

Green assessment of polymer microparticles production processes: a critical review

Hassan El Itawi, Sami Fadlallah, Florent Allais, Patrick Perre

• To cite this version:

Hassan El Itawi, Sami Fadlallah, Florent Allais, Patrick Perre. Green assessment of polymer microparticles production processes: a critical review. Green Chemistry, 2022, 10.1039/D2GC00578F . hal-03684328

HAL Id: hal-03684328 https://agroparistech.hal.science/hal-03684328

Submitted on 10 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Green assessment of polymer microparticles production processes: a critical review

Hassan El Itawi,*¹ Sami Fadlallah,*² Florent Allais,² Patrick Perré¹

¹ 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.

² 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.

Contents

Abl	breviatior	ns
1.	Introdu	ction
2.	Method	ology7
3.	Polymer	microparticles
4.	Applica	tions of polymer microparticles 10
5.	Sustaina	able assessment of common production methods
5	5.1. Ch	emical Processes
	Interfaci	al Polymerization 15
	Coacerva	ation
5	.2. Phy	vsical Processes
	Atomiza	tion
	Extrusio	n/Co-extrusion
	Microflu	idics
6.	Challen	ges of achieving green production
6	5.1. Gre	en production process
6	5.2. Gre	en raw material
	6.2.1.	Starch
	6.2.2.	Chitosan
	6.2.3.	Alginate
	6.2.4.	Lignin
	6.2.5.	PLA and PLGA
6	5.3. Gre	een solvents
7.	Summa	ry
8.	Conclus	ion
Acl	knowledge	ement
Ref	erences	

Abbreviations

AA:	Acrylic acid	PET:	Polyethylene terephthalate
Aam:	3-(((2-cyanopropan-2-	PGA:	Polyglycolic acid
	yl)oxy)(cyclohexyl)amino)-2,2-		
	dimethyl-3-phenylpropanenitrile		
AIBn:	Azobisisobutyronitrile	PHB:	Poly-β-hydroxybutyrate
APS:	Ammonium persulfate	PLA:	Polylactic acid
BSA:	Bis(trimethylsilyl)acetamide	PLGA:	Poly(lactic-co-glycolic acid)
DCM:	Dichloromethane	PMMA:	Poly(methyl methacrylate)
DEP:	Diethyl phthalate	PP:	Polypropylene
DMC:	Dimethyl carbonate	PS:	Polystyrene
DMF:	Dimethylformamide	PU:	Polyurethane
DOP:	Dioctyl phthalate	PUFAs:	Polyunsaturated fatty acids
DVB:	Divinylbenzene	PVA:	Poly(vinyl alcohol)
EGDMA:	Ethylene glycol dimethylacrylate	PVC:	Polyvinyl chloride
FLAP:	5-Lipoxygenase-activating protein	PVDF:	Polyvinylidene fluoride
GMA:	Glycidyl methacrylate	PVP:	Polyvinylpyrrolidone
HDDA:	1,6-Hexanediol diacrylate	SC CO ₂ :	Super-critical CO ₂
HPC:	Hydroxypropyl cellulose	SD:	Sustainable development
HPMC:	Hydroxypropyl methylcellulose	SDS:	Sodium dodecyl sulfate
IBOA:	Isobornyl acrylate	Span 20:	Sorbitan monolaurate
MYPC:	Dimyristylperoxydicarbonate	Span 80:	Polyoxyethylene (20) sorbitan monooleate
OCMTS:	Octamethylcyclotetrasiloxane	SPS:	Sodium persulfate
PA:	Polyamide	TEGDM	Triethylene glycol dimethacrylate
		A:	
PBMA:	Poly(butyl methacrylate)	TG:	Transglutaminase
PCL:	Polycaprolactone	THF:	Tetrahydrofuran
PDMS:	Polydimethylsiloxane	TPGDA:	Tripropylene glycol diacrylate
PE:	Polyethylene	VCM:	Vinyl chloride monomer
PEG:	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 $^{1-5}$. 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." ⁶. 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 ⁷. To this end, visual representations like the Venn diagram (Figure 1) have been proposed for better communication and more precise standards 8 , 9 .



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 ⁷. 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 ¹⁰. 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 ¹¹. 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 ¹². 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.*¹³.

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

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 ¹⁴ made from polymeric materials ranging in size from 1 to 1000 µm ¹⁵. 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 ¹⁶, cosmetics ¹⁷, biotechnology ^{18,19} and drug delivery ^{20–23} are derived from fossil fuel-based polymers/monomers. For example, commercial polymer microparticles are mainly made from poly(methyl methacrylate) (PMMA) ^{24,25}, polycaprolactone (PCL) ²⁶, 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 ^{16,17,27–30}. The microfluidic method is particularly important due to its thriftiness and controlled conditions advantage ¹⁵. 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) ^{12,31}. However, according to different literature studies ^{32–35}, 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 ³⁶. 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).

$$sEF = \frac{\sum m_{raw \ materials} + \sum m_{reagents} - m_{desired \ product}}{m_{desired \ product}}$$
(2)
$$cEF = \frac{\sum m_{raw \ materials} + \sum m_{reagents} + \sum m_{solvents} + m_{water} - m_{desired \ product}}{m_{desired \ product}}$$
(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_{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_{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.

$$E_{eff} = \frac{m_c}{m_{c0}} \quad (4)$$
$$PL = \frac{m_c}{m_{cap}} \quad (5)$$

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.* ³⁵:

$$V_{c} = \frac{Q_{c}}{Q_{d}} V_{d} \quad (6)$$

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 pharmaceutics, cosmetics, and the food industry. These examples are summarized in Table 1.

Polymer microparticles are synthesized for many applications ²⁸. 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 pharmaceutics, 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 $^{34,37-39}$. 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 40 . One year later, PE was implemented as another polymer for drug delivery 41 . 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) 21 .

Nowadays, several examples of polymer microparticles applications in pharmaceutics exist ⁴². 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 ⁴³. Poly(lactic-co-glycolic acid) (PLGA) microparticles loaded with chemotherapeutic drug doxorubicin (DOX) were fabricated for the controlled release to cancer cells ²². Similarly, PLGA microparticles were produced and loaded with DOX and paclitaxel (PTX) drugs for lung cancer treatment ⁴⁴, and PLGA microparticles were loaded with bupivacaine ³⁴. 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 ⁴⁵. Methotrexate (MTX)loaded gellan gum microparticles have been fabricated to treat human malignancies and autoimmune diseases like rheumatoid arthritis ⁴⁶. In addition to drug delivery, polymer microparticles are often used to deliver entrapped antigens or DNA vaccines ^{47,48}. 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 ¹⁷. Active ingredients in cosmetics like antioxidants ⁴⁹, essential oil and fragrances ⁵⁰, and sun filters ⁵¹ 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 nonpainful 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 ⁵², suspension polymerization ⁵³, and solvent evaporation ⁵⁴, respectively. Polysaccharide sodium alginate and sodium alginate with starch microparticles were synthesized for exfoliating dead skin cells without irritation ⁵⁵. 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 μ m⁵⁶. The contributions of polymer microparticles in pharmaceutics 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 ¹⁶. 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 ⁵⁷. 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 ⁵⁸. 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 ⁵⁹. 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 ⁶⁰. 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 ⁶¹. 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 ⁶². 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
	Alginate	Inflammatory bowel disease (IBL)	43
		treatment	
Dhammaaartiaa	PLGA	Lung cancer treatment	44
Pharmaceutics	CLC/PMMA	Smart drug delivery	45
	Gellan gums	Autoimmune diseases treatment	46
	PLGA, PLC, PLA, PLGA	Vaccine delivery	47,48
	PMMA	Antimicrobial and insect repellent	52–54
	Sodium alginate	Exfoliating dead skin	55
Cosmetics	Sodium alginate with starch		
	PLGA	Skin care	56
	Lignin	Sunscreen	63
	Polyacrylamide Gel	Continuous production of yogurt	58
F 1' 1 /	Alginate	Dairy desserts	59
Food industry	PMMA	Food preservation and flavoring	60
	Soybean protein	Masking odor of food product	62
Construction	PBH	Self-healing in cementitious materials	64
Agriculture	Lionin	Improving effectiveness of pesticides	65

Agriculture
Lignin
Improving effectiveness of pesticides
00

Table 1: Summary of some applications of polymer microparticles in pharmaceutics, cosmetics, food industry, and construction sectors.
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00
00</t

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 ⁶⁶ and was successfully implemented in industries such as paint, pharmaceutics, and food. A typical interfacial polymerization system consists of a continuous phase, dispersed phase (monomer), emulsifier (surfactant), and an initiator ⁶⁷. In most common interfacial polymerization processes, the continuous phase is mainly aqueous, and the monomer dispersed phase is usually organic (oil-in-water emulsion) ⁶⁸. 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 ⁶⁹. 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 ^{70,71}.

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 72 . 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 ³², polyacrylates, and poly(vinyl acetate) ^{73–75}. This process is frequently called a microbulk process because it is very similar to bulk polymerization, and the particle size produced is between 1 μ m and a few millimeters. Unlike suspension polymerization, the particle size produced in emulsion polymerization is less than 1 μ m. The initiator is dissolved in the continuous phase instead of the dispersed monomer ⁷⁶. 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 ^{77,78}.

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 ⁶⁷. High molecular weight products can be achieved quickly without further processing ⁷⁹. 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 ⁷⁹. These processes produce microparticles with a wide size distribution ⁸⁰.



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 ($\varphi = m_m/m_c$ 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 ^{67,70,74,79,81} but may be an organic solvent ⁸² 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 φ to unity or even more ⁷⁰. Unfortunately, this goal is hampered by the effect of less solvent on the properties of microparticles ³².

We take the example of PVC microparticle fabrication by suspension polymerization 32 reported in Table 2 (P1, P2, and P3). At $\varphi = 1.1$ (P3), the conversion rate is more than the P1 and P2 of lower φ . 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 φ 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 φ = 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. ⁸³ 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-3phenylpropanenitrile (Aam) and 2,2'-azobis (2-methylpropionitrile) (AIBN). The use of 0.15g of AIBN initiator (process P8) compared to 1.27 g Aam initiator (process P4) was not onlymore efficient (higher conversion rate) and greener (lower cEF; 3.6*vs.*4.6), but also six timesfaster. This result shows the importance of the proper choice of the initiator from theproduction and green points of view, especially when going from lab scale to industrial scalewhere the quantities are more important. Moreover, adding as small an amount as 45 mg ofNiNO₂ 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 15min.

