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# Green assessment of polymer microparticles production processes: a critical review

Hassan El Itawi,\*<sup>1</sup> Sami Fadlallah,\*<sup>2</sup> Florent Allais,<sup>2</sup> Patrick Perré<sup>1</sup>

<sup>1</sup> Université Paris-Saclay, CentraleSupélec, Laboratoire de Génie des Procédés et Matériaux, SFR Condorcet FR CNRS 3417, Centre Européen de Biotechnologie et de Bioéconomie (CEBB), 3 rue des Rouges Terres, Pomacle 51110, France.

<sup>2</sup> URD Agro-Biotechnologies Industrielles (ABI), CEBB, AgroParisTech, 51110, Pomacle, France.

\*hassan.el-itawi@centralesupelec.fr, sami.fadlallah@agroparistech.fr

## **Abstract:**

The fabrication of simple and core-shell polymer microparticles is of great importance due to their wide range of industrial applications, such as the food industry, cosmetics, and drug delivery. Regardless of their outstanding advantages, the vast majority of the targeted microparticles are produced using fossil raw materials whose depletion is inevitable, and there is an urgent need to develop innovative classes of sustainable microparticles from renewable resources. Several reviews discussed the common techniques to synthesize polymer microparticles for diverse real-life applications. Nonetheless, no reports were found on the sustainability evaluation of the diverse production methods or the microparticle raw materials and solvents used. In this critical review, the state of the art of polymer microparticles is first described. Next, the sustainability of the common production techniques, including microfluidics, is evaluated based on selected criteria, including waste generation, use of green solvents, atom- and energy efficiency. Furthermore, the challenges of achieving green production are discussed based on three elements: green production process, green raw material, and green solvents. Finally, room for improvement is discussed with highlights on future perspectives, including further investigations that should be accomplished to find renewable substitutes and green up the existing production strategies for better lives for future generations.

**Keywords:** Sustainability, polymer microparticles, microencapsulation, production processes, raw material, environmental factor.

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## Abbreviations

<b>AA:</b>	Acrylic acid	<b>PET:</b>	Polyethylene terephthalate
<b>Aam:</b>	3-(((2-cyanopropan-2-yl)oxy)(cyclohexyl)amino)-2,2-dimethyl-3-phenylpropanenitrile	<b>PGA:</b>	Polyglycolic acid
<b>AIBn:</b>	Azobisisobutyronitrile	<b>PHB:</b>	Poly-β-hydroxybutyrate
<b>APS:</b>	Ammonium persulfate	<b>PLA:</b>	Poly(lactic acid)
<b>BSA:</b>	Bis(trimethylsilyl)acetamide	<b>PLGA:</b>	Poly(lactic-co-glycolic acid)
<b>DCM:</b>	Dichloromethane	<b>PMMA:</b>	Poly(methyl methacrylate)
<b>DEP:</b>	Diethyl phthalate	<b>PP:</b>	Polypropylene
<b>DMC:</b>	Dimethyl carbonate	<b>PS:</b>	Polystyrene
<b>DMF:</b>	Dimethylformamide	<b>PU:</b>	Polyurethane
<b>DOP:</b>	Diethyl phthalate	<b>PUFAs:</b>	Polyunsaturated fatty acids
<b>DVB:</b>	Divinylbenzene	<b>PVA:</b>	Poly(vinyl alcohol)
<b>EGDMA:</b>	Ethylene glycol dimethylacrylate	<b>PVC:</b>	Polyvinyl chloride
<b>FLAP:</b>	5-Lipoxygenase-activating protein	<b>PVDF:</b>	Polyvinylidene fluoride
<b>GMA:</b>	Glycidyl methacrylate	<b>PVP:</b>	Polyvinylpyrrolidone
<b>HDDA:</b>	1,6-Hexanediol diacrylate	<b>SC CO<sub>2</sub>:</b>	Super-critical CO <sub>2</sub>
<b>HPC:</b>	Hydroxypropyl cellulose	<b>SD:</b>	Sustainable development
<b>HPMC:</b>	Hydroxypropyl methylcellulose	<b>SDS:</b>	Sodium dodecyl sulfate
<b>IBOA:</b>	Isobornyl acrylate	<b>Span 20:</b>	Sorbitan monolaurate
<b>MYPC:</b>	Dimyristylperoxydicarbonate	<b>Span 80:</b>	Polyoxyethylene (20) sorbitan monooleate
<b>OCMTS:</b>	Octamethylcyclotetrasiloxane	<b>SPS:</b>	Sodium persulfate
<b>PA:</b>	Polyamide	<b>TEGDM A:</b>	Triethylene glycol dimethacrylate
<b>PBMA:</b>	Poly(butyl methacrylate)	<b>TG:</b>	Transglutaminase
<b>PCL:</b>	Polycaprolactone	<b>THF:</b>	Tetrahydrofuran
<b>PDMS:</b>	Polydimethylsiloxane	<b>TPGDA:</b>	Tripropylene glycol diacrylate
<b>PE:</b>	Polyethylene	<b>VCM:</b>	Vinyl chloride monomer
<b>PEG:</b>	Polyethylene glycol		

## 1. Introduction

Sustainable development (SD) is defined literally as the development that can be continued either indefinitely or for the given time period <sup>1-5</sup>. SD was first introduced after the publication of the Brundtland Report (WCED, 1987), which proposed that “SD is the development that satisfies present needs without compromising future needs.” <sup>6</sup>. SD has become a moral, political, and environmental concern during the last three decades. The adoption of its principles is more an issue of the fate of future life on our planet than a choice that could be made. It can be seen from three points of view: (1) economic, which sees the financial health as an ultimate metric, (2) ecologic, based on its contribution to protecting the

natural environment, preserving clean air, pure water, and productive lands, and (3) social, which looks for contributions to the generation and sharing of knowledge <sup>7</sup>. To this end, visual representations like the Venn diagram (Figure 1) have been proposed for better communication and more precise standards <sup>8, 9</sup>.

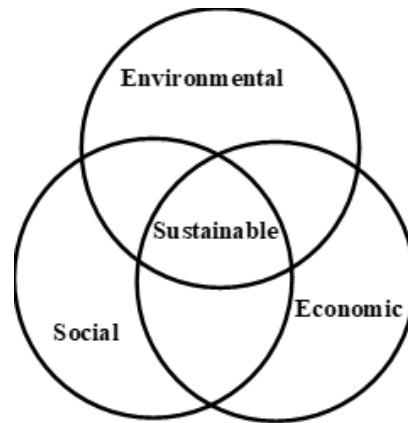


Figure 1: The sustainability Venn diagram.

Many of the Earth's resources, such as fossil fuels and ores, are employed in the fabrication of a wide range of materials. As an example, we consume a massive nine billion tons of attenuating fuels—oil and coal—per year. Fossil-based polymers like polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), polystyrene (PS), and polyethylene terephthalate (PET), on which we depend nowadays in daily life, are produced in billions of tons <sup>7</sup>. Fossil resources (coal, oil, and natural gas) are relatively able to satisfy present needs. However, they have two major issues: (1) the inevitable attenuation within less than a few hundred years due to the high consumption rate, (2) pollution due to the production of residues from the manufacturing process resulting in greenhouse gas emissions, climate change, altering the biological mix and plastics ending up in the ocean <sup>10</sup>. Population growth and change in consumption patterns make this situation even worse; Earth's material resources are insufficient to supply the growing needs of the planet's population. This

adversely affects future generations and their share of the Earth's resources and addresses the critical need of SD in the field of materials production.

For this purpose, it is crucial to conduct research to find bio-based, renewable, and sustainable substitutions for non-renewable fossil-based resources. However, are all renewable materials truly sustainable? It is an oversimplification to consider the sustainability of a given process only by the renewability of the employed starting materials. Fadlallah et al. have recently analyzed the procedures available for converting lignin-based compounds into different value materials by following the 12 principles of green chemistry<sup>11</sup>. The main conclusion of their work was that “renewable carbon should not be the only consideration while designing biobased alternative products.” Indeed, it was found that a major portion of the generated waste corresponds to the large volume of solvent(s) used in a chemical reaction. This necessitates the use of simple, accessible, and useful green metrics such as environmental factors (EF) to measure the greenness of the production processes<sup>12</sup>. EF measures the amount of waste generated by a certain process expressed in kg of waste per kg of product (Equation 1). The ideal EF of a process is 0, whereas a higher EF means more waste generation and, finally, greater negative environmental consequences. At the same time, most of the employed solvents are non-renewable and toxic. It is then important to consider replacing toxic and non-renewable solvents according to selection guides, *e.g.*, that of Pfizer. The green solvent selection guides are usefully reviewed by Clark *et al.*<sup>13</sup>.

$$EF = \frac{\sum m_{raw\ materials} + \sum m_{reagents} + \sum m_{solvents} - m_{desired\ product}}{m_{desired\ product}} \quad (1)$$

Simple and core-shell polymer microparticles are products of the material industry that are widely employed in daily life. Their use has been the scope of many research studies over the years because of their importance in a wide range of applications. By definition, polymer

microparticles are particles of different shapes<sup>14</sup> made from polymeric materials ranging in size from 1 to 1000  $\mu\text{m}$ <sup>15</sup>. In most studies, polymer microparticles refer to spherical particles that will be exclusively considered in this review. Most polymer particles produced for different applications such as the food industry<sup>16</sup>, cosmetics<sup>17</sup>, biotechnology<sup>18,19</sup> and drug delivery<sup>20–23</sup> are derived from fossil fuel-based polymers/monomers. For example, commercial polymer microparticles are mainly made from poly(methyl methacrylate) (PMMA)<sup>24,25</sup>, polycaprolactone (PCL)<sup>26</sup>, and poly(vinyl alcohol) (PVA), which are all derived from fossil fuels. Another issue is the production processes, which in most cases are not frugal, consume high energy, generate huge amounts of hazardous wastes that are expensive and hard to treat.

Several previous reviews described the chemical and physical production methods of polymer microparticles and their applications in detail<sup>16,17,27–30</sup>. The microfluidic method is particularly important due to its thriftiness and controlled conditions advantage<sup>15</sup>. However, and according to our knowledge, the sustainability of different production methods and that of the raw materials employed were never assessed. This critical review first shows the importance of polymer microparticles regarding sustainable development. Second, different chemical (interfacial polymerization and coacervation) and physical (atomization and extrusion) production processes, including microfluidics, are briefly described and evaluated according to their sustainability using different selected examples from the literature. The pros, cons, and challenges of the main polymer microparticle production processes are summarized in Table 9. Furthermore, the sustainability of the raw materials of the polymer microparticles is also discussed alongside the ramifications and constraints of the transition from fossil fuel-to bio-based microparticles. Finally, routes for improvements are considered while highlighting the future of bio-based microparticle production via microfluidics.

## 2. Methodology

This section begins by briefly describing the shapes and morphologies and the applications of polymer microparticles. The sustainability assessment of the production processes is based on four key aspects: waste generation, the quantity of solvents and their toxicity, energy consumption, and process duration. The waste is quantified by the EF, which has three different forms: simple E-factor (sEF), E-factor (EF), and the complete E-factor (cEF). The sEF excludes solvents while calculating the waste generated, and it is useful for the primary evaluation and comparison of different processes (Equation 2). The EF includes the solvents in waste evaluation except water because it is a green solvent (Equation 1) <sup>12,31</sup>. However, according to different literature studies <sup>32–35</sup>, water is often used in excessive quantities in certain processes. The excessive use of potable water and the difficulty of cleaning polluted water may lead to a water crisis by the 2040s, touching around 4.5 billion people, according to a UN projection <sup>36</sup>. Considering the difficulty of water treatment and recovery, it is then necessary to include water in the waste generation evaluation. The cEF thus estimates the waste generated, including the water used in the process (Equation 3).

$$sEF = \frac{\sum m_{raw\ materials} + \sum m_{reagents} - m_{desired\ product}}{m_{desired\ product}} \quad (2)$$

$$cEF = \frac{\sum m_{raw\ materials} + \sum m_{reagents} + \sum m_{solvents} + m_{water} - m_{desired\ product}}{m_{desired\ product}} \quad (3)$$

Although the EF is an indicator of the greenness of the process in terms of waste generation, it does not consider the toxicity of the substances and solvents employed. To that purpose, the nature of the solvents must be analyzed apart as a second key aspect. The third



aspect of this sustainability assessment is the temperature at which the process is done, which is related to energy consumption. Processes at room temperature are less energy-consuming than processes requiring heating or chilling, yet they may require more time and result in a lower yield. Accordingly, the final sustainability evaluation parameters are the duration of the process and its yield.

Due to the absence of some data, we made some reasonable assumptions to facilitate our calculations. Authors of some research on the interfacial polymerization process (P1 to P13 of Table 2) provided the conversion rate in their experiments without mentioning the yield. The calculation of the produced mass of microparticles in these cases assumes no loss of material during the purification process. The yield of these products is assumed to be equal to the conversion rate.

The authors of processes producing core-shell polymer microparticles, as in the case of coacervation, usually mention two key parameters estimated as a mean on a given sample of produced microparticles: the encapsulation efficiency ( $E_{\text{eff}}$ ) and the payload (PL). The encapsulation efficiency is the ratio between the mass of encapsulated core material ( $m_c$ ) and the mass of core material initially put in the process ( $m_{c0}$ ) (Equation 4). The payload is the mass ratio between the encapsulated core material ( $m_c$ ) and the total mass of the capsule ( $m_{\text{cap}}$ ) (Equation 5). The mass of encapsulated core material is calculated by Equation 4; then Equation 5 is used to calculate the mass of the capsules that represent the desired product.

$$E_{\text{eff}} = \frac{m_c}{m_{c0}} \quad (4)$$

$$PL = \frac{m_c}{m_{\text{cap}}} \quad (5)$$

Concerning microfluidic processes, authors usually give the flow rates of the two or three phases involved in the production process. We consider the production of a 1 ml volume

of simple polymer microparticles. The equivalent volume of continuous phase needed for this production is estimated with the help of the flowrate ratio between the continuous phase and the dispersed phase (Equation 6). The mass of the product is calculated using the yield of the process provided by the authors. This methodology was adopted in the recent study of Owen *et al.*<sup>35</sup>:

$$V_c = \frac{Q_c}{Q_d} V_d \quad (6)$$

where  $Q_c$  and  $Q_d$  are the flowrates of dispersed and continuous phases, respectively, and  $V_c$  and  $V_d = 1$  ml are their respective volumes. We perform the same procedure for core-shell microparticles with three fluids instead of two.

### 3. Polymer microparticles

In addition to shape, microparticles can also be classified according to their morphology as simple, core-shell, and Janus (Figure 2). The morphology of simple microparticles is a hydrophilic or hydrophobic full sphere that may be loaded with bioactive molecules for drug delivery applications. Core-shell microparticles, often called microcapsules, consist of an active ingredient (inner phase) in the form of solid or liquid coated within a solid polymer shell isolating it from the external environment to protect it, immobilize it and control its release at the appropriate time and place, and according to a targeted application. This production process of core-shell microparticles is often called microencapsulation, and the produced particle is called a microcapsule. Microcapsules have two different forms according to their composition: water-in-oil (W/O), where the inner phase is aqueous, and the shell is organic, or oil-in-water (O/W), where the inner phase is organic, and the shell is aqueous. It is possible also to classify microcapsules according to the structure

of the core material: mono-core where the inner phase is in the form of one particle, poly-core where inner material are several particles of different size and shape enclosed within the shell, and matrix where core materials are distributed homogeneously into the shell. Finally, Janus microparticles are particles with two or more different surfaces of distinct physical properties. The most common Janus particles have a hydrophilic half and a hydrophobic half.

