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Microwave-assisted polymer synthesis (MAPS) as a tool in biomaterials science: How new and how powerful

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ABSTRACT

Lack of reproducibility, difficult and expensive scale-up and standarization of synthetic processes are the main hurdles towards the industrial production of raw synthetic and semi-synthetic polymers for (bio)pharmaceutical applications. Time- and energy-consuming synthetic pathways that usually involve the use of volatile, flammable or toxic organic solvents are apparently cost-viable and environment-friendly for the synthesis at a laboratory scale. However, they are often not viable in industrial settings especially due to the impact they have on the product cost and the deleterious effect on the environment. This has presented hurdles to the incorporation of many new biomaterials displaying novel structural features into clinics. Nevertheless, owing to unique advantages such as shorter reaction times, higher yields, limited generation of by-products and relatively easy scale-up without detrimental effects, microwave-assisted organic synthesis has become an appealing synthetic tool. Regardless of these features, the use of microwave radiation in biomaterials science has been comparatively scarce. A growing interest in the basic aspects of the synthesis of either ceramic and polymeric biomaterials has been apparent during the last decade.

Abbreviations: 4-NPBC, *bis*-(4-nitrophenyl)carbonate; AFM, atomic force microscopy; AIST, National Institute of Advanced Industrial Science and Technology of Japan; BMA, butylmethacrylate; CL, ε-caprolactone; CROP, cationic ring opening polymerization; DMF, dimethylformamide; DMSO, dimethylsulfoxide; EHOx, 2-(3-ethylheptyl)-2-oxazoline; EMEA, European Medicines Agency; EtOx, poly(2-ethyl-2-oxazoline); FDA, US Food and Drug Administration; Fmoc, 9-fluorenylmethyloxycarbonyl; GA, glycolide; GPC, gel permeation chromatography; LA, lactide; MALDI-MS, matrix-assisted laser desorption/ionization mass spectrometry; MALDI-TOF, matrix-assisted laser desorption/ionization mass spectrometry with time-of-flight detector; MAOS, microwave-assisted organic synthesis; MAPS, microwave-assisted polymer synthesis; MMA, methylmethacrylate; MPEG–PLA, poly(ethylene glycol) monomethylether–poly(lactic acid) diblock; MPs, microparticles; MWs, microwaves; NMP, N-methylpyrrolidone; NPs, nanoparticles; PAA, polyacrylamide; PAA, poly(acrylic acid); PACs, poly(alkyl carbonate)s; PAN, polyacrylonitrile; PAsp, polyaspartic acid; PBMA, poly(butylmethacrylate); PCL, poly(ε-caprolactone); PDMS, polydimethylsiloxane; PEG, poly(ethylene glycol); PEGDMA, poly(ethylene glycol) dimethacrylate; PEG–PCL–PEG, poly(ε-caprolactone)–poly(ethylene glycol)–poly(ε-caprolactone) triblock; PEO, poly(ethylene oxide); PEO–PPO, poly(ethylene oxide)–poly(propylene oxide) block copolymers; PGA, poly(glycolic acid); PGlut, polyglutamic acid; PHEA, α,β-poly-(N-2-hydroxyethyl)-D,L-aspartamide; PHEMA, poly(2-hydroxyethyl methacrylate); PLA, poly(lactic acid); PLA–PEG–PLA, poly(lactic acid)–poly(ethylene glycol)–poly(lactic acid) triblock; PMAA, poly(methacrylic acid); PNIPAM, poly(N-isopropylacrylamide); PMMA, poly(methylmethacrylate); PNIPMAM, poly(*N*-isopropylmethacrylamide); POs, poly(2-oxazoline)s; PS, polystyrene; PTMC, polytrimethylenecarbonate; PTMC–PEG–PTMC, polytrimethylenecarbonate–poly(ethylene glycol)–polytrimethylenecarbonate triblocks; *p*-TsOH, *p*-toluene sulfonic acid; PUs, polyurethanes; PVP, polyvinylpyrrolidone; RAFT, reversible addition-fragmentation chain transfer polymerization; ROIP, ring opening insertion polymerization; ROP, ring opening polymerization; SiC, silicon carbide; SPPS, MW-supported solid phase polypeptide synthesis; SSA, solid super-acid; tan δ, loss tangent; TMC, trimethylenecarbonate; ε′, real part of the complex dielectric relative permittivity; ε″, imaginary part of the complex dielectric relative permittivity.

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This article reviews the most recent and prominent applications of MW as a versatile tool to synthesize and process organic and inorganic polymeric biomaterials, and discusses the unmet goals and the perspectives for a technology that probably has the potential to make biomaterials more accessible pharmaceutical excipients and the products that involve them more affordable to patients.

Contents

1. Introduction and scope

Lack of reproducibility, difficult and expensive scale-up and standarization of synthetic processes are the main hurdles towards the industrial production of raw synthetic and semi-synthetic polymers for (bio)pharmaceutical applications [1]. Time- and energy-consuming synthetic pathways that usually involve the use of volatile, flammable or toxic organic solvents are apparently cost-viable and environment-friendly for the synthesis at a laboratory scale. However, they are often not viable in industrial settings especially due to the impact they have on the product cost and the deleterious effect on the environment. This has presented hurdles to the incorporation of new biomaterials displaying novel structural features into clinics.

Green chemistry (also called sustainable chemistry) has emerged as a new philosophy that aims to minimize (i) the use of non-renewable resources and organic solvents, (ii) the generation of toxic secondary products and (iii) the consumption of energy and the emission of gases [2,3]. The first goal could be achieved by facilitating reactions under bulk conditions, while the latter by reducing substantially the reaction times.

Microwave-assisted organic synthesis (MAOS), first reported in the late 1980s [4,5], relies on the application of microwave (MW) irradiation as the energy source for organic reactions; MWs comprise electromagnetic radiation with a frequency between 0.3 and 300 GHz. To avoid interference with telecommunications and radars, MW frequency for domestic and synthetic purposes usually ranges between 2 and 8 GHz; e.g., most home-hold ovens operate at 2.45 GHz. Owing to a number of unique advantages such as shorter reaction times, higher yields, limited generation of by-products and the relatively easy scale-up without detrimental effects, this technology has steadily become an appealing synthetic tool [6].

The microwave heating process, the high temperatures attained and the ability to work under high pressure conditions for relatively short times make reactions faster than under conventional thermal conditions, and limit the ocurrence of slower side reactions [6]. Thus, greater yields are usually obtained. The ability to reduce reaction times from days and hours to minutes and seconds has motivated research areas such as combinatorial chemistry [7,8] and drug discovery [9,10]; these disciplines often rely on the generation of large libraries of compounds. Thus, MW-assisted synthesis has enhanced and diversified the capabilities of the synthetic chemist, since it enables faster and cleaner reactions and more pure products [6]; the longer the reaction time, the greater the amount of secondary products produced. Also, when one of the reactants is liquid, it can act as a solvent, and absorb MW sufficiently to homogenously heat the system, so that reactions can be conducted under solvent-free conditions [6,11]. Table 1

Table 1
Main differences between conventional thermal heating and MW heating.