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. ⁸². 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. ⁸⁴ produced PAA microparticles in an interesting suspension polymerization process in supercritical carbon dioxide (SC CO₂) ⁸⁴. SC CO₂ is a fluid state of inexpensive CO₂ gas held at or above its easily achievable critical temperature (31 °C) and critical pressure (73.8 bars). CO₂ accounted for 76% of the total EU greenhouse gas emissions in 2019 ⁸⁵. The use of SC CO₂ 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 CO₂ is considered a green non-organic, non-toxic, and nonexplosive solvent ⁸⁶. Despite these advantages, the main drawback of SC CO₂ 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_2 does not seem to be recycled and represents more than twice the amount of the monomer. Assuming the non-recycling of CO_2 and its release to the atmosphere, the two processes, P14 and P15, generate around 2.3 kg of CO_2 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_2 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	Т (°С)	time (h)	Yield (%)	sEF	EF	cEF	Ref.
P1	VCM/ PVC	MYPC	Span20 HPMC HPC	Water	50	24	68	0.7	0.7	4.3	32
P2	VCM/ PVC	MYPC	Span 20 HPMC HPC	Water	50	24	69	0.6	0.6	2.3	32
Р3	VCM/ PVC	MYPC	Span 20 HPMC HPC	Water	50	24	69.5	0.5	0.5	1.8	32
P4	MMA/ PMMA	AAm	PVA	Water	83	8	72	0.5	0.5	4.6	83
P5	MMA/ PMMA	AIBn NaNO ₂	PVA	Water	83	1.25	82	0.3	0.3	3.9	83
P6	BMA/ PBMA	AAm	PVA	Water	87	5	74	0.4	0.4	4.4	83
P7	BMA/ PBMA	AAm	PVA	Water	87	7	93	0.1	0.1	1.7	83
P8	MMA/ PMMA	AIBn	PVA	Water	83	1	88	0.2	0.2	3.6	83
Р9	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	55	1	60	3.8	28.9	39.9	82
P10	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	85	1	82.5	2.5	20.7	28.7	82
P11	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	75	1	97.5	2	17.4	24.2	82
P12	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	75	2	97.5	2	17.4	24.2	82
P13	AM/PAM	APS	Span80 Tween80	Plant oil (Organic)	75	0.333	65	3.4	26.6	36.7	82
P14	AA/PAA	SPS	PDMS	SC CO ₂	75	1.5	97	0.03	2.3	2.3	84
P15	AA/PAA	SPS	PDMS	SC CO ₂	75	1.5	97	0.04	2.3	2.3	84

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 1929⁸⁷. 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 colloid⁸⁸. 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)^{89,90}, 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)^{91,92} or complex (interaction of oppositely charged polymers^{93,94}.

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 95,96 . However, it is sensitive to several factors like physical parameters of core and shell material pressure, shearing, temperature, and pH, which limits its applications 97,98 . The effect of these physical parameters on the encapsulation efficiency and microparticle sizes and their wide size distribution was demonstrated by Xiao et al. 33 . 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 °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 ^{99–101}.



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. ⁸⁹ 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 ⁹⁸ 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 °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 ⁸⁹ (P19). PLA in dimethylformamide (DMF) solution of 15.7 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 ¹⁰². 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 ¹⁰³, one could recommend non-toxic alternatives such as CyreneTM derived from levoglucosenone, a cellulose-derived platform molecule ¹⁰⁴. CyreneTM 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[™] 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[™]. This will significantly increase production, reduce the price, and allow the efficient industrial implementation of green substitutes like Cyrene[™].

Lavender oil (LO), an essential oil widely employed in balms, salves, perfumes and cosmetics ¹⁰⁵, 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.³³ 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 ε amino group of polypeptide-bound lysines and the y-carboxamide group of polypeptidebound glutamines ¹⁰⁶. 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 ^{106–108}. 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.

	Туре	Core	Shell	Other reactants	T _r (°C)	T _d (°C)	t _r (h)	t _d (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	98
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	98
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	98
P19	Simple	Thyme oil	PLA	Tween 20 DMF OCMTS Pluronic F68 Ethanol	25	N/A	2	40	DMF	51.7	105	383	89
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	33
P21	Complex	Lavender oil	Gelatin and Arabic gum	Tranglutaminase	4	-10 to -50	9.3	72	Water	1.2	1.2	43.3	33

Table 3: A summary of some coacervation processes with their corresponding operating conditions.

Tr: temperature of the reaction, T_d : drying temperature, t_r : time of reaction, t_d : 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 µm in size or to encapsulate volatile, sensitive, and functional ingredients (core-shell)¹⁰⁹. 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 ¹¹⁰, dry tomato juice ¹¹¹, and coffee ¹¹². In addition to the food industry, 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 ¹¹⁶. 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 ^{109,117}. 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 ¹¹⁸ (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 ¹⁰⁹. This production technique can be scaled up easily by increasing the flow rate, disk size, and rotation speed ¹¹⁹. 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 ¹²⁰. The spray drying process is capable of producing microparticles from a very wide range of compounds ^{121,122} without a final drying step like solvent evaporation or freeze-drying, and without excessive use of solvents as in conventional techniques ¹²³. However, these processes have major drawbacks. First, air temperature in the drying chamber may reach up to 185 °C in certain spray drying reactors ¹²⁴ and may go down to -50 °C in spray chilling ¹²⁵, 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 ¹²⁶ and may decrease to less than 20% in some cases ¹²⁷. Moreover, the price of heat accounts for about 60% of the total cost of a spray drying unit ¹²⁷. In addition, spray drying/chilling is not adapted to coat solid matter that cannot be sprayed in a chamber ¹¹². 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 μ 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 ¹⁰⁹. Satellite droplets may also form at moderate rotation speeds, causing a loss of product and excessive raw material consumption ^{109,128}. 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 ¹²³ 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 ³⁵.

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 Mishra¹¹² with permission from *Taylor & Francis*, copyright 2015.

	Drying/ Chilling	Loaded drug/Core	Shell	T _{air} (°C)	Solvents	E _{eff} (%)	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	122
P23	Chilling	Erythropoietin	PLGA + 0.5% lactide	-50	Water DCM	100	37.1	37.1	1.7	53	55.7	120

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 ^{29,129}. Polymer solution or monomer droplets are extruded from a nozzle through dripping or jet break-up. Jet breaking can be generated through electrostatic mean ¹³⁰, coaxial flow ¹³¹, vibration ¹³², jet cutting ¹³³, or even the spinning disk described before ¹³⁴. 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 ¹³⁵. 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 ¹³⁶. 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 ¹³⁷.

Microfluidics

Microfluidics is an extrusion technique at the scale of 1 µm 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 ¹³⁸. In the last two decades, innovative microfluidic technology has been the scope of extensive studies ^{34,139,140} and diverse applications. For example, microfluidic techniques were proved to be very efficient in assisted reproductive technologies ¹⁴¹, bacteria separation and preconcentration ¹⁴², DNA compaction ¹⁴³, and fungus identification ¹⁴⁴. Microfluidics has emerged as an efficient technique for producing liposomes and nanoparticles ¹⁴⁵ and is important in the production of controlled size polymer microparticles ¹⁴⁶. 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 ¹⁴⁷. 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 ¹⁴⁸ 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 ¹⁴⁹, heating ¹⁵⁰, or other chemical reaction like ring-opening polymerization ¹⁵¹. 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.* ¹⁵², or off-chip by solvent evaporation after droplet collection ^{34,35}. Figure 9 shows a schematic of a simple microparticle production process where the solidification is performed by *in-situ* UV polymerization. The production of coreshell 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. ¹⁵³ 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 $E_{eff} \approx 59.7\%$ compared to CV $\approx 6.5\%$ and $E_{eff} \approx 47.4\%$ 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	d̄ (μm)	E _{eff} (%)	sEF	EF	cEF	Ref
P24	0.7 wt% Lignin and 0.01 wt%	PVA solution in water	Traditional solvent evaporation	25.3 ± 6.7	47.4 ± 3.5	6.9	138	2450	153
P25	Atarazine in DCM		Microfluidics + Solvent evaporation	50 ± 3	59.7 ± 8.2	1.2	119	228	153

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	\overline{d} (µm)	Yield (%)	sEF	EF	cEF	Ref
P26	GMA and EGDMA	3 wt% PVA in	In-situ UV	4 min	5.25	$110 \pm$	100	1.6	1.6	12.2	154
	co-monomer and	water	polymerization			3.3					
	DEP porogen		and post Off-								
	Monomer Phase	Continuous Phase	Method	Solidification time	Q_c/Q_d	\overline{d} (µm)	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 ± 2.25	100	2.2	2.2	32.7	154
P28	TPGDA and photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	20–900 s	60	104 ± 2	97	1.3	1.3	61.7	155
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 ± 3	100	1	1	49.8	148
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 ± 2.9	100	1	1	49.8	148
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 ± 12	100	0	16	18.2	150

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 mg.h⁻¹ in the dripping regime and up to 1 mg.h⁻¹ with a jet break-up ^{34,148,154,156–158}. 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 ³⁴. 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 $3.4 \text{ m}^2/\text{g}$, which means less porosity ¹⁵⁴.

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 $50 \times$ 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 ¹⁵⁹. 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.¹⁵², the solvent can still be substituted by a greener solvent like 2-methyltetrahydrofuran ¹⁶⁰. DMC was reported as a greener and more sustainable substitute for DCM in the atomization process section. Owen et al. ³⁵ 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	$\frac{Q_c/Q_d}{Q_c/Q_{cor}}$	Cores	d (µm)	Yield (%)	sEF	EF	cEF	Ref
P32	Silicone oil	HDDA with photoinitiator	2 wt% PVA in water	Off-chip UV polymerization	17.8 160	Monocore	135 ± 2.7	100	0.3	0.3	16.3	158
P33	Silicone oil	HDDA with thermal initiator	2 wt% PVA in water	Off-chip thermal polymerization	17.8 160	Monocore	135 ± 2.7	100	0.4	0.4	16.8	158
P34	Silicone oil	EGDMA with photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	66.7 444.4	Monocore	104 ± 2.6	100	1.2	1.2	58.1	157
P35	Silicone oil	EGDMA with photoinitiator	2 wt% SDS in water	<i>In-situ</i> UV polymerization	72.7 153.8	Polycore 2 cores	N/A	100	1	1	50.3	157
P36	Silicone	EGDMA with	2 wt% SDS in	In-situ UV	75	Polycore	N/A	100	1.2	1.2	57.8	157