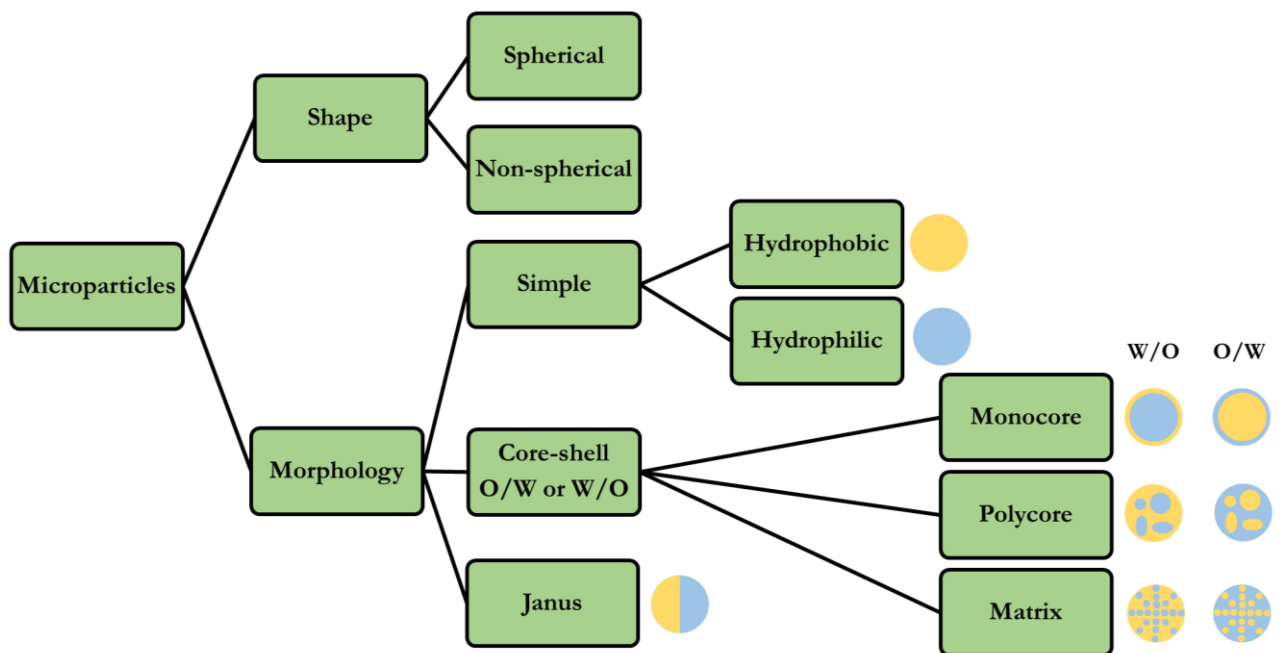


Figure 2: Classification of polymer microparticles according to shape and morphology. Yellow color corresponds to a hydrophobic content, while blue color corresponds to hydrophilic content.

## 4. Applications of polymer microparticles

This section reviews some examples of the SD concept as applied to the importance polymer microparticles in the domains of pharmaceuticals, cosmetics, and the food industry. These examples are summarized in Table 1.

Polymer microparticles are synthesized for many applications<sup>28</sup>. They help in handling and delivering drugs for several treatments. In addition, they are used to protect volatile materials from external environmental effects such as degradation, oxidation, and

reactions and ensure the safe handling of toxic materials. Core-shell microparticles help achieve controlled release of active ingredients and mask their odor if necessary. Polymer microparticles address important needs for society in terms of improving medical care and the quality of life of current and future generations. Thus, their sustainable production is of crucial importance.

In pharmaceuticals, drug-loaded polymer microparticles are often used as vehicles for drug delivery and targeted drug release necessary in many therapies approved by the US Food and Drug Administration <sup>34,37-39</sup>. The idea of using polymer microparticles as drug delivery vehicles dates to 1964, when silicone rubber was employed as a carrier for the controlled release of prolonged drug therapy <sup>40</sup>. One year later, PE was implemented as another polymer for drug delivery <sup>41</sup>. Despite the success of these implementations, both polymers have a low level of degradability, limiting their applications. This raises the need for degradable polymer microparticles for drug delivery and release. Degradable polymers can be natural such as polysaccharides (*e.g.*, alginate, gellan gum) or derived from natural monomers (*e.g.*, lactic acid, glycolic acids) <sup>21</sup>.

Nowadays, several examples of polymer microparticles applications in pharmaceuticals exist <sup>42</sup>. Alginate microparticles are frequently used for drug delivery due to their properties, especially their pH sensitiveness and biodegradability, which facilitate the controlled release making them efficient for treating diseases like inflammatory bowel disease (IBL) where drugs need to get through the stomach and small intestine for release in the large intestine <sup>43</sup>. Poly(lactic-co-glycolic acid) (PLGA) microparticles loaded with chemotherapeutic drug doxorubicin (DOX) were fabricated for the controlled release to cancer cells <sup>22</sup>. Similarly, PLGA microparticles were produced and loaded with DOX and paclitaxel (PTX) drugs for lung cancer treatment <sup>44</sup>, and PLGA microparticles were loaded with bupivacaine <sup>34</sup>. Another example of microparticle drug delivery application is the production of cholesterol liquid

crystal/PMMA (CLC/PMMA) microparticles with various cholesterol loading amounts by *in situ* suspension polymerization for smart drug delivery systems <sup>45</sup>. Methotrexate (MTX)-loaded gellan gum microparticles have been fabricated to treat human malignancies and autoimmune diseases like rheumatoid arthritis <sup>46</sup>. In addition to drug delivery, polymer microparticles are often used to deliver entrapped antigens or DNA vaccines <sup>47,48</sup>. Current and future generations benefit from the use of polymer microparticles for vaccination and the treatment of complex diseases.

The cosmetics sector represents a multi-billion-dollar global market in which polymer core-shell microparticles play a significant role <sup>17</sup>. Active ingredients in cosmetics like antioxidants <sup>49</sup>, essential oil and fragrances <sup>50</sup>, and sun filters <sup>51</sup> are volatile and sensitive to heat, light, and moisture. Core-shell microparticles offer the isolation and protection of desired volatile compounds in a polymeric shell and ensure their safe, effective, and non-painful targeted release on human skin. Polymers employed as shell material for cosmetics application can be natural (*i.e.*, polysaccharides, proteins, lipids) or synthetic (*i.e.*, acrylic polymers, polyvinyl alcohol (PVA), poly(vinylpyrrolidone) (PVP), poly (lactic acid) (PLA), and PLGA). Essential oils are important in the cosmetics sector because of their antimicrobial and insect repellent properties. Clove, ginger, and jasmine essential oils were all successfully encapsulated in acrylic polymer PMMA by solvent evaporation of O/W emulsion system <sup>52</sup>, suspension polymerization <sup>53</sup>, and solvent evaporation <sup>54</sup>, respectively. Polysaccharide sodium alginate and sodium alginate with starch microparticles were synthesized for exfoliating dead skin cells without irritation <sup>55</sup>. Urea is a penetrating moisturizer widely used in skincare and dermatological formulations; however, it is unstable in water. Urea readily decomposes into ammonia and carbon dioxide in cosmetics products containing water, leading to emulsion instability and biological nonavailability. To avoid this drawback, urea was encapsulated in a PLGA shell to form microcapsules ranging between 1 and 5  $\mu\text{m}$  <sup>56</sup>. The contributions of

polymer microparticles in pharmaceuticals and cosmetics are similar. Despite the benefits to skin care brought by their wide implementation, attention should be paid to the sustainability of the compounds used and how they are produced.

Core-shell microparticles are widely used in the food industry to incorporate food ingredients, enzymes, cells, and other materials<sup>16</sup>. Microcapsules have crucial importance not only in protecting against oxygen, light, or extreme conditions such as moisture and heat but also in the controlled release of aromas and flavors<sup>57</sup>. In the dairy industry, microencapsulation is applied to immobilize lactic acid-producing bacteria in polyacrylamide gel, a required step for the continuous production of yogurt<sup>58</sup>. The consumption of probiotic bacteria is associated with several health benefits. Its encapsulation in alginate beads allows the bacteria to survive in fermented dairy desserts<sup>59</sup>. Essential oils are also a valuable key product in the food industry for their fragrance and interesting antimicrobial, antifungal, antibiotic biological properties, making them very important for food preservation and flavoring. Because some components are highly volatile, essential oils need to be stabilized, and encapsulation is the best choice for this purpose. Essential oil was encapsulated in PMMA and crosslinked with a tetrafunctional monomer, triethylene glycol dimethacrylate (TEGDMA), through suspension polymerization<sup>60</sup>. Fish oil is another important product in the food industry because of its n-3 polyunsaturated fatty acid (n-3 PUFAs) and its valuable health benefits<sup>61</sup>. However, it has an undesired odor, making its incorporation into the food very difficult unless encapsulated. Fish oil was successfully encapsulated in soybean protein particles by emulsification and spray drying<sup>62</sup>. The application of polymer microparticles in the food industry offers safer, less expensive, and healthier food, as seen from the above examples. This will ensure humans food chain, contribute to expanding the human life span and is beneficial for future generations of life on Earth.

Despite all benefits for human wellness, the employment of non-renewable resources and energy-consuming processes generating difficult-to-treat wastes remains a violation of sustainable development. These two contradicting facts address the necessity of employing sustainable production processes and renewable raw materials. Many improvements are still necessary at the environmental level, especially when considering the production processes and renewability of raw materials (*vide infra*).

Domain	Polymer microparticles	Application	Reference
Pharmaceutics	Alginate	Inflammatory bowel disease (IBL) treatment	43
	PLGA	Lung cancer treatment	44
	CLC/PMMA	Smart drug delivery	45
	Gellan gums	Autoimmune diseases treatment	46
	PLGA, PLC, PLA, PLGA	Vaccine delivery	47,48
Cosmetics	PMMA	Antimicrobial and insect repellent	52-54
	Sodium alginate Sodium alginate with starch	Exfoliating dead skin	55
	PLGA	Skin care	56
	Lignin	Sunscreen	63
Food industry	Polyacrylamide Gel	Continuous production of yogurt	58
	Alginate	Dairy desserts	59
	PMMA	Food preservation and flavoring	60
	Soybean protein	Masking odor of food product	62
Construction	PBH	Self-healing in cementitious materials	64
Agriculture	Lignin	Improving effectiveness of pesticides	65

Table 1: Summary of some applications of polymer microparticles in pharmaceutics, cosmetics, food industry, and construction sectors.

## 5. Sustainable assessment of common production methods

Regardless of the nature of raw materials (non-renewable, fossil-based, or bio-based) used in the synthesis of microparticles, the sustainability and thriftiness of the production process itself remain questionable. This section offers a critical review of the state of the art of common production processes and assesses their sustainability. Production processes may be divided into two major categories: chemical processes (*i.e.*, interfacial polymerization and coacervation) and physical processes (*i.e.*, atomization and extrusion techniques, including microfluidics). Figure 3 summarizes the different production processes discussed in the present review.

## 5.1. Chemical Processes

Chemical processes or emulsion-based processes rely on emulsification to form droplets, followed by the formation of a shell or matrix through a chemical reaction (interfacial polymerization) or phase separation (coacervation).

### Interfacial Polymerization

The interfacial polymerization process was first introduced in 1932 by Luther and Heuck<sup>66</sup> and was successfully implemented in industries such as paint, pharmaceuticals, and food. A typical interfacial polymerization system consists of a continuous phase, dispersed phase (monomer), emulsifier (surfactant), and an initiator<sup>67</sup>. In most common interfacial polymerization processes, the continuous phase is mainly aqueous, and the monomer dispersed phase is usually organic (oil-in-water emulsion)<sup>68</sup>. The chemical reaction is a free-radical polymerization that starts with the initiation reaction using an initiator that is soluble in either the dispersed phase or the continuous phase<sup>69</sup>. Interfacial polymerization can be conventionally called suspension polymerization, emulsion polymerization, or dispersion polymerization depending on four criteria: the initial state of the polymerization mixture, polymerization kinetics, mechanism of particle formation, and the shape and size of the final polymer particles<sup>70,71</sup>.

In suspension polymerization, a solution containing the monomer and the initiator is dispersed in a heterogeneous mixture with the continuous phase by mechanical agitation to prevent coalescing<sup>72</sup>. Suspension of an aqueous monomer in an organic solvent (*e.g.*, acrylamide) is referred to as an inverse suspension polymerization process. While maintaining



the suspension throughout the whole polymerization process, polymerization is initiated at a controlled temperature between 20 and 100 °C, occurs inside the droplet and continues until completion. The monomer microdroplets solidify under these conditions and form microparticles (Figure 4). Examples of polymer microparticles produced by suspension polymerization include PS, PVC<sup>32</sup>, polyacrylates, and poly(vinyl acetate)<sup>73-75</sup>. This process is frequently called a microbulk process because it is very similar to bulk polymerization, and the particle size produced is between 1 µm and a few millimeters. Unlike suspension polymerization, the particle size produced in emulsion polymerization is less than 1 µm. The initiator is dissolved in the continuous phase instead of the dispersed monomer<sup>76</sup>. This process requires a surfactant (mainly anionic) dissolved in the continuous phase at a concentration above the critical micelle concentration to form micelles ranging from 5 to 10 nm in size. MMA and PVC/clay nanocomposites are examples of polymers produced by emulsion polymerization<sup>77,78</sup>.

Like any process, interfacial polymerization processes have pros and cons despite being very useful in the industry. An advantage is that interfacial polymerization is simple to operate and easy to perform. The process avoids issues related to chain transfer, heat transfer or overheating because the system remains fluid during the polymerization reaction, and the heat generated by the exothermic free radical polymerization dissipates in the continuous phase that acts as a heat sink<sup>67</sup>. High molecular weight products can be achieved quickly without further processing<sup>79</sup>. However, surfactants and other polymer adjuvants remain in the polymer and are difficult to remove, making the polymer microparticles incompatible with applications requiring high purity materials. In the case of dry polymers, solvent use and recovery induce high energy consumption and cost, limiting its commercial utilization to

polycarbonates, aliphatic polysulfides, and aromatic polyamides<sup>79</sup>. These processes produce microparticles with a wide size distribution<sup>80</sup>.

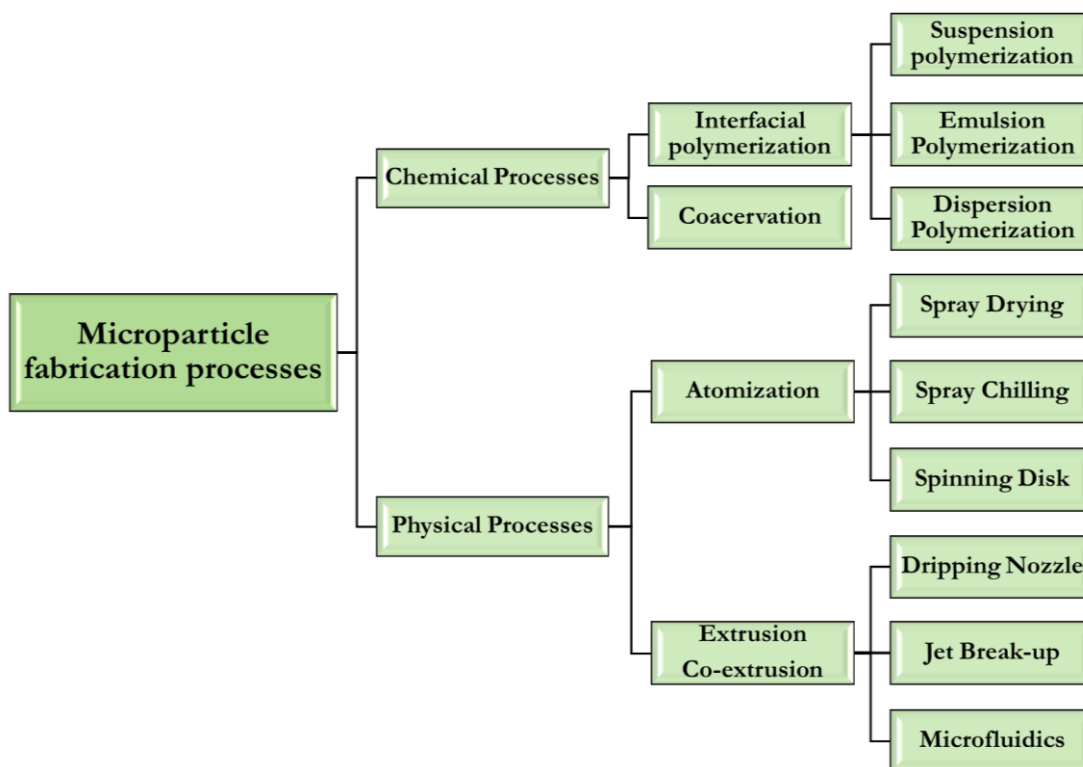


Figure 3: The classification of different processes used to produce polymer microparticles.

