natural or natural derived polymer. Then, the design of the experiment, the process parameters analyzed are shown. Finally, the morphological characterization and evaluation of the performance of the products are presented.

3.1 Introduction

The spray drying technique has been already introduced in Chapter I. Briefly, spray drying is a unit operation by which a liquid product is atomized passing through a nozzle in a hot gas flow contained in a chamber, to instantaneously obtain a powder.[1] The total time required for transforming the liquid product into powder is in the range of few milliseconds to few seconds.[2] The liquid product, namely the feeding, can be in solution, suspension, emulsion or paste form. The resulting dried powder is recovered through a cyclone separator. The application of this process in microencapsulation involves four steps[3]: preparation of the dispersion or emulsion; homogenization of the dispersion; atomization of the infeed emulsion; dehydration of the atomized particles. The first stage is the formation of a stable emulsion of the core material in the shell solution. Emulsion viscosity and initial particle size distribution have significant effects on microencapsulation by spray drying. High viscosities, indeed, interfere with the atomization process, leading to the formation of large and elongated droplets with a negative impact to the drying rate.[4] The composition and the properties of the emulsion, and the drying conditions affect the core material retention.[1] The feed solution is then atomized into the drying chamber filled by a heated air stream and the evaporation of the solvent leads to the formation of microcapsules. The efficiency of this method highly depends on the spray drying conditions; the main factors to be optimized are feed temperature, air inlet temperature and air outlet temperature.[5] The feed temperature influences the viscosity and thus, the fluidity of the feed solution; consequently, its capacity to be homogenously sprayed changes. The air inlet temperature must be appropriately adjusted: low inlet temperature leads to low evaporation rate, causing formation of microcapsules with high density membranes, poor fluidity and easiness of agglomeration; high inlet temperature, on

the other hand, causes excessive evaporation resulting in cracks in the membrane and subsequent premature release and degradation of the encapsulated material, besides the loss of volatiles.[6] The outlet temperature cannot be directly controlled because it depends on the inlet temperature and on the drying characteristics of the material. For the encapsulation of flavor ingredients, the range 50-80°C has been reported. In figure III-1 a schematic diagram of spray drying and product quality affecting factors is represented.

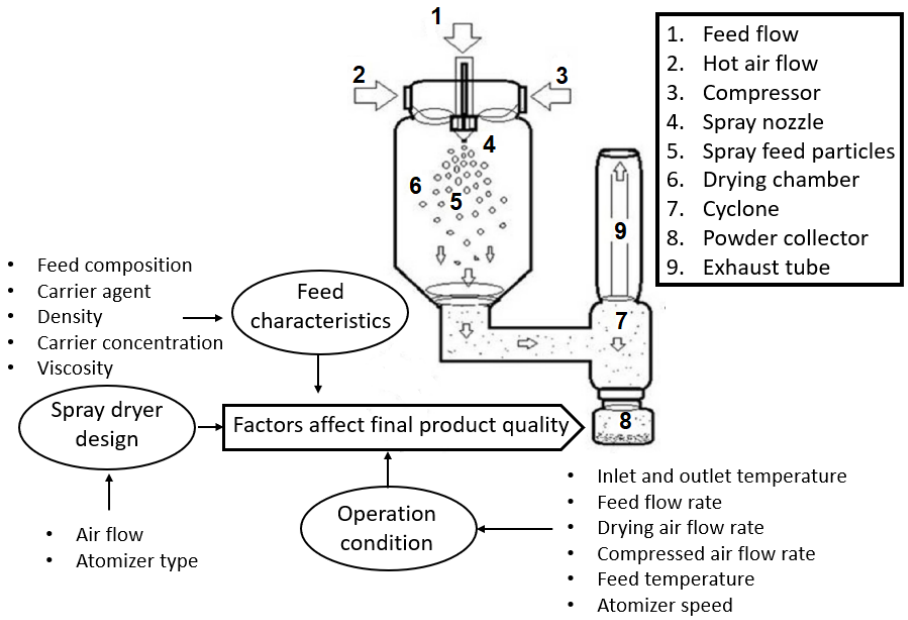


Figure III-1 Schematic diagram of spray drying and product quality affecting factors (adapted from Shishir et al[7])

This method is widely used at industrial scale, especially for the encapsulation of food bioactive compounds.[7,8] In recent years, various publications focus on the use of natural or naturally derived materials. Estevinho *et al*[9] studied the possibility to encapsulate β-galactosidase using different biopolymers as shell material. β-Galactosidase is one of the most important enzymes used in pharmaceutical and food industries. A significant percentage of the world population suffers from lactose intolerance or has difficulty in consuming milk and dairy products

caused by the lack of β-galactosidase activity[10,11]; this is the reason why it is important to immobilize this enzyme and release it in a controlled manner through biocompatible systems. They created and compared different β-galactosidase microparticle systems, evaluating the different biopolymers (arabic gum, chitosan, water soluble chitosan, calcium alginate and sodium alginate) as enzyme encapsulating materials. In particular, the effect of the encapsulation on enzyme activity, morphology and size of particles was studied. With their work, they demonstrated that the encapsulation of β-galactosidase enzyme using different biopolymers by the spray drying technique is possible. Calcium alginate and sodium alginate-based microcapsules presented a very smooth surface, while the microcapsules formed with arabic gum presented the smallest decrease of enzymatic activity. Paramita *et al*[12] investigated the impact of emulsifiers on the microencapsulation of *d*-limonene for the wall materials gum arabic, maltodextrin and their blend. Limonene is the major component in the oil of citrus fruit peels. The *d*-isomer, occurring more commonly in nature as the fragrance of oranges, is a flavoring agent in food and personal care manufacturing. By comparing the emulsion properties and the flavor retention of the different combination wall material-emulsifier, they found out that the recommended system among those studied, was gum arabic/polyglycerol ester. Furthermore, they discovered that is possible to enhance the retention of the encapsulated flavor, by using emulsifier to prepare the carrier solution.

In our case, we decided to firstly test our system with the spray drying technique because is a common technique used for polymeric capsules and it is an economic and industrially available process.

3.2 Experimental section

3.2.1 Materials

Cellulose acetate (Mn ≈30.000 $gmol^{-1}$) and Acetone were purchased from Sigma Aldrich. Glacial acetic acid was purchased from Scharlau. All the compounds were used as received without any further purification. The technical accord called Sweet & Smart was prepared by Procter & Gamble as descripted in Chapter II.

3.2.2 Microcapsules Preparation

Microcapsules based on cellulose acetate were prepared by a spray drying process. The polymeric solutions in different ratio were prepared by mixing the different compounds for 24h under magnetic stirring. In addition, the bottles must be perfectly closed, since it could penetrate water vapor (humidity of the environment) that could cause precipitation of the polymer. The range of polymer concentration was 3-6% and microparticles were prepared without perfume, and in ratio polymer:active of 1:1 and 1:3. The apparatus used was a Buchi Mini Spray-Dryer B290, as presented in figure III-2. It was equipped with a 0,7 mm diameter nozzle tip. An Inert Loop B-295 was connected to the apparatus, to enable the spray dryer to handle organic solvents safely. The rotameter, that is the indicator for the gas flow, was always set at a 30mm height, resulting in a spray gas flow of 357L/h.

The polymeric solution was then used as feed solution into the apparatus; different process parameters were analyzed, such as the inlet temperature, the pump and the aspiration. It is not possible to control the outlet temperature in a spray drying process, but it is reported as well in our experiments, as it can influence the final structure

of the products. After the preparation, the microcapsules were washed with distilled water and collected into vials for further analysis.

Figure III-2 Spray dryer and Inert Loop

3.2.3 Characterization

Microcapsules morphology was investigated by means of ESEM FEI Quanta 600 apparatus. To obtain microcapsules cross-section micrographs without modifying their structure, they were cryogenically cut.[13] First microcapsules were attached over a specimen disc with a freezing medium. An embedding medium for frozen tissue specimens was used (Tissue-Tek, OCT Compound, Sakura Tissue). Once the capsules were fixed over the specimen disc, the disc was immersed into a liquid nitrogen bath in order to freeze the sample. Next, the specimen disc was located in the cryochamber. Then, the sample was cut with thickness intervals of 1 μm at −20 °C and deposited over a glass. Finally, the cross-sections were analyzed by ESEM.

Thermogravimetric analysis (TGA) and Gas Chromatography-Mass Spectroscopy (GC-MS) were used to determine the activity of the capsules. Capsule activity is defined as the weight percentage of active

encapsulated in the capsule. Different methods have been proposed to calculate the activity of the capsules[14], presenting slightly difference in the results. TGA is a thermal analysis in which the changes in weight of a sample are constantly measured over time as the temperature changes. The heating rate needs to be set to avoid the overlap between the evaporation temperature of the encapsulated active and the temperature of degradation of the shell. TGA response curves of the pure components, the active and the shell, are needed for a comparison between their response profiles and that of the capsules. This correlation is used to determine the temperature range where only the mass loss of encapsulated active occurs. Once the correct temperature range is identified, it is possible to estimate the mass of the encapsulated active (active in capsules) as the weight loss of the capsules in that temperature range. The encapsulation efficiency (EE) can be defined as the mass of encapsulated active compared to the mass of the active added to the initial formulation[15]. The encapsulation efficiency was calculated through the equation III-1:

$$EE = \frac{Active\ in\ capsules}{total\ active} \qquad \text{(III-1)}$$

TGA was carried out with a Mettler TGA/SDTA 851e thermo-balance. The samples with an approximate weight of 10 mg were degraded between 30 and 600 °C at a heating rate of 10°C min^{-1} in nitrogen (100 mL min^{-1}) measured under normal conditions.

In the Total oil test, the active is extracted from the capsules via ethanol extraction at 60°C for 30 min. After cooling, the solution is mixed with an internal standard and filtered through a 0.45µm PVDF syringe filter. The perfume is analyzed by Gas Chromatography – Flame

Ionization Detector (GC-FID) versus a reference perfume. For analysis a non-polar capillary column (Type DB5) 5m x 0.32mm with a 1µm film-thickness is used. The resulting peaks are compared to obtain the concentration of each perfume raw material (PRM), as explained in Equation III-2 and III-3.

$$RRF = \frac{Area_{istd} W_{std}}{\sum Area_i \; W_{istd}} \quad \text{(III-2)}$$

where RRF is the relative response factor, $Area_{istd}$ is the area of the internal standard, $\sum Area_i$ is the sum of all perfume peaks, and W_{std} and W_{istd} are the weight of the reference perfume and internal standard solution, respectively;

$$\% \, Total \; oil = \frac{\sum Area_i \; RRF \; W_{istd}}{Area_{istd} \; W_{sa}} 100 \quad \text{(III-3)}$$

where W_{sa} is the weight of the analyzed sample.

The result of this test shows the presence and the concentration of the PRMs and, consequently, the activity of the capsules.

The stability of the capsules was assessed in different condition by using different techniques. The stability of dried capsules was evaluated by means of TGA analysis, as described before. Samples of the capsules were stored in ambient condition and the TGA was performed at different time. The activity of the capsules at t=0 (freshly prepared capsules), was compared to the activity after six months and one year.