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

 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 µm (P26 and P27), 2.5 times more solvent waste was generated. Similarly, the reduction of PLGA microparticles of P42 from 42 to 12 µm 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		Yield (%)	sEF	EF	cEF	Ref
P40	5 wt% PVC in	20 wt% NaCl	Solvent	< 20 s	7	170 ±	97	37	56.5	204	152
	THF	in water	dissolution			5.1					
P41	1 wt% PVC in	20 wt% NaCl	Solvent	< 20 s	7	$80 \pm$	97	185	287	1024	152
	THF	in water	dissolution			2.4					
P42	40 g/l PLGA	1 wt% PVA in	Off-chip	3 min	4	42 ±	100	1.33	33.6	165	34
	and 25%	tris buffer	solvent			1.6					
	bupivicaine in		evaporation								
	DCM		_								
P43	40 g/l PLGA	1 wt% PVA in	Off-chip	3 min	20	12 ±	100	6.6	39	696	34
	and 25%	tris buffer	solvent			0.46					
	bupivicaine in		evaporation								
	DĈM		-								

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

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 ($\overline{d} = 75 \ \mu m$) are around 1.4 times higher than those of P26 ($\overline{d} = 110 \ \mu m$), knowing that the two processes use the same fluids but with different Q_c/Q_d . Similarly, the sEF of P43 ($\overline{d} = 12 \ \mu m$) is five times higher than that of P40 $(\overline{d} = 42 \ \mu m)$, 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 µm. 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 ^{162,163}. 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 Nisisako¹⁵⁸, in which Janus droplets were generated in a microfluidic device and transformed into a coreshell 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 nitrogennitrogen 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. ¹⁵⁷ 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	 Simplicity Easy to operate Low cost Capsules stability 	 Relatively low purity of polymer Wide size distribution Solvent removal complications Excessive use of solvents High sensitivity to physical parameters 	 Optimization solvents quantities with respect to particle properties Best choice of initiators and stabilizers Energy consumption optimization (temperature, duration) Green solvent substitutes: cost vs. properties Optimizing encapsulation efficiency 			
Coacervation	• High E _{eff} possible	 Expensive post-processing Common use of toxic crosslinkers Wide size distribution 	 Best choice of crosslinkers Post-processing energy consumption optimization (temperature, duration) Reducing the quantity of water used Green solvent substitutes: cost vs. properties 			
Atomization	 Scalability and high production rate No post processing High E_{eff} at industrial scale 	 Energy-consuming Wide size distribution Not adapted to encapsulate solid matter Toxic solvents and wastes 	 Green solvent substitutes: cost vs. properties Reducing energy consumption Reducing and recovering wastes 			
Atomization + spinning disk	 Scalability No post processing Size control 	 Energy-consuming Not adapted to encapsulate solid matter Toxic solvents and wastes Large surface requirement Satellite droplets (loss of matter) Unadopted to particles less than 100 µm Production rate less than classical atomization and limited to rotation speeds 	 Green solvent substitutes: cost vs. properties Reducing energy consumption Reducing wastes Recovering satellite droplets 			
Extrusion/ Co-extrusion	ScalabilityNo post processingSize control	 Limited production rate/nozzle Unadopted to high viscosities without heating Not advanced compared to other older processes 	 Recycling the continuous phase Optimizing energy consumption Good knowledge and assessment for successful implementation 			
Monomer- based microfluidics	 Size control Content control and morphology Yield close to 100% High E_{eff} Scalability Fast and cheap Tuning material properties 	 Dependency between flow rates and wastes Limited production rate/microfluidic chip 	 Recycling the continuous phase Optimizing energy consumption 			
Polymer solution-based microfluidics	 Size control Content control and morphology Yield close to 100% High Eeff Scalability Fast and cheap Tuning material properties No heating or UV 	 Dependency between flow rates and wastes Limited production rate/microfluidic chip Waste due to droplet solvent evaporation Use of toxic solvents 	 Recycling the continuous phase Recycling the polymer solvent of the droplet phase Green solvent substitutes: greenness vs. properties 			

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 biobased material and synthetic polysaccharides employed in the production of polymer microparticles is proposed.

45



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) ¹⁶⁴. It was used for the preparation of polymer microparticles mainly by spray drying processes. For example, Böger et al. ¹⁶⁵, Wang et al. ¹⁶⁶, and Baltrusch et al. ¹⁶⁷ 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 ¹⁶⁸. Despite these qualities, starch still suffers three main disadvantages, namely: hydrophilic nature, mechanical properties and processability ¹⁶⁹.

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 T_g is for the same kind of starch. Liu et al. ¹⁷⁰ 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 Tg 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 ¹⁶⁹. Furthermore, the mechanical properties of starch are sensitive to storage duration due to retrogradation. In this context, Cano et al. ¹⁷¹ 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 ¹⁷². 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 ^{173,174}.

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 ^{175,176}.

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 ^{177,178}. 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%) 179 , whereas at RH > 60% water molecules penetrated more intensively the chitosan chains which increased the moisture content significantly ¹⁸⁰. 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 181. 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. ¹⁸² 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 -dmannuronic (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 ⁴³. For example, alginate microspheres loaded by Soy isoflavone and Insulin were synthesized by extrusion and spray drying techniques respectively ^{183,184}. 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 ¹⁸⁵. Alginate is poorly stable because its depolymerization may start at 40 °C as shown in the study of Mao et al. ¹⁸⁶. In addition, alginate microparticles precipitate at low pH ¹⁸⁵ 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 ¹⁸⁷.

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%)¹⁸⁸. 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 ¹⁸⁸. Mechanical processes like high-shear homogenization method and ultrasonic method are also employed to produce lignin microparticles ^{188,189}. 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. ¹⁵³ 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.¹⁹⁰ 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 L.h^{-1}) of the colloidal suspension, a drying air flow rate at 536 L.h⁻¹ and an inlet air temperature of 150 °C was the most efficient atomization configuration. 72% (w/w) of lignin was recovered in this study, a comparable result to the study of Marguez-Gomez et al.¹⁹¹ 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 ¹⁸⁹. In addition to the controlled release for pesticides systems and encapsulation of volatile materials mentioned above, Qian et al.¹⁹² synthesized lignin colloidal spheres of different sizes and structures by self-assembly method for sunscreen. Ago et al. ¹⁹³ proved lignin microparticles of sizes between 0.03 and 2 µm as good options for stabilizing oil-water Pickering emulsion. The study of Zhu et al. ¹⁹⁴ 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 recalcitrate structure with several major types of functional groups: hydroxyl, methoxyl, carbonyl, and carboxyl^{195,196}. 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 ¹⁹⁷. PLA polymer microparticles were produced for drug, antigen and vaccine delivery ^{47,48,198} 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 ¹⁹⁹, and dodecane filled biodegradable PLA capsules were prepared in a microreactor setup ²⁰⁰.

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^{201,202}. In addition, its degradation rate cannot meet a wide range of application-specific requirements ²⁰³. 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 ²⁰⁴. 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 ²⁰⁵. 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 ²⁰⁶ 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 ²⁰⁷.

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 ²⁰⁸. In this context, Haddadi et al. ⁵⁶ encapsulated urea inside PLGA using DCM conventional solvent evaporation for skincare application. Feng et al. ⁴⁴ 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 ³⁴.

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 ²⁰⁹. In addition, protein release from PLGA matrices was not successfully achieved, instead, an incomplete release was attained because of the protein instability ²¹⁰. This causes a loss of therapeutic activity and complications regarding immunogenicity and toxicity ²¹¹. To resolve this problem chemical modifications like PEGylation may be used to stabilize the protein ²¹². However, this is extensive and may compromise the mechanical strength of the polymer as well as the loss of targeting 213 .

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 ^{214,215}. Fischer et al. were among the first scientists to pose the question of green solvents in their article dating to 2007 ²¹⁶. 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 ²¹⁷. 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 ²¹⁸. 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 ²¹⁹. GSK solvent guide also includes banned solvents ²²⁰ 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 ²²¹ 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 ²²². 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 27,92 . 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^{71,223}. 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. ¹⁵² used both water and THF to prepare PVC polymer microparticles (P40 and P41), and Xu et al. ³⁴ used both water and DCM for the production of PLGA dug-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 ²²³. 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 ³⁶, 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 ²¹⁵, 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 ^{224–227}. 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 ²¹⁷.

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 ^{34,56,120,153,199}. 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.³⁵ 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. ³⁴ 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 ²²⁸, 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 ^{229–231}. For example, ethyl cellulose hollow microcapsules were prepared by combining microfluidics and solvent evaporation ²³². 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 ^{152,233,234}. 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 ¹⁶⁰. 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 ²³⁵, 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 ^{89,233,236,237}. In addition, DMF, known for its hepatotoxicity and reproductive toxicity ¹³, 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 ²¹⁷. 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 drugloaded microparticles as in the study of Brzeziński et al. ¹⁹⁸. 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	AstraZeneca	GSK	Pfizer	Sanofi	CHEM21
Watar	N.	Veek	Na	(°C)	Crear	Crear	Duefermed	Deserves and ad	December
water	INO	res*	INO	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	Undesirable	Banned	Highly
						issues			Hazardous
DCM	Yes	No	Yes	40	Yellow	Major	Undesirable	Substitution	Hazardous
						issues		advisable	
DMC	Low	No	Yes	91	N/A	Some	N/A	N/A	Recommended
						issues			
Ethyl acetate	Yes	Yes	Yes	77.1	Green	Green	Preferred	Recommended	Recommended
THF	Yes	No	Yes	66	Red	Major	Usable	Substitution	Problematic
						issues		advisable	
2MeTHF	Yes	Yes	Yes	78-80	N/A	Some	Usable	Recommended	N/A
						issues			
DMF	Yes	No	low	153	Yellow	Major	Undesirable	Substitution	Hazardous
						issues		requested	
Acetonitrile	Yes	No	Yes	82	Red	Some	Usable	Recommended	Problematic

						issues						
Cyrene ^{тм}	No	Yes	No	226	N/A	N/A	N/A	N/A	Problematic			
Ta	Table 10: The characteristics of frequently employed solvents in the polymer microparticles production											

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, CyreneTM represents a potential non-cytotoxic environmental friendlier replacement of both DMF and acetonitrile, especially to dissolve lignin and lignin-derived molecules ^{13,223,238}. However, it is classified problematic according to CHEM21 guidelines because of its suffering in the environmental assessment. CyreneTM 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 dissoluted from high concentrated NaCl solution to non-concentrated one ¹⁵². The Resolute project mentioned in section 4.1 aims to efficiently implement industrial production of CyreneTM 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 ^{239,240} and pan coating ²⁴¹ 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),

60

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 μ 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 ^{34,146,156}, 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.

Acknowledgement

This study was carried out in the Centre Européen de Biotechnologie et de Bioéconomie (CEBB), supported by the Région Grand Est, Département de la Marne, Greater Reims and the European Union. In particular, the authors would like to thank the Département de la Marne, Greater Reims, Grand Est region and the European Union along with the European Regional Development Fund (ERDF Champagne Ardenne 2014-2020) for their financial support of the Chair of Biotechnology of CentraleSupélec and URD ABI-AgroParisTech.