Property	Conventional thermal heating	MW heating
Heating rate	Slow	Fast
Maximum reaction temperature	Limited by the boiling point of the solvent (usually under reflux)	Overheating above the boiling point of the solvent of up to (i) 100 °C in closed-vessel reactions and (ii) 40 °C in open-vessel reactions
Reaction time	Long time	Short time
Pressure	High pressure reactions are more dangerous due to longer reaction times	High pressure reactions are less dangerous
Homogeinity of heating	Low; "wall effect" cannot be prevented	High; no "wall effect"
Yield	Low	High
Amount of secondary products	High	Low
Solvent conditions	Difficult to conduct without solvent	Easy to conduct under solvent-free conditions
Reproducibility[a]	Low	High

[a] A higher reproducility of MW reactions is commonly claimed, though this phenomenon depends on the sophistication of the employed equipment, as domestic MW ovens lack optimal reproducibility.

summarizes the most relevant differences between conventional thermal heating and MW heating that make the latter an especially attractive tool in biomaterials synthesis; the differences need to be understood as general and they should be evaluated appropriately in each specific case.

Due to the very different temperature profiles attained in reaction containers heated by microwaves and those heated via an external bath, some experts have noted that care must be taken to make valid comparisons between these two arrangements [6]. The significantly greater heating rates of MW led to the rationalization of the MW effect in terms of thermal/kinetic effects [6]. However, there may exist other effects defined as "specific microwave effects" that stem from this unique dielectric heating mechanism and that are still "thermal" in nature. These effects are (i) superheating of solvents at normal pressure, (ii) selective heating of strongly microwave-absorbing heterogeneous catalysts or reagents dispersed in a less absorbing reaction medium, (iii) the formation of "molecular radiators" by direct coupling of the microwaves to specific reagents in homogeneous solution (microscopic hotspots) and (iv) the elimination of wall effects. On the other hand, the possibility of non-thermal effects related to changes of the activation energy in the Arrhenius equation has been also proposed and it is a matter of scientific debate [6].

Most research groups initially employed multimode domestic MW ovens. Their main advantage is their affordability. In that context, they are a valuable tool for preliminary explorative work. On the other hand, they work under constant power output and the power level in the oven is regulated by means of "on–off" cycles (see below). Moreover, the homogeinity of the irradiation inside the oven cavity (applicator) is small and it is usually concentrated in specific areas. The main reason is that microwaves are launched into the rectangular metal box and undergo multiple reflections with the walls [12]. Thus, the field distribution within the load depends not only on dielectric permeability or dielectric loss, but also on the size and location of the load within the applicator. To improve this aspect, a rotating reflector can be introduced. A crucial disadvantage of these ovens for scientific purposes is that since the spatial distribution of field strength is unknown, the results cannot be generalized and a scale-up stage may not be fully reliable. Professional microwave ovens commercially available for a decade enable controlled and reproducible reaction conditions, optimal for relatively easy scale-up and technology transfer [6]; syntheses can be scaled-up quite reliably from a few milligrams to several hundred grams without modifying the reaction conditions. On the other hand, since this equipment has been designed for use in the laboratory, it often limits the scalability of the process and demands batch reactions or the design of semi-continuous and continuous processes [13–15]. For example, Diaz-Ortiz et al. reported that heating of different parallel arrays in domestic ovens offers the possibility to perform multiple solvent-free reactions in one irradiation experiment, blending the advantages of MW heating technology and parallel chemistry. A typical solvent-free reaction described in a domestic oven was reproduced in monomode reactor, scaled-up in a controlled multimode oven and reproduced in parallel, using a multiwell plate to assure identical conditions for each individual reaction. This result opens new possibilities in reproducibility, scalability and combinatorial chemistry and permits to take advantage of many synthetic procedures described in domestic ovens [16]. Conversely, the relatively high price of these ovens when compared to domestic ones still appears to be a main constraint, especially for less affluent research groups.

The capacity of a certain material (e.g., solvents) to absorb the electromagnetic microwave irradiation of a given frequency and convert it into heat is intimately associated with its dielectric properties and these factors can be considered using the loss tangent ($\tan\delta$). This parameter is calculated by taking the ratio between the imaginary part, ε'', of the complex dielectric relative permittivity ε^* and the real part, ε', of the complex dielectric relative permittivity and it depends on the temperature and the irradiation frequency. The loss factor ε'' describes the efficiency of the conversion of the electromagnetic energy into heat, while ε' is a measure of the ability of a dielectric material to store electrical potential energy under the influence of an electric field. Based on the loss tangent, compounds are classified into three groups: high ($\tan\delta > 0.5$), medium ($0.1 < \tan\delta < 0.5$) and low microwave absorbing ($\tan\delta < 0.1$) materials. It is noticeable that solvents that show similar solubilization capability and boiling point can be distinguished based on a different interaction with microwave irradiation; e.g., dimethylsul-

foxide (DMSO) and *N*,*N*-dimethylformamide (DMF) display relatively high boiling point though very different tan δ values being 0.825 and 0.165, respectively [6]. Thus, this property can be capitalized to control the maximum temperature attained during the reaction by using a solvent that absorbs MWs less efficiently than the reactants and dissipates the heat generated in the reaction mixture. On the other hand, it should be noticed that since tan δ is calculated as the $\varepsilon''/\varepsilon'$ ratio, materials could display high tan δ but low ε'', so that the resulting MW energy absorbed will be limited, and the heating efficiency will be weak. In this context, while most of the studies exclusively refer to tan δ values to assess MW reactivity, it could also be misleading and the value of ε'' should also be evaluated.

In addition, by selecting appropriately an absorbing solvent or by adding ionic liquids [17], reactions can proceed even when the reagents do not absorb the radiation; an ionic liquid is an organic salt with melting point below 100 °C and that displays good polymer solubilization capacity, the latter attribute being important for MW reactions [18]. The use of strongly microwave-absorbing silicon carbide (SiC) vials to improve heating rates has been recently reported [19].