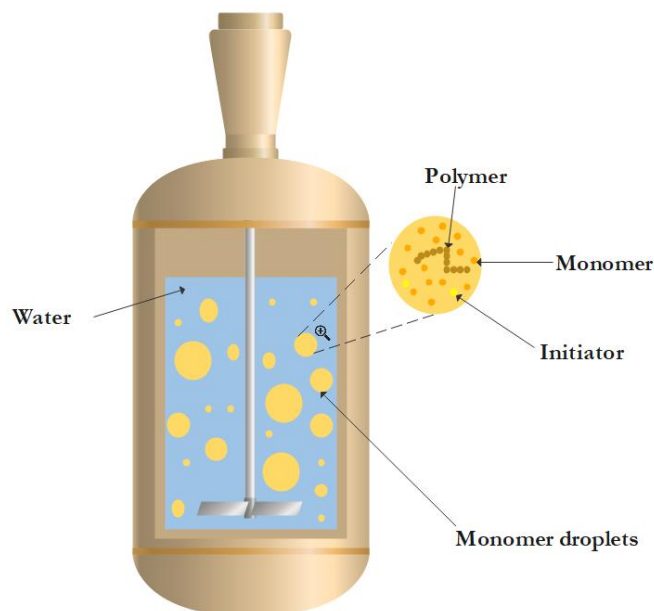


Figure 4: The suspension polymerization process scheme.

Because this review is focused on polymer particles at the micro-scale, the sustainability of suspension polymerization is selected for evaluation from the other interfacial polymerization processes. According to the literature, high use of solvents is recorded in several suspension polymerization processes for either the continuous phase or the formation of a solution of monomer, initiator, and surfactants. The mass ratio of the dispersed phase (monomer) to the continuous phase ( $\phi = m_m/m_c$  where  $m_m$  is the mass of the monomer and  $m_c$  is the mass of continuous phase) ranges between 0.1 and 0.5 in most studies. The continuous phase uses from twice to 10 times as much solvent as the dispersed phase. The continuous phase is frequently water<sup>67,70,74,79,81</sup> but may be an organic solvent<sup>82</sup> in the case of hydrophilic monomer-dispersed phases like polyacrylamide (PAM) and poly(acrylic acid) (PAA). The use of water and solvents should be optimized; the goal is to increase  $\phi$  to unity or even more<sup>70</sup>. Unfortunately, this goal is hampered by the effect of less solvent on the properties of microparticles<sup>32</sup>.

We take the example of PVC microparticle fabrication by suspension polymerization<sup>32</sup> reported in Table 2 (P1, P2, and P3). At  $\phi = 1.1$  (P3), the conversion rate is more than the P1 and P2 of lower  $\phi$ . In addition, the produced microparticles have a slightly higher bulk density and thus better mechanical resistance. The total amount of generated waste is also less (cEF = 1.8), signifying a more eco-friendly process than the P1 (cEF = 4.3) and P2 (cEF = 2.3) of the same study. However, particle shapes and size distributions are adversely impacted. Precisely, although increasing  $\phi$  from 0.41 (P1) to 1.1 (P3) for PVC microparticle formation reduced the quantity of solvent waste by an approximate factor of 2.3, it resulted in wider size distribution and poor control of particle size. In addition, a higher agglomeration degree was recorded, and less porosity and irregular shapes were observed at  $\phi = 1.1$ . These results suggest a compromise between the greenness of the process in terms of solvent use and

the properties of the synthesized microparticles when optimizing for the best quality of microparticles with the least solvent consumption.

Ballard et al.<sup>83</sup> studied the nitroxide-mediated suspension polymerization of MMA and BMA by varying the operating conditions of temperature, the type and quantity of reagents (monomer, initiator, and stabilizers) and solvents. The suspension polymerization of MMA was performed at 83 °C with the same quantity of monomer and two different initiators: 3-(((2-cyanopropan-2-yl)oxy)(cyclohexyl)amino)-2,2-dimethyl-3-phenylpropanenitrile (Aam) and 2,2'-azobis (2-methylpropionitrile) (AIBN). The use of 0.15 g of AIBN initiator (process P8) compared to 1.27 g Aam initiator (process P4) was not only more efficient (higher conversion rate) and greener (lower cEF; 3.6 vs. 4.6), but also six times faster. This result shows the importance of the proper choice of the initiator from the production and green points of view, especially when going from lab scale to industrial scale where the quantities are more important. Moreover, adding as small an amount as 45 mg of NiNO<sub>2</sub> in the continuous phase to the AIBN-initiated suspension polymerization (process P5) increased the conversion rate by 6% and reduced the time needed for polymerization by 15 min.

Unlike PVC, PMMA and PBMA, PAM is a hydrophilic polymer, so its production by suspension polymerization requires an organic solvent as a continuous phase. In addition to waste generation, organic solvents are usually less green than aqueous solvents because they undergo strict hazardous waste management that requires further energy consumption. Suspension polymerization of PAM was performed at different temperatures and durations (P9 to P13) in the study of Yao et al.<sup>82</sup>. Both water and organic solvents were used, which justifies the relatively high cEF and EF for processes P9 to P13 in the range of 24.2–39.9 and 17.4–28.9, respectively. At a relatively low temperature (55 °C), the conversion rate is 60%

(P9) due to a low initiation rate; this results in more waste of reagents (sEF = 3.8). Although increasing the temperature to 75 °C (P11) requires more energy, it allows a higher conversion rate for the same duration and, consequently, less waste (sEF = 2). An excessive increase of temperature (P10) is useless due to the faster transfer rate of chains that will terminate the reaction and reduce the conversion rate to 82.5%, which means more waste (sEF = 2.5). In addition to using organic solvents, a large amount of water was used in these processes to prepare the monomer and emulsifier solutions. This justifies the gap between EF and the cEF and makes this process more waste-producing. Moreover, the results of this study show no variation of the conversion rate and amount of waste generated for the same reaction at a prolonged duration. The optimal conditions of temperature and duration for this process are 75 °C and 1 h. Optimizing the reaction conditions and the quantities of reagents and raw materials is a key step for sustainable production using this process.

Hussain et al.<sup>84</sup> produced PAA microparticles in an interesting suspension polymerization process in supercritical carbon dioxide (SC CO<sub>2</sub>)<sup>84</sup>. SC CO<sub>2</sub> is a fluid state of inexpensive CO<sub>2</sub> gas held at or above its easily achievable critical temperature (31 °C) and critical pressure (73.8 bars). CO<sub>2</sub> accounted for 76% of the total EU greenhouse gas emissions in 2019<sup>85</sup>. The use of SC CO<sub>2</sub> for diverse applications conditioned by its recycling after use is very interesting in terms of reducing atmospheric emissions and limiting greenhouse effect consequences. Moreover, SC CO<sub>2</sub> is considered a green non-organic, non-toxic, and non-explosive solvent<sup>86</sup>. Despite these advantages, the main drawback of SC CO<sub>2</sub> remains its expensive extraction equipment; however, the possibility of using a lower temperature during extraction avoids the thermal degradation of the labile compounds reduces the maintenance costs and renders the process attractive. In the present study, the AA monomer is diluted in water to neutralize it. The neutralized mixture, including water, was transformed into a polymer product with a 97% yield, justifying an sEF close to zero in both P14 and P15.

However, only 64% of the total monomer was transformed into microparticles, with the rest transforming into “large pieces” of polymer. The claimed large pieces could be used for other applications instead of being considered wastes, which increases sEF to 0.6 for both P14 and P15. Water is not considered a solvent in the cEF determination. The used CO<sub>2</sub> does not seem to be recycled and represents more than twice the amount of the monomer. Assuming the non-recycling of CO<sub>2</sub> and its release to the atmosphere, the two processes, P14 and P15, generate around 2.3 kg of CO<sub>2</sub> waste for every one kg of AA polymer microparticles with large pieces. This ratio can reach up to 4 if the large pieces are considered wastes. This result justifies the need for recycling the extracted CO<sub>2</sub> for multiple uses. This optimization may reduce the generation of waste to a value close to zero, making the process green and sustainable.

Process	Monomer /Polymer	Initiator	Emulsifier(s)	Continuous phase	T (°C)	time (h)	Yield (%)	sEF	EF	cEF	Ref.
P1	VCM/ PVC	MYPC	Span20 HPMC HPC	Water	50	24	68	0.7	0.7	4.3	<sup>32</sup>
P2	VCM/ PVC	MYPC	Span 20 HPMC HPC	Water	50	24	69	0.6	0.6	2.3	<sup>32</sup>
P3	VCM/ PVC	MYPC	Span 20 HPMC HPC	Water	50	24	69.5	0.5	0.5	1.8	<sup>32</sup>
P4	MMA/ PMMA	AAM	PVA	Water	83	8	72	0.5	0.5	4.6	<sup>83</sup>
P5	MMA/ PMMA	AIBn NaNO <sub>2</sub>	PVA	Water	83	1.25	82	0.3	0.3	3.9	<sup>83</sup>
P6	BMA/ PBMA	AAM	PVA	Water	87	5	74	0.4	0.4	4.4	<sup>83</sup>
P7	BMA/ PBMA	AAM	PVA	Water	87	7	93	0.1	0.1	1.7	<sup>83</sup>
P8	MMA/ PMMA	AIBn	PVA	Water	83	1	88	0.2	0.2	3.6	<sup>83</sup>
P9	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	55	1	60	3.8	28.9	39.9	<sup>82</sup>
P10	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	85	1	82.5	2.5	20.7	28.7	<sup>82</sup>
P11	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	75	1	97.5	2	17.4	24.2	<sup>82</sup>
P12	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	75	2	97.5	2	17.4	24.2	<sup>82</sup>
P13	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	75	0.333	65	3.4	26.6	36.7	<sup>82</sup>
P14	AA/PAA	SPS	PDMS	SC CO <sub>2</sub>	75	1.5	97	0.03	2.3	2.3	<sup>84</sup>
P15	AA/PAA	SPS	PDMS	SC CO <sub>2</sub>	75	1.5	97	0.04	2.3	2.3	<sup>84</sup>

Table 2: A summary of some suspension polymerization processes with their corresponding operating conditions. The yield is assumed to be equivalent to conversion for P4-P15.

## Coacervation

Coacervation, often called phase separation, was first explained in detail by Bungenberg de Jong in 1929<sup>87</sup>. The International Union of Pure and Applied Chemistry (IUPAC) defines coacervation as the separation of a colloidal solution into two liquid phases: a coacervate rich in colloid and another liquid phase poor in colloid<sup>88</sup>. The coacervation process consists of four steps: (1) emulsification: formation of an O/W or W/O emulsion depending on the nature of the core and shell material, (2) coacervation: deposition of the coating polymer solution and its separation into two phases: the coacervate (coating) and the solvent, followed by the precipitation of the coacervate around the core under stirring, and (3) hardening: solidification and stabilization of the coating, which can be done by UV, thermal crosslinking or solvent removal technique (Figure 5)<sup>89,90</sup>, and (4) drying: post-processing through an energy-consuming process like spray drying or freeze drying. There are two classifications of coacervation systems based on the phase separation mechanism occurring in the second step: simple (salting out)<sup>91,92</sup> or complex (interaction of oppositely charged polymers)<sup>93,94</sup>.

Coacervation is an efficient encapsulation technique that offers the production of mechanically stable microcapsules of high payload up to 99% with excellent controlled release characteristics<sup>95,96</sup>. However, it is sensitive to several factors like physical parameters of core and shell material pressure, shearing, temperature, and pH, which limits its applications<sup>97,98</sup>. The effect of these physical parameters on the encapsulation efficiency and microparticle sizes and their wide size distribution was demonstrated by Xiao et al.<sup>33</sup>. In addition, this process requires time- and energy-consuming post-processing. For example, freeze-drying can take up to three days where temperatures can go down to  $-50\text{ }^{\circ}\text{C}$  to dry the produced capsules compared to physical processes like spray drying or chilling where no

further processing is needed. The common use of toxic reactants like glutaraldehyde in complex coacervation for crosslinked coacervate shells is a drawback. Glutaraldehyde can irritate the eyes, nose, and throat and burn the skin at higher concentrations, and must be carefully used according to the different regulations, especially in the food industry<sup>99–101</sup>.

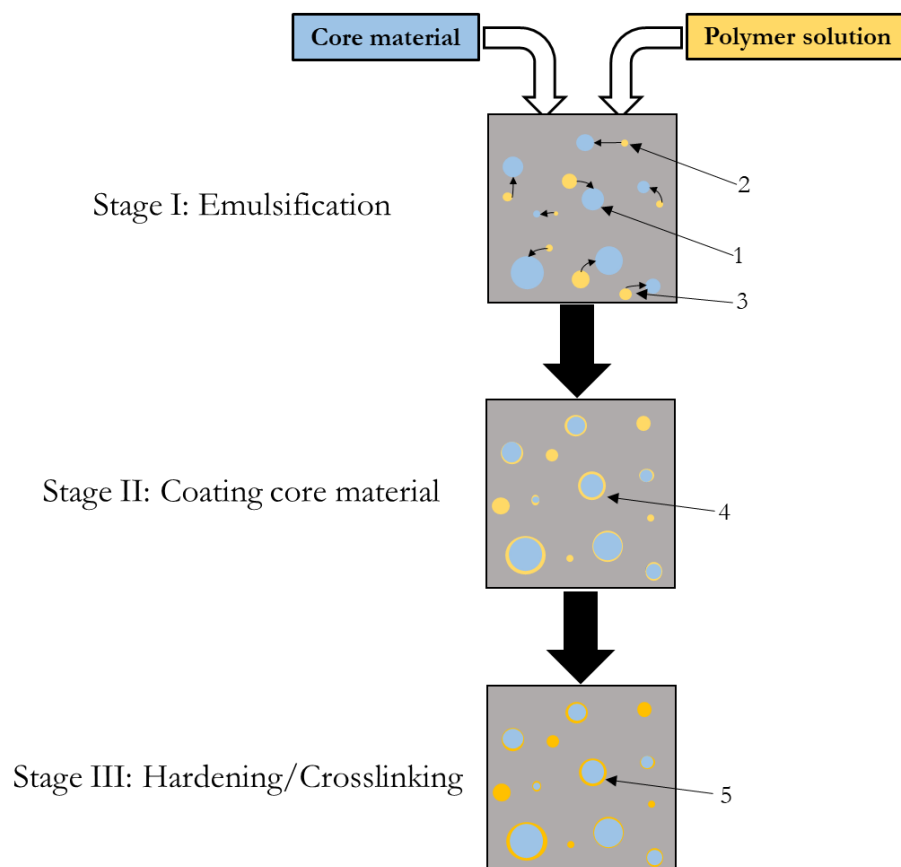


Figure 5: Coacervation process scheme. (1) core material; (2) polymer; (3) deposition of the polymer coating upon core material; (4) coated core materials, (5) microcapsules. Reproduced from Martins et al.<sup>89</sup> with permission from *Taylor & Francis*, copyright 2009.

Table 3 summarizes the conditions (reactants, temperature, and duration) and the corresponding EFs of different coacervation processes. Ocak and Gülümser<sup>98</sup> encapsulated tea tree oil, a volatile essential oil, in gelatin by coacervation using glutaraldehyde as a crosslinker and studied the effect of concentration of the core material, polymer solution, and the crosslinker on the encapsulation efficiency. Process P16 represents the highest encapsulation efficiency recorded in this study *ca.* 88%. In the best cases, 12% of the precious



volatile tea tree oil is not encapsulated; this is not a bad result if a feasible recovery system for non-encapsulated material is integrated with the process. In addition, the  $cEF = 5.5$  seems high due to the possible excessive use of water as a solvent. This result opens room for improvement to optimize the quantity of water used without affecting the efficiency. Using less polymer solution in P17 led to a lower encapsulation efficiency and a higher generation of waste ( $cEF = 7.2$ ). In P18, using a larger volume of polymer solutions to encapsulate more tea tree oil resulted in an encapsulation efficiency of 70% compared to 88% in P16. This is explained by the smaller mass ratio of polymer solution to core material. This process is energy-consuming as post-processing freeze drying requires cooling to  $-30\text{ }^{\circ}\text{C}$ . The encapsulation process took 10 h, and further freeze-drying was carried out for two days. This is a relatively slow process compared to other chemical and physical processes.