References

- 1 S. M. Lélé, Sustainable development: A critical review, *World Dev.*, 1991, **19**, 607–621.
- 2 J. Dernbach, Sustainable Development as a Framework for National Governance, *Case West. Reserve Law Rev.*, 1998, **49**, 1–103.
- 3 J. Dernbach, Achieving Sustainable Development: The Centrality and Multiple Facets of Integrated Decisionmaking, *Indiana J. Glob. Leg. Stud.*, 2003, **10**, 247.
- 4 H. Stoddart, A Pocket Guide to Sustainable Development Governance Edited by SECOND EDITION Commonwealth Secretariat Stakeholder Forum, 2011.
- 5 J. Mensah, Sustainable development: Meaning, history, principles, pillars, and implications for human action: Literature review, *Cogent Soc. Sci.*, 2019, **5**, 1653531.
- R. Goodland and H. Daly, Environmental Sustainability: Universal and Non-Negotiable, *Ecol. Appl.*, 1996, 6, 1002–1017.
- 7 M. F. Ashby, Chapter 1 Background: Materials, Energy and Sustainability, 2016.
- 8 R. Lozano, Envisioning sustainability three-dimensionally, J. Clean. Prod., 2008, 16, 1838–1846.
- D. Mebratu, Sustainability and sustainable development: Historical and conceptual review, *Environ*.
 Impact Assess. Rev., 1998, 18, 493–520.
- 10 G. Chichilnisky, Source L. Econ., 1997, 73, 467–491.
- 11 S. Fadlallah, P. S. Roy, G. Garnier, K. Saito and F. Allais, *Green Chem.*, 2021, 23, 1495–1535.
- 12 R. A. Sheldon, The: E factor 25 years on: The rise of green chemistry and sustainability, Green Chem.,

2017, **19**, 18–43.

- 13 F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. Robert McElroy and J. Sherwood, Tools and techniques for solvent selection: green solvent selection guides, *Sustain. Chem. Process.*, 2016, 4, 1–24.
- 14 D. Dendukuri, D. C. Pregibon, J. Collins, T. A. Hatton and P. S. Doyle, Continuous-flow lithography for high-throughput microparticle synthesis, *Nat. Mater.*, 2006, 5, 365–369.
- 15 C. A. Serra and Z. Chang, *Chem. Eng. Technol.*, 2008, 31, 1099–1115.
- B. F. Gibbs, S. Kermasha, I. Alli and C. N. Mulligan, Encapsulation in the food industry: A review, *Int. J. Food Sci. Nutr.*, 1999, 50, 213–224.
- F. Casanova and L. Santos, Encapsulation of cosmetic active ingredients for topical application-a review,
 J. Microencapsul., 2016, **33**, 1–17.
- 18 D. Deveci and S. Egginton, Development of the fluorescent microsphere technique for quantifying regional blood flow in small mammals, *Exp. Physiol.*, 1999, **84**, 615–630.
- 19 S. A. Eucker, B. D. Hoffman, R. Natesh, J. Ralston, W. M. Armstead and S. S. Margulies, Development of a fluorescent microsphere technique for rapid histological determination of cerebral blood flow, *Brain Res.*, 2010, **1326**, 128–134.
- 20 G. Tiwari, R. Tiwari, S. Bannerjee, L. Bhati, S. Pandey, P. Pandey and B. Sriwastawa, Drug delivery systems: An updated review, *Int. J. Pharm. Investig.*, 2012, **2**, 2–11.
- S. Freiberg and X. X. Zhu, Polymer microspheres for controlled drug release, *Int. J. Pharm.*, 2004, 282, 1–18.
- 22 W. Liu, S. Wen, M. Shen and X. Shi, Doxorubicin-loaded poly(lactic-co-glycolic acid) hollow microcapsules for targeted drug delivery to cancer cells, *New J. Chem.*, 2014, **38**, 3917–3924.
- K. Farbod, K. Sariibrahimoglu, A. Curci, A. Hayrapetyan, J. Hakvoort, J. Van Den Beucken, M. Iafisco,
 N. Margiotta and S. Leeuwenburgh, Controlled Release of Chemotherapeutic Platinum-Bisphosphonate
 Complexes from Injectable Calcium Phosphate Cements, *Tissue Eng. Part A*, 2016, 22, 788–800.
- F. Ahangaran, A. H. Navarchian and F. Picchioni, Material encapsulation in poly(methyl methacrylate)
 shell: A review, J. Appl. Polym. Sci., 2019, 136, 1–21.
- 25 B. Wang, C. S. Ho and D. A. Weitz, Fabrication of monodisperse toroidal particles by polymer solidification in microfluidics, *ChemPhysChem*, 2009, **10**, 641–645.
- 26 S. Yadavali, H. H. Jeong, D. Lee and D. Issadore, Silicon and glass very large scale microfluidic droplet

integration for terascale generation of polymer microparticles, Nat. Commun., 2018, 9, 1-9.

- 27 J. Oxley, Overview of Microencapsulation Process Technologies, Elsevier Inc., 2014.
- R. Dubey, T. C. Shami and K. U. Bhasker Rao, Microencapsulation technology and applications, *Def. Sci. J.*, 2009, **59**, 82–95.
- 29 O. P. Bamidele and M. N. Emmambux, Encapsulation of bioactive compounds by "extrusion" technologies: a review, *Crit. Rev. Food Sci. Nutr.*, 2020, **61**, 3100–3118.
- 30 W. J. Duncanson, T. Lin, A. R. Abate, S. Seiffert, R. K. Shah and D. A. Weitz, Microfluidic synthesis of advanced microparticles for encapsulation and controlled release, *Lab Chip*, 2012, **12**, 2135–2145.
- R. A. Sheldon, The E Factor: Fifteen years on, *Green Chem.*, 2007, 9, 1273–1283.
- 32 N. Etesami, M. Nasr Esfahany and R. Bagheri, Effect of the Phase Ratio on the Particle Properties of Poly(vinyl chloride) Resins Produced by Suspension Polymerization, J. Appl. Polym. Sci., 2010, 110, 2748–2755.
- Z. Xiao, W. Liu, G. Zhu, R. Zhou and Y. Niu, Production and characterization of multinuclear microcapsules encapsulating lavender oil by complex coacervation, *Flavour Fragr. J.*, 2014, 29, 166–172.
- Q. Xu, M. Hashimoto, T. T. Dang, T. Hoare, D. S. Kohane, G. M. Whitesides, R. Langer, D. G.
 Anderson and H. David, Preparation of monodisperse biodegradable polymer microparticles using a microfluidic flow-focusing device for controlled drug delivery, *Small*, 2009, 5, 1575–1581.
- 35 M. J. Owen, J. H. N. Yik, C. Ye, B. Netto, D. R. Haudenschild and G. yu Liu, A Green Approach to Producing Polymer Microparticles for Local Sustained Release of Flavopiridol, *Chem. Res. Chinese* Univ., 2021, 37, 1116–1124.
- 36 A. Baer, Not enough water to go round?, *Int. Soc. Sci. J.*, 1996, **48**, 277–292.
- 37 N. Tahir, A. Madni, W. Li, A. Correia, M. M. Khan, M. A. Rahim and H. A. Santos, Microfluidic fabrication and characterization of Sorafenib-loaded lipid-polymer hybrid nanoparticles for controlled drug delivery, *Int. J. Pharm.*, 2020, 581, 119275.
- 38 P. Sundararajan, J. Wang, L. A. Rosen, A. Procopio and K. Rosenberg, Engineering polymeric Janus particles for drug delivery using microfluidic solvent dissolution approach, *Chem. Eng. Sci.*, 2018, **178**, 199–210.
- 39 X. T. Sun, R. Guo, D. N. Wang, Y. Y. Wei, C. G. Yang and Z. R. Xu, Microfluidic preparation of polymer-lipid Janus microparticles with staged drug release property, *J. Colloid Interface Sci.*, 2019,

553, 631–638.

- 40 J. Folkman and D. M. Long, The use of silicone rubber as a carrier for prolonged drug therapy, *J. Surg. Res.*, 1964, **4**, 139–142.
- 41 S. J. Desai, P. Singh, A. P. Simonelli and W. I. Higuchi, Investigation of factors influencing release of solid drug dispersed in inert matrices ii quantitation of procedures, *J. Pharm. Sci.*, 1965, **54**, 1459–1464.
- 42 M. Lengyel, N. Kállai-Szabó, V. Antal, A. J. Laki and I. Antal, Microparticles, microspheres, and microcapsules for advanced drug delivery, *Sci. Pharm.*, 2019, **87**, 20.
- 43 L. Agüero, D. Zaldivar-Silva, L. Peña and M. Dias, Alginate microparticles as oral colon drug delivery device: A review, *Carbohydr. Polym.*, 2017, **168**, 32–43.
- 44 T. Feng, H. Tian, C. Xu, L. Lin, Z. Xie, M. H. W. Lam, H. Liang and X. Chen, Synergistic co-delivery of doxorubicin and paclitaxel by porous PLGA microspheres for pulmonary inhalation treatment, *Eur. J. Pharm. Biopharm.*, 2014, **88**, 1086–1093.
- 45 H. K. Ju, J. W. Kim, S. H. Han, I. S. Chang, H. K. Kim, H. H. Kang, O. S. Lee and K. Do Suh, Thermotropic liquid-crystal/polymer microcapsules prepared by in situ suspension polymerization, *Colloid Polym. Sci.*, 2002, 280, 879–885.
- 46 M. Dhanka, C. Shetty and R. Srivastava, Methotrexate loaded gellan gum microparticles for drug delivery, *Int. J. Biol. Macromol.*, 2018, **110**, 346–356.
- D. O'Hagan, Microparticles as vaccine delivery systems, *Immunopotentiators Mod. Vaccines*, 2006, 123–147.
- 48 M. Singh, A. Chakrapani and D. O'Hagan, Nanoparticles and microparticles as vaccine-delivery systems, *Expert Rev. Vaccines*, 2007, **6**, 797–808.
- 49 M. H. Lee, S. G. Oh, S. K. Moon and S. Y. Bae, Preparation of silica particles encapsulating retinol using o/w/o multiple emulsions, *J. Colloid Interface Sci.*, 2001, **240**, 83–89.
- 50 A. Sansukcharearnpon, S. Wanichwecharungruang, N. Leepipatpaiboon, T. Kerdcharoen and S. Arayachukeat, High loading fragrance encapsulation based on a polymer-blend: Preparation and release behavior, *Int. J. Pharm.*, 2010, **391**, 267–273.
- 51 P. D. Marcato, J. Caverzan, B. Rossi-Bergmann, E. F. Pinto, D. Machado, R. A. Silva, G. Z. Justo, C. V. Ferreira and N. Durán, Nanostructured polymer and lipid carriers for sunscreen. Biological effects and skin permeation, *J. Nanosci. Nanotechnol.*, 2011, **11**, 1880–1886.
- 52 J. Abdullah, F. M. Marsin, N. N. Ting, F. Ilyana, A. Razak, W. Aini and W. Ibrahim, Poly(methyl

methacrylate) -microencapsulated clove oil slow release formulation, *eProceedings Chem.*, 2017, 2, 267–273.