The design and synthesis of on-demand biomaterials has become an emerging area of (bio)pharmaceutical research [20]. Biomaterials perform not only as inert drug carriers but also as more complex systems able to interact intimately with the biological environment. An example of this trend is the change in the definition of the term "biomaterial". Biomaterial was first defined as "*a non viable material used in a medical device, intended to interact with biological systems*" [21]. However, in 2009, it was redefined as "*a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine*" [22]. In this framework, only a few scientists have addressed the systematic design and synthesis of biomaterial libraries by means of combinatorial chemistry to produce biomaterials that fulfill the requirements for a specific application [23,24]. This approach relies on the ability to synthesize a great number of derivatives in a very fast and efficient manner, a goal certainly difficult when using conventional, time-consuming synthetic methods.

As mentioned above, scale-up and technology transfer from academia (and lab scale) to industry of thermally driven reactions remains, in many cases, very challenging and a main reason for failure of that transition. A clear example that we recently faced in our laboratory involved the linear (poloxamers, Pluronic®) and branched (poloxamines, Tetronic®) temperature-sensitive poly(ethylene oxide)–poly(propylene oxide) block copolymers (PEO–PPO), extensively investigated as drug nanocarriers [25]. They are produced and commercialized by BASF (NJ, US). Due to their proven biocompatibility several poloxamers have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) as pharmaceutical excipients. A doxorubicin-containing poloxamer mixed system, SP1049C (Supratek Pharma Inc., Montreal, Canada), is currently in Phase III clinical evaluation [26,27]. In a recent work, we observed a significant gap between the theoretical molecular weight provided by the supplier and the value determined by gel permeation chromatography (GPC) [28]; the molecular weight of the copolymer is a key feature that governs self-aggregation and drug encapsulation. These findings together with the well-known batch-to-batch variability [29,30] reveal the low reproducibility of the synthetic process challenging one of the main advantages claimed for synthetic over natural polymers pertaining to the better reproducibility of the properties among batches of synthetic polymers.

Regardless of the remarkable advantages shown by MW chemistry, the use of this technology in polymer and biomaterials science has been comparatively scarce [31,32]. A search of "microwave + biomaterials" in Scopus® resulted in approximately 150 articles (search field = article title + abstract + keywords). A growing interest in the basic aspects of the synthesis of either ceramic [33] or polymeric biomaterials [31] has been apparent only during the last decade. A landmark in this regard is the construction of the first industrial plant by the National Institute of Advanced Industrial Science and Technology of Japan (AIST) for the microwave-assisted production of lactic acid oligomers at a commercial level [34]; poly(lactic acid) (PLA) constitutes one the most popular and broadly used biodegradable polyesters in drug delivery (see below). In addition to mass production of high-quality polymers in shorter manufacturing times (as claimed in the website), the reduction of 70% of CO_2 emissions is envisioned [34].

MW radiation has been mainly investigated in the production of different poly(ester)s [35–37]. Other applications such as the *in situ* production of micro and nanoparticles [38], the crosslinking and curing of hydrogels and resins [39], the production of hybrid composites [40] and the modification of carbohydrate and other macromolecular templates [41] have been also pursued, but in most of these cases, only a few studies are available in the literature.

This article reviews the most recent and prominent applications of MWs as a versatile tool to synthesize and process organic and inorganic polymeric biomaterials, and discusses the perspectives of this technology in the near future. A goal of the journal Progress in Polymer Science is to stress the developments of the last decade. In the case of microwave-assisted biomaterial synthesis, this goal can be easily accomplished, as the scientific literature on this topic is almost negligible before the year 2000. It is worth mentioning that MW radiation has been investigated for production of non-polymeric ceramic biomaterials (e.g., hydroxyapatite), though these studies are out of the scope of the present review. However, in this regard, in addition to organic polymeric biomaterials, inorganic biomaterials that display a polymeric architecture will be also addressed.

2. Synthesis of organic biomedical polymers

2.1. Aliphatic poly(ester)s and poly(ester) block copolymers

Aliphatic poly(ester)s are the most broadly investigated biodegradable synthetic biomaterials to date

[42]. Not surprisingly, most of the investigations at the interface of biomaterials science and MWs focused on them. First, the most prominent aliphatic poly(ester)s, namely poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL) homopolymers, their combinations as well as their block copolymers with poly(ethylene glycol) (PEG) will be briefly introduced. Then, the beneficial aspects of MWs to optimize their synthesis by means of two synthetic pathways, polycondensation of hydroxyacids or ring opening polymerization (ROP) of lactones, will be discussed. MW-assisted ROP reactions using solid particle initiators to obtain composites will be described in a separate section.

2.1.1. Poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and copolymers (PLGA)

PGA and PLA are the most extensively investigated poly(ester)s for biomedical applications. PGA, the simplest linear poly(ester), is highly crystalline and displays a high glass transition temperature T_g and melting temperature T_m, and low solubility in organic solvents. PGA was employed for the production of the first synthetic bioresorbable suture, known as Dexon™. The synthesis is carried out by the ROP of glycolide (GA). Due to the relatively high hydrophilicity, PGA homopolymers undergo hydrolysis over 2–4 weeks. Thus, to increase the hydrophobicity and broaden its applicability, GA was copolymerized with lactide (LA), a more hydrophobic counterpart. PLA can be semi-crystalline or totally amorphous, the crystallization process and the thermal behavior being related to the stereochemistry of the LA precursor. L-lactide (L-LA) and D-lactide (D-LA) give enantiopure crystallizable homopolymers, while D,L-lactide (D,L-LA) give the racemic amorphous product. Despite the relevance of the PGA, only a few studies have assessed the potential of MWs in the synthesis of PGA/PLA copolymers and none have addressed pure PGA. Pandey et al. prepared PGA/PLA chloroformic solutions of both homopolymers and mixed them to obtain blends which were then exposed to MW irradiation (260 W), over 25 min [35]. Chloroform is a weakly absorbing solvent with a low dielectric constant at 2450 MHz ($\tan\delta = 0.091$, $\varepsilon'' = 0.218$). Under the reaction conditions, it served as both solvent and heat sink, providing a cooling effect by draining the heat generated by the efficient MW-absorbing PLLA and PGA and contributing to maintain a mild and homogeneous temperature; this phenomenon led to solvent evaporation. IR, NMR and DSC data suggested that transesterification and crosslinking takes place to generate a homogeneous copolymer. A very important aspect of consideration is that the reactivity of the system under MWs gradually decreases over polymerization due to a decrease of the ε''. For example, the ε'' of aqueuos lactic acid is >6–8 in a wide temperature range (25–120 °C), while that of lactic acid oligomers is <2 [43]. Thus, a lower MWs absorption is expected as the reaction progresses. LA is expected to display a lower absorbing capacity than lactic acid. It should be remembered that the reaction progress under MWs may not only be dictated by the dielectric properties of the reaction mixture. For example, despite the high ε'' of lactic acid, the polycondensation is a relatively challenging reaction, even under MWs, due to the generation of water molecules that must be gradually eliminated to displace the equilibrium towards the formation of ester bonds. More recently, Li et al. reported the synthesis of PLGA copolymers by the ROP of GA and L-LA mixtures at 120 °C in the presence of octadecanol as the initiator and tin 2-ethylhexanoate (stannous octanoate, SnOct) as the catalyst [44]. Yields were between 69 and 89%, and the greatest molecular weight was attained after 5 min irradiation, this reaction time being substantially shorter than that of the conventional reactions (2–3 h) [42]. However, it should be remarked that conventional thermal reactions under similar conditions were not conducted in this study. Irradiation times longer than 9 min led to the thermal degradation of the copolymer and the carbonization of unreacted monomer. Five GA/LA molar ratios were investigated; the higher the GA content, the larger the molecular weight and the greater the polydispersity observed. In other words, GA had a higher reaction activity than L-LA in the copolymerization. These findings would suggest that GA displays a greater ε'' value (no data on ε'' is available for GA).