3.2.4 Results and discussion

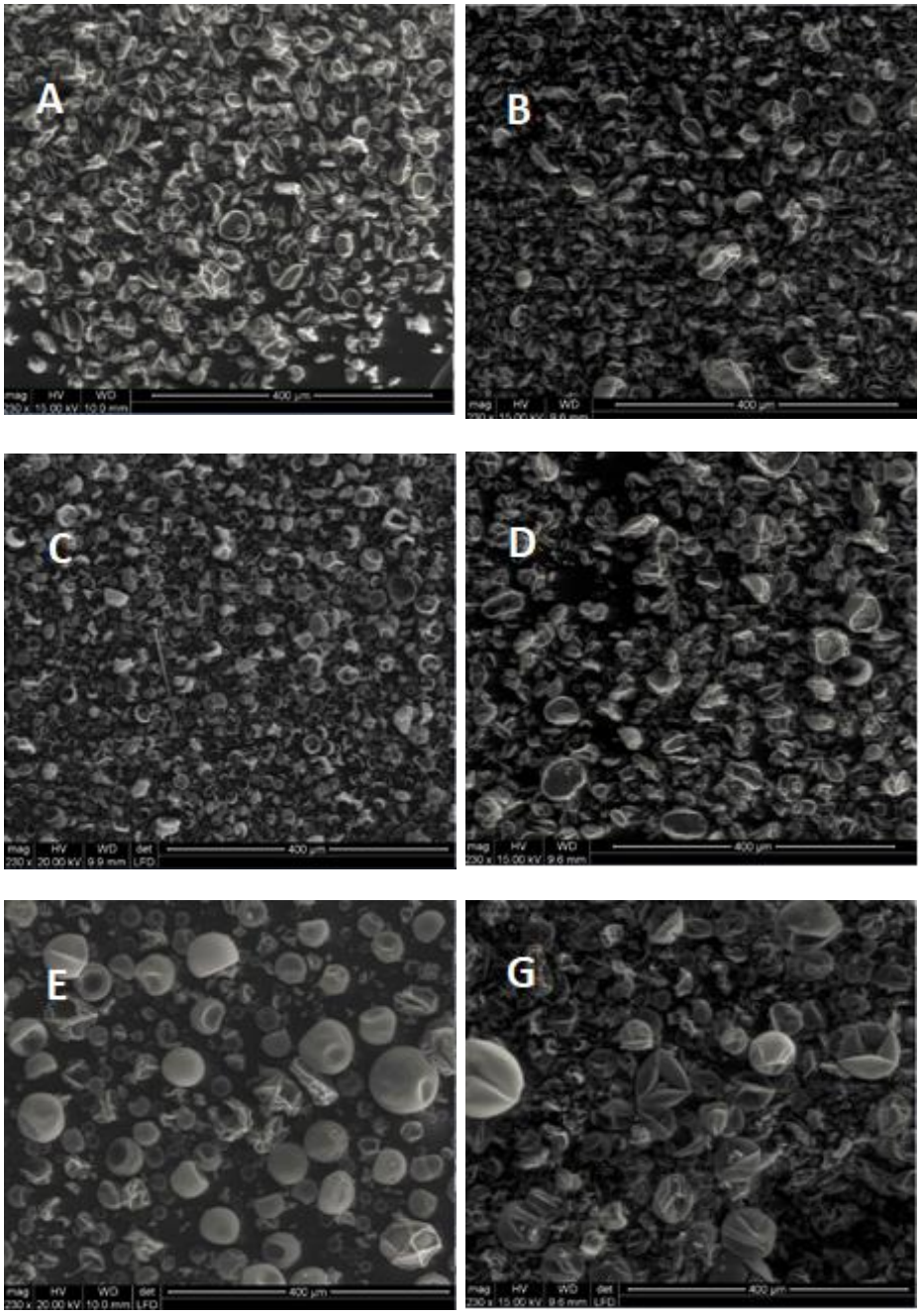
The aim of this chapter was the preparation of cellulose acetate microcapsules containing the active Sweet & Smart by the spray drying

technique. ESEM micrographs of the resulting products are showed. In figure III-3 it is possible to notice the difference in the morphology resulting from the different inlet temperature set on the spray dryer machine. The sample showed in figure III-3 were prepared with different inlet temperature, according to the values reported in table III-1.

Sample	CA concentration [%]	IT [°C]
A	3	60
B	3	90
C	3	105
D	3	120
E	3	150
F	3	170
G	3	200

Table III-1 Spray drying capsules prepared with different IT

In figure III-3.A, the microparticles prepared at IT 60°C, are completely opened and not formed. Increasing the inlet temperature, the amount of structures completely formed increase as well; in figure III-3.F, the inlet temperature was set at 170°C and the large majority of capsules are well formed. At 200°C, the capsules present cracks and they seem collapsed on themselves probably due to the high temperature in the chamber, as shown in figure III-3.G. Numerous studies have been done on the influence of spray dryer inlet and outlet temperatures.[4,8,16,17] It is shown that a high enough inlet air temperature leads to a rapid formation of a semi-permeable membrane on the droplet surface, giving optimum retention; on the other hand, too high inlet temperatures cause heat damage to the dry product or excessive bubble growth and surface imperfections which increase losses during drying[18] or cause the particles to become sticky and cake.[19,20] The influence of the outlet temperature is still not clear and well documented.


A
B
C
D
E
G

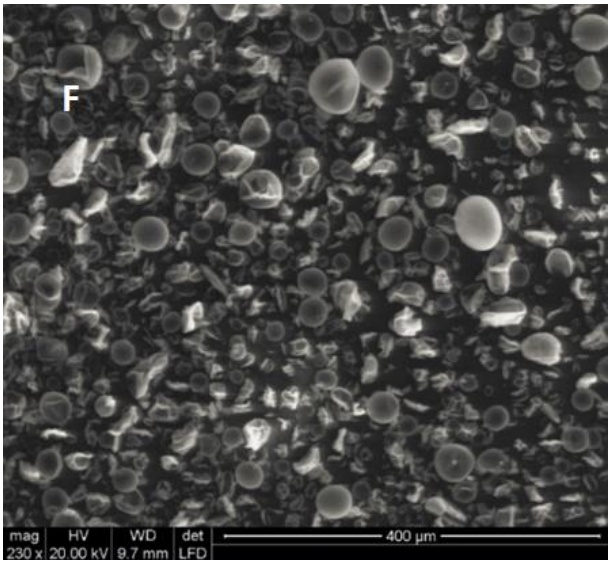


Figure III-3 ESEM micrographs of the spray dryer capsules prepared at different inlet temperature. a) 60°C; b) 90°C; c) 105°C; d) 120°C; e)150°C; f)170°C; g) 200°C

The feed flow was another parameter evaluated, controlled by the pump percentage of the spray dryer. In figure III-4 the resulting microparticles are presented in increasing feed flow order, from 3ml/min to 7.5ml/min. In this case, there are not clearly visible differences in the products, which include a mix of formed and unformed microcapsules. It means that the feed flow in the investigated range (3ml/min - 7,5ml/min) has no influence on our system.

Moreover, no crucial tendency has been found on the morphology of the capsules while analyzing the composition of the feed solution (6% of CA instead of 3%, presence and content of the active).

The best spray dryer process parameters that have been found in this study are reported in Table III-2.

Composition	Core:shell ratio	Inlet T [°C]	Outlet T [°C]	Pump [ml/min]
CA 3%	*1:1*	*170*	*115-120*	*5*

Table III-2 Optimal process parameters for SD capsules preparation

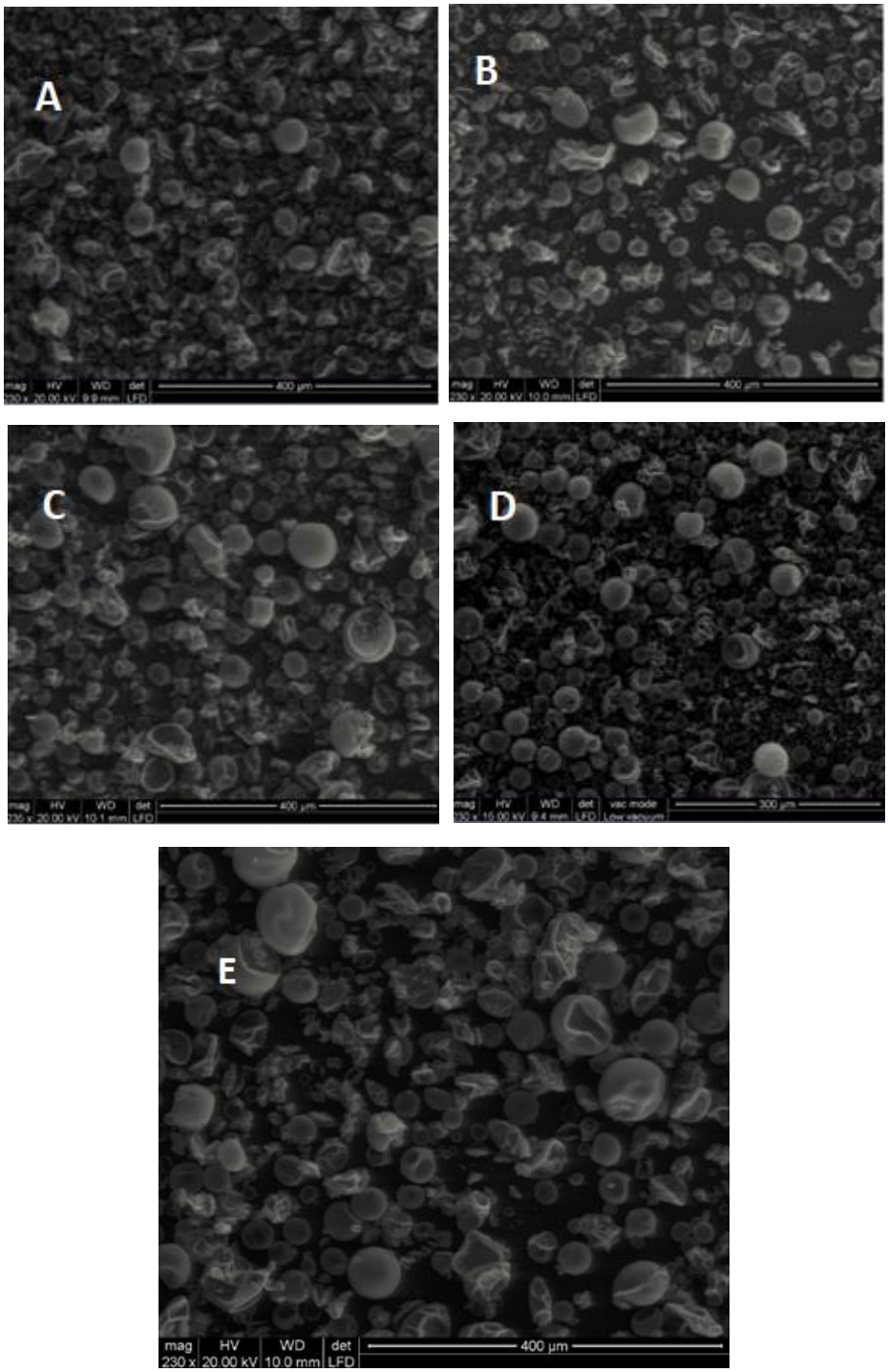


Figure III-4 ESEM micrographs of the spray dryer capsules prepared at different feed flow. a) 3ml/min; b) 4ml/min; c) 5ml/min; d)6,2ml/min; e)7,5ml/min

In figure III-5, micrographs of the capsules made with these parameters are shown. They present a satisfactory spherical shape and homogeneous formation.