- 53 A. L. Tasker, J. P. Hitchcock, L. He, E. A. Baxter, S. Biggs and O. J. Cayre, The effect of surfactant chain length on the morphology of poly(methyl methacrylate) microcapsules for fragrance oil encapsulation, *J. Colloid Interface Sci.*, 2016, **484**, 10–16.
- 54 P. Teeka, A. Chaiyasat and P. Chaiyasat, Preparation of poly (methyl methacrylate) microcapsule with encapsulated jasmine oil, *Energy Procedia*, 2014, **56**, 181–186.
- 55 J. Kozlowska, W. Prus and N. Stachowiak, Microparticles based on natural and synthetic polymers for cosmetic applications, *Int. J. Biol. Macromol.*, 2019, **129**, 952–956.
- 56 A. Haddadi, R. Aboofazeli, M. Erfan and E. S. Farboud, Topical delivery of urea encapsulated in biodegradable PLGA microparticles: O/W and W/O creams, *J. Microencapsul.*, 2008, **25**, 379–386.
- 57 W. Sliwka, Microencapsulation, Angew. Chemie Inernational Ed., 1975, 14, 539–550.
- 58 M. H. Siess and C. Divies, Behaviour of Saccharomyces cerevisiae cells entrapped in a polyacrylamide gel and performing alcoholic fermentation, *Eur. J. Appl. Microbiol. Biotechnol.*, 1981, **12**, 10–15.
- 59 N. P. Shah and R. . Ravula, Microencapsulation of probiotic bacteria and their survival in frozen fermented dairy desserts, *Aust. J. dairy Technol.*, 2000, **55**, 139.
- 60 A. Racoti, E. Rusen, A. Diacon, A. Dinescu, M. Buleandra and I. Calinescu, Ginger essential oil encapsulation in PMMA microcapsules. I, *Mater. Plast.*, 2016, 53, 357–360.
- 61 S. Higgins, Y. L. Carroll, N. M. O'Brien and P. A. Morrissey, Use of microencapsulated fish oil as a means of increasing n-3 polyunsaturated fatty acid intake, *J. Hum. Nutr. Diet.*, 1999, **12**, 265–271.
- 62 L. Di Giorgio, P. R. Salgado and A. N. Mauri, Encapsulation of fish oil in soybean protein particles by emulsification and spray drying, *Food Hydrocoll.*, 2019, **87**, 891–901.
- 43 Y. Qian, X. Zhong, Y. Li and X. Qiu, Fabrication of uniform lignin colloidal spheres for developing natural broad-spectrum sunscreens with high sun protection factor, *Ind. Crops Prod.*, 2017, **101**, 54–60.
- 64 L. Souza and A. Al-Tabbaa, Microfluidic fabrication of microcapsules tailored for self-healing in cementitious materials, *Constr. Build. Mater.*, 2018, **184**, 713–722.
- 65 C. A. Busatto, M. E. Taverna, M. R. Lescano, C. Zalazar and D. A. Estenoz, Preparation and Characterization of Lignin Microparticles-in-Alginate Beads for Atrazine Controlled Release, *J. Polym. Environ.*, 2019, 27, 2831–2841.
- 66 M. Luther and C. Heuck, Ger 558890= USP 1864078, *In Chem. Abstr*, 1932, **26**, 4505.

- 67 Q. Wang, S. Fu and T. Yu, Emulsion polymerization, *Prog. Polym. Sci.*, 1994, **19**, 703–753.
- 68 I. A. M. Appelqvist, M. Golding, R. Vreeker and N. J. Zuidam, Emulsions as delivery systems in foods, Encapsulation Control. Release Technol. Food Syst. Second Ed., 2016, 129–172.
- 69 C. S. Chern, Emulsion polymerization mechanisms and kinetics, *Prog. Polym. Sci.*, 2006, **31**, 443–486.
- R. Arshady, Suspension, emulsion, and dispersion polymerization: A methodological survey, *Colloid Polym. Sci.*, 1992, 270, 717–732.
- 71 F. Salaün, Microencapsulation by Interf acial Polymerization, 2013.
- R. Arshady and A. Ledwith, Suspension polymerisation and its application to the preparation of polymer supports, *React. Polym. Ion Exch. Sorbents*, 1983, 1, 159–174.
- A. F. Cebollada, M. J. Schmidt, J. N. Farber, N. J. Capiati and E. M. Vallés, Suspension polymerization of vinyl chloride. I. Influence of viscosity of suspension medium on resin properties, *J. Appl. Polym. Sci.*, 1989, 37, 145–166.
- 74 O. H. Gonçalves, J. M. Asua, P. H. H. De Araújo and R. A. F. Machado, Synthesis of PS/PMMA coreshell structured particles by seeded suspension polymerization, *Macromolecules*, 2008, **41**, 6960–6964.
- 75 M. S. Islam, J. H. Yeum and A. K. Das, Synthesis of poly(vinyl acetate-methyl methacrylate) copolymer microspheres using suspension polymerization, *J. Colloid Interface Sci.*, 2012, **368**, 400–405.
- J. W. Vanderhoff, Mechanism of Emulsion Polymerization., J. Polym. Sci. Polym. Symp., 1985, 198, 161–198.
- 77 M. Pan, X. Shi, X. Li, H. Hu and L. Zhang, Morphology and properties of PVC/clay nanocomposites via in situ emulsion polymerization, *J. Appl. Polym. Sci.*, 2004, 94, 277–286.
- 78 X. Huang and W. Brittain, Synthesis and Characterization of PMMA Nanocomposites by Suspension and Emulsion Polymerization Xinyu, *Macromolecules*, 2001, 34, 3255–3260.
- 79 G. Odian, Principles of Polymerization Engineering., 2004.
- 80 V. Chaudhary and S. Sharma, Suspension polymerization technique: parameters affecting polymer properties and application in oxidation reactions, *J. Polym. Res.*, 2019, **26**, 1–12.
- 81 M. S. Islam, J. H. Yeum and A. K. Das, Synthesis of poly(vinyl acetate-methyl methacrylate) copolymer microspheres using suspension polymerization, *J. Colloid Interface Sci.*, 2012, **368**, 400–405.
- C. Yao, G. Lei, X. Gao and L. Li, Controllable preparation, rheology, and plugging property of microngrade polyacrylamide microspheres as a novel profile control and flooding agent, *J. Appl. Polym. Sci.*, 2013, 130, 1124–1130.

- 83 N. Ballard, M. Aguirre, A. Simula, J. R. Leiza, S. van Es and J. M. Asua, Nitroxide mediated suspension polymerization of methacrylic monomers, *Chem. Eng. J.*, 2017, **316**, 655–662.
- Y. A. Hussain, T. Liu and G. W. Roberts, Synthesis of cross-linked, partially neutralized poly(acrylic acid) by suspension polymerization in supercritical carbon dioxide, *Ind. Eng. Chem. Res.*, 2012, 51, 11401–11408.
- 85 J. G. J. Peters and J. A. H. . Olivier, *Trends in global CO2 and total greenhouse gas emissions*, 2020.
- T. Gu, Pretreatment of Lignocellulosic Biomass Using Supercritical Carbon Dioxide as a Green Solvent,
 2013.
- H. G. Bungenberg de Jong and H. R. Kruyt, Coacervation (partial miscibility in colloid systems), *Proc. K. Ned. Akad. Wet*, 1929, **32**, 849–856.
- A. D. McNaught and A. Wilkinson, *Compendium of chemical terminology. IUPAC recommendations*, Oxford (United Kingdom) Blackwell, 1997.
- 89 I. M. Martins, S. N. Rodrigues, F. Barreiro and A. E. Rodrigues, Microencapsulation of thyme oil by coacervation, J. Microencapsul., 2009, 26, 667–675.
- K. Zhang, H. Zhang, X. Hu, S. Bao and H. Huang, Synthesis and release studies of microalgal oil-containing microcapsules prepared by complex coacervation, *Colloids Surfaces B Biointerfaces*, 2012, 89, 61–66.
- 91 O. Siddiqui and H. Taylor, Physical factors affecting microencapsulation by simple coacervation of gelatin, *J. Pharm. Pharmacol.*, 1983, **35**, 70–73.
- 92 S. S. Deveci and G. Basal, Preparation of PCM microcapsules by complex coacervation of silk fibroin and chitosan, *Colloid Polym. Sci.*, 2009, **287**, 1455–1467.
- B. Mohanty and H. B. Bohidar, Systematic of alcohol-induced simple coacervation in aqueous gelatin solutions, *Biomacromolecules*, 2003, 4, 1080–1086.
- 94 X. L. Gu, X. Zhu, X. Z. Kong and Y. Tan, Comparisons of simple and complex coacervations for preparation of sprayable insect sex pheromone microcapsules and release control of the encapsulated pheromone molecule, *J. Microencapsul.*, 2010, 27, 355–364.
- 95 C. Yan and W. Zhang, *Coacervation Processes*, Elsevier Inc., 2014.
- K. Zhang, H. Zhang, X. Hu, S. Bao and H. Huang, Synthesis and release studies of microalgal oil-containing microcapsules prepared by complex coacervation, *Colloids Surfaces B Biointerfaces*, 2012, 89, 61–66.