More profuse research has been conducted on PLA homopolymers. Most studies employ the ROP synthetic pathway, owing to the higher molecular weight attainable. The first work on the MAPS of D,L-LA with SnOct as catalyst appeared in 2001 [45]. The reaction was conducted in toluene ($\tan\delta = 0.040$, $\varepsilon'' = 0.096$). High molecular weights between 39 and 67 kDa and low polydispersity index (1.3–1.7) were reported. Relatively low power (85–170 W) and short reaction times between 15 and 60 min were used; reactions were conducted under isothermal conditions (130 °C). Then, the same group described the optimization of the reaction and the production of PDLLA (molecular weight of 100 kDa) with a yield greater than 90%, under irradiation power of 255 W; a slightly higher power, 340 W, promoted degradation of the polymer [46]. This is an interesting issue of consideration as studies consistently show the serious detrimental effect of over-irradiation in terms of both power and time on the final product. Koroskenyi and McCarthy reported high monomer conversion and molecular weight within 6 min under non-isothermal conditions [47]. A main additional advantage of MWs is that since reactions proceed very rapidly, they can be conducted under normal atmosphere with very high yields (~90%), and molecular weights as high as 200 kDa can be produced [48]. Similar results were reported by Nikolic et al., with M_{wGPC} of up to 310 kDa within 30 min at 100 °C [49]. Zhang et al. have recently modified a domestic MW oven to enable continuous microwave irradiation (90 W, 10 min, 0.56 wt% SnOct) [50], this novel setting led to a more rapid temperature increase.

The novel nature of this research field has also motivated researchers to study the performance of less conventional catalysts such as *cone*-25,27-dipropyloxy-26,28-dioxo-calix[4]arene titanium (IV) dichloride [51]; reactions were conducted under bulk conditions. Conventional thermal heating led to M_{wGPC} of up to 30 kDa in 3 h. When the LA/catalyst molar ratio was up to 500, conversion extents were greater than 90%. In contrast, lower monomer/catalyst ratios resulted in a deleterious effect. MW irradiation increased the polymerization rate, the 95%

conversion being attained after 80 min; it is worth stressing that the reaction temperature was not reported. On the other hand, lower control of the molecular weight and the molecular weight distribution was observed with MWs, as expressed by the slightly smaller molecular weights and the broader molecular weight distributions obtained; e.g., polydispersity values were between 1.4–1.5 and 1.2–1.3 under MWs and the conventional heating method, respectively. Even if advantageous for purposes of the reaction, the use of more novel (and eventually effective) catalysts of unproven toxicity/biocompatibility remains a main limitation towards the clinical use of these products.

The polycondensation of lactic acid is more challenging because (i) the monomer contains >15% water and (ii) water is produced upon condensation. Since water needs to be eliminated over time to displace the reaction equilibrium towards the formation of new ester bonds, polycondensation reactions usually demand longer reactions and lead to remarkably lower molecular weights. The main advantage of lactic acid over LA resides in its substantially lower price. In that context, this would be a very attractive synthetic strategy to pursue. The first attempts based on microwave radiation resulted in faster reaction times, though molecular weights were very low. For example, Miklos's group polycondensed racemic lactic acid and compared the results to those obtained by the conventional thermal method [52,53]. Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) analysis revealed that the reaction temperature controls the formation of linear and cyclic oligomers. Molecular weights were between 500 and 1000 Da. Aiming to make the process more efficient, Nagahata et al. introduced a binary catalyst of $SnCl_2$ and *p*-toluene sulfonic acid (*p*-TsOH) and conducted the reaction under reduced pressure (~30 mmHg) to gradually remove the generated water [54]; this catalyst showed the maximum efficiency among a broad variety investigated. PLA of much greater molecular weight (16 kDa) was produced within 30 min, at 200 °C. Cao and co-workers further innovated and used solid super-acid (SSA) as green catalyst, obtaining 20 kDa molecular weight PLA after 1 h reaction [55]. The reaction was conducted at 260 °C. Since the reaction takes place on the surface of the heterogenous catalyst, it can be easily recycled up to 5 times. Remarkably, this technique saved approximately 90% of the energy demanded by the thermal reaction. Additional sophistication and optimization of the experimental setting by incorporating progressive heating ramps and water removal steps under vacuum, enabled the production of even greater molecular weights of approximately 30 kDa within 2–3 h instead of 24–48 h by the conventional method [34]; the reaction was conducted under catalyst-free conditions. A main requirement for the industrial-scale production of PLA under is to develop a method to monitor the reaction progress. In fact, the application of MWs in polymer/biomaterials synthesis has mainly been exploited to improve reaction rates and yields. Conversely, the fundamental aspects of the MWs remain to be thoroughly investigated. In this context, the study by Nakamura and coinvestigators that measured the dielectric properties of the reaction mixture and showed that they decrease over time constitutes an interesting approach to gain further insight into these parameters [43]; their setup is presented in Fig. 1. This study constitutes the first of its kind and stresses the potential of this technology.

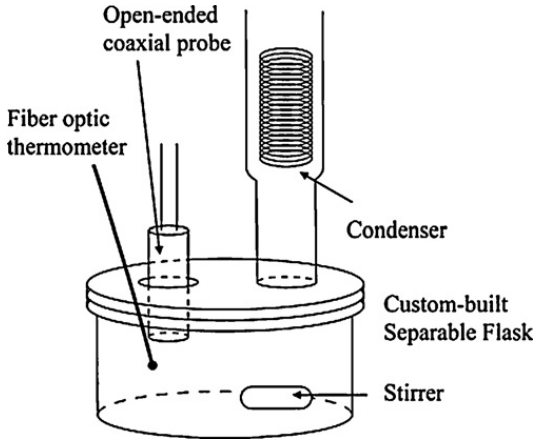


Fig. 1. Schematic illustration of a set for open-ended coaxial probe measurement. (Reproduced with permission of Elsevier from Ref. [43].)