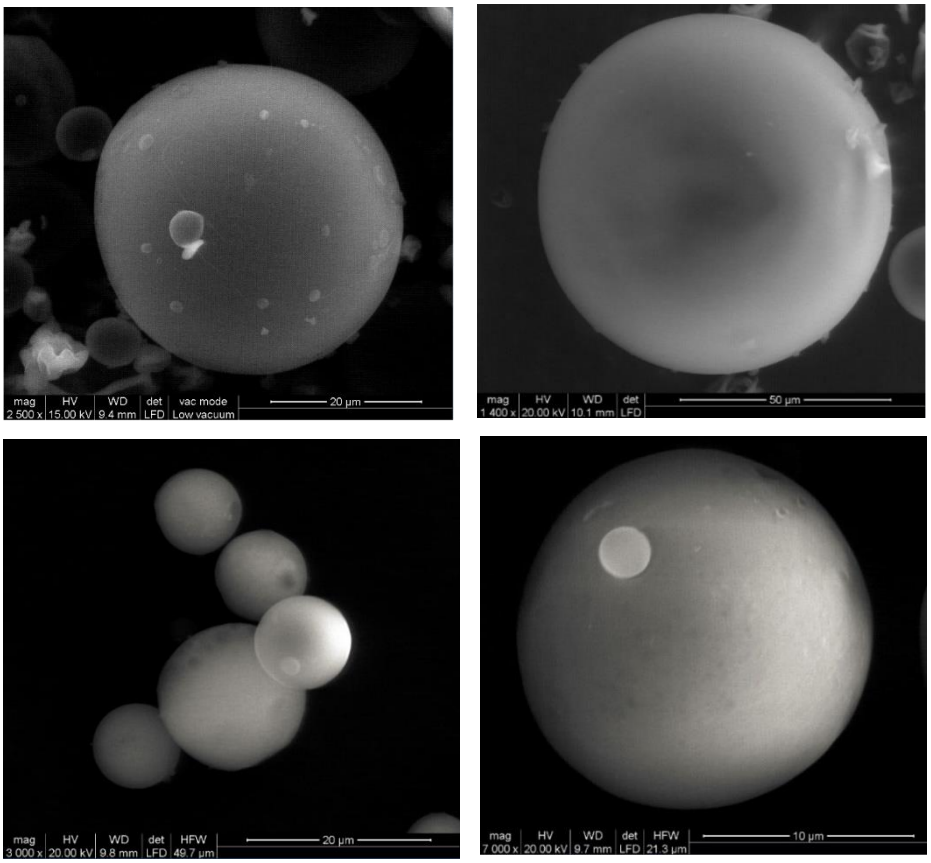


Figure III-5 Micrographs of capsules made with the best parameters found

The internal structure represented in figure III-6 is obtained from the cross section of the capsules after being cryogenically cut. The images show a thin dense layer of few µm of the shell surrounding an internally empty structure, characteristic of a core-shell morphology.

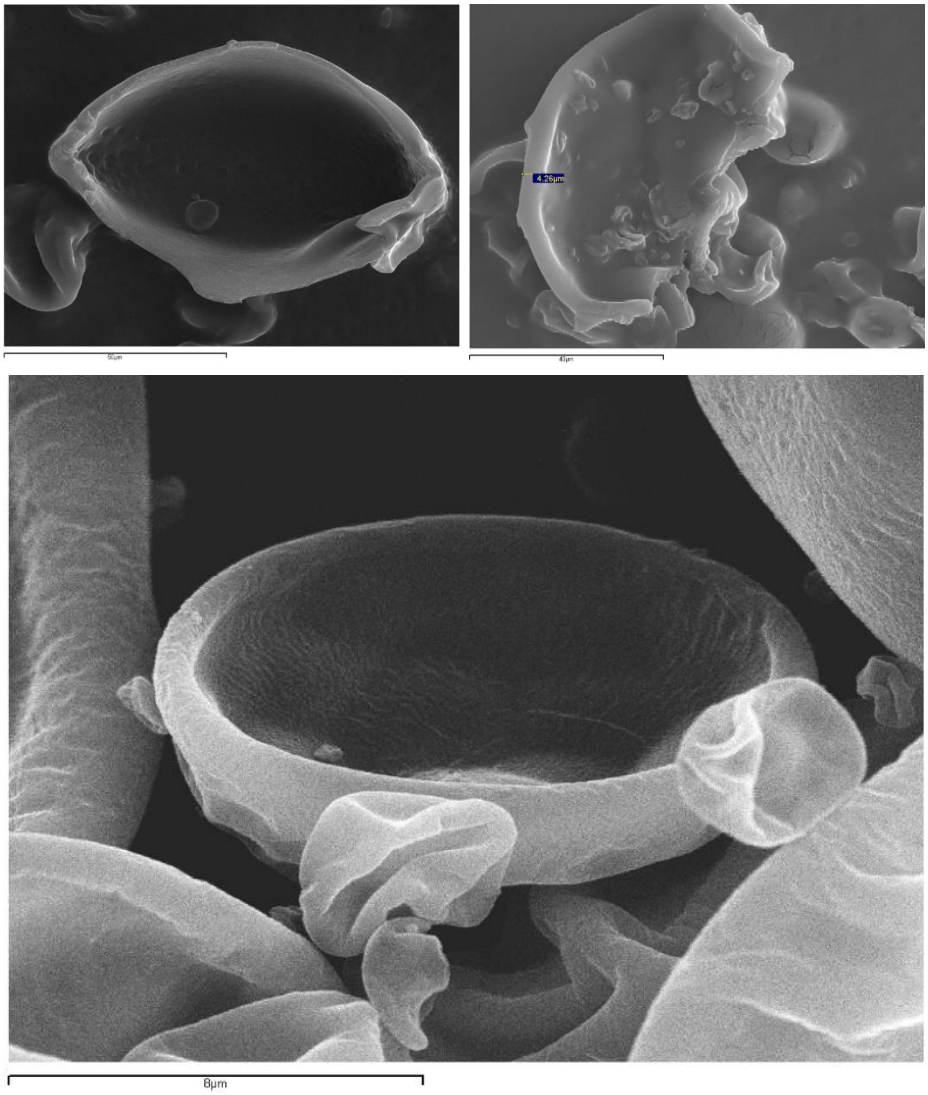


Figure III-6 Cross section of SD capsules

By means of TGA analysis, we were able to determine the activity of the capsules, defined as the active encapsulated inside the capsules. Previous analysis on the active and the polymeric system were required. For the polymeric system we prepared CA microparticles without adding the active in the feed solution. In figure III-7, the TGA results of core and shell of our system are presented.

The TGA profiles of the two samples show a wide plateau between the evaporation temperature of the active (≈250°C) and the degradation temperature of the polymer (≈300°C). Therefore, it was possible to choose a temperature included in this range to pick up the active content value, affecting the result with a negligible error.

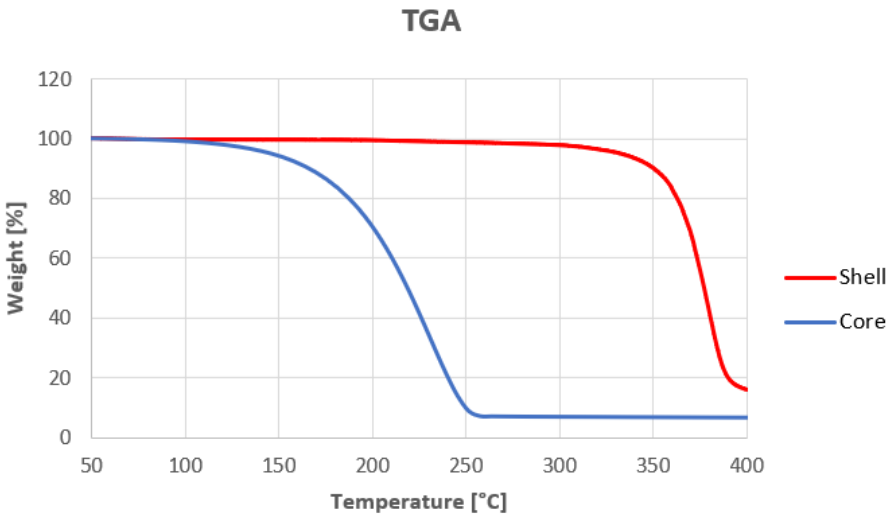


Figure III-7 TGA reference profiles

Three different profiles are shown in figure III-8, chosen as examples of all those analyzed. The blue line represent the sample made with core:shell ratio 1:1 and a low inlet temperature (up to 120°C); the red line is referred to a sample with the same core:shell ratio of the previous, but prepared using a higher inlet temperature (150°C-170°C), while the green one was made with the same inlet temperature, but with a core:shell ratio 3:1. In the first case, the weight loss at 250°C is ≈20%, indicating also the activity of the sample; the second one presents an activity ≈25%, while in the third case the activity is ≈50%.

In table III-3 the values of activity and encapsulation efficiency are reported for the different samples.

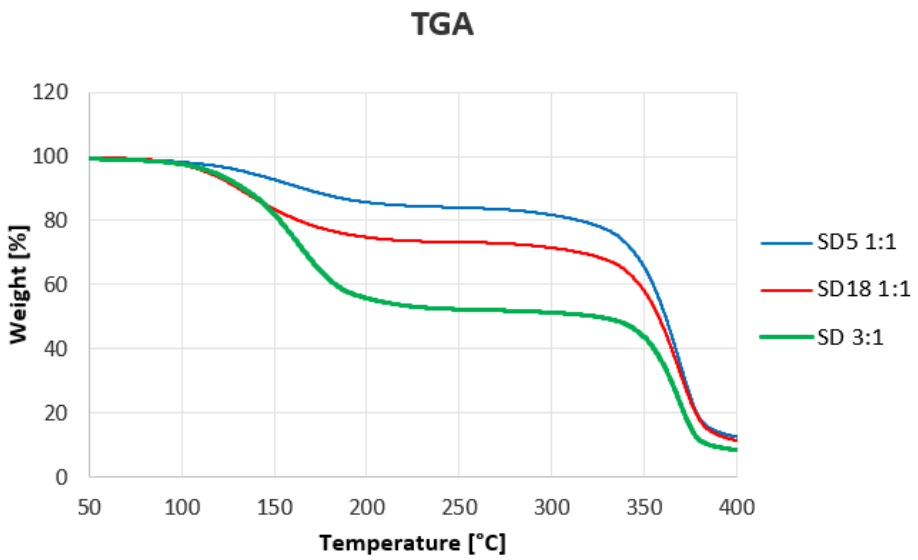


Figure III-8 TGA profiles of different SD capsules

Sample	Core:shell ratio	Inlet Temperature [°C]	Activity [%]	EE [%]
SD5	*1:1*	*120*	*18*	*36*
SD18	*1:1*	*150*	*28*	*56*
SD23	*3:1*	*150*	*50*	*66.6*
SD30	*1:1*	*170*	*25*	*50*

Table III-3 Activity and EE of different SD capsules prepared

The difference in active content found between the sample made with lower and higher inlet temperature reflects the difference shown in morphology and follows what is described in the literature, according to which high enough inlet air temperature leads to better retention[20,21]. The encapsulation efficiency was increasing while the active content was increasing in the feed solution, suggesting that the microcapsules were not completely filled with the core.

The explanation of the active loss stays in the volatility of the missing PRMs; the temperature of the process conflicted with the boiling

point (BP), leading to rapid evaporation of part of the loading. The kinetics of formation of the capsules were slower than the speed at which part of the perfume evaporates. Nevertheless, due to the formation of proper capsules only when the process temperature was reaching at least 150°C, it was not possible to decrease the temperature to encapsulate more active.

3.3 Conclusions

The spray drying technique is one of the most common microencapsulation technologies and widely used at industrial scale. Several natural or natural derived polymer have been employed to encapsulate actives by using this technique. The main aim of this study was the preparation of cellulose acetate microcapsules *via* spray drying process for the encapsulation of the technical accord S&S. It was chosen as encapsulation process due to its easiness and low cost. A characterization of the capsules was firstly carried out to evaluate the morphology and the retention of fragrance. Then, standard industrial test to verify the stability of the capsules in finish products and the applicability in real applications were carried out.

ESEM studies showed that the cellulose acetate microcapsules were successfully prepared. Depending on the inlet temperature of the spray dryer we get different shapes and degree of formation of the capsules, that were spherical and completely formed when the IT was 170°C. The internal morphology of the capsules prepared at this IT is a typical core-shell structure, with a thin polymeric shell and an internal empty space to contain the active. Lower IT lead to incomplete formation of the shell, while by using higher IT, the micrographs show collapsed microcapsules.