- 97 C. J. F. Souza, E. E. Garcia Rojas, N. R. Melo, A. Gaspar and J. F. C. Lins, Complex coacervates obtained from interaction egg yolk lipoprotein and polysaccharides, *Food Hydrocoll.*, 2013, **30**, 375– 381.
- B. Ocak, G. Gülümser and E. Baloğlu, Microencapsulation of melaleuca alternifolia (tea tree) oil by using simple coacervation Method), *J. Essent. Oil Res.*, 2011, 23, 58–65.
- 99 S. Petrusic and V. Koncar, *Controlled release of active agents from microcapsules embedded in textile structures*, Elsevier Ltd, 2016.
- 100 R. Malviya, P. Shukla and P. Srivastava, Preparation, characterization and evaluation of chitosan-gum arabic coacervates as excipient in fast dissolving/disintegrating dosage form, *Fabad J. Pharm. Sci.*, 2009, **34**, 13–23.
- 101 R. Dai, G. Wu, W. Li, Q. Zhou, X. Li and H. Chen, Gelatin/carboxymethylcellulose/dioctyl sulfosuccinate sodium microcapsule by complex coacervation and its application for electrophoretic display, *Colloids Surfaces A Physicochem. Eng. Asp.*, 2010, **362**, 84–89.
- 102 O. Bayraktar, I. Erdogan, M. D. Köse and G. Kalmaz, Nanocarriers for Plant-Derived Natural Compounds, *Nanostructures Antimicrob. Ther. Nanostructures Ther. Med. Ser.*, 2017, 395–412.
- M. Cave, K. C. Falkner and C. McClain, *Occupational and Environmental Hepatotoxicity*, Elsevier Inc.,
 Sixth Edit., 2012.
- 104 S. H. Krishna, D. J. McClelland, Q. A. Rashke, J. A. Dumesic and G. W. Huber, Hydrogenation of levoglucosenone to renewable chemicals, *Green Chem.*, 2017, 19, 1278–1285.
- 105 H. Chograni, Y. Zaouali, C. Rajeb and M. Boussaid, Essential oil variation among natural populations of Lavandula multifida L. (lamiaceae), *Chem. Biodivers.*, 2010, 7, 933–942.
- 106 Z. J. Dong, S. Q. Xia, S. Hua, K. Hayat, X. M. Zhang and S. Y. Xu, Optimization of cross-linking parameters during production of transglutaminase-hardened spherical multinuclear microcapsules by complex coacervation, *Colloids Surfaces B Biointerfaces*, 2008, **63**, 41–47.
- 107 Z. Dong, Y. Ma, K. Hayat, C. Jia, S. Xia and X. Zhang, Morphology and release profile of microcapsules encapsulating peppermint oil by complex coacervation, J. Food Eng., 2011, 104, 455– 460.
- 108 A. S. Prata, M. H. A. Zanin, M. I. Ré and C. R. F. Grosso, Release properties of chemical and enzymatic crosslinked gelatin-gum Arabic microparticles containing a fluorescent probe plus vetiver essential oil, *Colloids Surfaces B Biointerfaces*, 2008, 67, 171–178.
- 109 Y. Senuma, C. Lowe, Y. Zweifel, J. G. Hilborn and I. Marison, Alginate hydrogel microspheres and microcapsules prepared by spinning disk atomization, *Biotechnol. Bioeng.*, 2000, **67**, 616–622.
- 110 V. Westergaard, Milk Powder Technology Evaporation and Spray Drying, 2011.
- 111 K. Masters, Spray Drying Handbook, 1st edn. London, U.K.: George Godwin Ltd., 1976.
- 112 M. Mishra, *Microencapsulation by Annular Jet Process*, 2015.
- 113 M. Dixit, A. G. Kini and P. K. Kulkarni, Preparation and characterization of microparticles of piroxicam by spray drying and spray chilling methods., *Res. Pharm. Sci.*, 2010, **5**, 89–97.
- B. Albertini, N. Passerini, M. Di Sabatino, B. Vitali, P. Brigidi and L. Rodriguez, Polymer-lipid based mucoadhesive microspheres prepared by spray-congealing for the vaginal delivery of econazole nitrate, *Eur. J. Pharm. Sci.*, 2009, **36**, 591–601.
- 115 Y. J. Fu, S. S. Shyu, F. H. Su and P. C. Yu, Development of biodegradable co-poly(D, L-lactic/glycolic acid) microspheres for the controlled release of 5-FU by the spray drying method, *Colloids Surfaces B Biointerfaces*, 2002, 25, 269–279.
- J. D. Oxley, Spray cooling and spray chilling for food ingredient and nutraceutical encapsulation,
 Elsevier Masson SAS., 2012.
- Y. Senuma, Generation of monodispersed polymer microspheres by spinning disk atomization, 1999, 207.
- 118 B. B. Fogler and R. V. Kleinschmidt, Spray Drying, Ind. Eng. Chem., 1938, 30, 1372–1384.
- 119 E. Teunou and D. Poncelet, Rotary disc atomisation for microencapsulation applications-prediction of the particle trajectories, *J. Food Eng.*, 2005, **71**, 345–353.
- B. Bittner, M. Morlock, H. Koll, G. Winter and T. Kissel, Recombinant human erythropoietin (rhEPO) loaded poly(lactide-co- glycolide) microspheres: Influence of the encapsulation technique and polymer purity on microsphere characteristics, *Eur. J. Pharm. Biopharm.*, 1998, 45, 295–305.
- 121 C. Anish, A. K. Upadhyay, D. Sehgal and A. K. Panda, Influences of process and formulation parameters on powder flow properties and immunogenicity of spray dried polymer particles entrapping recombinant pneumococcal surface protein A, *Int. J. Pharm.*, 2014, **466**, 198–210.
- 122 B. Tobar-Grande, R. Godoy, P. Bustos, C. von Plessing, E. Fattal, N. Tsapis, C. Olave and C. Gómez-Gaete, Development of biodegradable methylprednisolone microparticles for treatment of articular pathology using a spray-drying technique, *Int. J. Nanomedicine*, 2013, 8, 2065–2076.
- 123 A. Sosnik and K. P. Seremeta, Advantages and challenges of the spray-drying technology for the

production of pure drug particles and drug-loaded polymeric carriers, *Adv. Colloid Interface Sci.*, 2015, **223**, 40–54.

- R. Wisniewski, in 45th International Conference on Environmental Systems, Bellevue, Washington, 2015, pp. 1–9.
- 125 P. K. Okuro, F. Eustáquio de Matos and C. S. Favaro-Trindade, Technological challenges for spray chilling encapsulation of functional food ingredients, *Food Technol. Biotechnol.*, 2013, **51**, 171–182.
- M. G. Bordón, N. P. X. Alasino, Á. Villanueva-Lazo, C. Carrera-Sánchez, J. Pedroche-Jiménez, M. del C. Millán-Linares, P. D. Ribotta and M. L. Martínez, Scale-up and optimization of the spray drying conditions for the development of functional microparticles based on chia oil, *Food Bioprod. Process.*, 2021, **130**, 48–67.
- 127 F. Cheng, X. Zhou and Y. Liu, in E3S Web of Conferences, 2018, vol. 53, pp. 4–6.
- 128 Y. Senuma and J. G. Hilborn, High speed imaging of drop formation from low viscosity liquids and polymer melts in spinning disk atomization, *Polym. Eng. Sci.*, 2002, **42**, 969–982.
- M. Whelehan and I. W. Marison, Microencapsulation using vibrating technology, J. Microencapsul., 2011, 28, 669–688.
- 130 B. G. Amsden and M. F. A. Goosen, An examination of factors affecting the size, distribution and release characteristics of polymer microbeads made using electrostatics, *J. Control. Release*, 1997, 43, 183–196.
- 131 Y. He, Application of flow-focusing to the break-up of an emulsion jet for the production of matrixstructured microparticles, *Chem. Eng. Sci.*, 2008, **63**, 2500–2507.
- 132 A. Zvonar, J. Kristl, J. Kerč and P. A. Grabnar, High celecoxib-loaded nanoparticles prepared by a vibrating nozzle device, *J. Microencapsul.*, 2009, 26, 748–759.
- 133 U. Prüße, B. Fox, M. Kirchhoff, F. Bruske, J. Breford and K. D. Vorlop, The jet cutting method as a new immobilization technique, *Biotechnol. Tech.*, 1998, **12**, 105–108.
- 134 Y. Senuma, S. Franceschin, J. G. Hilborn, P. Tissières, I. Bisson and P. Frey, Bioresorbable microspheres by spinning disk atomization as injectable cell carrier: From preparation to in vitro evaluation, *Biomaterials*, 2000, 21, 1135–1144.
- 135 V. T. Tran, J. P. Benoît and M. C. Venier-Julienne, Why and how to prepare biodegradable, monodispersed, polymeric microparticles in the field of pharmacy?, *Int. J. Pharm.*, 2011, **407**, 1–11.
- 136 M. Whelehan and I. W. Marison, Microencapsulation by dripping and jet break up. Bioencapsulation

Research Group, 2011.

- 137 T. Brandau, Annular Jet-Based Processes, Elsevier Inc., 2014.
- 138 Elveflow.com, Microfluidics: A general overview of microfluidics.
- 139 X. Li, N. Visaveliya, L. Hafermann, G. A. Gross, A. Knauer and J. M. Köhler, Hierarchically structured particles for micro flow catalysis, *Chem. Eng. J.*, 2017, **326**, 1058–1065.
- 140 A. Igder, S. Pye, A. H. M. Al-Antaki, A. Keshavarz, C. L. Raston and A. Nosrati, Vortex fluidic mediated synthesis of polysulfone, *RSC Adv.*, 2020, **10**, 14761–14767.
- 141 M. Khodamoradi, S. R. Tafti, S. A. M. Shaegh, B. Aflatoonian, M. Azimzadeh and P. Khashayar, Recent microfluidic innovations for sperm sorting, *Chemosensors*, 2021, 9, 1–18.
- 142 V. V. Ryzhkov, A. V. Zverev, V. V. Echeistov, M. Andronic, I. A. Ryzhikov, I. A. Budashov, A. V. Eremenko, I. N. Kurochkin and I. A. Rodionov, Cyclic on-chip bacteria separation and preconcentration, *Sci. Rep.*, 2020, **10**, 1–12.
- A. Estévez-Torres and D. Baigl, DNA compaction: Fundamentals and applications, *Soft Matter*, 2011, 7, 6746–6756.
- 144 S. Iftikhar, Fungus identification and research using microfluidics, 2020.
- B. Yu, R. J. Lee and L. J. Lee, Microfluidic Methods for Production of Liposomes, *Methods Enzymol.*, 2009, 465, 129–141.
- 146 D. Boskovic and S. Loebbecke, Synthesis of polymer particles and capsules employing microfluidic techniques, *Nanotechnol. Rev.*, 2013, **3**, 27–38.
- A. J. DeMello, Control and detection of chemical reactions in microfluidic systems, *Nature*, 2006, 442, 394–402.
- 148 P. C. Lewis, R. R. Graham, Z. Nie, S. Xu, M. Seo and E. Kumacheva, Continuous synthesis of copolymer particles in microfluidic reactors, *Macromolecules*, 2005, **38**, 4536–4538.
- S. Xu, Z. Nie, M. Seo, P. Lewis, E. Kumacheva, H. A. Stone, P. Garstecki, D. B. Weibel, I. Gitlin and G.
 M. Whitesides, Generation of Monodisperse Particles by Using Microfluidics: Control over Size, Shape, and Composition, *Angew. Chemie*, 2005, **117**, 734–738.
- 150 B. Yang, Y. Lu and G. Luo, Controllable preparation of polyacrylamide hydrogel microspheres in a coaxial microfluidic device, *Ind. Eng. Chem. Res.*, 2012, **51**, 9016–9022.
- 151 D. D. Harrier, P. J. A. Kenis and D. Guironnet, Ring-Opening Polymerization of Cyclic Esters in an Aqueous Dispersion, *Macromolecules*, 2020, 53, 7767–7773.