An interesting study described the fast (20–30 min) MW synthesis of D,L-LA from racemic lactic acid under a temperature ramp [56]. The 2-step mechanism involves the initial polycondensation to form oligolactic acid, with the later depolymerizing to give the lactone. However, the yield was up to 36% employing a catalysis system based on $SnCl_2$ and a patented "cat-A". Using a similar approach (though with a zinc powder catalyst), Yang and Liu obtained D,L-LA with 40.3% yield in 3.2 h [57]; a temperature ramp up to 170 °C was used. Then, the produced D,L-LA can be polymerized to obtain high molecular weight PLA. More recently, Hirao and collaborators investigated comparatively the racemization during the production of LA from enantiopure L-lactic acid under MWs and conventional heating [58]. The amounts of LA produced under microwave irradiation (25 mmHg, 180 °C, 12 h), including L,L-, D,D-, and meso-LA, was approximately 2.7 times higher than the corresponding amount found under conventional thermal treatment; the ratio of the number of D,L-LA to the total number of lactone was approximately 9-fold greater with MWs. In addition, this phenomenon was more noticeable at longer reaction times and higher temperatures. Conversely, when the vacuum was lower than 15 mmHg, the ratios for the MWs and the conventional heating process were comparable. The sublimation of LA is required to displace the equilibrium towards the generation of more product. Thus, it is expected that under a weaker vacuum, sublimation becomes the rate-limiting step and the benefits of MWs are reduced. These findings stress the need for a careful fine-tuning of the experimental conditions.

2.1.2. Poly(ε-caprolactone) (PCL)

Poly(ε-caprolactone) (PCL) is a highly hydrophobic and semicrystalline poly(ester) that, owing to its proven biocompatibility, has been used in different biomedical devices [59,60]. PCL is permeable to hydrophilic and hydrophobic drugs and has been employed in the production of solid and injectable implants and micro and

nanoparticles for drug delivery [61–63]. PCL withstands hydrolysis better than PGA and PLA [64,65] and sustains the release of the encapsulated drugs for longer times [66]. The low glass transition temperature (−60 °C) and melting temperature (<60 °C) [67] were exploited to produce drug-loaded implants by mild processes, such as melt molding/compression, without affecting the chemical stability of the encapsulated drug [68,69]. The synthesis of PCL entails a main advantage over PLA and PGA and copolymers: the precursor, ε-caprolactone (CL), is remarkably cheaper than LA or GA. This is probably the reason that even though PCL is less broadly used in clinics than PLA and PLGA, more extensive research has been conducted on the use of MWs in PCL synthesis. A preliminary work by Albert et al. that compared the thermal and MW methods concluded that "*conversion, measured by means of viscosity build-up, and number-average molecular weight of poly(ε-caprolactone) were similar for both processes and did not indicate advantages relating to the use of microwave irradiation*" [70]. Since then, profuse research around PCL that studied different initiators (e.g., carboxylic acids) and catalysts (e.g., lanthanide halides, Zn powder, lipase) [35,71–74] has come out. All these studies contradict Albert's statement. Reactions were usually conducted under bulk conditions, and the most common catalyst was SnOct [75]; as opposed to the solid LA and GA, CL is liquid and can serve as solvent for both initiator and catalyst. However, in a few trials, syntheses were assessed in ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate [76]. Findings consistently indicate that the use of MWs increases the reaction rates and the synthetic efficiency. These phenomena would rely on the fast temperature increase due to the relatively high MW absorption of CL, $\tan\delta$ and ε'' being approximately 0.35 and 14.7, respectively [77]. However, they also suggested that a non-thermal microwave effect would take place [78]. For example, Zhuo et al. reported on the fast temperature increase from 20 to 355 °C within 5 min irradiation at 680 W [79]. The temperature was then self-regulated at approximately 360 °C, probably due to the lower ε'' displayed by the polymer with respect to that of the monomer, as previously shown for lactic acid and low molecular weight PLA [43]. It is interesting to note that most of the investigations employed conventional microwave ovens and power levels were reported as average values; these equipments often maintain constant effective irradiation power and regulate "on–off" cycles [6]. In general, the effective irradiation power is calculated as the product of the "power level" and the maximum power of the oven. For example, if a power level of 5 (out of 10) in an oven of 900 W power is employed, the "average irradiation effective power" reported is 450 W. This procedure is not fully reliable and can be certainly misleading. Also, the reaction conditions could be probably not reproducible with different ovens. This issue as well as the relatively limited reproducibility are crucial disadvantages of domestic equipments and counterbalance the benefits of their cheapness. In this regard, MAOS have undergone a transition over the last 2 decades, during which research groups gradually moved from domestic to professional ovens; currently, MAOS employing domestic ovens is hardly publishable. In this context, a similar phenomenon can be expected over the next years in polymer and biomaterials science, this process being probably hastened by the more affordable prices available today in the market.

Yu et al. polymerized CL using carboxylic acids (e.g., benzoic acid and chlorinated acetic acid) as initiator without catalyst [37]; temperature conditions were not monitored. The initiator is incorporated into the polymer chain. When a mixture of CL and benzoic acid (25/1 molar ratio) was irradiated at 680 W over 4 h, the M_{wGPC} was 44.8 kDa and the PDI 1.6. A similar reaction mixture under conventional heating at 210 °C led to M_{wGPC} of 12.1 kDa (PDI = 4.2). Even though the mechanism involved in this improvement was not discussed, the faster and more efficient polymerization of monomer bearing polar functional groups has been consistently reported [37].

In addition, the polymerization employing maleic, succinic and adipic acid as initiators under MW irradiation was evaluated (360 W, 85 min) [80,81]. The reaction temperature is a crucial parameter, as excessive heating (>230 °C) may result in chain degradation over chain propagation [82]. The same research group conducted the SnOct-catalysed synthesis of PCL in a self-designed industrial oven of 6000 W maximum power, the temperature of the reaction being recorded online (Fig. 2) [83]. Monomer amounts ranged between 750 and 2450 g and the irradiation time between 12 and 59 min. The temperature profiles attained depended on the power level and the monomer mass. The maximum temperature attained when 750 g CL was irradiated at 850 W (power/mass 1.13 W/g) was 86.3 °C after 13 min. In addition, the monomer conversion was >90% after 24 min, the M_w (GPC) being 66,200 Da. Greater power/mass ratios of 2.27 and 3.4 W/g led to the highest recorded temperature (114.1 °C) at 17 and 9 min, respectively. The produced PCL polymers displayed M_w of 66.3 and 66.9 kDa after 23 and 12 min, respectively, conversions being 90–94%. Overall, the findings indicate that both the combinations of high power level/short reaction time and low power level/long reaction time can be capitalized in PCL synthesis. The derivatives obtained are suitable for a broad spectrum of bio(pharmaceutical) applications, such as particles, monolithic implants and scaffolds. Finally, a different kind of initiator, hydrogen phosphonates (e.g., diisopropyl hydrogen phosphonate), has been explored [84]. The mechanism of the reaction is more complex and comprises two stages: (i) coordination and (ii) insertion; the reaction is known as ring opening insertion polymerization (ROIP). First, the P atom attacks the carbonyl moiety of CL to break the ester bond, forming the coordination intermediate (Scheme 1). Then, the P alkoxide undergoes cleavage, generating an acyl-alkoxide bond (Scheme 1). However, in an additional work, the same group suggested another mechanism implying the initiation of the ROP of CL by trace water amounts and the subsequent transesterification between the oligo(ε-caprolactone) (oligoCL) and the hydrogen phosphonate to form an oligoCL bearing a terminal hydrogen phosphonate [85]. This intermediate would catalyse the polymerization, once the phosphonate is consumed.