The TGA analysis and the total oil test provide the activity of the capsules and, through it, the EE. It was found the for microcapsules with a core:shell ratio of 1:1 the activity was in the range 18-28%, increasing with the increase of the IT; the capsules with a core:shell ratio of 3:1 reveal an activity of 50%. The EE, high up to ≈65%, was not enough for industrial purpose in both cases.

3.4 Bibliography

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4. Preparation and characterization of capsules *via* Vapour Induced Phase Separation (VIPS)

In this chapter the preparation of microcapsules via the Vapour Induced Phase Separation is presented. This method, considered as an implement of the most common Phase inversion by immersion precipitation (IPS), is introduced in its technical aspect and the main related applications are provided. A comparison with capsules made by the IPS is provide as well as the reason why an implement to this technique has been attempted. Then, the experimental design the process parameters analyzed are shown. The morphological characterization and evaluation of the performance are presented. Moreover, our theory about the non-optimal encapsulation of the active is provided.

4.1 Introduction

A common method for membranes and microcapsules production is the phase inversion precipitation. This technique has been already introduced in Chapter II. Briefly, this technique is based on the interaction of at least three compounds: a polymer, a solvent for the chosen polymer and a non-solvent for the polymer. Solvent and non-solvent should be miscible with each other[1].

Between the several different ways in which it is possible to induce the phase separation, the immersion precipitation technique (IPS) is probably the most common for microcapsules production. Several studies and patent are focused on the preparation of capsules by using this technique, for many different applications, from the absorption of toxic compounds from wastewater to DNA encapsulation for medical purpose, up the perfume conservation[2–8]. IPS involved the use of liquid water as non-solvent for the precipitation bath. This process is very fast and it is usually completed within a few seconds, which makes it almost impossible to determine the kinetics[9].

Vapour induced phase separation (VIPS) is a similar process that involves a dry-wet casting process; the dope solution is exposed to nonsolvent vapor prior to immersion in a coagulation bath. The VIPS was first introduced by Zsigmondy in 1918[10] and described in the 1930s by Elford[11]. It can be considered as an intermediate process between the IPS and the controlled solvent evaporation. In solvent evaporation, however, the nonsolvent is originally contained in the solution, along with the polymer and a more volatile solvent. Due to that, the phenomenon responsible for phase separation is the solvent outflow, while in VIPS is the nonsolvent outflow. For that reason, VIPS is more assimilable as a wet method, where the initial solution composed by polymer and solvent is immersed in a nonsolvent bath. By using nonsolvent vapor instead of the liquid nonsolvent, the process becomes

much slower and controlling the whole process becomes possible. The mass transfer rates, indeed, are considerably reduced compared to those associated to a wet process[12]. Due to this advantage, VIPS became a quite common technique for membrane preparation and several articles can be found[9,13–18]. The most mentioned polymers are polyvinylidene difluoride (PVDF)[19–22], polysulfone (PSf)[23–26], poly(ether sulfone) (PES)[27–29], and poly(ether imide) (PEI)[30–32]. However, studies with other synthetic polymers have been reported, as well as the use of natural biopolymers, such as chitin and chitosan[33–35]. Despite the great interest in this technique regarding the production of membranes, it is not a common method for microcapsules preparation. As far as we know, polysulfone microcapsules were prepared by using that technique[36], but apart from that, no other publications have been found in literature.

In this work, we started preparing capsules by IPS, but, after analyzing the morphology of the prepared microcapsules, we were focusing our attention on the VIPS, because of the interesting possibilities offered from this technique.

4.2 Experimental section

4.2.1 Materials

Cellulose acetate (Mn ≈30.000 $gmol^{-1}$) and Acetone were purchased from Sigma Aldrich. Glacial acetic acid was purchased from Scharlau. All the compounds were used as received without any further purification. The technical accord called Sweet & Smart was prepared by Procter & Gamble as descripted in Chapter II.

4.2.2 Microcapsules preparation *via* phase inversion by immersion precipitation (IPS)

A polymeric solution was prepared and maintained under stirring for 24 hours before microcapsules production. In addition, the bottles must be perfectly closed, since it could penetrate water vapor (humidity of the environment) that could cause precipitation of the polymer. In Figure IV-1 a schematic setup of the equipment is represented.

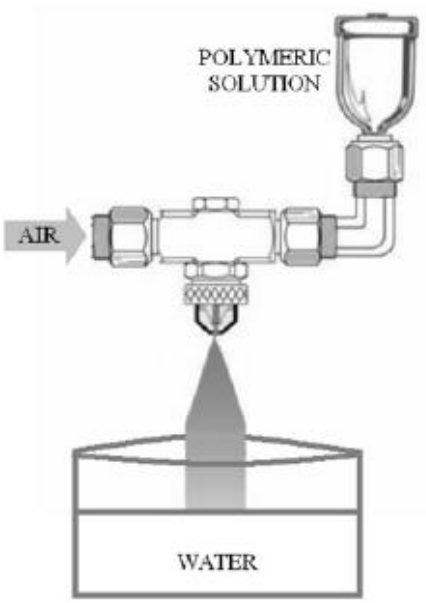


Figure IV-1 Schematic diagram of the atomization set-up for microcapsules production by IPS[36]

An airbrush, constituted by an air-atomizing nozzle (0.8 mm diameter) was used to disperse the polymeric solution by a simple shearing action, which was provided by a compressed air stream. Air pressure was set at 2.5 bar. In Figure IV-2 a picture of the airbrush used, and the nozzle are shown.

The airbrush was positioned in such a way that the outlet flow direction was perpendicular to the surface of a water precipitation bath.

The nozzle was located at different distances from the precipitation bath and the water content of the bath was varied as well, to observe possible influence of the microcapsules production. The precipitation bath was always stirred. When the polymeric solution microdroplets were in contact with the precipitation bath, microparticles began floating on it immediately. Particles removal was necessary after a while to avoid collision with the new microdroplets and aggregates. Therefore, the production of particles was stopped regularly and the liquid in the precipitation bath was filtered using a 0.8 µm nylon filter. The microparticles were then collected into a vial and stored for further analysis.

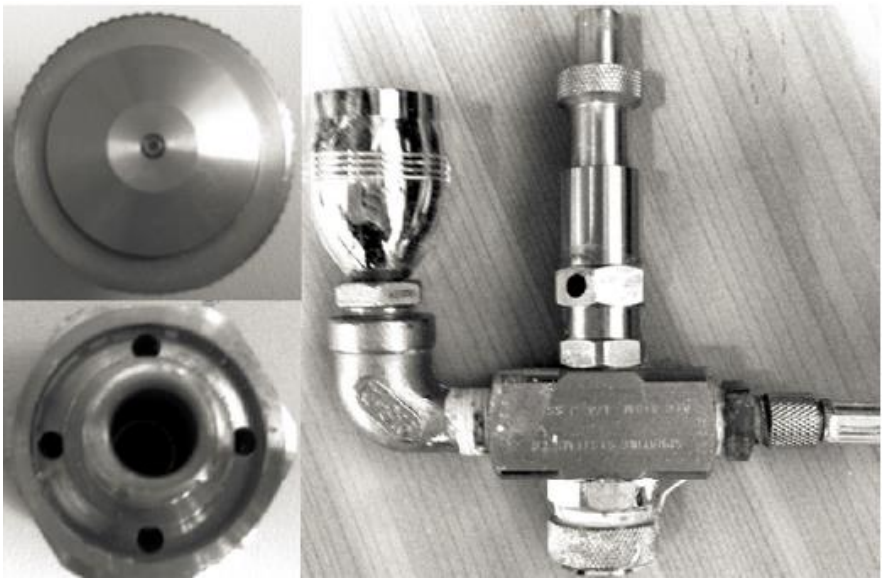


Figure IV-2 Airbrush and nozzle used for IPS technique

4.2.3 Microcapsules preparation *via* vapour induced phase separation (VIPS)

The main difference between the previous technique and this one stays in the use of nonsolvent vapor prior to immersion in the

coagulation bath. For this purpose, the airbrush was placed into a chamber, which has been specially designed and built for this work. Chamber dimension were 110 x 30 x 30 cm^3 (length x width x height). The chamber was designed with this dimension after the observation of the outflowing sprayed flux of solution at the selected pressure of 2.5 bar. Considering a sprayed angle of ≈14° and after selecting the length of the chamber, we got all the parameters to arrange the chamber as desired. In Figure IV-3 a picture of the airbrushing spraying the solution is shown.

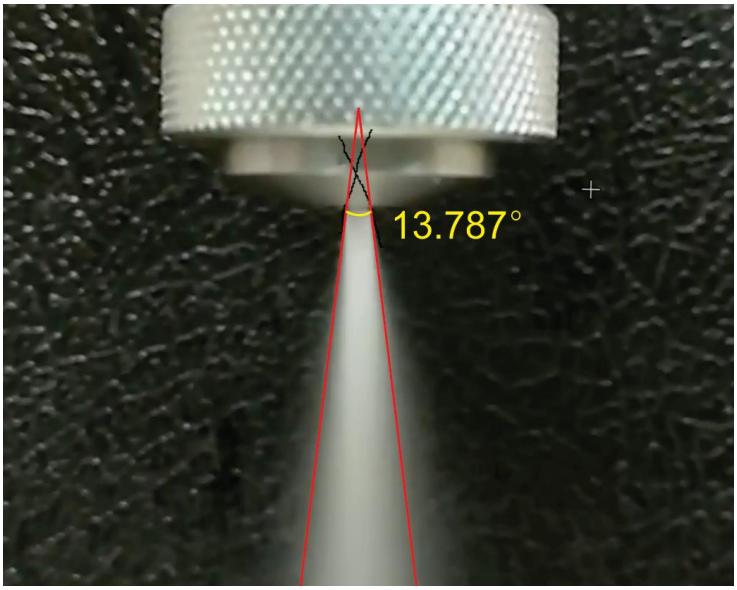


Figure IV-3 Estimated angle of the sprayed solution at 2.5 bar

For achieving a highly humid atmosphere inside the chamber, a compressed air flow was forced to pass through a bubble bottle containing distilled water and, in addition, heated to 80°C in a water bath, to increase water content in the air flow. The conditions of temperature and relative humidity inside the chamber were controlled through a hygrometer and they were 25°C and 95%, respectively. At the bottom of the chamber, a 300 ml water precipitation bath was placed to complete the solvent-nonsolvent exchange and complete the particles

formation. When the surface of the water bath was covered by the microparticles, the production was stopped. The resulting products were filtered using a 0.8µm nylon filter. The microparticles were then collected into a vial and stored for further analysis. A schematic diagram of the setup is represented in figure IV-4.