- 152 Y. Zhang, R. W. Cattrall and S. D. Kolev, Fast and environmentally friendly microfluidic technique for the fabrication of polymer microspheres, *Langmuir*, 2017, **33**, 14691–14698.
- 153 C. A. Busatto, M. E. Taverna, M. R. Lescano, C. Zalazar and D. A. Estenoz, Preparation and Characterization of Lignin Microparticles-in-Alginate Beads for Atrazine Controlled Release, *J. Polym. Environ.*, 2019, 27, 2831–2841.
- 154 S. Dubinsky, H. Zhang, Z. Nie, I. Gourevich, D. Voicu, M. Deetz and E. Kumacheva, Microfluidic synthesis of macroporous copolymer particles, *Macromolecules*, 2008, **41**, 3555–3561.
- 155 M. Seo, Z. Nie, S. Xu, M. Mok, P. C. Lewis, R. Graham and E. Kumacheva, Continuous microfluidic reactors for polymer particles, *Langmuir*, 2005, **21**, 11614–11622.
- 156 P. W. Chen, R. M. Erb and A. R. Studart, Designer polymer-based microcapsules made using microfluidics, *Langmuir*, 2012, 28, 144–152.
- 157 Z. Nie, S. Xu, M. Seo, P. C. Lewis and E. Kumacheva, Polymer particles with various shapes and morphologies produced in continuous microfluidic reactors, *J. Am. Chem. Soc.*, 2005, **127**, 8058–8063.
- S. Xu and T. Nisisako, Polymer Capsules with Tunable Shell Thickness Synthesized via Janus-to-core shell Transition of Biphasic Droplets Produced in a Microfluidic Flow-Focusing Device, *Sci. Rep.*, 2020, 10, 1–10.
- 159 D. Zhao, S. Yu, B. Sun, S. Gao, S. Guo and K. Zhao, Biomedical applications of chitosan and its derivative nanoparticles, *Polymers (Basel).*, 2018, **10**, 462.
- 160 V. Pace, 2-Methyltetrahydrofuran: A versatile eco-friendly alternative to THF in Organometallic chemistry, *Aust. J. Chem.*, 2012, **65**, 301–302.
- 161 J. H. Xu, H. Zhao, W. J. Lan and G. S. Luo, A novel microfl uidic approach for monodispersed chitosan microspheres with controllable structures, *Adv. Healthc. Mater.*, 2012, **1**, 106–111.
- 162 M. Abkarian, E. Loiseau and G. Massiera, Continuous droplet interface crossing encapsulation (cDICE) for high throughput monodisperse vesicle design, *Soft Matter*, 2011, 7, 4610–4614.
- 163 H. El Itawi, B. Lalanne, G. Massiera, N. Le Sauze and O. Masbernat, Numerical simulation of the crossing of a liquid-liquid interface by a droplet, *Phys. Rev. Fluids*, 2020, **5**, 093601.
- 164 R. Hoover, T. Hughes, H. J. Chung and Q. Liu, Composition, molecular structure, properties, and modification of pulse starches: A review, *Food Res. Int.*, 2010, **43**, 399–413.
- 165 B. R. Böger, L. B. Acre, M. C. Viegas, L. E. Kurozawa and M. T. Benassi, Roasted coffee oil microencapsulation by spray drying and complex coacervation techniques: Characteristics of the

particles and sensory effect, Innov. Food Sci. Emerg. Technol., 2021, 72, 102739.

- 166 Y. F. Wang, J. X. Jia, Y. Q. Tian, X. Shu, X. J. Ren, Y. Guan and Z. Y. Yan, Antifungal effects of clove oil microcapsule on meat products, *LWT Food Sci. Technol.*, 2018, **89**, 604–609.
- 167 K. L. Baltrusch, M. D. Torres, H. Domínguez and N. Flórez-Fernández, Spray-drying microencapsulation of tea extracts using green starch, alginate or carrageenan as carrier materials, *Int. J. Biol. Macromol.*, 2022, 203, 417–429.
- 168 J. Ju, Y. Xie, Y. Guo, Y. Cheng, H. Qian and W. Yao, Application of starch microcapsules containing essential oil in food preservation, *Crit. Rev. Food Sci. Nutr.*, 2020, **60**, 2825–2836.
- 169 L. Ribba, N. L. Garcia, N. D'Accorso and S. Goyanes, *Disadvantages of Starch-Based Materials, Feasible Alternatives in Order to Overcome These Limitations*, Elsevier Inc., 2017.
- 170 P. Liu, L. Yu, X. Wang, D. Li, L. Chen and X. Li, Glass transition temperature of starches with different amylose/amylopectin ratios, *J. Cereal Sci.*, 2010, **51**, 388–391.
- A. Cano, E. Fortunati, M. Cháfer, J. M. Kenny, A. Chiralt and C. González-Martínez, Properties and ageing behaviour of pea starch films as affected by blend with poly(vinyl alcohol), *Food Hydrocoll.*, 2015, 48, 84–93.
- A. Cano, E. Fortunati, M. Cháfer, J. M. Kenny, A. Chiralt and C. González-Martínez, Properties and ageing behaviour of pea starch films as affected by blend with poly(vinyl alcohol), *Food Hydrocoll.*, 2015, 48, 84–93.
- 173 M. S. B. Reddy, D. Ponnamma, R. Choudhary and K. K. Sadasivuni, A comparative review of natural and synthetic biopolymer composite scaffolds, *Polymers (Basel).*, 2021, **13**, 1105.
- 174 M. R. Roslan, N. F. M. Nasir, E. M. Cheng and N. A. M. Amin, Tissue engineering scaffold based on starch: A review, *Int. Conf. Electr. Electron. Optim. Tech. ICEEOT 2016*, 2016, 1857–1860.
- 175 A. Kujur, S. Kiran, N. K. Dubey and B. Prakash, Microencapsulation of Gaultheria procumbens essential oil using chitosan-cinnamic acid microgel: Improvement of antimicrobial activity, stability and mode of action, *LWT - Food Sci. Technol.*, 2017, 86, 132–138.
- 176 Y. Li, C. Wu, T. Wu, L. Wang, S. Chen, T. Ding and Y. Hu, Preparation and characterization of citrus essential oils loaded in chitosan microcapsules by using different emulsifiers, *J. Food Eng.*, 2018, 217, 108–114.
- 177 E. Szymańska and K. Winnicka, Stability of chitosan A challenge for pharmaceutical and biomedical applications, *Mar. Drugs*, 2015, **13**, 1819–1846.

- F. Croisier and C. Jérôme, Chitosan-based biomaterials for tissue engineering, *Eur. Polym. J.*, 2013, 49, 780–792.
- 179 M. Mucha, S. Ludwiczak and M. Kawinska, Kinetics of water sorption by chitosan and its blends with poly(vinyl alcohol), *Carbohydr. Polym.*, 2005, **62**, 42–49.
- 180 H. K. No and W. Prinyawiwatkul, Stability of chitosan powder during long-term storage at room temperature m, *J. Agric. Food Chem.*, 2009, **57**, 8434–8438.
- J. M. Viljoen, J. H. Steenekamp, A. F. Marais and A. F. Kotzé, Effect of moisture content, temperature and exposure time on the physical stability of chitosan powder and tablets, *Drug Dev. Ind. Pharm.*, 2014, 40, 730–742.
- 182 L. Y. Lim, E. Khor and C. E. Ling, Effects of dry heat and saturated steam on the physical properties of chitosan, J. Biomed. Mater. Res., 1999, 48, 111–116.
- 183 M. Elmowafy, K. Shalaby, A. Salama, G. M. Soliman, N. K. Alruwaili, E. M. Mostafa, E. F. Mohammed, A. E. G. A. Moustafa and A. Zafar, Soy isoflavone-loaded alginate microspheres in thermosensitive gel base: attempts to improve wound-healing efficacy, *J. Pharm. Pharmacol.*, 2019, **71**, 774–787.
- 184 K. Bowey, B. E. Swift, L. E. Flynn and R. J. Neufeld, Characterization of biologically active insulinloaded alginate microparticles prepared by spray drying, *Drug Dev. Ind. Pharm.*, 2013, **39**, 457–465.
- 185 R. G. Puscaselu, A. Lobiuc, M. Dimian and M. Covasa, Alginate: From food industry to biomedical applications and management of metabolic disorders, *Polymers (Basel).*, 2020, **12**, 1–30.
- 186 S. Mao, T. Zhang, W. Sun and X. Ren, The depolymerization of sodium alginate by oxidative degradation, *Pharm. Dev. Technol.*, 2012, **17**, 763–769.
- 187 J. J. Chuang, Y. Y. Huang, S. H. Lo, T. F. Hsu, W. Y. Huang, S. L. Huang and Y. S. Lin, Effects of pH on the Shape of Alginate Particles and Its Release Behavior, *Int. J. Polym. Sci.*, 2017.
- 188 K. Chen, S. Wang, Y. Qi, H. Guo, Y. Guo and H. Li, State-of-the-Art: Applications and Industrialization of Lignin Micro/Nano Particles, *ChemSusChem*, 2021, 14, 1284–1294.
- 189 M. Tortora, F. Cavalieri, P. Mosesso, F. Ciaffardini, F. Melone and C. Crestini, Ultrasound driven assembly of lignin into microcapsules for storage and delivery of hydrophobic molecules, *Biomacromolecules*, 2014, 15, 1634–1643.
- 190 M. C. S. Aguiar, M. F. das Graças Fernandes da Silva, J. B. Fernandes and M. R. Forim, Evaluation of the microencapsulation of orange essential oil in biopolymers by using a spray-drying process, *Sci. Rep.*,

2020, **10**, 1–11.