In another study, thyme oil was encapsulated inside PLA through coacervation<sup>89</sup> (P19). PLA in dimethylformamide (DMF) solution of  $15.7\text{ g L}^{-1}$  was prepared. The encapsulation efficiency of the process is relatively low (30.5%), given that the coacervation process efficiency can achieve higher than 85% efficiency<sup>102</sup>. Because only the concentration of PLA in DMF was given in the study, not the mass of PLA nor the volume of DMF, we assume that the mass of PLA identified as the shell material of the capsule is equal to 40% of the encapsulated thyme oil mass to proceed to calculations. According to this assumption, the process generates waste close to 400 times the mass of produced capsules ( $cEF = 383$ ). The assumption of less quantity of PLA is irrelevant; in other words,  $cEF = 383$  is in the best case for this process. Optimization experiments are recommended to reduce the quantity of solvents and raw materials employed in these experiments. In addition to DMF, which is known for its hepatotoxicity<sup>103</sup>, one could recommend non-toxic alternatives such as Cyrene<sup>TM</sup> derived from levoglucosenone, a cellulose-derived platform molecule<sup>104</sup>. Cyrene<sup>TM</sup> is a green, non-toxic, and biodegradable solvent with no effect on aquatic life. It can be

recycled without any problem by distillation under reduced pressure. However, Cyrene<sup>TM</sup> is ten times more expensive than DMF due to its high production cost. The Resolute project with 11 European partners and a total budget of 23M € aims to build factories at an industrial scale to convert waste cellulosic biomass into safe, environmentally friendly chemicals like Cyrene<sup>TM</sup>. This will significantly increase production, reduce the price, and allow the efficient industrial implementation of green substitutes like Cyrene<sup>TM</sup>.

Lavender oil (LO), an essential oil widely employed in balms, salves, perfumes and cosmetics<sup>105</sup>, is highly volatile and chemically unstable due to its oxidation, chemical interactions, or volatilization in the presence of oxygen, light, water and heat. However, it is a high-value chemical due to its applicability in the perfumery industry as a pleasant fragrance and an antimicrobial agent. Benefiting from its advantages requires encapsulation to protect the oil from the external environment and ensure safe handling. For this purpose, Xiao et al.<sup>33</sup> studied the encapsulation of LO by complex coacervation in gelatin and Arabic gum. According to this study, P19, P20, and P21 are the optimum encapsulation process conditions concerning the mass ratio between the polymer solution and the core material (3:2). The gap between cEF and both sEF and the EF in processes P19, P20, and P21 is due to the use of water as a solvent. Using glutaraldehyde (P20), the most popular crosslinker, resulted in an encapsulation efficiency of 43.5%, with the best individualized spherical capsules containing 47.5% LO. However, the toxic character of glutaraldehyde boosts the need to search for a safer crosslinker given the context of sustainable development. Transglutaminase (TG) is a naturally occurring enzyme that catalyzes the formation of isopeptide bonds between the  $\epsilon$ -amino group of polypeptide-bound lysines and the  $\gamma$ -carboxamide group of polypeptide-bound glutamines<sup>106</sup>. The result of using TG as a crosslinking agent (P21) showed no difference in shape compared to microcapsules with glutaraldehyde as a crosslinker, while the encapsulation efficiency slightly increased with higher loading content (57.7%) and slightly

less waste generated. Even if TG seems to be a safer and better substitute for the toxic glutaraldehyde, it is accompanied by several inconveniences in terms of sustainable development. TG crosslinking of coacervate made the process 3 h slower than P20, and in some reports, coacervation with TG as a crosslinker took more than 12 h<sup>106–108</sup>. TG is more expensive than other crosslinkers, which will increase the production cost; moreover, strict storage conditions, such as a very cold and dry place (freezer) and hermetic packaging, are required. These results show the importance of the choice of the crosslinker on the sustainability of the coacervation process in terms of efficiency and waste generation and in terms of cost, duration and difficulty of handling and storage of raw materials.

	Type	Core	Shell	Other reactants	T <sub>r</sub> (°C)	T <sub>d</sub> (°C)	t <sub>r</sub> (h)	t <sub>d</sub> (h)	Solvent	sEF	EF	cEF	Ref.
P16	Simple	Tea tree oil	Gelatin	Glutaraldehyde Tween 80 Sodium sulfate Sulfuric acid Acetic acid Methanol	40	-30	10	48	Water	0.7	0.7	5.5	<sup>98</sup>
P17	Simple	Tea tree oil	Gelatin	Glutaraldehyde Tween 80 Sodium sulfate Sulfuric acid Acetic acid Methanol	40	-30	10	48	Water	0.5	0.5	7.2	<sup>98</sup>
P18	Simple	Tea tree oil	Gelatin	Glutaraldehyde Tween 80 Sodium sulfate Sulfuric acid Acetic acid Methanol	40	-30	10	48	Water	1.2	1.2	5.1	<sup>98</sup>
P19	Simple	Thyme oil	PLA	Tween 20 DMF OCMTS Pluronic F68 Ethanol	25	N/A	2	40	DMF	51.7	105	383	<sup>89</sup>
P20	Complex	Lavender oil	Gelatin and Arabic gum	Acetic acid Sodium hydroxide Glutaraldehyde	4	-10 to -50	6.3	72	Water	1	1	38.9	<sup>33</sup>
P21	Complex	Lavender oil	Gelatin and Arabic gum	Tranglutaminase	4	-10 to -50	9.3	72	Water	1.2	1.2	43.3	<sup>33</sup>

Table 3: A summary of some coacervation processes with their corresponding operating conditions. Tr: temperature of the reaction, T<sub>d</sub>: drying temperature, t<sub>r</sub>: time of reaction, t<sub>d</sub>: drying time.

## 5.2. Physical Processes

Physical processes are characterized by the use of drying, congealing or gelling of an atomized droplet to form a matrix or a shell. In this section, we describe physical processes like atomization and extrusion processes, including microfluidics, and discuss their sustainability.

### Atomization

Atomization processes are continuous physical processes involving spray drying or chilling widely employed in several domains, especially in the food industry, to produce simple polymeric microparticles between 5 and 1000  $\mu\text{m}$  in size or to encapsulate volatile, sensitive, and functional ingredients (core-shell) <sup>109</sup>. The first patent of this technology dates to the early 1870s. Spray drying is a continuous process in which a liquid feed (solution, suspension, or paste) is transformed into dry powder microparticles by a hot drying medium such as hot air. In the first stage, the liquid feed is sprayed into a drying chamber, where it contacts the drying medium to evaporate and dry. The product is recovered at the bottom of the chamber or by separation from the air for small particles. Spray drying is widely used to produce dry milk <sup>110</sup>, dry tomato juice <sup>111</sup>, and coffee <sup>112</sup>. In addition to the food industry, spray drying/chilling is also used in drug delivery <sup>113-115</sup>. Figure 6 represents a one-stage spray drying plant. Spray chilling, also called spray cooling or spray congealing, is an atomization technology like spray drying. Instead of a drying chamber, the feed is atomized into a cooling chamber whose temperature is below the melting point of the feed <sup>116</sup>. The feed solidifies without mass transfer, and the microparticles are obtained in the form of powder.

Spinning disk technology may be used as an atomizer in a spray dryer/chiller to improve control of the size and distribution of the formed droplets <sup>109,117</sup>. Spinning disk

atomization is a system where a rotating disk, which can take the form of a wheel, plate, bowl, or cup, induces forces to break up the feed fluid <sup>118</sup> (Figure 7). The liquid is distributed onto the spinning disk, forming a film due to the centrifugal force and the wettability. The liquid film spreads to the disk rim, where it is thrown off tangentially as droplets, forming the spray of controlled droplet sizes <sup>109</sup>. This production technique can be scaled up easily by increasing the flow rate, disk size, and rotation speed <sup>119</sup>. Finally, the combination of spinning disk atomization with a spray drying device prevents clogging because the pressure nozzle is absent.

Spray drying/chilling is a simple, rapid, high throughput, robust, reproducible, and continuous process. This makes it scalable without modification, reaching a high production rate of microparticles up to 30 ton/h with a high encapsulation efficiency that can reach up to 100% in some optimized processes at an industrial scale <sup>120</sup>. The spray drying process is capable of producing microparticles from a very wide range of compounds <sup>121,122</sup> without a final drying step like solvent evaporation or freeze-drying, and without excessive use of solvents as in conventional techniques <sup>123</sup>. However, these processes have major drawbacks. First, air temperature in the drying chamber may reach up to 185 °C in certain spray drying reactors <sup>124</sup> and may go down to -50 °C in spray chilling <sup>125</sup>, meaning the process has an energy requirement constraint. Spray drying/chilling is a high energy-consuming unit operation where thermal efficiency is 73% at most in recent studies <sup>126</sup> and may decrease to less than 20% in some cases <sup>127</sup>. Moreover, the price of heat accounts for about 60% of the total cost of a spray drying unit <sup>127</sup>. In addition, spray drying/chilling is not adapted to coat solid matter that cannot be sprayed in a chamber <sup>112</sup>. In the absence of spinning disks, particle size cannot be controlled, and the size distribution of the produced particles is wide (Figure 6). A spinning disk is ideal for optimizing size control in atomization processes; however, it requires a large surface or volume to collect the produced particles without damage. The

production of small microparticles, less than 100  $\mu\text{m}$  in size, requires increased rotation speed or reduced liquid viscosity. However, the increase of rotation speed may cause the vibration of the disk and the production of satellite droplets<sup>109</sup>. Satellite droplets may also form at moderate rotation speeds, causing a loss of product and excessive raw material consumption<sup>109,128</sup>. The impact of this issue may be reduced by integrating a recovering system for the satellite droplets to be reused later, if possible. The reduction of fluid viscosity to achieve smaller sizes may seriously affect the shape of the droplet. Therefore, spinning disk technology is not compatible with producing sub-hundred-micron microparticles.

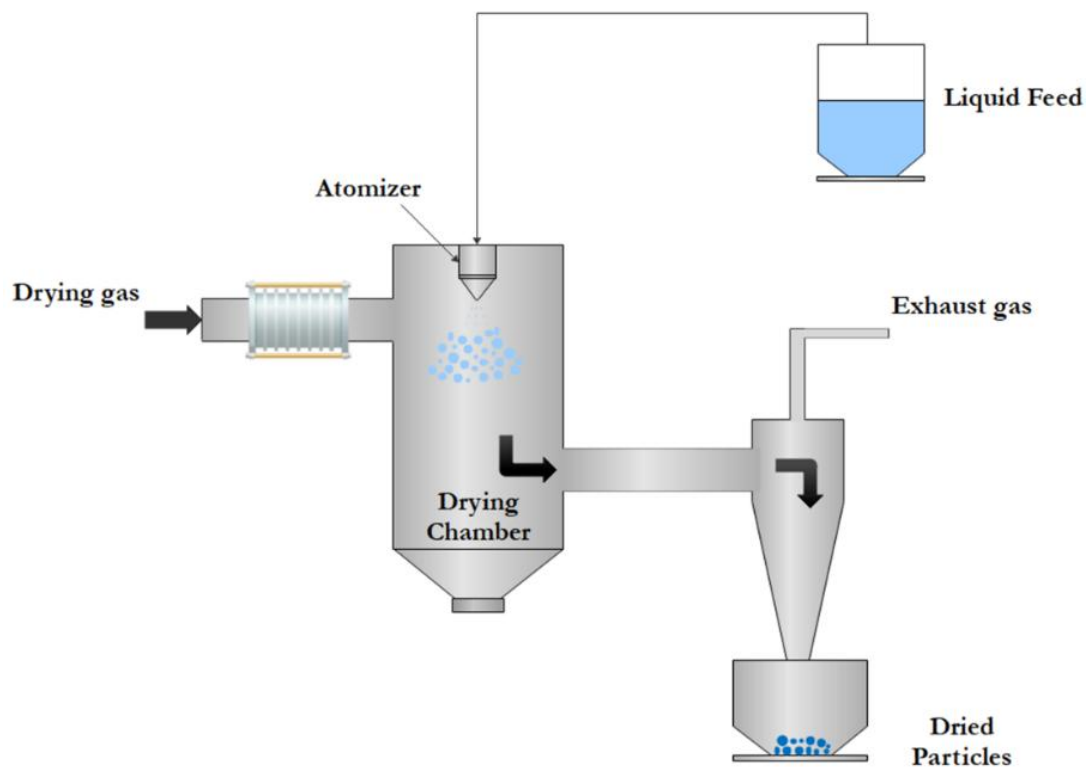


Figure 6: Schematic one-stage spray drying plant. Reproduced from Sonsnik & Seremeta<sup>123</sup> with permission from *Elsevier*, copyright 2015.

Waste generation is also an issue for atomization processes at the laboratory scale. For example, the yield in process P22 of Table 4 performed at laboratory scale is 35%. Most (65%) of the input material is lost, which is an excessive consumption of raw material. Considering the encapsulation efficiency, the total yield of the process is reduced to around

32%, and with the excessive use of water and ethanol as solvents, the cEF reaches a huge value of 883. The spray chilling process reported in P23 to encapsulate erythropoietin in PLGA has 100% encapsulation efficiency; however, its total yield is less by one-third due to the use and evaporation of the dichloromethane (DCM) organic solvents. This results in a huge amount of waste (cEF = 55.7). In addition, DCM is known for its toxicity and may be substituted by a green solvent like dimethyl carbonate (DMC), which is less toxic and has higher biocompatibility and efficacy. DMC is a much greener solvent than DCM by approximately one order of magnitude; the sEF and cEF of DMC are only a fraction of those of DCM, indicating greater sustainability<sup>35</sup>.

In brief, the scale-up may optimize the atomization process to reach a yield of up to 100%. However, the process may still be a high producer of waste due to the evaporation of solvents of the dried microparticles, which contributes to the final cEF. This shows the importance of using green solvents in the process.

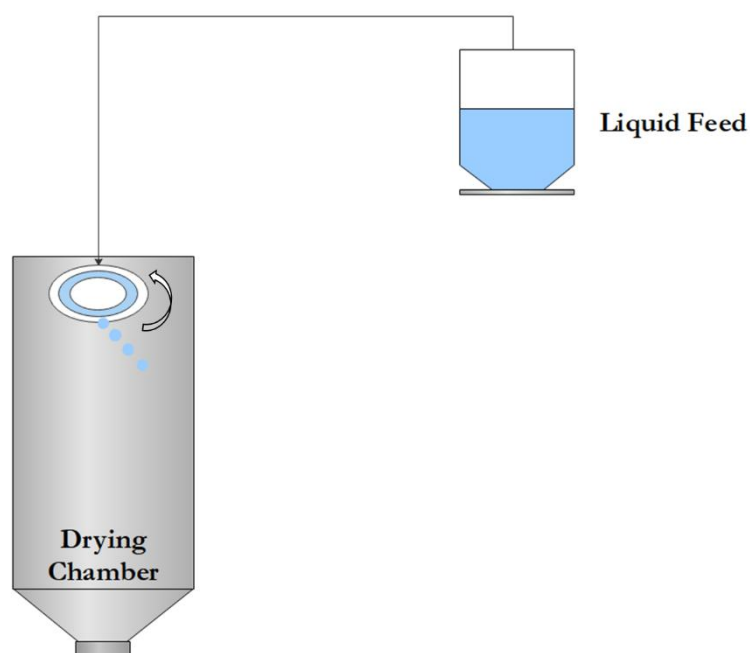


Figure 7: A scheme of a spinning disk device integrated into a drying chamber. Reproduced from Mishra <sup>112</sup> with permission from *Taylor & Francis*, copyright 2015.

	Drying/ Chilling	Loaded drug/Core	Shell	T <sub>air</sub> (°C)	Solvents	E <sub>eff</sub> (%)	Yield (%)	Total Yield (%)	sEF	EF	cEF	Ref.
P22	Drying	Methylprednisolone	Albumin Hyaluronic acid Chondroitin sulfate	100 to 140	Water Ethanol	92	35	32.2	2.1	225	884	<sup>122</sup>
P23	Chilling	Erythropoietin	PLGA + 0.5% lactide	-50	Water DCM	100	37.1	37.1	1.7	53	55.7	<sup>120</sup>

Table 4: A summary of some spray drying/chilling processes with their corresponding operating conditions.