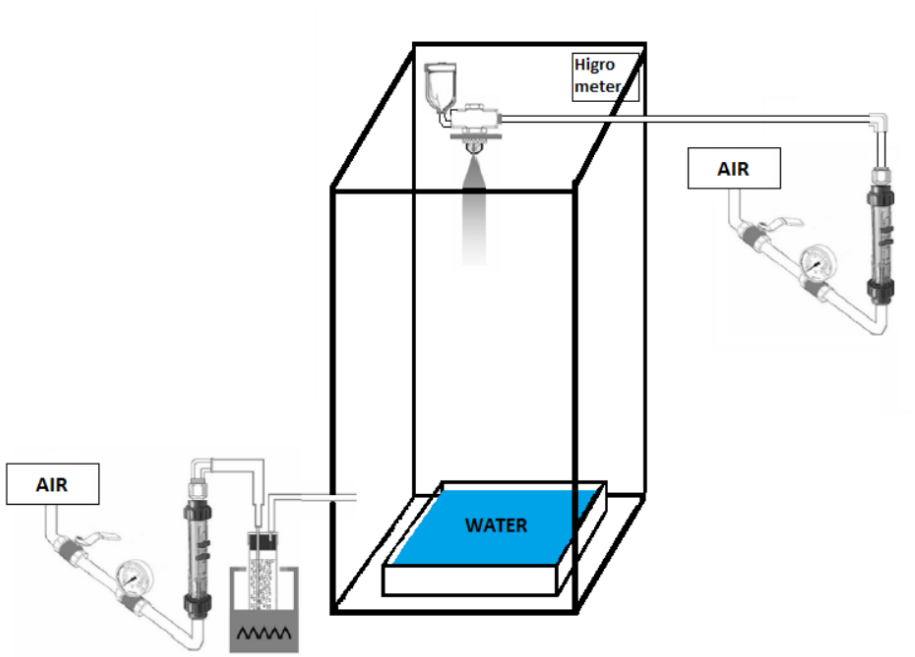


Figure IV-4 Schematic diagram of the VIPS technique

4.2.4 Characterization

Microcapsules morphology was investigated by means of ESEM FEI Quanta 600 apparatus. To obtain microcapsules cross-section micrographs without modifying their structure, they were cryogenically cut[37]. First microcapsules were attached over a specimen disc with a freezing medium. An embedding medium for frozen tissue specimens was used (Tissue-Tek, OCT Compound, Sakura Tissue). Once the capsules were fixed over the specimen disc, the disc was immersed into a liquid nitrogen bath in order to freeze the sample. Next, the specimen

disc was located in the cryochamber. Then, the sample was cut with thickness intervals of 1 μm at −20 °C and deposited over a glass. Finally, the cross-sections were analyzed by ESEM.

Thermogravimetric analysis (TGA) was used to determine the activity of the capsules. Capsule activity is defined as the weight percentage of active encapsulated in the capsule. Different methods have been proposed to calculate the activity of the capsules[38], presenting slightly difference in the results. TGA is a thermal analysis in which the changes in weight of a sample are constantly measured over time as the temperature changes. The heating rate needs to be set to avoid the overlap between the evaporation temperature of the encapsulated active and the temperature of degradation of the shell. TGA response curves of the pure components, the active and the shell, are needed for a comparison between their response profiles and that of the capsules. This correlation is used to determine the temperature range where only the mass loss of encapsulated active occurs. Once the correct temperature range is identified, it is possible to estimate the mass of the encapsulated active (active in capsules) as the weight loss of the capsules in that temperature range. The encapsulation efficiency (EE) can be defined as the mass of encapsulated active compared to the mass of the active added to the initial formulation[39]. The encapsulation efficiency was calculated through the equation IV-1:

$$EE = \frac{active\ in\ capsules}{total\ active} \qquad \text{(IV-1)}$$

TGA was carried out with a Mettler TGA/SDTA 851e thermo-balance. The samples with an approximate weight of 10 mg were degraded between 30 and 600°C at a heating rate of 10°C min^{-1} in nitrogen (100 mL min^{-1}) measured under normal conditions.

4.3 Results and discussion

4.3.1 IPS

The aim of this work was the preparation of cellulose acetate microcapsules containing the active Sweet & Smart by IPS technique. In Table IV-1, the different polymeric solutions prepared and process parameters tested are indicated. the composition of the solution has been decided after some tests and is influenced by the need for a low viscosity of the feed solution that must pass through the airbrush; higher viscosities led to a discontinuous and not optimal flow for the process since the solution remained attached to the walls of the equipment.

Sample	CA [wt.%]	Distance nozzle/bath [cm]	H_2O Bath [ml]
IPS1	10	20	200
IPS2	6	20	200
IPS3	3	50	1300
IPS4	6	80	1300

Table IV-1 Sample composition and process parameters of the IPS microparticles

In figure IV-5 the ESEM micrographs of IPS1 are showed. IPS1 was our first attempt to make particles *via* this technique and the concentration of CA inside the solution was 10%, making its viscosity low enough to flow homogeneously inside the airbrush. However, it is possible to notice the formation of filamentous and other shaped structures instead of spherical shapes.

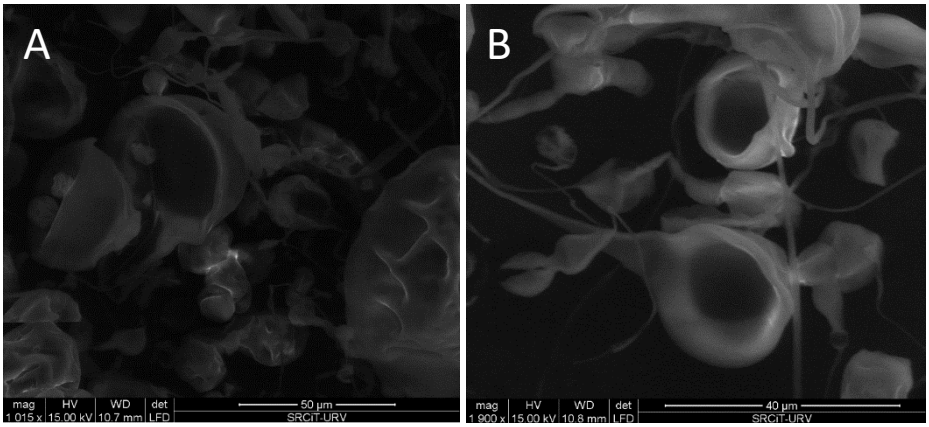


Figure IV-5 IPS1 micrographs

Following the indication of Li *et al*[42], we decided to decrease the concentration of CA for the subsequent experiments. In their study, in fact, they were producing CA microcapsules containing phase change materials (PCMs) *via* solution spray method. They prepared solution with different CA concentration, from 6wt% up to 15wt%. When analyzing the effect of CA concentration on morphology and microstructure, they noticed that higher than 6% CA concentration solutions lead to filamentous and irregular spherical microspheres. They assumed that the increased viscosity resulted in large surface tension and other applied force among the liquid drop. Therefore, the molecular motion was restricted when the solution was sprayed, thus resulting in non-spherical or near spherical shapes during falling process. In Figure IV-6, IPS2 microparticles are showed. The CA concentration of the solution was 6wt%, according to the optimal value found by Li *et al.*[42] The filaments of polymer present in the previous particles production was completely absent, but non-spherical shapes were still visible. Moreover, the formation of the shell was interrupted before a complete spherical structure was reached.

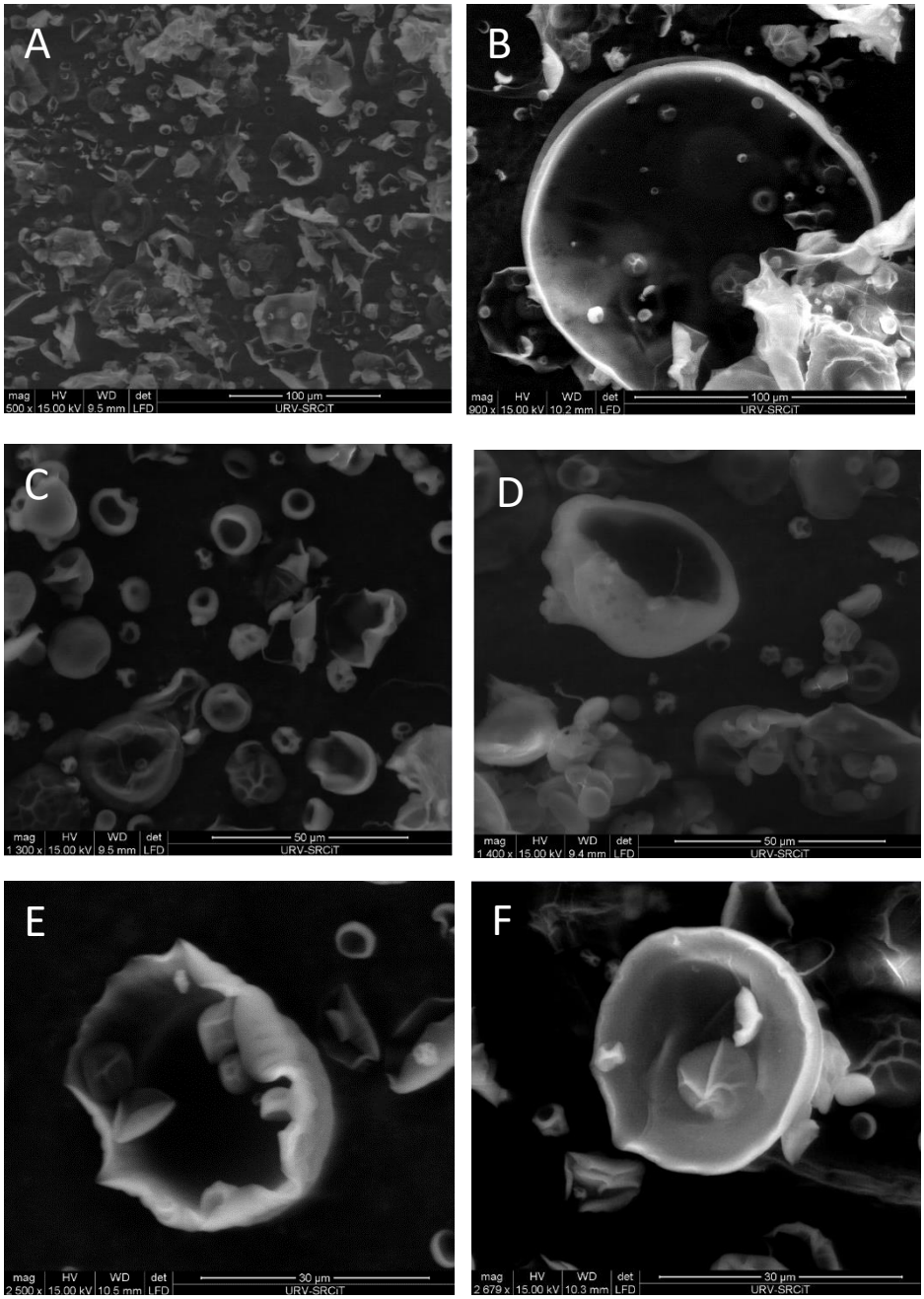
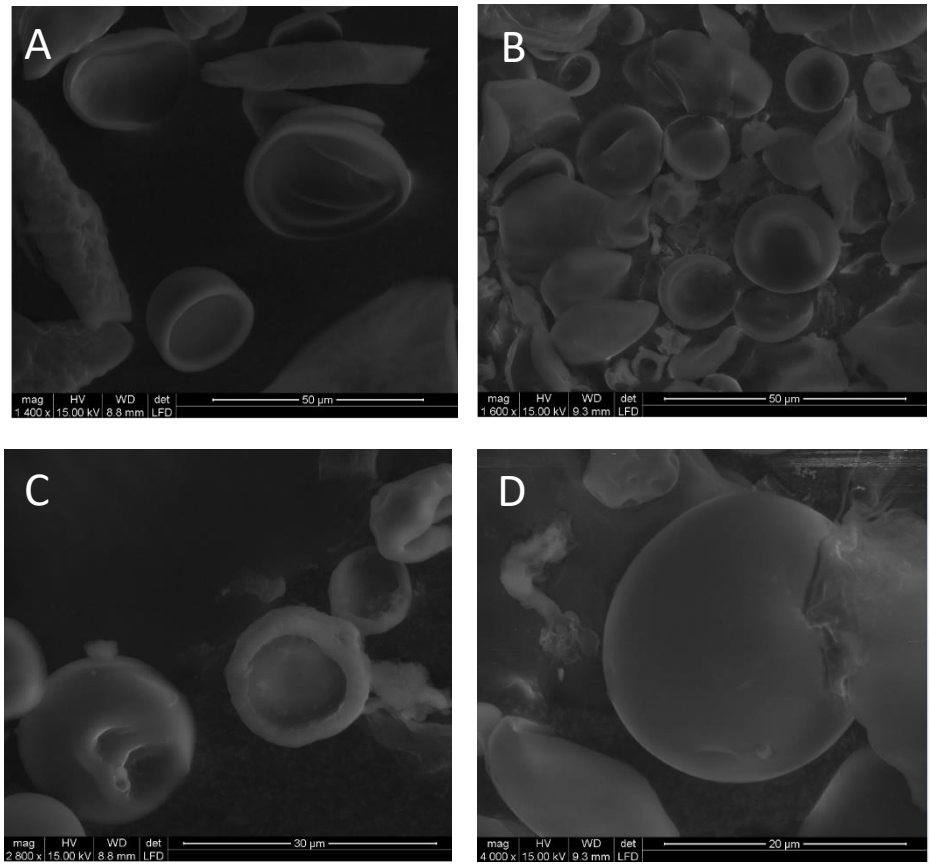


Figure IV-6 IPS2 micrographs

In the next attempt we further decreased the CA composition of the solution to a 3wt%. In addition, we increased the distance between the nozzle of the airbrush and the precipitation bath.