- 191 M. Márquez-Gómez, T. Galicia-García, R. Márquez-Meléndez, M. Ruiz-Gutiérrez and A. Quintero-Ramos, Spray-dried microencapsulation of orange essential oil using modified rice starch as wall material, J. Food Process. Preserv., 2018, 42, e13428.
- 192 Y. Qian, X. Zhong, Y. Li and X. Qiu, Fabrication of uniform lignin colloidal spheres for developing natural broad-spectrum sunscreens with high sun protection factor, *Ind. Crops Prod.*, 2017, **101**, 54–60.
- M. Ago, S. Huan, M. Borghei, J. Raula, E. I. Kauppinen and O. J. Rojas, High-throughput synthesis of lignin particles (~30 nm to ~2 μm) via aerosol flow reactor: Size fractionation and utilization in pickering emulsions, ACS Appl. Mater. Interfaces, 2016, 8, 23302–23310.
- 194 Z. Zhu, S. Fu and L. A. Lucia, Tuning the Morphology of Microparticles from Spray Drying of Cellulose Nanocrystal Suspensions by Hydrophobic Lignin, ACS Sustain. Chem. Eng., 2019, 7, 5376–5384.
- H. Wang, Y. Pu, A. Ragauskas and B. Yang, From lignin to valuable products-strategies, challenges, and prospects, *Bioresour. Technol.*, 2019, **271**, 449–461.
- A. Vishtal and A. Kraslawski, Challenges in industrial applications of technical lignins, *BioResources*, 2011, 6, 3547–3568.
- J. Payne, P. McKeown and M. D. Jones, A circular economy approach to plastic waste, *Polym. Degrad. Stab.*, 2019, **165**, 170–181.
- 198 M. Brzeziński, M. Socka and B. Kost, Microfluidics for producing polylactide nanoparticles and microparticles and their drug delivery application, *Polym. Int.*, 2019, **68**, 997–1014.
- 199 G. T. Vladisavljević, W. J. Duncanson, H. C. Shum and D. A. Weitz, Emulsion templating of poly(lactic acid) particles: Droplet formation behavior, *Langmuir*, 2012, 28, 12948–12954.
- 200 D. Lensen, K. Van Breukelen, D. M. Vriezema and J. C. M. Van Hest, Preparation of biodegradable liquid core PLLA microcapsules and hollow PLLA microcapsules using microfluidics, *Macromol. Biosci.*, 2010, **10**, 475–480.
- 201 P. VanWouwe, M. Dusselier, E. Vanleeuw and B. Sels, Lactide Synthesis and Chirality Control for Polylactic acid Production, *ChemSusChem*, 2016, 9, 907–921.
- J. Payne, P. McKeown and M. D. Jones, A circular economy approach to plastic waste, *Polym. Degrad. Stab.*, 2019, 165, 170–181.
- 203 Y. Cheng, S. Deng, P. Chen and R. Ruan, Polylactic acid (PLA) synthesis and modifications: A review, *Front. Chem. China*, 2009, 4, 259–264.

- J. Payne and M. D. Jones, The Chemical Recycling of Polyesters for a Circular Plastics Economy:Challenges and Emerging Opportunities, *ChemSusChem*, 2021, 14, 4041–4070.
- M. Nazareth, M. R. C. Marques, M. C. A. Leite and Í. B. Castro, Commercial plastics claiming biodegradable status: Is this also accurate for marine environments?, *J. Hazard. Mater.*, 2019, 366, 714–722.
- 206 B. Tyler, D. Gullotti, A. Mangraviti, T. Utsuki and H. Brem, Polylactic acid (PLA) controlled delivery carriers for biomedical applications, *Adv. Drug Deliv. Rev.*, 2016, **107**, 163–175.
- 207 E. Espino-Pérez, J. Bras, G. Almeida, C. Plessis, N. Belgacem, P. Perré and S. Domenek, Designed cellulose nanocrystal surface properties for improving barrier properties in polylactide nanocomposites, *Carbohydr. Polym.*, 2018, **183**, 267–277.
- 208 M. Hirenkumar and S. Steven, Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier, *Polymers (Basel).*, 2012, **3**, 1–19.
- 209 R. H. Ansary, M. B. Awang and M. M. Rahman, Biodegradable poly(D,L-lactic-co-glycolic acid)-based micro/nanoparticles for sustained release of protein drugs - A review, *Trop. J. Pharm. Res.*, 2014, 13, 1179–1190.
- 210 D. J. Hines and D. L. Kaplan, Poly(lactic-co-glycolic) acid-controlled-release systems: Experimental and modeling insights, *Crit. Rev. Ther. Drug Carrier Syst.*, 2013, **30**, 257–276.
- M. van de Weert, W. E. Hennink and W. Jiskoot, Protein instability in PLGA MPs, *Pharm. Res.*, 2000, 17, 1159–1167.
- 212 A. Taluja and Y. H. Bae, Role of a novel multifunctional excipient poly(ethylene glycol)-blockoligo(vinyl sulfadimethoxine) in controlled release of lysozyme from PLGA microspheres, *Int. J. Pharm.*, 2008, **358**, 50–59.
- T. Y. Lim, C. K. Poh and W. Wang, Poly (lactic-co-glycolic acid) as a controlled release delivery device,
 J. Mater. Sci. Mater. Med., 2009, 20, 1669–1675.
- 214 F. Pena-Pereira, A. Kloskowski and J. Namieśnik, Perspectives on the replacement of harmful organic solvents in analytical methodologies: A framework toward the implementation of a generation of ecofriendly alternatives, *Green Chem.*, 2015, **17**, 3687–3705.
- D. Prat, J. Hayler and A. Wells, A survey of solvent selection guides, *Green Chem.*, 2014, 16, 4546–4551.
- 216 C. Capello, U. Fischer and K. Hungerbühler, What is a green solvent? A comprehensive framework for

the environmental assessment of solvents, Green Chem., 2007, 9, 927-93.

- 217 K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation, *Green Chem.*, 2008, **10**, 31–36.
- 218 L. J. Diorazio, D. R. J. Hose and N. K. Adlington, Toward a More Holistic Framework for Solvent Selection, Org. Process Res. Dev., 2016, 20, 760–773.
- 219 P. Isnard, E. Guntrum, T. Senac and P. Cruciani, Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes, *Org. Lett.*, 2013, **17**, 1517–1525.
- R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, Expanding GSK's solvent selection guide embedding sustainability into solvent selection starting at medicinal chemistry, *Green Chem.*, 2011, 13, 854–862.
- 221 C. S. Slater and M. Savelski, A method to characterize the greenness of solvents used in pharmaceutical manufacture, J. Environ. Sci. Heal. - Part A Toxic/Hazardous Subst. Environ. Eng., 2007, 42, 1595– 1605.
- 222 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2015, **18**, 288–296.
- 223 S. Fadlallah, L. M. M. Mouterde, G. Garnier, K. Saito and F. Allais, Cellulose-Derived Levoglucosenone, a Great Versatile Chemical Platform for the Production of Renewable Monomers and Polymers, ACS Symp. Ser., 2020, 1373, 77–97.
- Y. Baimark, P. Srihanam, Y. Srisuwan and P. Phinyocheep, Preparation of Porous Silk Fibroin Microparticles by a Water-in-Oil Emulsification-Diffusion Method, J. Appl. Polym. Sci., 2010, 118, 1127–1133.
- 225 N. Bolourtchian, K. Karimi and R. Aboofazeli, Preparation and characterization of ibuprofen microspheres, J. Microencapsul., 2005, 22, 529–538.
- 226 S. Kikuchi, S. Yoshida, S. Kanehashi, G. H. Ma and K. Ogino, Fabrication of core-shell, janus, dumbbell, snowman-like and confetti-like structured microspheres of blends of poly(4-butyl triphenylamine) and poly(methyl methacrylate) by solvent evaporation method, *J. Fiber Sci. Technol.*, 2021, **75**, 22–28.
- A. M. Deliormanlı and A. C. Yenice, Preparation of hollow pcl microspheres by o/w single emulsionsolvent evaporation method in the presence of graphene nanopowders, *Express Polym. Lett.*, 2021, **15**,

641-653.

- 228 H. J. Kuenen, H. J. Mengers, A. G. J. van der Ham and A. A. Kiss, *Novel Process for Conversion of CO2 to Dimethyl Carbonate using Catalytic Membrane Reactors*, Elsevier Masson SAS, 2016, vol. 38.
- 229 A. Otte, F. Sharifi and K. Park, Interfacial tension effects on the properties of PLGA microparticles, *Colloids Surfaces B Biointerfaces*, 2020, **196**, 111300.
- F. T. Meng, G. H. Ma, W. Qiu and Z. G. Su, W/O/W double emulsion technique using ethyl acetate as organic solvent: Effects of its diffusion rate on the characteristics of microparticles, *J. Control. Release*, 2003, 91, 407–416.
- 231 Z. Yang, H. Peng, W. Wang and T. Liu, Crystallization behavior of poly(ε-caprolactone)/layered double hydroxide nanocomposites, J. Appl. Polym. Sci., 2010, 116, 2658–2667.
- 232 L. Liu, J. P. Yang, X. J. Ju, R. Xie, L. Yang, B. Liang and L. Y. Chu, Microfluidic preparation of monodisperse ethyl cellulose hollow microcapsules with non-toxic solvent, *J. Colloid Interface Sci.*, 2009, **336**, 100–106.
- 233 M. Jafari-Nodoushan, J. Barzin and H. Mobedi, Size and morphology controlling of PLGA microparticles produced by electro hydrodynamic atomization, *Polym. Adv. Technol.*, 2015, 26, 502–513.
- F. J. Ruiz, S. Rubio and D. Pérez-Bendito, Water-induced coacervation of alkyl carboxylic acid reverse micelles: Phenomenon description and potential for the extraction of organic compounds, *Anal. Chem.*, 2007, **79**, 7473–7484.
- V. Pace, P. Hoyos, L. Castoldi, P. Domínguez De María and A. R. Alcántara, 2-Methyltetrahydrofuran (2-MeTHF): A biomass-derived solvent with broad application in organic chemistry, *ChemSusChem*, 2012, 5, 1369–1379.
- X. Wang, Y. Hu, L. Song, H. Yang, W. Xing and H. Lu, In situ polymerization of graphene nanosheets and polyurethane with enhanced mechanical and thermal properties, *J. Mater. Chem.*, 2011, 21, 4222–4227.
- K. H. Kim, J. K. Park, S. H. Im and B. J. Park, Waterproof Light-Emitting Metal Halide Perovskite–
 Polymer Composite Microparticles Prepared via Microfluidic Device, *Part. Part. Syst. Charact.*, 2021,
 38, 2100006.
- A. Duval and L. Avérous, Dihydrolevoglucosenone (CyreneTM) as a versatile biobased solvent for lignin fractionation, processing, and chemistry, *Green Chem.*, 2022, **24**, 338–349.

- K. Dewettinck and A. Huyghebaert, Fluidized-bed-coating-in-food-technology, *Trends Food Sci. Technol.*, 1999, **10**, 163–168.
- 240 C. Frey, Fluid Bed Coating-Based Microencapsulation, Elsevier Inc., 2014.
- 241 P. Pandey, R. Turton, N. Joshi, E. Hammerman and J. Ergun, Scale-up of pan-coating process, *AAPS PharmSciTech*, 2006, **7**, E1–E8.