### Extrusion/Co-extrusion

The extrusion process is another physical process based on mechanical techniques, permitting the production of simple and core-shell microparticles <sup>29,129</sup>. Polymer solution or monomer droplets are extruded from a nozzle through dripping or jet break-up. Jet breaking can be generated through electrostatic mean <sup>130</sup>, coaxial flow <sup>131</sup>, vibration <sup>132</sup>, jet cutting <sup>133</sup>, or even the spinning disk described before <sup>134</sup>. Droplets take a spherical shape due to the surface tension and then solidify through a physical or chemical technique like cooling, crosslinking, or solvent evaporation. At optimal conditions, it is possible to synthesize uniform and homogeneous simple polymer microparticles with controlled size and narrow size distribution. Co-extrusion is the process allowing the production of core-shell



microparticles. The core and shell materials are extruded from a concentric nozzle through dripping or jet breaking to form an emulsion. Once the emulsion is formed, the shell should solidify while maintaining the core-shell morphology. Figure 8 shows the extrusion and co-extrusion process in the dripping regime.

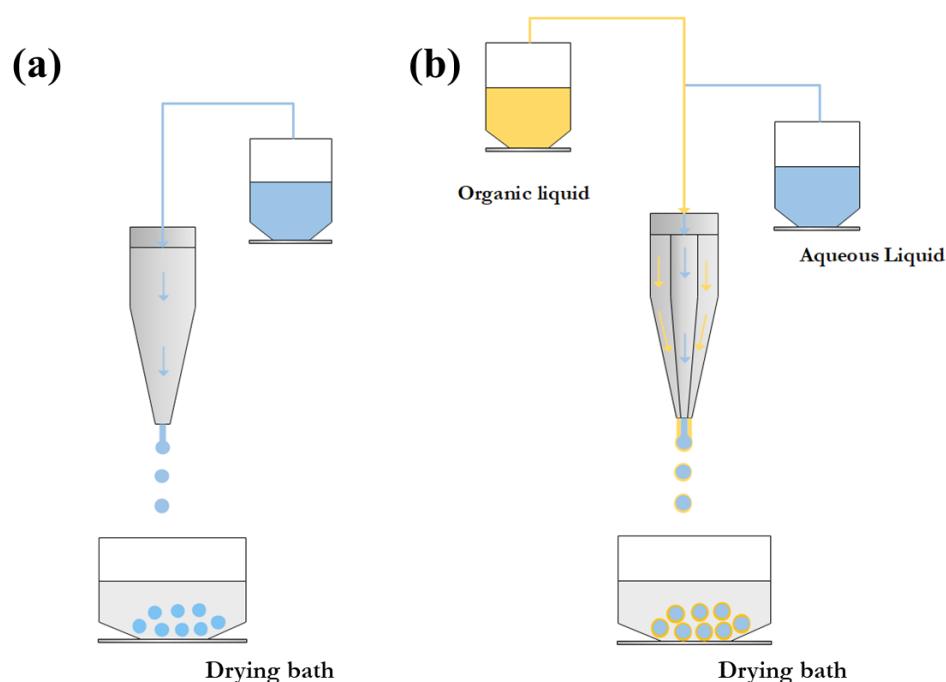


Figure 8: A scheme of (a) extrusion process in dripping mode, (b) co-extrusion process in dripping mode.

Extrusion and co-extrusion techniques are straightforward to set up and very simple to operate compared to other techniques. They can produce simple and core-shell microparticles with controlled size, size distribution, and content. The scale-up could be achieved by parallelization, in other words, by increasing the number of nozzles that produce simple microparticles and microcapsules simultaneously<sup>135</sup>. However, the production rate per nozzle is constrained due to the limitation of the maximal flow rate. Another disadvantage of this technique is the impossibility of extruding viscous polymers, limiting its use to a low polymer concentration, and may lead to the production of microparticles with limited mechanical resistance<sup>136</sup>. This limitation could be resolved by reducing the viscosity through heating the polymer solution but would require more energy. The device “Encapsulator B-390” supplied

by Büchi is an example of an apparatus capable of heating and maintaining the polymer solution and the nozzle at a controlled temperature. Moreover, the dependency on an external source to break the liquid jet makes the process energy consuming. These techniques are not as advanced as older technologies like spray drying, so they demand a good knowledge and assessment of materials for successful implementation<sup>137</sup>.

## **Microfluidics**

Microfluidics is an extrusion technique at the scale of 1  $\mu\text{m}$  to a few millimeters. It can be defined as (1) the science allowing the study of fluid behavior at a tiny scale inside micro-channels, and (2) a technology permitting the production of microminiaturized devices containing inlets, outlets, and tunnels through which a fluid flow is confined<sup>138</sup>. In the last two decades, innovative microfluidic technology has been the scope of extensive studies<sup>34,139,140</sup> and diverse applications. For example, microfluidic techniques were proved to be very efficient in assisted reproductive technologies<sup>141</sup>, bacteria separation and preconcentration<sup>142</sup>, DNA compaction<sup>143</sup>, and fungus identification<sup>144</sup>. Microfluidics has emerged as an efficient technique for producing liposomes and nanoparticles<sup>145</sup> and is important in the production of controlled size polymer microparticles<sup>146</sup>. Microfluidic flow is characterized by a high surface-to-volume ratio that enhances heat and mass transfer in reactive processes and allows exothermic and high-temperature reactions to be carried out in a controllable, isothermal, and efficient manner<sup>147</sup>. Microfluidic reactors facilitate the design of accurate, multistep reaction processes.

Microfluidic assisted techniques allow the synthesis of simple and core-shell polymer microparticles. The production of simple polymer microparticles requires a two-step process: (1) droplet formation by shearing a continuous external fluid (simple emulsion) in a microfluidic device and (2) droplet solidification. The fluids constituting the droplets

(dispersed phase) and the continuous phase are pumped by an external device such as a pressure regulator system, peristaltic pump, or syringe pump. The size of the formed droplets is controlled by the shearing of the continuous phase that breaks the dispersed phase into droplets and may be tuned by the fluid's physical parameters (density, viscosity, and surface tension), the flow rates, and the microfluidic device geometry. The droplet formation step may be done in a dripping or a jetting regime where droplets are formed at a higher frequency.

The dispersed phase may be a mixture of monomer(s) and initiator<sup>148</sup> or a polymer solution, and the continuous phase is usually a surfactant solution ensuring the stability of the emulsion. The second solidification step depends on the nature of the dispersed phase. The monomer/initiator mixture may be solidified through two different treatments: (1) *in-situ* polymerization, where solidification happens along the trajectory of the droplets or (2) off-chip polymerization, where the droplets are solidified after the collection of the emulsion. The two treatments can be done through UV light irradiation<sup>149</sup>, heating<sup>150</sup>, or other chemical reaction like ring-opening polymerization<sup>151</sup>. After the droplets are formed, solvent removal is used to solidify polymer solution droplets. It may be *in-situ* where the polymer solvent of the droplet dissolves into another liquid present in a collection beaker or tank with no further treatments, as in the study of Zhang *et al.*<sup>152</sup>, or off-chip by solvent evaporation after droplet collection<sup>34,35</sup>. Figure 9 shows a schematic of a simple microparticle production process where the solidification is performed by *in-situ* UV polymerization. The production of core-shell microparticles requires the same steps using three fluids (core material to be encapsulated, monomer or polymer solution, continuous phase) instead of two.

Busatto *et al.*<sup>153</sup> produced lignin microparticles loaded by atrazine drug using both traditional solvent evaporation process and microfluidics before encapsulating them in alginate beads (P24 and P25 of Table 5). The raw materials (lignin polymer, atrazine drug,

and PVA surfactant) were added at the same concentrations with respect to the solvents. However, the usage of more water in the traditional solvent evaporation process implies more surfactants quantities to keep the same concentration. As a result, microfluidic processes produced around 8 times less reagents wastes and 10 times less solvents waster (sEF = 1.2 and cEF = 228) than the traditional solvent evaporation process (sEF = 6.9 and cEF = 2450). In addition, microparticles with lower size dispersion and higher encapsulation efficiency were produced by microfluidics with  $CV \approx 6.1\%$  and  $E_{\text{eff}} \approx 59.7\%$  compared to  $CV \approx 6.5\%$  and  $E_{\text{eff}} \approx 47.4\%$  in the traditional solvent evaporation process. This results show the privilege of microfluidic processes on traditionally employed processes not only from an environmental point of view but also in terms of efficiency and size control quality.

	Polymer solution Phase	Continuous Phase	Method	$\bar{d}$ ( $\mu\text{m}$ )	$E_{\text{eff}}$ (%)	sEF	EF	cEF	Ref
P24	0.7 wt% Lignin and 0.01 wt%	PVA solution in water	Traditional solvent evaporation	$25.3 \pm 6.7$	$47.4 \pm 3.5$	6.9	138	2450	<sup>153</sup>
P25	Atarazine in DCM		Microfluidics + Solvent evaporation	$50 \pm 3$	$59.7 \pm 8.2$	1.2	119	228	<sup>153</sup>

Table 5: Comparison between traditional and microfluidic processes to produce Lignin polymer microparticles with the same quantities of ingredients.

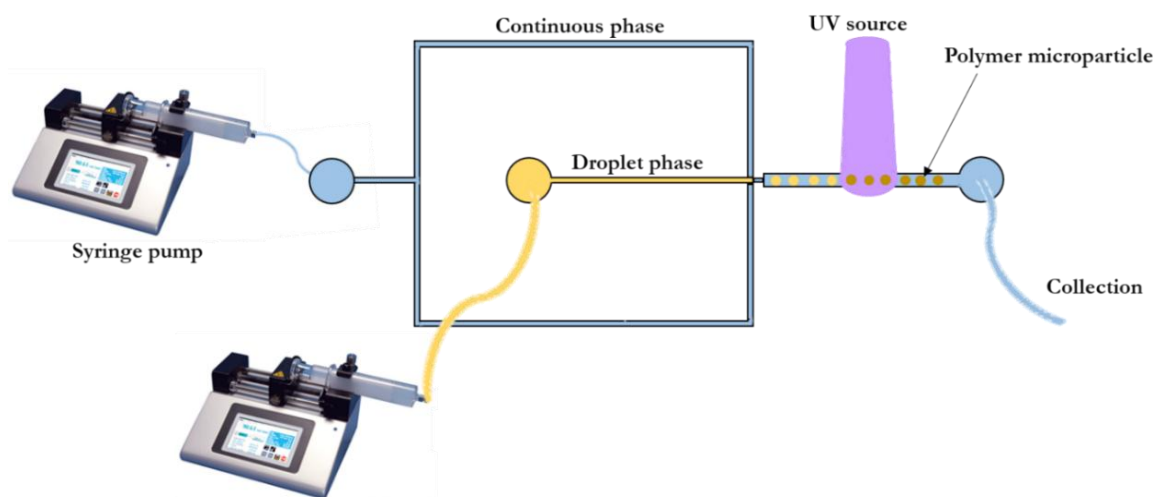


Figure 9: A setup of a droplet generator chip. The two phases are pumped by two syringe pumps, and the droplets are solidified by *in-situ* UV treatment.

	Monomer Phase	Continuous Phase	Method	Solidification time	$Q_c/Q_d$	$\bar{d}$ ( $\mu\text{m}$ )	Yield (%)	sEF	EF	cEF	Ref
P26	GMA and EGDMA co-monomer and DEP porogen	3 wt% PVA in water	<i>In-situ</i> UV polymerization and post Off-	4 min	5.25	$110 \pm 3.3$	100	1.6	1.6	12.2	<sup>154</sup>

	Monomer Phase	Continuous Phase	Method	Solidification time	$Q_c/Q_d$	$\bar{d}$ ( $\mu\text{m}$ )	Yield (%)	sEF	EF	cEF	Ref
			chip polymerization								
P27	GMA and EGDMA co-monomer and DOP porogen	3 wt% PVA in water	<i>In-situ</i> UV polymerization and post Off-chip polymerization	4 min	15	$75 \pm 2.25$	100	2.2	2.2	32.7	<sup>154</sup>
P28	TPGDA and photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	20–900 s	60	$104 \pm 2$	97	1.3	1.3	61.7	<sup>155</sup>
P29	95 wt% TPGDA and 5 wt% AA	2 wt% SDS in water	<i>In-situ</i> UV polymerization	10 s to several min	50	$153 \pm 3$	100	1	1	49.8	<sup>148</sup>
P30	92 wt% TPGDA and 8 wt% AA	2 wt% SDS in water	<i>In-situ</i> UV polymerization	10 s to several min	50	$143 \pm 2.9$	100	1	1	49.8	<sup>148</sup>
P31	AA and APS initiator	0.2 wt% SDS in water	<i>In-situ</i> thermal initiated polymerization at 90 °C	2 h	8	$300 \pm 12$	100	0	16	18.2	<sup>150</sup>

Table 6: The production processes of polymer microparticles by combining microfluidics and monomer droplet polymerization.

Table 6 summarizes some examples of simple polymer microparticle microfluidic production processes based on monomer/initiator mixture droplets and their corresponding environmental factors. Table 7 shows the same information for the microfluidic production of core-shell microparticles. Finally, Table 8 focuses on the production of particles by polymer solution droplets. The polymerization time reported in the three tables ranges from a few seconds to a few minutes, which is much faster than traditional processes like coacervation and suspension polymerization, where reactions may last a few days. The yield is almost 100%, with a size dispersion of less than 5%. These complementary advantages allow a typical lab-scale microfluidic chip to produce size-controlled polymer microparticles at a mean of  $0.4 \text{ mg}\cdot\text{h}^{-1}$  in the dripping regime and up to  $1 \text{ mg}\cdot\text{h}^{-1}$  with a jet break-up<sup>34,148,154,156–158</sup>. A thousand parallel microfluidic chip devices in a jetting regime should be able to generate up to 24 kg/day of microparticles. This level of productivity is probably less expensively achieved using the microfluidic technique than using alternative technologies<sup>34</sup>. The strong control in microfluidics is not only limited to microparticle size and composition but also applies to structure properties like porosity. The porosity of the formed microparticles

was shown to be tunable through the choice of a porogen in the dispersed phase and its solubility to the formed polymer (P26 and P27 of Table 6). The employment of the DEP porogen in P26, which is less soluble in poly(GMA-co-EGDMA) than the DOP porogen of P27, reduced the specific area of the microparticle from 28.7 to 3.4 m<sup>2</sup>/g, which means less porosity<sup>154</sup>.

Microfluidic monomer-based processes seem to be of similar greenness to the processes mentioned above when considering sEFs that range between 0 and 2 (Table 6 and Table 7). However, although evidence of its recycling is reported in the literature, the continuous phase in all processes of this section was considered a solvent waste in the evaluation of EF and cEF. Except P47, the continuous phase of all microfluidic processes reported in Tables 6, 7, and 8 is aqueous and enter only in the evaluation of cEF, and not in either sEF or EF. The flowrate ratio  $Q_c/Q_d$  ranges between 4 and 444 is equivalent to the consumption ratio of the continuous phase to the dispersed one. This explains the 50× gap between cEF and both sEF and EF and shows the importance of recycling the continuous phase as a vital additional step in the process. Without recycling, it is incorrect to declare microfluidics as a green and sustainable process. An industrial-scale pilot with *in-situ* polymerization and a back-loop to recycle the continuous phase seems ideal for this purpose. Moreover, the cEF of polymer solution-based processes reported in Table 8 are unsurprisingly higher by two or even three orders of magnitude than those of monomer-based processes reported in Table 6 and Table 7. The polymer solvent of the droplet is evaporated or dissolved in another liquid, forming a solvent waste in addition to the continuous phase. In cases where the polymer solution dissolves in another continuous fluid rather than evaporates, as in P40 and P41, a final separation step would allow the recovery of solvents but would surely add an energy and time constraint to the process. However, even though polymer solution-based processes generate much more waste than monomer-based processes, they are

important in the case of some naturally occurring polymers like chitosan, which has a wide range of applications in drug, antibiotic, and gene delivery <sup>159</sup>. So, using less solvents to be recycled and using solvents that are less toxic than THF of processes P40 and P41 and DCM of processes P42-P45 (Table 8), which are known for their toxicity, is recommended. Even though THF was used as a modeling solvent for laboratory experiments in Zhang *et al.* <sup>152</sup>, the solvent can still be substituted by a greener solvent like 2-methyltetrahydrofuran <sup>160</sup>. DMC was reported as a greener and more sustainable substitute for DCM in the atomization process section. Owen *et al.* <sup>35</sup> proved DMC to be a greener substitute through an environmental factor approach. At the same time, monomer-based processes generate less waste but require energy that can be non-renewable or partially renewable for both UV and heat treatment. On a lab scale, a heat plate consumes an average of 0.6 kWh, like a 1-inch UV lamp. Taking the maximum production rate of one chip (24 g/day), the energy consumption of these processes is estimated at 0.6 kWh/g of microparticles at best. This is considered a huge consumption in terms of scaling-up; however, at an industrial scale, the energy consumption is not equivalent to 1 hot plate per chip, and the consumption of the heating system or UV lamps may be less than 0.6 kWh of the lab-scale.