Our theory was that the precipitation of the CA when in contact with the nonsolvent was immediate or in any case too fast to maintain the droplet shape, thus not forming complete microparticles. Increasing the distance nozzle/bath, the solvent-nonsolvent exchange could start during the falling of the solution droplet, providing more time to the CA to precipitate proerly.

Figure IV-7 shows the ESEM images of the IPS3. The distance between nozzle and bath was set at 50cm. The products were more homogeneous compared to the previous attempts and less amorphous structures were present. Spherical particles can be found, even if the majority were still not completed particles. The morphology of the products allows us to check the internal structure of the particles composed by a thin shell layer and completely empty inside.



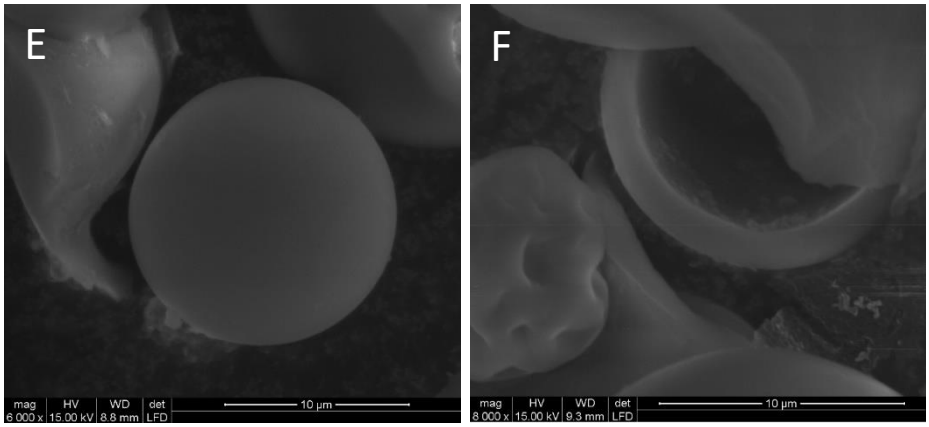


Figure IV-7 IPS3 micrographs

Due to that result, the distance nozzle/bath was increased to 80cm. Images of the IPS4 are showed in figure IV-8.

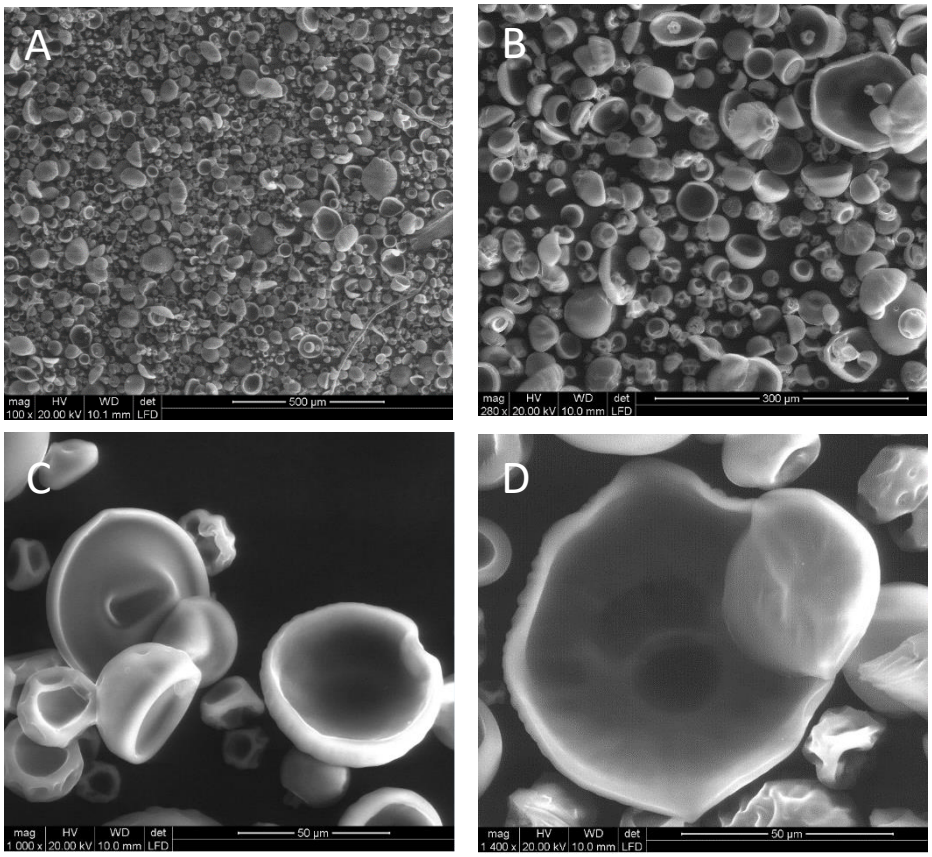


Figure IV-8 IPS4 micrographs

In this case, the morphology of products was very homogeneous. Amorphous structures were not present, but still all the particles were not completely formed. Their internal structure is showed; it is composed again by a thin polymeric layer surrounding the empty internal volume.

Due to the unsatisfactory morphology reached, no further characterization was carried out on IPS particles.

4.3.2 VIPS

Our strategy was to continue with the phase separation technique, implementing the IPS used so far. The idea was to control the precipitation rate of the encapsulation material in the nonsolvent thanks to the longer exposition time to the vapor of the nonsolvent and the distance between the drop formation and the collection bath. This is possible through the VIPS technique. Below, in table IV-2 the microcapsules prepared by the VIPS technique are reported.

Sample	CA [wt.%]	S&S:CA	RH [%]
VIPS1	3	1:1	95
VIPS2	3	3:1	95
VIPS3	3	5:1	95

Table IV-2 Sample composition and process parameters of the VIPS microparticles

In Figure IV-9, generic images of the microcapsules are shown. They have a spherical and complete structure, unlike those previously shown and prepared through the IPS technique. The distribution is quite wide, in fact both large capsules (> 50 µm), and much smaller capsules (≤10 µm) are present.

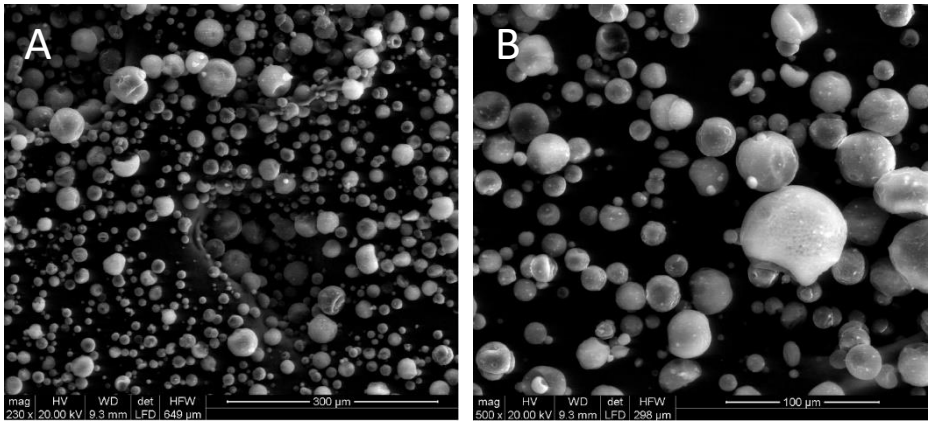
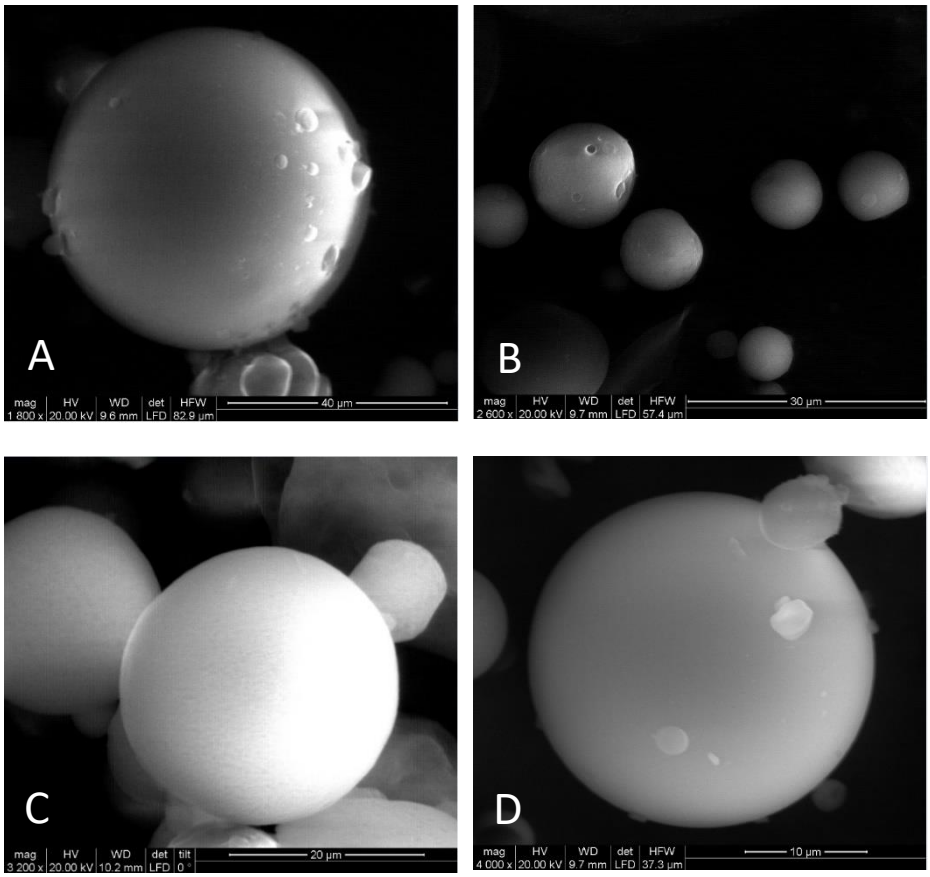


Figure IV-9 SEM of VIPS capsules micrographs with small magnitude

In Figure IV-10 SEM images of the microcapsules as listed in Table 2 are presented. The microcapsules have a rounded outer surface that show continuous walls with no fissures, cracks or interruptions.