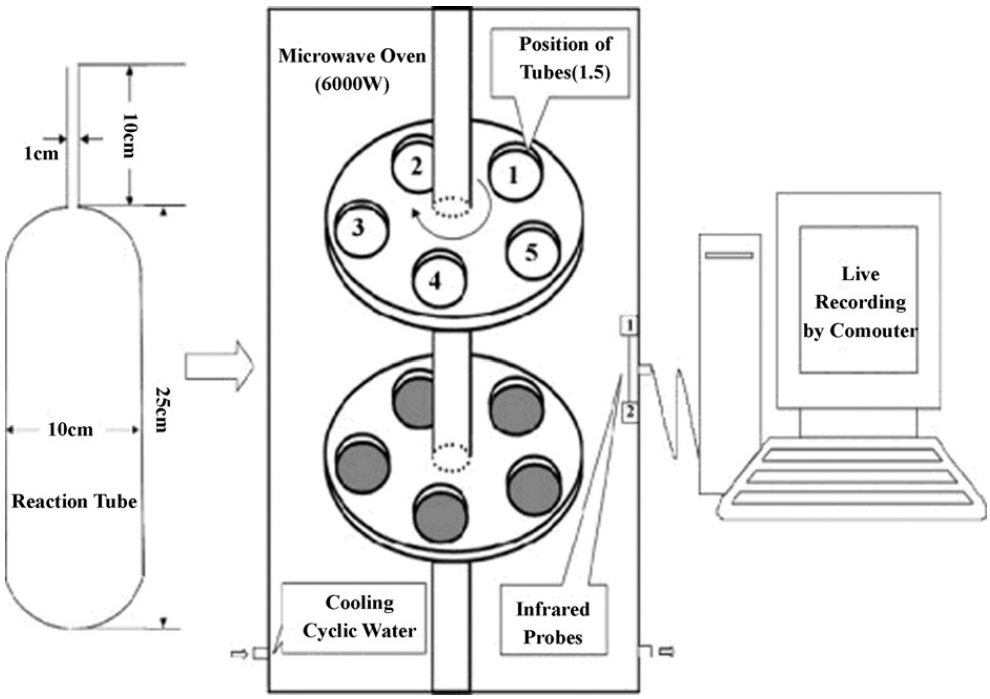
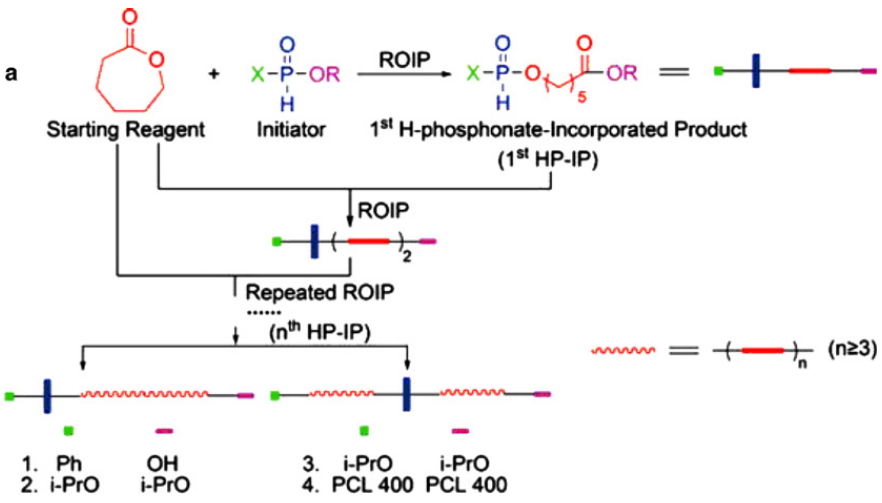


Fig. 2. Schematic illustration of polymerization reactor for the large-scale microwave-assisted ROP of CL. (Reproduced with permission of Elsevier from Ref. [83].)

2.2. Poly(ester)–poly(ethylene oxide) block copolymers

As mentioned above, poly(ester)s are relatively hydrophobic biomaterials, and this characteristic not only constrains their biodegradability in a biological environment but also their applicability due to their very low aqueous solubility. Aiming to increase their water affinity and solubility, poly(ester)s have been copolymerized with highly hydrophilic blocks of poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO) [86–89]; PEG and PEO are used as initiators of the ROP of LA and CL. For a brief description of PEG and PEO and their applications see Section 2.7. It is worth mentioning that depending on the hydrophilic–lipophilic balance and the molecular weight of the copolymer, polymeric micelles, polymeric vesicles (polymersomes) and hydrogels can be obtained. Regardless of the key role of these copolymers, only a few reports on MAPS have been published. Yu and Liu synthesized bifunctional PCL–PEG–PCL triblocks with M_n of approximately 20 kDa and used the copolymers for the sustained release of ibuprofen for over 24 days, the release period being associated with the PCL/PEG ratio [90]. Conversely, Ahmed et al. employed monofunctional PEG monomethyl ethers, resulting in monofunctional PEG–PCL diblocks [91]. Zhang et al. synthesized PLA–PEG–PLA triblocks by reacting a PEG (2 kDa) initiator with L-LA in bulk over 3 min at 100 °C [92]. Conversions were greater than 92% and molecular weights up to 28 kDa. Similarly, they produced monofunctional MPEG–PLA diblocks with molecular weights between 7.3 and 116.7 kDa, the reaction conditions being



Scheme 1. Mechanism of H-phosphonate-initiated ROIP of ε-caprolactone. (Reproduced with permission of Wiley & Sons from Ref. [84].)

Table 2
Different PCL–PEG–PCL block copolymers synthesized by MAPS (adapted with permission of Elsevier from Ref. [93]).