	Core	Shell	Continuous Phase	Method	$Q_c/Q_d$	Cores	$\bar{d}$ ( $\mu\text{m}$ )	Yield (%)	sEF	EF	cEF	Ref
					$Q_c/Q_{cor}$							
P32	Silicone oil	HDDA with photoinitiator	2 wt% PVA in water	Off-chip UV polymerization	17.8	Monocore	$135 \pm 2.7$	100	0.3	0.3	16.3	<sup>158</sup>
					160							
P33	Silicone oil	HDDA with thermal initiator	2 wt% PVA in water	Off-chip thermal polymerization	17.8	Monocore	$135 \pm 2.7$	100	0.4	0.4	16.8	<sup>158</sup>
					160							
P34	Silicone oil	EGDMA with photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	66.7	Monocore	$104 \pm 2.6$	100	1.2	1.2	58.1	<sup>157</sup>
					444.4							
P35	Silicone oil	EGDMA with photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	72.7	Polycore 2 cores	N/A	100	1	1	50.3	<sup>157</sup>
					153.8							
P36	Silicone	EGDMA with	2 wt% SDS in	<i>In-situ</i> UV	75	Polycore	N/A	100	1.2	1.2	57.8	<sup>157</sup>

	Core	Shell	Continuous Phase	Method	$Q_c/Q_d$	Cores	$\bar{d}$ ( $\mu\text{m}$ )	Yield (%)	sEF	EF	cEF	Ref
					$Q_c/Q_{cor}$							
	oil	photoinitiator	water	polymerization	240	3 cores						
P37	Silicone oil	EGDMA with photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	58 166.7	Polycore 4 cores	N/A	100	0.9	0.9	43.6	<sup>157</sup>
P38	Silicone oil	EGDMA with photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	60.6 192.3	Polycore n cores	N/A	100	0.96	0.96	46.6	<sup>157</sup>
P39	2 wt% PVA in water	IBOA + surfactant Span 85 + photoinitiator	2wt % PVA	Off-chip UV polymerization	10 20	Monocore	$150 \pm 6$	99	0.2	0.2	7.2	<sup>156</sup>

Table 7: The production processes of core-shell microparticles by combining microfluidics and monomer droplet polymerization.

P26 and P27 are made in the same experimental conditions except for the ratio  $Q_c/Q_d$ , which shows the dependency of the droplet size on this ratio. The droplet size decreased when  $Q_c/Q_d$  increased. In a typical microfluidic chip, the droplet size is inversely proportional to  $Q_c/Q_d$  for a given fluid system because the continuous phase shears the dispersed phase to form the droplets. This means that to form smaller microparticles, more continuous phase is needed than dispersed phase, and thus more solvent wastes are generated. For example, to reduce the size of poly (GMA-*co*-EGDMA) microparticles from 110 to 75  $\mu\text{m}$  (P26 and P27), 2.5 times more solvent waste was generated. Similarly, the reduction of PLGA microparticles of P42 from 42 to 12  $\mu\text{m}$  in P43 generates over four times the quantity of solvent wastes (see cEF of P26 and P27 and of P42 and P43).

	Polymer solution Phase	Continuous Phase	Method	Solidification time	$Q_c/Q_d$	$\bar{d}$ ( $\mu\text{m}$ )	Yield (%)	sEF	EF	cEF	Ref
P40	5 wt% PVC in THF	20 wt% NaCl in water	Solvent dissolution	< 20 s	7	$170 \pm 5.1$	97	37	56.5	204	<sup>152</sup>
P41	1 wt% PVC in THF	20 wt% NaCl in water	Solvent dissolution	< 20 s	7	$80 \pm 2.4$	97	185	287	1024	<sup>152</sup>
P42	40 g/l PLGA and 25% bupivacaine in DCM	1 wt% PVA in tris buffer	Off-chip solvent evaporation	3 min	4	$42 \pm 1.6$	100	1.33	33.6	165	<sup>34</sup>
P43	40 g/l PLGA and 25% bupivacaine in DCM	1 wt% PVA in tris buffer	Off-chip solvent evaporation	3 min	20	$12 \pm 0.46$	100	6.6	39	696	<sup>34</sup>



	Polymer solution Phase	Continuous Phase	Method	Solidification time	$Q_c/Q_d$	$\bar{d}$ ( $\mu\text{m}$ )	Yield (%)	sEF	EF	cEF	Ref
P44	10 g/l PLGA and 1.2% FLAP in DCM	1 wt% PVA in water	Off-chip solvent evaporation	15 min	80	$15.1 \pm 0.6$	93	85.4	226	8764	<sup>35</sup>
P45	10 g/l PLGA and 1.2% FLAP in DMC	1 wt% PVA in water	Off-chip solvent evaporation	15 min	60	$15.1 \pm 0.6$	92	64.8	180	6653	<sup>35</sup>
P46	40 mg/ml PLGA and 0.9% FLAP in DMC	1 wt% PVA in water	Off-chip solvent evaporation	15 min	60	$32.4 \pm 1$	93	16	43.7	1639	<sup>35</sup>
P47	2 wt% Chitosan 0.33 wt% Acetic acid 0.2 wt% BSA drug in water	n -octanol with 2 wt% Span80	n-octane solidification bath	10–35 min	80	$67 \pm 0.33$	100	60.4	3018	3062	<sup>161</sup>

Table 8: The production processes of simple polymer microparticles by combining microfluidics to droplet solvent evaporation.

Because some raw materials like surfactants are dissolved in the continuous phase, more raw material wastes are also generated to produce smaller microparticles and not only solvent wastes. For example, the sEF and EF of P27 ( $\bar{d} = 75 \mu\text{m}$ ) are around 1.4 times higher than those of P26 ( $\bar{d} = 110 \mu\text{m}$ ), knowing that the two processes use the same fluids but with different  $Q_c/Q_d$ . Similarly, the sEF of P43 ( $\bar{d} = 12 \mu\text{m}$ ) is five times higher than that of P40 ( $\bar{d} = 42 \mu\text{m}$ ), meaning more consumption of raw materials with ratios that are very important for industrial-scale production. The impact of this dependency between the droplet size and waste can be avoided by tuning the microparticle size through the concentration of compositions forming the monomer phase as in P29 and P30. The increase of AA concentration from 5 to 8 wt% with respect to TPGDA in the monomer phase slightly reduced the droplet size from 153 to 143  $\mu\text{m}$ . Even if this size reduction has no environmental impact (P29 and P30 have the same environmental factors), it remains modest compared to the change of material concentration. The size tuning seems to be limited through this procedure without neglecting the possible impact on the mechanical and thermal properties uninvestigated in the study. Similarly, the decrease of PVC concentration in THF from 5 to 1 wt% significantly reduced the size of the droplet to more than half (P40 and P41,

respectively). This reduction is simply due to the dissolution of 99% of solvents constituting the droplet phase instead of 95%, which obviously yields five times more solvent wastes (cEF increased from 204 to 1024). Microfluidic systems where the droplet size is determined by an external force like a centrifugal force instead of shearing as in the continuous process of interface crossing encapsulation are another option to eliminate this dependency<sup>162,163</sup>. The environmental impact of the dependency between the droplet size and the flow rates may also be eliminated through the recycling of the continuous phase.

P32 and P33 are two interesting results of the recent study of Xu and Nisisako<sup>158</sup>, in which Janus droplets were generated in a microfluidic device and transformed into a core-shell shape along their pathway. The polymerization of the transformed core-shell microparticle was performed via both off-chip thermally and photo-induced polymerization. This study showed no effect on the microparticle size, and no environmental effect related to waste generation due to the polymerization method but did show an impact on the capsule morphology. UV polymerization produces microcapsules with smooth surfaces. In contrast, thermal polymerization generates microcapsules with a porous surface due to the nitrogen-nitrogen double bond cleavage of the V-65 thermal initiator in the HDDA monomer, which produces nitrogen during the polymerization reaction. Tuning the shell thickness by controlling the  $Q_c/Q_d$  ratio allowed the release of the nitrogen directly without accumulation, which resulted in smoother surfaces. This result demonstrates the importance of the method of polymerization for both the efficiency of the process and for the morphology of the produced microparticles. The study also depicts the potential of microfluidics for tuning material properties, such as the porosity of porous microparticles.

Nie et al.<sup>157</sup> encapsulated silicone oil in a poly(EGDMA) shell and defined the conditions to produce mono-core and poly-core from one to numerous numbers of

microspheres inside the capsule (P34 to P38). This study shows the capacity of microfluidic platforms in tuning the morphology content of the microcapsules by simply adjusting the fluid flow rates. The cEF is not a function of the number of microspheres but rather a function of the flow rates as they represent the quantity of matter and solvents involved in the process.

Process	Pros	Cons	Sustainability challenges
Interfacial polymerization	<ul style="list-style-type: none"> <li>• Simplicity</li> <li>• Easy to operate</li> <li>• Low cost</li> </ul>	<ul style="list-style-type: none"> <li>• Relatively low purity of polymer</li> <li>• Wide size distribution</li> <li>• Solvent removal complications</li> <li>• Excessive use of solvents</li> </ul>	<ul style="list-style-type: none"> <li>• Optimization solvents quantities with respect to particle properties</li> <li>• Best choice of initiators and stabilizers</li> <li>• Energy consumption optimization (temperature, duration)</li> <li>• Green solvent substitutes: cost vs. properties</li> </ul>
Coacervation	<ul style="list-style-type: none"> <li>• Capsules stability</li> <li>• High <math>E_{eff}</math> possible</li> </ul>	<ul style="list-style-type: none"> <li>• High sensitivity to physical parameters</li> <li>• Expensive post-processing</li> <li>• Common use of toxic crosslinkers</li> <li>• Wide size distribution</li> </ul>	<ul style="list-style-type: none"> <li>• Optimizing encapsulation efficiency</li> <li>• Best choice of crosslinkers</li> <li>• Post-processing energy consumption optimization (temperature, duration)</li> <li>• Reducing the quantity of water used</li> <li>• Green solvent substitutes: cost vs. properties</li> </ul>
Atomization	<ul style="list-style-type: none"> <li>• Scalability and high production rate</li> <li>• No post processing</li> <li>• High <math>E_{eff}</math> at industrial scale</li> </ul>	<ul style="list-style-type: none"> <li>• Energy-consuming</li> <li>• Wide size distribution</li> <li>• Not adapted to encapsulate solid matter</li> <li>• Toxic solvents and wastes</li> </ul>	<ul style="list-style-type: none"> <li>• Green solvent substitutes: cost vs. properties</li> <li>• Reducing energy consumption</li> <li>• Reducing and recovering wastes</li> </ul>
Atomization + spinning disk	<ul style="list-style-type: none"> <li>• Scalability</li> <li>• No post processing</li> <li>• Size control</li> </ul>	<ul style="list-style-type: none"> <li>• Energy-consuming</li> <li>• Not adapted to encapsulate solid matter</li> <li>• Toxic solvents and wastes</li> <li>• Large surface requirement</li> <li>• Satellite droplets (loss of matter)</li> <li>• Unadapted to particles less than 100 <math>\mu\text{m}</math></li> <li>• Production rate less than classical atomization and limited to rotation speeds</li> </ul>	<ul style="list-style-type: none"> <li>• Green solvent substitutes: cost vs. properties</li> <li>• Reducing energy consumption</li> <li>• Reducing wastes</li> <li>• Recovering satellite droplets</li> </ul>
Extrusion/ Co-extrusion	<ul style="list-style-type: none"> <li>• Scalability</li> <li>• No post processing</li> <li>• Size control</li> </ul>	<ul style="list-style-type: none"> <li>• Limited production rate/nozzle</li> <li>• Unadapted to high viscosities without heating</li> <li>• Not advanced compared to other older processes</li> </ul>	<ul style="list-style-type: none"> <li>• Recycling the continuous phase</li> <li>• Optimizing energy consumption</li> <li>• Good knowledge and assessment for successful implementation</li> </ul>
Monomer-based microfluidics	<ul style="list-style-type: none"> <li>• Size control</li> <li>• Content control and morphology</li> <li>• Yield close to 100%</li> <li>• High <math>E_{eff}</math></li> <li>• Scalability</li> <li>• Fast and cheap</li> <li>• Tuning material properties</li> </ul>	<ul style="list-style-type: none"> <li>• Dependency between flow rates and wastes</li> <li>• Limited production rate/microfluidic chip</li> </ul>	<ul style="list-style-type: none"> <li>• Recycling the continuous phase</li> <li>• Optimizing energy consumption</li> </ul>
Polymer solution-based microfluidics	<ul style="list-style-type: none"> <li>• Size control</li> <li>• Content control and morphology</li> <li>• Yield close to 100%</li> <li>• High <math>E_{eff}</math></li> <li>• Scalability</li> <li>• Fast and cheap</li> <li>• Tuning material properties</li> <li>• No heating or UV</li> </ul>	<ul style="list-style-type: none"> <li>• Dependency between flow rates and wastes</li> <li>• Limited production rate/microfluidic chip</li> <li>• Waste due to droplet solvent evaporation</li> <li>• Use of toxic solvents</li> </ul>	<ul style="list-style-type: none"> <li>• Recycling the continuous phase</li> <li>• Recycling the polymer solvent of the droplet phase</li> <li>• Green solvent substitutes: greenness vs. properties</li> </ul>

Table 9: Summary of the pros, cons, and sustainability challenges of the main polymer microparticle production processes.

## 6. Challenges of achieving green production

To achieve the ambitious goal of green production of polymer microparticles, three elements of the production process will be considered and discussed in this section, namely: green production process, green raw materials, and green solvents.

### 6.1. Green production process

The EF, energy consumption, thermal efficiency, and cost are important criteria when choosing a process and evaluating its sustainability. Table 9 summarizes the pros, cons, and sustainability challenges of the processes mentioned in the present review. The waste generation was evaluated, analyzed, and commented through an environmental factor approach. The sEF ranges between 0 and 185 along all the 47 examples corresponding to 5 different processes of section 4, EF ranges between 0.1 and 3018, and cEF ranges between 1.7 and 6653. However, the three environmental factors are independent of the chosen process. In other words, the chosen process is not the main source of the environmental wastes, but rather the proper usage of the quantities of raw material, reagents, and solvents. In all processes, the usage of smaller amounts of solvents, as well as the greenness of the chosen solvent and its recycling have proven to be of crucial importance when speaking about greening of the production processes. Moreover, the choice of the process is made according to the targeted application and rate of production. Applications that do not require a narrow size distribution of the microparticles but do require a high production rate, like milk powder, powder juice, or coffee, are often produced by spray-drying atomization due to its 100% yield and high production rate at an industrial scale. In contrast, the control of size distribution is significant in applications requiring a controlled release like drug delivery. The challenge in both cases is to compromise between the economy in energy, reagents, raw material, and solvents (recycling and optimizing quantities) while conserving a profitable production rate and the

targeted quality of microparticles. Briefly, a green process should be compatible with the targeted application, while using optimized quantities of raw material and solvent to yield the best ratio between quality/production rate and environmental concerns.