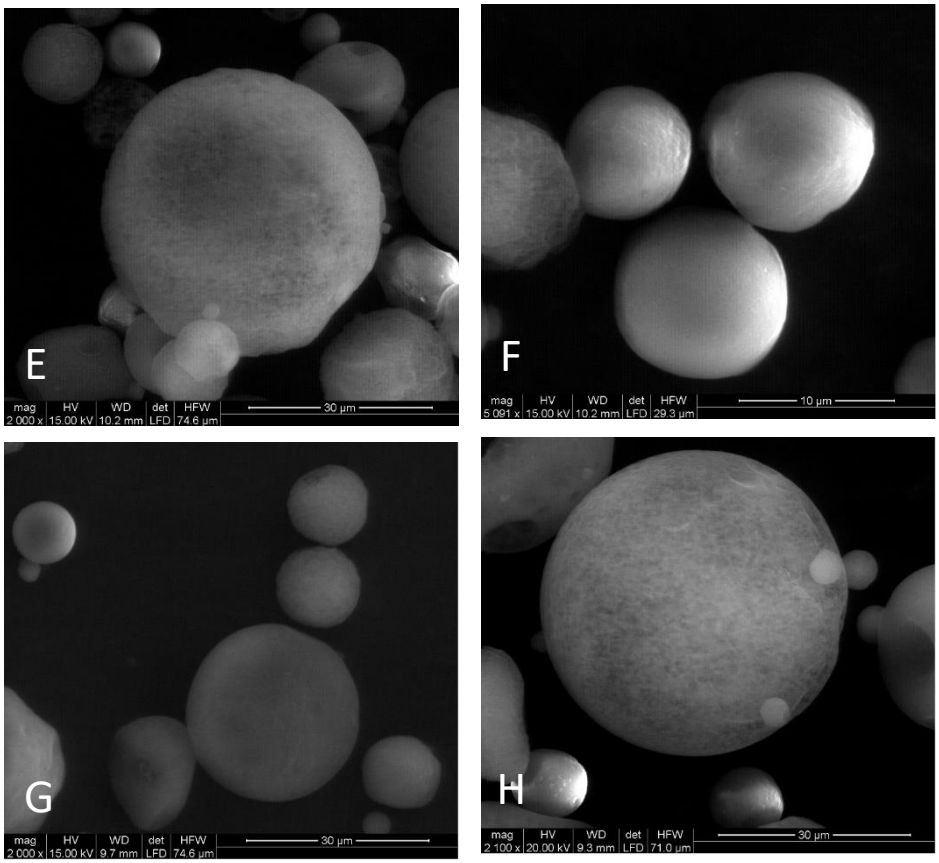


Figure IV-10 ESEM pictures of microcapsules prepared by VIPS technique. A-C) VIPS 1; D-F) VIPS 2; G-H) VIPS 3

Evaluating Fig. IV-10A–H, it is possible to see the microcapsules formed with different core concentration and conclude that it is not interfering in microcapsule morphology. Ortiz *et al*[43] and Rocha *et al*[44] also observed that the core concentration did not interfere on particle morphology when casein hydrolysate was encapsulated using soybean protein isolate and when lycopene was encapsulated using modified starch, respectively. The internal structure represented in figure IV-11, is obtained from the cross section of the capsules after being cryogenically cut. The images show a layer of the polymeric shell surrounding an internally empty structure, typical of a core-shell morphology. Furthermore, the polymeric shell does not show porosity,

appearing as a dense, compact and homogeneous layer. This is an essential quality to ensure lower gas permeability, better protection and fragrance retention.

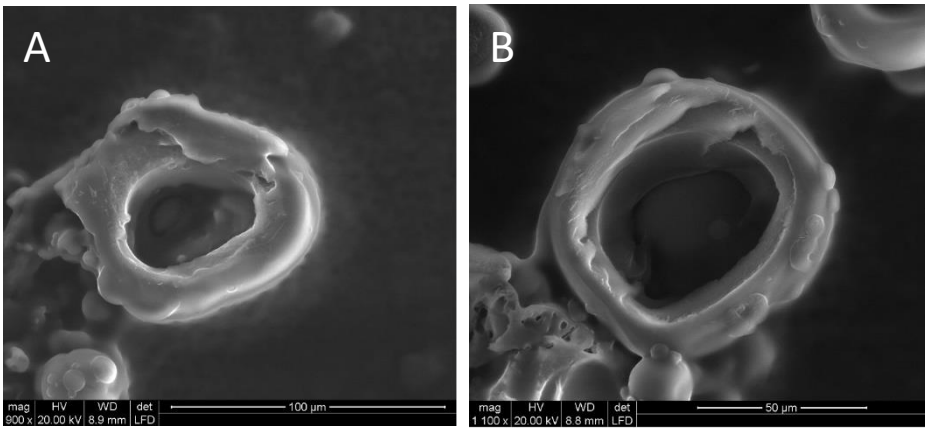


Figure IV-11 Cross section of VIPS capsules

By means of TGA analysis, we were able to determine the activity of the capsules, defined as the active encapsulated inside the capsules. As mentioned in chapter III, previous analysis on the active and the polymeric system were required. To obtain the reference of the polymeric system, CA microparticles without adding the active were prepared. In figure IV-12, the TGA results of core and shell of our system are presented.

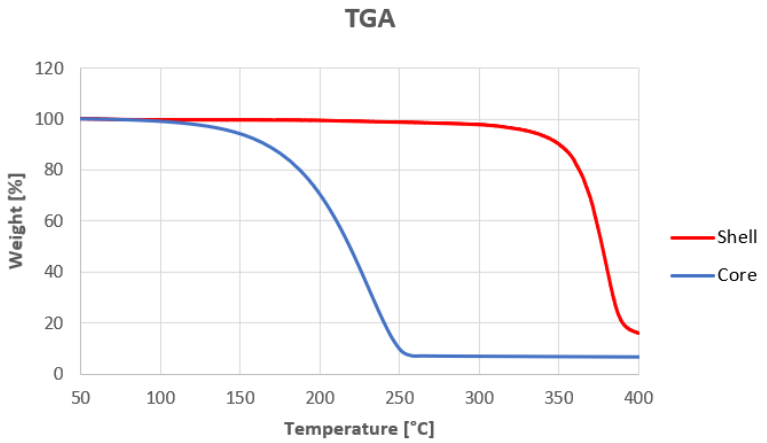


Figure IV-12 TGA reference profiles

In the interval between the evaporation temperature of the active (≈250°C) and the degradation temperature of the polymer (≈300°C) it is possible to choose a temperature and evaluate the active content value, associable to the weight loss at that determined temperature. The temperature of 260°C has been chosen to consider the weight loss of the samples and consequently determine the activity. In Table IV-3, the activity and the encapsulation efficiency for the VIPS capsules prepared with different core:shell ratio are presented. It is possible to notice that increasing the active content in the polymeric solution, the activity of the capsules and thus the encapsulation efficiency increase as well.

Sample	Activity [%]	EE [%]
VIPS 1:1	*30*	*60*
VIPS 3:1	*62*	*82.5*
VIPS 5:1	*74*	*88.5*

Table IV-3 Activity and encapsulation efficiency of VIPS capsules

The explanation of this phenomenon could be in the saturation of the chamber. It means that once a certain concentration limit has been reached for each PRM, it is no longer possible for the active to spread within the internal space of the chamber, which is then forced to remain inside the polymeric shell of the capsule.

4.3 Conclusions

Microcapsules containing S&S active have been tried to be prepared through the IPS technique. Following the failed proper creation of the capsules, we went on to study and use of the VIPS technique. VIPS technique is an implement of the IPS, mostly used for the preparation of capsules. The main difference lies in the use of

solvent vapor to promote better precipitation of the polymer through a solvent-non-solvent exchange of the solution, in a more controllable manner. To do this, a chamber was built and filled with water vapor before starting the spray of the polymer solution using an airbrush.

Through the SEM images, it was possible to notice the different morphology reached through the two techniques and the decided increase in the achievement of a spherical and complete structure. the preparation of cellulose acetate capsules was therefore successful with the use of the VIPS technique. The key factors were the longer exposition time to the vapor of the non-solvent and the distance between the drop formation and the collection bath. The obtainment of a core-shell structure and a thin and dense polymer wall was confirmed by the morphological analysis of the cross section of the capsules.

Activity and EE of the products have been evaluated through the TGA and reach a maximum of 74% and 88.5%, respectively, in the case of a core:shell ratio 5:1. Furthermore, these 2 parameters increase as the amount of active added to the initial solution increases.

VIPS technique resulted suitable for our chemistry, leading to the complete formation of spherical capsules. Despite this, improvements to the technique are necessary to achieve better results. The influence of RH%, water bath and airbrush nozzle need to be further investigated for a deeper understanding and a better control of the process.

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5. Preparation and characterization of capsules *via* solvent evaporation with pickering emulsifier

In this chapter the preparation of microcapsules via solvent evaporation is described. The microcapsules are produced after emulsification through pickering emulsifier. The base of pickering emulsification will be introduced and the reasons that led us to choose this technique rather than the most common emulsion with molecular surfactants will be explained. Then, the design of the process to prepare microcapsules and their characterization will be described.

5.1 Introduction

Microencapsulation by solvent evaporation technique is widely used, especially in pharmaceutical and cosmetic industries to obtain the controlled release of active. There are different methods to use this technique, but basically it consists of four major steps[1]:

1. Dissolution of the active in an organic solvent containing the polymer;
2. Emulsification of the organic phase in an inorganic phase (called dispersed and continuous phase, respectively);
3. Transformation of the droplets of dispersed phase into solid particles through solvent extraction accompanied by solvent evaporation;
4. Recovery and drying of the microparticles to eliminate the residual solvent.

In figure V-1 a scheme of a common solvent evaporation process is represented.

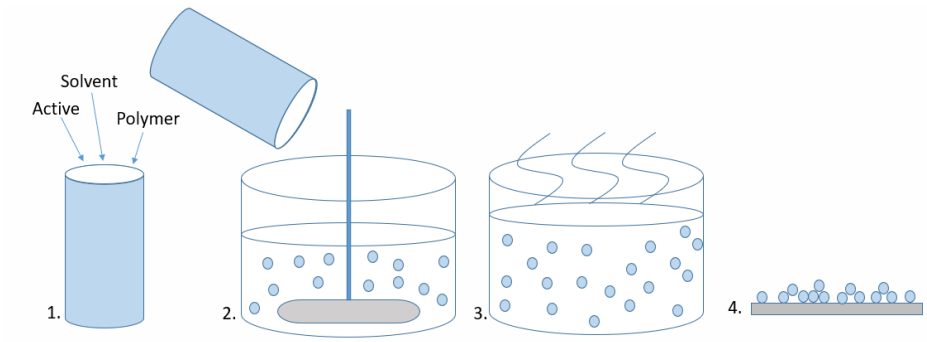

Figure V-1 Scheme of microencapsulation by solvent evaporation

An important step of this process is the emulsification: depending on the properties and the stability of the emulsion, the properties of the resulting products changes. Emulsions are widely used in many different fields, such us pharmaceutic, drug delivery, cosmetics,

food industry and so on. The advances of the last decades have made them even more attractive and suitable for different applications. An emulsion stabilized by solid particles instead of surfactants, is called Pickering emulsion.

Pickering emulsion was discovered a century ago, in 1907, by Pickering[2]. He reported the formation of a stable emulsion of paraffin oil stabilized by solid particles adsorbed at the oil droplet surface. He gave evidence for the adsorption of solid particles, showing the improved stability of such emulsion with respect to emulsion based on surfactants. Even if some advantages of Pickering emulsion were already clear, the technique was largely ignored for a long period. Recently, it has drawn significant research interest due to the following advantages[3]:

- Solid particles reduce the possibility of coalescence, improving the stability of the emulsion
- The surfactant-free character makes them attractive to several application fields, such as cosmetics and pharmaceutical applications where surfactants often show adverse effects (irritancy, hemolytic behavior..)
- some food-grade solid particles have lower toxicity, thus leading to higher safety for *in vivo* usage
- many solid particles can provide the prepared materials useful characteristics such as conductivity, stimuli-responsiveness, porosity and so on.

The mechanism of stabilization in Pickering emulsion is based on the formation of a steric barrier by solid particles adsorbing at the oil-water interface[4]. In figure V-1 a sketch of a classical and a Pickering emulsion is represented. The particles can irreversibly attach the oil-water interface, leading to a more efficient stabilization than surfactant

adsorption. This mechanism is commonly accepted and demonstrated through theoretical approaches and thermodynamic calculations[5–7].