PCL–PEG–PCL copolymer	CL/EO molar ratio[a]	M_n [a] (Da)	M_n [b] (Da)	M_w [b] (Da)	PDI[b]
1050–6000–1050	0.14	8100	12,250	13,400	1.10
1450–6000–1450	0.19	8900	11,000	15,200	1.38
2550–6000–2550	0.33	11,100	13,000	15,000	1.16
1300–10000–1300	0.10	12,600	15,400	16,950	1.10
2600–10000–2600	0.20	15,200	16,700	19,700	1.18
3700–10000–3700	0.29	17,400	18,300	23,200	1.27
4500–10000–4500	0.35	19,000	16,000	19,000	1.19
1500–20000–1500	0.06	23,000	21,600	25,950	1.20
3800–20000–3800	0.15	27,600	21,600	26,200	1.21
7850–20000–7850	0.30	35,700	24,850	26,850	1.08

[a] Calculated by ^{1}H NMR.
[b] Calculated by GPC. PDI: polydispersity calculated as M_w/M_n.

20 min at 100 °C. As consistently shown in different studies, extending the irradiation time did not improve the conversion extent and led to chain scission and molecular weight decrease. Very recently, our research group investigated the molecular features governing the encapsulation of the antituberculosis drug rifamcpicin within PCL–PEG–PCL flower-like polymeric micelles [93]. Three PEG initiators with average molecular weights of 6, 10 and 20 kDa were used, the CL/EG molar ratio ranging between 0.06 and 0.33 (Table 2). Relatively low polydispersity values were obtained. The amphiphiles were efficiently obtained (conversion was greater than 90%) after 15 min irradiation in a domestic MW oven at average irradiation of 240–400 W (see below). As opposed to most studies, in this case, MW irradiation was used as a support tool to enable fast and reproducible synthesis of the materials and not as the inherent goal of the work. In this context, the different parameters affecting the progress of the reaction (e.g., irradiation time, effective power, solvent type and concentration, etc.) were not thoroughly investigated. Following a similar approach, though with the aim to produce highly hydrophobic PCL–PEG–PCL derivatives, the ROP of CL was performed using a low molecular weight PEG (400 Da) in the presence of SnOct under bulk or solvent conditions [94]. The PEG central block was used to calculate the M_n also by means of ^{1}H NMR. The effect of irradiation time and catalyst concentration was investigated. M_{wGPC} as high as 66 kDa was attained after 14 min irradiation. On the other hand, when very high CL to EO molar feeding ratios were employed, a homopolymerization pathway was favored; this phenomenon decreased the maximum molecular weight attainable. Aiming to maintain the viscosity of the system relatively low over the whole reaction and favor the complete monomer conversion the use of solvents displaying different MW absorbing properties (dimethylformamide, DMF and dimethylsulfoxide, DMSO) was explored. DMSO displays a higher absorbing capacity ($\tan\delta = 0.825$, $\varepsilon'' = 37.1$) than DMF ($\tan\delta = 0.161$, $\varepsilon'' = 6.07$) [6], thus faster reactions and higher polymerization efficiencies than those attained with DMF were envisioned. The synthesis of PCL–PEG–PCL copolymers with moderate molecular weight (~20 kDa) in solutions with up to 30 wt% DMF was efficient and similar to under bulk conditions. Conversely, greater DMF concentrations resulted in a smaller degree of polymerization and a clear smaller monomer conversion. In the case of DMSO, even 5% solvent led to smaller molecular weights. This phenomenon probably stemmed from solvent overheating and polymer thermal degradation. An additional (and not negligible) advantage of this technique would be the higher content of triblock molecules than those found in the commercial products that contained greater concentrations of diblocks, as shown recently by MALDI-TOF for low molecular weight PEG initiators [95]. This improvement could be probably ascribed to the more homogeneous heating process in MW synthesis. In general, commercial triblocks are synthesized by conventional thermal methods in relatively large scales, this process favoring an even less homogeneous molecular size distribution.

2.3. Poly(2-oxazoline)s (POs)

POs are obtained by a "living" cationic ring-opening polymerization (CROP) of pristine and substituted 2-oxazoline, resulting in materials with controlled molecular weight and narrow molecular weight distribution [96]. Due to their chemical versatility and biocompatibility, they are gradually gaining more attention [97,98]. Vesicles [99,100], polymeric micelles [101,102] and pH-responsive hydrogels [103] for drug delivery and, more recently, vectors for gene transfection [104] have been described. Schubert's group has embraced MW technology for the fast and systematic synthesis of POs displaying different block arrangements and architectures [105–108]; this combinatorial strategy may enable the design of derivatives with new and more predictable features [109–111]. For example, the polymerization of optically active 2-butyl-4-ethyl-2-oxazolines and the racemic mixture led to formation of solvent-dependent secondary structures in solution [107]. Interestingly, both enantiopure and racemic polymers generate a random coiled structure when solubilized in a good solvent, such as trifluoroethanol-d_3. Conversely, when the POs were dissolved in a bad solvent (methanol-d_4), the enantiopure derivatives generated a more compact, elongated structure compared to the racemic one. These results indicated that these synthetic polymers generate a dynamic secondary structure similar to polyproline type II helices that can be dictated by the properties of the solvent [107]. Conversely, the combination of hydrophilic and hydrophobic oxazolines in a sequential manner during the polymerization resulted in the generation of amphiphiles that self-assemble into polymeric micelles [112–114].

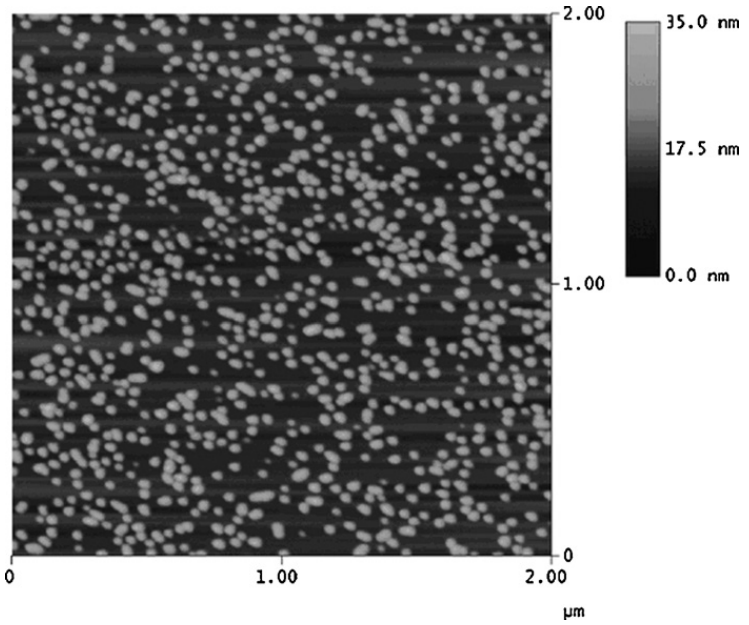


Fig. 3. AFM height contrast images of block copolymer micelles prepared from the p(MeOx-*b*-EtOx-*b*-PhOx-*b*-NonOx) tetrablock quarterpolymer. These micelles were prepared from initial acetone solutions of the polymers at 1.0 g/L. (Reproduced with permission of the American Chemical Society from Ref. [113].)