## **6.2. Green raw material**

The sustainability and challenges of the employed raw material (monomers/polymers, initiators, and surfactants), produced microparticles, and solvents classified as organic and aqueous are crucial parameters when evaluating the greenness of a given production method. The produced polymer microparticles may be classified according to their origin: fossil-based, synthetic bio-based, and naturally occurring bio-based (Figure 10). The origin of the monomers/polymers puts the sustainability of the production process under question even if the environmental factor is 0. Polymer microparticles made from PMMA (MMA monomer), PBH (mixture of 1,6-hexanediol diacrylate and bisphenol A glycerolate dimethacrylate), and polyacrylamide (acrylamide monomer) are of great importance in diverse applications like cosmetics, drug delivery, food preservation, and even construction as shown in Table 1. However, their fossil-based origin makes them unsustainable by definition and affects their wide advantages due to the environmental consequences of consuming fossil fuels in their production processes. For example, 2 kg of petroleum are needed to produce 1 kg of PMMA. Natural occurring and synthetic bio-based polymers mentioned in Figure 10 may have less environmental disadvantages than fossil-based monomers/polymers if their production processes are optimized to minimize the use of hazardous substances and the quantity of waste generated. However, they have different constraints concerning their quality and functionalities. In what follows, a brief state-of-the art on the main naturally occurring bio-based material and synthetic polysaccharides employed in the production of polymer microparticles is proposed.

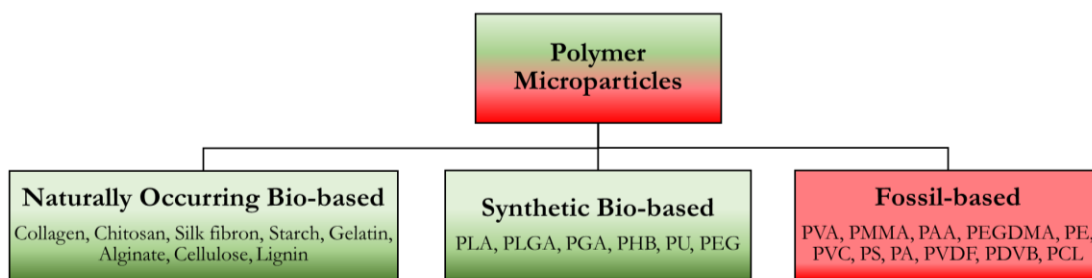


Figure 10: Classification of polymers employed in microparticle production according to origin.

### 6.2.1. Starch

Starch is a non-toxic, biocompatible, and biodegradable natural occurring polymeric carbohydrate with thermoplastic behavior. It is mostly composed by a mixture of two biopolymers: 15 – 30% amylose (straight chain) and amylopectin (branched chain) <sup>164</sup>. It was used for the preparation of polymer microparticles mainly by spray drying processes. For example, Böger et al. <sup>165</sup>, Wang et al. <sup>166</sup>, and Baltrusch et al. <sup>167</sup> used starch to successfully encapsulate roasted coffee oil, clove oil and tea extracts respectively by spray drying. Results showed a strong heat and corrosion resistance of the produced microparticles, in addition to high entrapment rate and yield, and good sustained release <sup>168</sup>. Despite these qualities, starch still suffers three main disadvantages, namely: hydrophilic nature, mechanical properties and processability <sup>169</sup>.

Starch chains are held together using strong hydrogen bonds that cause non-solubility of starch granules in cold water. However, water may act as a plasticizer agent of starch that can turn it into a thermoplastic product by employing mechanical and heat energy. Consequently, water molecules interact with hydroxyl groups and cause the partial solubilization of starch granules in water. The result is low water stability and high moisture sensitivity, which makes starch-based materials difficult to employ. Moreover, starch glass transition temperature ( $T_g$ ) is dependent on the amylose content, the higher the amylose content, the higher the  $T_g$  is for the same kind of starch. Liu et al. <sup>170</sup> showed that  $T_g$  was

increased from about 52 to 60 °C with increasing amylose content from 0 to 80% for the samples containing about 13% moisture. Due to its structure, its  $T_g$  is relatively high which yields a brittle behavior that increases with time at room temperature. Therefore, starch thermoplastic-based materials have very bad mechanical properties compared with other thermoplastics which limits their use to very specific applications associated with soft plastics<sup>169</sup>. Furthermore, the mechanical properties of starch are sensitive to storage duration due to retrogradation. In this context, Cano et al.<sup>171</sup> compared the mechanical properties of films based on pea starch after 1 and 5 weeks of storage at 25 °C and 53% relative humidity (RH). The results showed that every parameter related with mechanical properties significantly changed during storage<sup>172</sup>. Mechanical properties are also impacted by material processing. Indeed, water addition is necessary to process starch which can influence the mechanical properties of the final material due to water evaporation during the processing. The results are instabilities, increase in moisture content and occluded bubbles. Finally, starch is difficult to modify and tune which makes it less competitive than other fossil-based polymers. The chemical modification of starch may lead to toxic byproducts and is likely to reduce its degradation rate<sup>173,174</sup>.

### **6.2.2. Chitosan**

Chitosan is another non-toxic and non-allergic naturally occurring and biodegradable polymer important for its anti-inflammatory activity and in drug delivery and tissue engineering applications. As an example from literature, Chitosan was used to encapsulate Citrus and Gaultheria procumbens L. essential oils through emulsion polymerization and spray drying processes respectively<sup>175,176</sup>.

Despite the great potentials of chitosan, its poor long-term stability, poor mechanical and thermal properties, and its rapid *in vivo* degradation rate are substantial limitations of the



scaling-up of Chitosan applications<sup>177,178</sup>. Namely, the storage conditions of chitosan may affect its functionalities and alter its functional groups. Chitosan absorbed 14-16 wt% of water within less than four hours at ambient conditions (T= 25 °C and RH= 60%)<sup>179</sup>, whereas at RH > 60% water molecules penetrated more intensively the chitosan chains which increased the moisture content significantly<sup>180</sup>. As a result, chitosan hydrolytic damage accelerates, the polymer's physicochemical and biological properties dramatically change, and chitosan functional groups are diluted. Apart from RH, Chitosan was also shown to be sensitive to temperatures. The storage of chitosan solution at ambient temperatures results in faster degradation of its chains, and Chitosan powder dehydrated and decreased in hardness and mechanical strength at 40 °C<sup>181</sup>. Moreover, the processing of Chitosan represent another dramatic limitation. As an example, sterilization methods like filter sterilization, saturated steam sterilization, or exposure to dry heat and ethylene oxide which are necessary in pharmaceutical applications, can physically or chemically affect chitosan and irreversibly alter its structure and function. The study of Lim et al.<sup>182</sup> showed that the sterilization of chitosan by saturated steam decreased its viscosity by 20 to 50% and resulted in a loss of 30% of its molecular weight, while the sterilization by heating at 160 °C for 2 h and by autoclaving caused darkening of chitosan powder to yellow.

### **6.2.3. Alginate**

Alginate is an unbranched heteropolysaccharide of 1–4 glycosidically linked -d-mannuronic (M) and -l-guluronic (G) acids in varying compositions and sequences. It is a very popular biocompatible and biodegradable polysaccharide with different block configurations that give rise to different material properties. It is known for its applications mainly in medicine<sup>43</sup>. For example, alginate microspheres loaded by Soy isoflavone and Insulin were synthesized by extrusion and spray drying techniques respectively<sup>183,184</sup>. However, the employment of alginate has disadvantages that make its application difficult is

some occasions, and necessitate combining it with other bio-based or fossil-based polymer namely: poor dimensional stability, low mechanical and barrier properties, incompatibility with heavy metals and heat treatment instabilities<sup>185</sup>. Alginate is poorly stable because its depolymerization may start at 40 °C as shown in the study of Mao et al.<sup>186</sup>. In addition, alginate microparticles precipitate at low pH<sup>185</sup> and tend to change in shape as seen in the study of Chuang et al. where spherical alginate droplets contained in low pH gelation solutions turned to be oblate<sup>187</sup>.

#### **6.2.4. Lignin**

Lignin is a waste product of pulp and paper industry formed by connecting one or more of three phenylpropane structural units, namely p-coumaryl, coniferyl and sinapyl alcohols through carbon-carbon bonds (20–35%) and ether bonds (60–75%)<sup>188</sup>. Due to its non-toxic, bio-renewable, corrosion-resistance and UV resistance characteristics, it has attracted the attention of researchers working in the domain of polymer microparticles in the last few years. In addition to microfluidic processes and atomization, lignin microparticles can be prepared by chemical processes like self-assembly method and emulsion inversion where the final product is a solvent containing microparticles<sup>188</sup>. Mechanical processes like high-shear homogenization method and ultrasonic method are also employed to produce lignin microparticles in powder form without control on neither the size nor the shape of the microparticles<sup>188,189</sup>. The principle of high-shear homogenization is to blend the lignin suspension by mechanical shearing action, whereas the ultrasonic method provides energy for lignin to break its molecular bonds through ultrasonic wave.

Busatto et al.<sup>153</sup> used microfluidics and conventional solvent evaporation to prepare atrazine-loaded lignin microparticles for controlled release systems in P24 and P25 detailed in Table 5. This study showed that lignin-based formulations are safe according to

phytotoxicity test and can potentially improve the effectiveness of pesticides and reduce their undesirable environmental impact contrary to phytotoxic commercial atrazine. In a different study, Aguiar et al.<sup>190</sup> encapsulated orange essential oil in lignin through a spray-drying process. This study showed that a combination of a low flow transfer rate ( $0.15 \text{ L.h}^{-1}$ ) of the colloidal suspension, a drying air flow rate at  $536 \text{ L.h}^{-1}$  and an inlet air temperature of  $150 \text{ }^\circ\text{C}$  was the most efficient atomization configuration. 72% (w/w) of lignin was recovered in this study, a comparable result to the study of Marquez-Gomez et al.<sup>191</sup> where powder recoveries of 29, 36, and 73% were reported by using maltodextrin, hydrolyzed protein, and rice starch, a wall material respectively. This data indicates that lignin is a viable alternative for the encapsulation processes. Additionally, the encapsulation efficiency was up to 97% according to some experiments of the study which confirms the retention capacity of lignin microparticles. Moreover, Oil-filled microcapsules of kraft lignin were synthesized by high intensity, ultrasound-assisted cross-linking of lignin at the water/oil interface. These microcapsules were shown to be biocompatible for potential use in the biomedical field<sup>189</sup>. In addition to the controlled release for pesticides systems and encapsulation of volatile materials mentioned above, Qian et al.<sup>192</sup> synthesized lignin colloidal spheres of different sizes and structures by self-assembly method for sunscreen. Ago et al.<sup>193</sup> proved lignin microparticles of sizes between  $0.03$  and  $2 \text{ }\mu\text{m}$  as good options for stabilizing oil-water Pickering emulsion. The study of Zhu et al.<sup>194</sup> showed that the addition of hydrophobic lignin into cellulose suspension in spray drying processes increased the water evaporation kinetics and permitted the control of the microparticle morphology.

The above examples from recent literature demonstrate the great potential of lignin microparticles for drug delivery applications, encapsulation of volatile materials, UV blockers, and emulsion stabilization. However, there are still several aspects restricting the employment of lignin starting from its complex and recalcitrant structure with several major

types of functional groups: hydroxyl, methoxyl, carbonyl, and carboxyl <sup>195,196</sup>. In addition, problems related to biomass fractionation make the conversion of lignin into desired products more complicated. Since lignin is a bio-based polymer with high molecular weight, it should be depolymerized before transforming it into chemical compounds. Depolymerized lignin fractions are highly reactive which leads to uncontrollable side reactions, including repolymerization and condensation. This necessitates fundamental scientific understanding of different chemical structures effects on lignin processibility and reactivity.

### **6.2.5. PLA and PLGA**

PLA is a renewable and biodegradable aliphatic polyester sourced from the microbial fermentation of starch-rich feedstocks, such as corn and sugar <sup>197</sup>. PLA polymer microparticles were produced for drug, antigen and vaccine delivery <sup>47,48,198</sup> by polymer solution-based microfluidics processes. As an example, monodisperse coherent PLA particles with a smooth surface were formed by microfluidics and DCM evaporation at room temperature <sup>199</sup>, and dodecane filled biodegradable PLA capsules were prepared in a microreactor setup <sup>200</sup>.

PLA is a thermally stable synthetic bio-based polymer with excellent mechanical strength; however, it has many drawbacks limiting its employment. First, it has a high production cost compared to traditional synthetic polymers because of the complexity of the fermentation and purification of lactic acid, which accounts for around 50% of total production costs <sup>201,202</sup>. In addition, its degradation rate cannot meet a wide range of application-specific requirements <sup>203</sup>. Although declared as bio-degradable, the degradation process of PLA still requires elevated temperatures (60°C) and high relative humidity in the presence of thermophilic microbes <sup>204</sup>. Moreover, recent studies have shown that PLA

degradation persists marine environment where no degradation was recorded within one year under laboratory conditions simulating static sea water despite mass losses due to dynamic conditions<sup>205</sup>. The relatively low melting point (160-180 °C) of PLA is another disadvantage that renders it impossible to recycle with other polymers, and consequently increases its recycling cost. Finally, PLA has a relatively high permeability<sup>206</sup> allowing moisture and oxygen to pass more easily leading to less efficient encapsulation and incompatibility with for long-term storage applications. This defect can however be corrected by adding CNC, another bio-sourced polymer<sup>207</sup>.

PLGA is a copolymer of lactide and glycolic acid. It is considered as the best-defined biomaterial available for drug delivery with respect to design and performance<sup>208</sup>. In this context, Haddadi et al.<sup>56</sup> encapsulated urea inside PLGA using DCM conventional solvent evaporation for skincare application. Feng et al.<sup>44</sup> produced doxorubicin and paclitaxel drug loaded PLGA microparticles for lung cancer treatment through emulsification and conventional solvent evaporation method. Similarly, Xu et al. produced bupivacaine drug-loaded PLGA microparticles by combining polymer solution-based microfluidics and solvent evaporation of DCM<sup>34</sup>.

PLGA is a synthetic bio-based co-polymer with a hydrophobic and hydrophilic part and good mechanical properties. It is approved by the US FDA for the use of drug delivery. However, several obstacles remain for its usage in controlled release applications. Precisely, the degradation of PLGA during the drug release process generates lactic and glycolic acid that reduces the pH of the microenvironment and denatures the encapsulated materials<sup>209</sup>. In addition, protein release from PLGA matrices was not successfully achieved, instead, an incomplete release was attained because of the protein instability<sup>210</sup>. This causes a loss of therapeutic activity and complications regarding immunogenicity and toxicity<sup>211</sup>. To resolve this problem chemical modifications like PEGylation may be used to stabilize the protein<sup>212</sup>.

However, this is extensive and may compromise the mechanical strength of the polymer as well as the loss of targeting<sup>213</sup>.

In brief, fossil-based and synthetic bio-based microparticles have relatively better mechanical and thermal properties than microparticles of naturally occurring polymers. However, fossil-based microparticles are non-sustainable, and synthetic bio-based microparticles have many challenges limiting their activities and applications. The utilization of bio-based raw materials is needed to render processes green and sustainable. However, challenges arise concerning the properties of the produced microparticles and waste management. These contradictory effects of the three different types of raw materials employed in polymer microparticle production leave plenty of room for improvement. Possible improvement routes are based on the exploration of bio-based platform molecules that can be a key to producing polymer microparticles with competitive properties and fewer complications than existing materials.

### **6.3. Green solvents**

Solvents have received much attention in the framework of green chemistry due to their use in chemical reactions, especially at purification stages, and in formulations<sup>214,215</sup>. Fischer et al. were among the first scientists to pose the question of green solvents in their article dating to 2007<sup>216</sup>. They considered that solvents are evaluated as green or non-green according to a two-two assessment tool: (1) energy demand and environmental, health and safety (EHS), (2) life-cycle assessment (LCA). Furthermore, pharmaceutical companies like Pfizer, AstraZeneca, GSK, and Sanofi developed data-rich solvent guides to help scientists in selecting greener solvents for their applications. Pfizer published a simple two-page document where most classical solvents are classified into three categories: “preferred”, “usable”, and

“undesirable” with a given substitution advice<sup>217</sup>. Furthermore, AstraZeneca published a table of 46 solvents with ten different evaluation criteria scored between 1 and 10 with a 3-color code: green, yellow, and red. The ten criteria involve two safety criteria, one health criterion and seven environmental criteria, including life cycle analysis<sup>218</sup>. Moreover, the Sanofi’s guide classifies solvents in four classes: “recommended”, “substitution advisable”, “substitution requested” and “banned” according to safety, Health and Environmental hazards, and industrial issues<sup>219</sup>. GSK solvent guide also includes banned solvents<sup>220</sup> and classifies solvents according to a 3-color code: green, yellowish green (few issues), yellow (some issues), red (major issues). In addition to these principal solvents guide, other public resources like Rowan University<sup>221</sup> excel tool are available to help solvent selection.