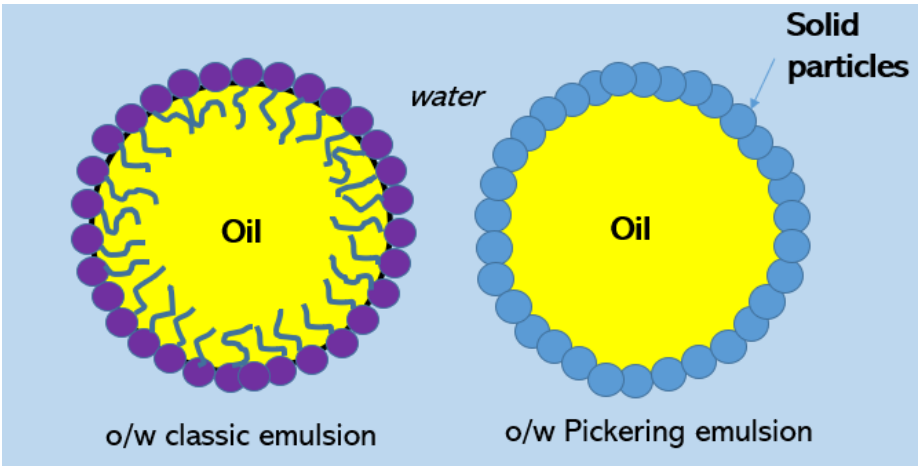

Figure V-2 Sketch of a classical and a Pickering emulsion

The mechanism of adsorption is very different of surfactants however, since the solid particles do not need being amphiphilic. The origin of the strong anchoring of solid particles at the oil–water interface is the partial wetting of the surface of the solid particles: in fact, only when the contact angle θ (the angle at the three-phase boundary of solid particles, continuous and dispersed phase, in figure V-2), is relatively close to 90°, the particle can effectively work as a Pickering stabilizer. Equation V-1 shows the change in interfacial energy (ΔE) when a solid sphere is adsorbed at the interface with a contact angle θ,

$$\Delta E = -\Pi r^2 \gamma_{ow} (1 \pm \cos\theta)^2 \qquad \text{(V-1)}$$

Where *r* and γ_{ow} are the radius of the particle and oil/water interfacial tension, respectively. In this respect, the adsorption is the strongest when θ = 90°C; the energy required to desorb the particles from the interface is order of magnitude higher than that of soluble surfactants[8].

Particles tend to remain dispersed if they are too hydrophilic or too hydrophobic[9]. Surface modification of the solid particles can be necessary to meet condition of partial wetting by water and oil.

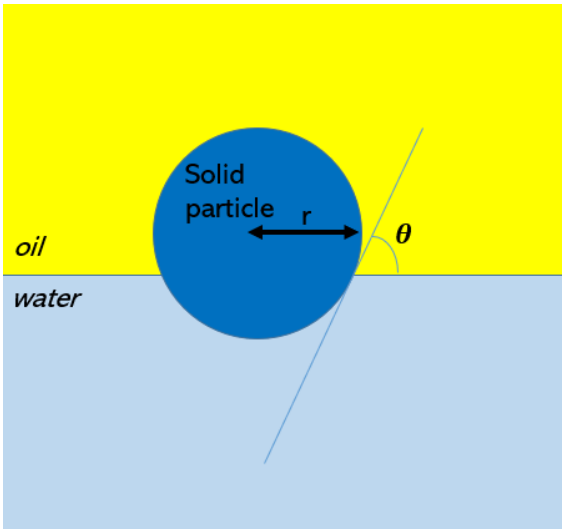

Figure V-3 Solid particle at the oil/water interface

Several solid particles, either organic or inorganic, have been used as stabilizers for Pickering emulsion. Some examples are graphene dioxide[10], clays (laponite[11,12], montmorillonite[13]), carbon nanotubes[14], magnetic particles[15], polymer particles[16,17], titanium dioxide[18] and silica nanoparticles[19–21]. Among them, silica is the most popular solid material because it is easily obtained and modified[3]. Bare silica particles are generally unable to stabilize Pickering emulsion because of the total wetting of silica in water. Therefore, modification of silica particles properties is needed to modify their hydrophilicity. They can be modified by chemical reaction[22,23] and physical pre-adsorption of various materials, such as salts[24,25], low molecular weight surfactants[26] and polymers[27,28]. Hydrophobic particles are obtained by grafting organosilanes obtaining fumed silica particles. Grafting dichloromethylsilane or hexamethyldisilazane to silica leaves hydrophobic dimethylsilylr groups attached at the surface of silica; the

grafting degree controls the hydrophobic character of silica and its wetting to water and oil[29]. Such fumed particles are available from different manufacturers, such as Evonik, Wacker and Cabot. During synthesis, these nanoparticles (*diam* 10-25 nm) are irreversibly stuck together[30]; the size of the aggregates is of the order of 100nm or more, thus resulting in submicron particles rather than nanoparticles.

The state of aggregated silica particles strongly influences the stability of Pickering emulsions and that aggregation can be effectively controlled by addition of inorganic salts. Silica aggregates prepared by changes in salt concentrations have been used[31,32], and their stability, interfacial and rheological properties have been discussed in literature.[33,34]

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6. General conclusions

This thesis deals with the production and characterization of solvent stable microcapsules to provide the perfume deliver technology to consumer goods. All this had to be done following sustainability criteria.

The general conclusions of the work are the following:

1. The material selected as shell of our capsules system was respecting both the prerequisites exposed in the objective: cellulose acetate is a natural derived polymer, known as biodegradable in literature. Titanium dioxide is an inorganic compound occurring in nature. Screening test confirmed the suitability of both polymer and blend of polymer with titanium nanoparticles as a barrier between active and full formulation products. The absence of benefits referable to the titanium dioxide nanoparticles and the possible health risks attributable to these nanoparticles are the reasons why its use has been cancelled during the work;
2. Three different encapsulation techniques were studied. The spray dryer is a common encapsulation process, due to its easiness. The solvent evaporation *via* Pickering emulsifier is lately attracting more attention because of the presence of inorganic particles as stabilizer instead of surfactants and its benefits. The Vapor Induced Phase Separation is a technique developed during this work, which allowed us to see improvements compared to more commonly used encapsulation techniques.
3. In every case we succeed to produce microcapsules. The morphology observed for all the capsules prepared in this work, by spray drying, by VIPS technique and by solvent evaporation is a core-shell type. They show an empty space surrounded by

a dense and thin polymeric wall. Moreover, the optical microscopy images of the capsules prepared by solvent evaporation with Pickering emulsifier confirmed that morphology, due to the way in which the release of the active occurs when the capsules are mechanically stressed, typical of that kind of structure. The encapsulation efficiency, that is a crucial value for industrial purpose due to the high cost of the perfume compound, was found higher in the VIPS capsules, where value of ≈90% was reached. The low active loss is associated with the use of water vapor during the process. In fact, the most water-soluble PRMs are those which are not encapsulated or less encapsulated since they are transported out of the solution drop before the polymeric shell can form. As reported in literature, therefore, the PRMs that present a lower logP, result those more difficult to encapsulate; in our case, more specifically, the more difficult to encapsulate are the most water-soluble materials. The SD capsules, with a maximum EE of ≈67%, suffer from a large loss of perfume due to the high process temperature, in contrast with the BP of some of the PRMs present in the S&S composition. The high temperature was however necessary to obtain a complete sphere and a proper capsule morphology. Solvent evaporation by Pickering emulsifier is a promising technique for our chemistry because of the easy formation of core-shell capsules. Nevertheless, a deeper knowledge on how to isolate the capsules and to characterize them would be required.

VIPS technique is the process that gave the best results in our work. First, it has improved the production of the capsule with respect to the IPS, promoting a better precipitation of the polymer and a spherical morphology. Furthermore, considering the results of activity and EE, the technique is very promising and several studies for optimization of the

apparatus and process can be attempted. It would be interesting to perform more simulations, taking into account the atomization pattern and the time required for the precipitation of the droplets through a flow simulation study for a better design of the chamber. Also, the acquisition of new atomization nozzles may allow a finer adjustment of the parameters and a narrow size distribution.

Appendixes

Appendix A - List of abbreviations

APIs	Active pharmaceutical ingredients
BP	Boiling point
CA	Cellulose acetate
CTA	Cellulose triacetate
DS	Degree of substitution
DV	Drop volume
DST	Dynamic surface tension
ECHA	European Chemical Agency
EE	Encapsulation efficiency
ESEM	Environmental scanning electron microscopy
FID	Flame iodization detector
FP	Finish product
GC-MS	Gas Chromatography – Mass Spectrometry
HDL	Heavy duty liquid
IPS	Immersion precipitation technique
IARC	International Agency for Research on Cancer
LCD	Liquid crystal displays

LFE	Liquid fabric enhances
LLE	Liquid liquid extraction
LOQ	Limit of quantification
MF	Melanine-formaldehyde
NPs	Nanoparticles
P	Partition coefficient
PCMs	Phase change materials
PEI	Poly(ether imide)
PES	Poly(ether sulfone)
PMC	Perfume Microcapsule
PSF	Polysulfone
PVDF	Polyvinylidene difluoride
scCO2	Supercritical carbon dioxide
SD	Spray dryer
SPME	Solid-phase microextraction
S&S	Sweet & Smart
TEM	Transmission Electron Microscopy
TGA	Thermogravimetric analysis

UF	Urea-formaldehyde
VIPS	Vapour induced phase separation
WSCA	Water-soluble cellulose acetate

Appendix B - List of figures and tables

Appendix C - Congresses and contributions

Authors: M. Ammendola, R. Rodrigo Gomez, R. Garcia-Valls
Title: Permeability studies on sustainable composite membranes
Congress: 15th Doctoral day 2018
Format (poster or oral): Poster
Date: 23 May 2018 **Place**: Tarragona, Spain

Authors: M. Ammendola, R. Rodrigo Gomez, R. Garcia-Valls
Title: Permeability studies on sustainable composite membranes
Congress: 16th NYM (Network Young Membrains) 2018
Format (poster or oral): Oral
Date: 5-7 July 2018 **Place**: Valencia, Spain

Authors: M. Ammendola, R. Rodrigo Gomez, R. Garcia-Valls
Title: Permeability studies on sustainable composite membranes
Congress: 21st Advanced Materials Congress
Format (poster or oral): Poster
Date: 3-6 September 2018 **Place**: Stockholm, Spain

Authors: M. Ammendola, R. Rodrigo Gomez, R. Garcia-Valls
Title: Spray drying Microencapsulation by natural and natural derived polymers
Congress: International Symposium on Encapsulation Technologies
Format (poster or oral): Oral
Date: 22-24 October 2018 **Place**: Tarragona, Spain

Authors: M. Ammendola, J. Ma, D. Pirone, R. del Pezzo, G. Colace
Title: SMARTMEM: Bridging the emerging technology platform around smart-membranes and consumer goods products
Congress: 2019 MCAA General Assembly & Conference
Format (poster or oral): Poster

Date: 24-25 February 2019 **Place**: Vienna, Austria

Authors: M. Ammendola, R. Rodrigo Gomez, R. Garcia-Valls
Title: o Spray drying capsules by natural derived polymer
Congress: 8th Conference Bubble&Drop
Format (poster or oral): Oral
Date: 24-28 June 2019 **Place**: Sofia, Bulgaria

Authors: M. Ammendola, R. Rodrigo Gomez, R. Garcia-Valls
Title: Sustainable microcapsules via vapour induces phase separation (VIPS)
Congress: 26th International Conference on Bioencapsulation
Format (poster or oral): Poster
Date: 27-29 August 2019 **Place**: Strasbourg, France