The thresholds that define the conclusion regarding a solvent and its color-coded score are set according to the preference of the guide’s designers and may not be consistent between tools or relevant to the applied regulations. For example, THF is classified red by AstraZeneca’s guide, whereas it is considered usable according to Pfizer’s guide, “substitution advisable” according to Sanofi, and a product with major issues (red color) according to GSK. In a recent attempt to establish a solvent selection guide with a more insistence on regulatory controls, scientists from Sanofi, GSK, Pfizer, the University of York, and Charnwood consultants were involved in a collaborative research project known as the CHEM21<sup>222</sup>. As a result, solvents were classified into six categories, namely: “recommended”, “recommended or problematic?”, “problematic”, “problematic or hazardous?”, “hazardous” and “highly hazardous”.

The solvents were employed in all the processes described in section 5 of the present review. Indeed, both hydrophilic (*e.g.*, water in P17 and P18) or hydrophobic (*e.g.*, DMF in P19) solvents are necessary for the synthesis of core-shell microparticles through coacervation<sup>27,92</sup>. On the other hand, the preparation of microparticles by suspension polymerization

necessitates at least one non-solvent. In other words, the production of hydrophobic microparticles requires at least an aqueous solvent as the case of P1-P3 to prepare PVC microparticles and P3-P9 to prepare PMMA and PBMA microparticles, whereas hydrophilic monomers require organic solvents that are generally less green than water as in P9-P13 where plant oil was used in the preparation of PAM microparticles<sup>71,223</sup>. This is contrary to atomization process that necessitates a solvent for the dissolution of the material to be dried through chilling or heating (P22 and P23). Finally, the microfluidic and extrusion techniques require at least one solvent to act as a continuous phase in monomer-based processes and may require two or more solvents in polymer solution-based processes. For example, Zhang et al.<sup>152</sup> used both water and THF to prepare PVC polymer microparticles (P40 and P41), and Xu et al.<sup>34</sup> used both water and DCM for the production of PLGA drug-loaded polymer microparticles (P42-P44). These facts render solvents inevitable and compulsory in all the production processes described in the present critical review. To this end, it is of crucial environmental importance not only to optimize the quantity of solvents but also to use the greenest solvents possible for each process. The main solvents used in polymer microparticles production are classified in Table 10 according to their toxicity, nature, volatility, boiling point, and their classification according to the solvent selection guides published by AstraZeneca, Pfizer, GSK, Sanofi, and CHEM21.

Water is a non-toxic, natural solvent that is preferably used in chemistry over other common organic solvents<sup>223</sup>. However, it is not always possible to use it for all cases (*e.g.*, inverse suspension polymerization, hydrophobic polymer solutions and atomization with hydrophobic polymer). In addition, the gap between cEF on one hand, and EF and sEF on the other, is huge (3 to 50×) and was observed in all the 47 processes evaluated in section 4. This large gap is due to the excessive use of water which evidently shows its impact on the waste generated from a production process. The alarming reality of a water crisis touching more



than 4 billion people by the 2040s<sup>36</sup>, shows the importance and necessity of economizing water and recycling it in all life domains including polymer microparticles production. Moreover, water is considered as an involatile solvent with boiling point at 100 °C making it incompatible with polymer solution-based microfluidic processes and conventional solvent evaporation that usually require a volatile solvent. Ethanol is considered as a green solvent according to the modified version of the conclusion to the survey of solvent selection guides<sup>215</sup>, and all the solvent selection guides. It is primarily made from biomass nowadays because of its energy uses. Due to its 78.37 °C boiling point, ethanol is considered volatile and compatible with processes requiring solvent evaporation as a prerequisite.

Most organic solvents widely employed in all the microparticles production processes like chloroform, DCM, THF, and DMF, are derived from fossil fuels, thus non-sustainable. Chloroform was frequently used in the preparation of polymer microparticles as a solvent for polymers like PMMA and PCL<sup>224-227</sup>. However, it is a toxic and non-renewable solvent with major issues according to GSK's guide and banned by Sanofi's, leading to consider it highly hazardous according to CHEM21. Pfizer guide classifies chloroform as undesirable solvent and recommends DCM as a substitution<sup>217</sup>.

DCM is a volatile solvent of 40 °C boiling point. Due to these characteristics, it was widely employed in solvent evaporation processes (conventional and combined with microfluidics) to produce PLGA drug-loaded polymer microparticles for drug delivery mainly, and also lignin, PMMA, and PLA microparticles<sup>34,56,120,153,199</sup>. However, the non-renewable and toxic characteristic of DCM makes it non-sustainable. Even though it was suggested as a substitution to chloroform due to its better score according to Pfizer's guide, DCM is still considered undesirable according to the same evaluation procedure. Moreover, GSK's guide classifies it as a solvent with major issues and both Sanofi and AstraZeneca's guide recommend its substitution, while CHEM21 classifies it as hazardous. DMC is a

carbonated ester recently used as a solvent that is exempt from the restrictions placed on most volatile organic compounds that has the potential to replace DCM. DMC was used in the study of Owen et al.<sup>35</sup> for the production process of PLGA-drug loaded microparticles and showed comparable results to microparticles prepared using DCM in the study of Xu et al.<sup>34</sup> with less environmental impact. DMC is much less hazardous than DCM according to the classification of GSK (green with some issues) and CHEM21 (recommended) solvent selection guides, knowing that there is no available data concerning it in AstraZeneca, Pfizer, and Sanofi guides. However, it has a much higher boiling point (91 °C) that makes it less volatile than DCM and harder to evaporate. Not to forget that DMC is still a fossil-based and toxic solvent, even if the toxicity is relatively low<sup>228</sup>, this classifies it as non-sustainable. Ethyl acetate is one of the most important bio-based solvents derived from cellulosic biomass that can replace DCM especially in solvent evaporation processes<sup>229–231</sup>. For example, ethyl cellulose hollow microcapsules were prepared by combining microfluidics and solvent evaporation<sup>232</sup>. Ethyl acetate is classified as green by all solvent selection guides. However, it is less volatile than DCM with a higher boiling point (77.1 °C) making the evaporation process more difficult than DCM. In addition, it is highly flammable and toxic when ingestion or inhaled according to its safety data sheet.

THF is a cyclic ester volatile solvent of relatively low boiling point (66 °C) used in the production processes of polymer microparticles, like coacervation, atomization, and microfluidics<sup>152,233,234</sup>. However, it is also toxic, fossil-based, and classified red according to AstraZeneca and GSK solvent selection guides. Sanofi's guide advises its substitution and CHEM21 guide finds it problematic, whereas only Pfizer's guide classifies it as usable. The article of Pace dating to 2012 suggests the substitution of THF by 2Me-THF<sup>160</sup>. The latter is recommended by Sanofi's guide and classified usable according to Pfizer guidelines, and a "product with some issues" according to GSK's guide. Furthermore, 2Me-THF is derived

from renewable biomass resources <sup>235</sup>, however, it is toxic when breathed, flammable, and a dangerous fire hazard according to its safety data sheet.

DMF is classified yellow according to AstraZeneca’s solvent selection guide. However, it is considered hazardous according to CHEM21 guidelines, undesirable according to Pfizer’s, and a major issue product according to GSK. Furthermore, Sanofi’s guide requests its substitution despite being employed in many polymer microparticles production processes <sup>89,233,236,237</sup>. In addition, DMF, known for its hepatotoxicity and reproductive toxicity <sup>13</sup>, is low volatile with a relatively high boiling point (153 °C) making it non-compatible with solvent evaporation processes. Pfizer’s guidelines recommend its substitution by the more volatile acetonitrile (boiling point: 82 °C). Acetonitrile is also recommended according to Sanofi’s guide <sup>217</sup>. However, it is controversially classified red according to AstraZeneca’s guidelines, while being ranked usable by Pfizer, “some” issues by GSK, and problematic by CHEM21 guide. Acetonitrile was useful to fabricate polymer microparticles like PLGA and PEG drug-loaded microparticles as in the study of Brzeziński et al. <sup>198</sup>. However, it is also toxic according to its safety data sheet and derived from non-renewable resources. These observations confirm acetonitrile as a better substitution of DMF, but not an ideal one.

Solvent	Toxicity	Renewable	Volatility	Boiling Point (°C)	AstraZeneca	GSK	Pfizer	Sanofi	CHEM21
Water	No	Yes*	No	100	Green	Green	Preferred	Recommended	Recommended
Ethanol	No	Yes	Yes	78.37	Green	Green	Preferred	Recommended	Recommended
Chloroform	Yes	No	Yes	61.2	N/A	Major issues	Undesirable	Banned	Highly Hazardous
DCM	Yes	No	Yes	40	Yellow	Major issues	Undesirable	Substitution advisable	Hazardous
DMC	Low	No	Yes	91	N/A	Some issues	N/A	N/A	Recommended
Ethyl acetate	Yes	Yes	Yes	77.1	Green	Green	Preferred	Recommended	Recommended
THF	Yes	No	Yes	66	Red	Major issues	Usable	Substitution advisable	Problematic
2MeTHF	Yes	Yes	Yes	78-80	N/A	Some issues	Usable	Recommended	N/A
DMF	Yes	No	low	153	Yellow	Major issues	Undesirable	Substitution requested	Hazardous
Acetonitrile	Yes	No	Yes	82	Red	Some	Usable	Recommended	Problematic

						issues			
Cyrene™	No	Yes	No	226	N/A	N/A	N/A	N/A	Problematic

Table 10: The characteristics of frequently employed solvents in the polymer microparticles production processes and their classification according to solvent guides established by big pharmaceutical companies.

\*Water is renewable, but its excessive use may lead to water crisis.

Since it is issued from the Levoglucosenone renewable molecule derived from biomass, Cyrene™ represents a potential non-cytotoxic environmental friendlier replacement of both DMF and acetonitrile, especially to dissolve lignin and lignin-derived molecules<sup>13,223,238</sup>. However, it is classified problematic according to CHEM21 guidelines because of its suffering in the environmental assessment. Cyrene™ is not volatile and has a relatively high production cost and very high boiling point compared to other conventional solvents (226 °C). The latter represents a big limitation for its employment in solvent evaporation processes, yet, it is still possible to use it in solvent dissolution production processes as in the study of Zhang et al. where THF was dissolved from high concentrated NaCl solution to non-concentrated one<sup>152</sup>. The Resolute project mentioned in section 4.1 aims to efficiently implement industrial production of Cyrene™ and reduce its price which would ameliorate its environmental assessment and thus its CHEM21 classification.

According to the above analysis of solvents employed in the production processes of polymer microparticles, there is no ideal solvent for a process. Even water that is considered a green non-harmful solvent suffers today from issues related to its excessive use that may lead to a human crisis. However, some solvents are less harmful to human beings and environment than others. The choice and employment of solvents should be made with much care and attention. The ideal case is a bio-based solvent, as less hazardous as possible to be, handling with high attention, using quantities not more than the production process needs. The rooms of optimization and improvement are wide for this purpose, and scientific research should be conducted to discover less hazardous and adaptable solvents.

## 7. Summary

This review discussed the different shapes and morphologies of polymer microparticles, highlighting their importance in different application fields. The main chemical and physical processes for their production were described mentioning their advantages, drawbacks, and challenges to render them sustainable. The pros, cons, and sustainability challenges are summarized in Table 9 and in the graphical abstract. The sustainability of the processes was evaluated according to environmental factors describing waste generation, process energy consumption, and the nature of solvents employed in different experimental conditions and scales. Other processes like fluidized bed coating<sup>239,240</sup> and pan coating<sup>241</sup> enable coating solid particles and forming a microcapsule of the solid core.

Interfacial polymerization, the first chemical process discussed, is a simple and easy to operate process that can produce microparticles with wide size distribution at a low cost. Excessive use of organic and aqueous solvents was reported, whereas using less solvent showed microparticles with weaker characteristics. Using the appropriate initiator and raw material is vital to reduce waste. Room for improving this process exists in optimizing the quantities of the solvent to compromise the quantity (cEF) vs. the properties of microparticles, the choice of materials, finding green substitutes for employed solvents, and energy consumption optimization. The coacervation process was the second chemical process that produces stable capsules with high encapsulation efficiency but always with a large size dispersion. This process is relatively slow compared to other processes and necessitates a slow and energy-consuming post-processing step like freeze-drying to dry the capsules. It is also very sensitive to physical parameters, and toxic crosslinkers like glutaraldehyde are widely employed. This process faces several sustainability challenges such as optimizing encapsulation efficiency, the best choice of crosslinkers (capsules quality vs. cytotoxicity),

optimizing post-processing energy and time consumption, reducing the quantity of solvents, and finding green substitutes for toxic solvents (cost vs. properties).

Two different categories of physical processes were also discussed. The atomization process allows large-scale production but always with poor size control. These processes are highly scalable and do not require any post-processing, with an encapsulation efficiency and yield up to 100% at an industrial scale. However, in addition to the wide size distribution of microparticles, it is the most energy-consuming of the processes discussed in the current review and normally uses solvents that generate toxic waste. To this end, the challenges facing the sustainability of the current process are the use of green solvent substitutes, improving the thermal efficiency and optimizing energy consumption, and recovering the evaporated solvent wastes.

Integrating a spinning disk into the atomization process allows the production of controlled size droplets. However, the spinning disk requires a larger reactor surface because the droplets deviate everywhere, and satellite droplets mean a loss of matter. Furthermore, dependency on the disk rotation speed makes the process less productive and limits output to droplet sizes of more than 100  $\mu\text{m}$ . Extrusion and co-extrusion processes do not require any post-processing like atomization processes. The polymer microparticles produced by these processes had a small size dispersion (< 5%); however, the production rate/nozzle was limited and could not handle high viscosities without heating. This process is not advanced compared to other processes and requires good knowledge and assessment for successful implementation.

Microfluidic processes propose a fast and less expensive wide range of possibilities with perfect control of conditions, durations, homogeneity, and reproducibility. Note that the size and its dispersion affect the mechanism of flavors and aromas released in the case of core-shell microparticles and the speed at which drugs are delivered and released<sup>34,146,156</sup>, and

the time needed between treatments in the case of simple polymer microparticles. Unlike traditional processes that have poor size control, microfluidics does not require a large installation and is superior. However, the microparticle size in these classical microfluidic techniques is dependent on the flow rates, which in turn fixes the quantity of solvent wastes generated by the process. This dependency can be harnessed in systems with an external force (*i.e.*, centrifugal force) controlling the size of the generated droplets. Nevertheless, the recycling of the continuous phase and the recovery of involved solvents is especially critical in polymer solution-based processes. This step was shown to be a vital step for the sustainability of the process, not only from an environmental point of view but also for reducing the wastes generated when reducing the particle sizes.

The choice of production process depends on the targeted application, production rate, particle size dispersion, and waste generation characterized by the EFs. Therefore, a green process for a targeted application is the process in which the ratio of quality/production rate compared to environmental concern is optimized.

The present review discussed environmental factors as another crucial parameter to be considered for the process choice criteria. The next step in choosing the appropriate process for a specific application is the choice of raw materials based on their properties and sustainability. In this context, fossil-based materials cannot be candidates for sustainable production due to the depletion of their source and their environmental consequences. Although naturally occurring and synthetic bio-based materials cover a wide range of applications that cannot be underestimated, they were shown to be either mechanically or thermally weak, difficult to tune and modify, dimensionally unstable, or inappropriate for many applications, limiting their accessibility to numerous domains.

## 8. Conclusion

This critical review showed the pros, cons, and sustainability challenges of the polymer microparticle production processes. The microfluidic technique is a thrifty, inexpensive, fast, and sustainable process, if and only if the continuous phase is recycled. It allows the production of microparticles with perfectly controlled size, content, and morphology. The present review also introduced the importance of discovering bio-based platform molecules that can produce tunable monomers, polymers and solvents with competitive characteristics compared to fossil-based microparticles while keeping the renewability advantage of bio-based products. These renewable materials should be produced exclusively through truly sustainable processes. The combination of the optimized microfluidic process, bio-based tunable monomers, and greenest solvents possible is a sustainable area of improvement in the production field of polymer microparticles.

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