Fig. 3 shows the morphology of PO micelles visualized by atomic force microscopy (AFM) [114]. Following a similar rationale, water-soluble poly(2-ethyl-2-oxazoline) (EtOx) homopolymers were primarily synthesized by CROP using the heteroinitiator α-bromoisobutyrylbromide and then reacted with styrene by atom transfer radical polymerization to produce polystyrene blocks conjugated to the polyoxazoline [115]. Since the hydrophilic segment was shorter than the hydrophobic one, polymeric micelles were obtained by means of the cosolvent method; the copolymer was dissolved in DMF and micellization was triggered by pouring the organic solution into water. Hydrodynamic radii ranged between 77 and 141 nm. Polymeric micelles are among the most promising drug carriers [116]. The effect of different halide leaving groups in the benzyl-initiated CROP of EtOx and 2-phenyl-2-oxazoline (PhOx) has also been shown [117]. In contrast, when the initiator was aliphatic, namely acetyl chloride, acetyl bromide and acetyl iodide, different halides did not lead to differences in the polymerization profile [118]. One of the main advantages claimed for MW chemistry is the ability to conduct reactions under bulk conditions or to use more environment-friendly solvents. In this context, they also evaluated the synthetic efficiency of POs in bulk or reduced solvent contents [119] and water-soluble ionic liquids [120]. Another example of this versatile family of compounds is the fast synthesis of fully amorphous branched 2-(3-ethylheptyl)-2-oxazoline (EHOx) homopolymer that displays T_g below 0 °C [108], and could be exploited in the development of thermoplastic injectable implants [121]. Copolymers combining different EtOx contents were also obtained and characterized [108]; T_g values gradually increased for derivatives containing greater EtOx (Fig. 4). Reactions times were under 15 s, and the polydispersity index values <1.28 indicated a narrow molecular weight distribution. A main issue in the synthesis of biomaterials towards their clinical use is production at a greater scale than laboratory. A complementary facet of the work by Schubert and collaborators was to investigate approaches to increase the working scale from a few to several hundreds of mL by means of batch [122] or continuous-flow modes [123] and in ionic liquid medium [124]. In this context, an automated workflow mode has been also proposed [109] (Fig. 5). The contribution of this comprehensive work is not limited and useful only to the synthesis of this specific family of biomaterials, but it also sheds light on the fundamental aspects of this technology. In addition, it probably constitutes the most extensive and comprehensive work in the field conducted to date. Most effort has been devoted to understand the more basic parameters affecting the synthetic process, while their usefulness in specific biomedical applications still needs evaluation. On the other hand, some systems have been explored with

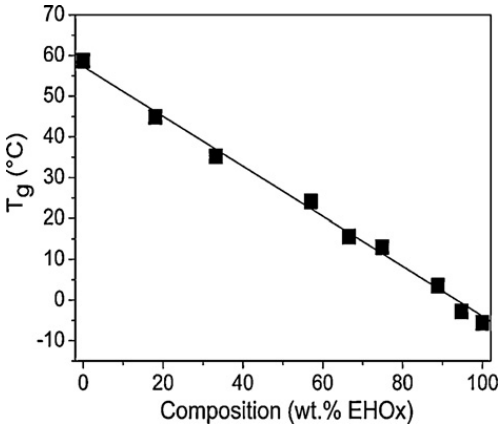


Fig. 4. Dependence of T_g of p(EtOx-r-EHOx) random copolymers on the weight percent of 2-(3-ethylheptyl)-2-oxazoline. (Reproduced with permission of the American Chemical Society from Ref. [108].)

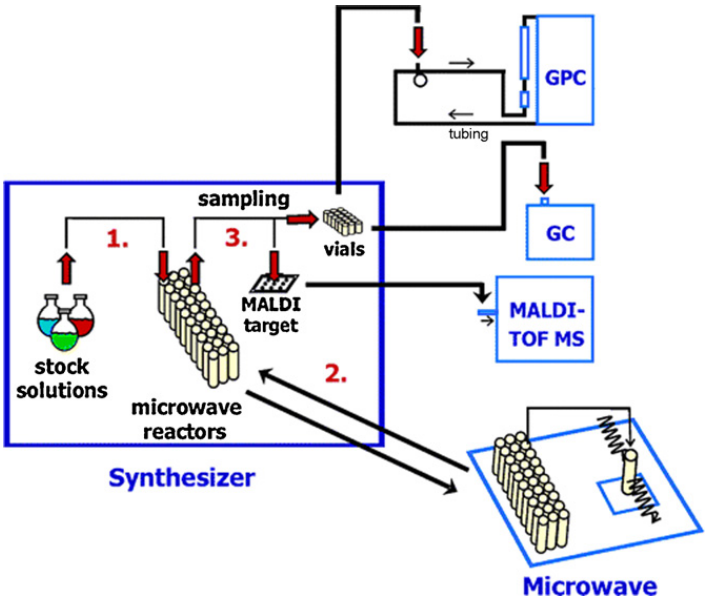


Fig. 5. Schematic representation of the automated workflow, including the microwave synthesizer and the peripheral characterization equipment. All arrows going outside or inside the ASW2000 synthesis robot (synthesizer) represent manual steps. (Reproduced with permission of the American Chemical Society from Ref. [109].)

more emphasis on applications. For example, the potential role of hydrophilic polyoxazolines as substitutes of poly(ethylene glycol) (PEG) in the PEGylation process of nanocarriers (e.g., liposomes) [125] and active molecules [126–128] has been addressed; PEGylation is the conjugation of PEG blocks to alter the response of the biological environment, usually extending the circulation time *in vivo* [129]. For example, the protein trypsin and the pyrimidine analog cytosine arabinose were selected as high- and low-molecular weight drug models and were conjugated to modified polyEtOx chains synthesized by MW-assisted CROP of 2-ethyl-2-oxazoline in acetonitrile ($\tan\delta = 0.062$, $\varepsilon'' = 2.325$) over 450 s [128]. The monomer conversion was 95%. Since acetonitrile is a relatively weak MW-absorbing solvent, the reaction temperature was controlled at 140 °C. Further chemical modifications and conjugations were carried out under conventional conditions.

The main advantages that support the use of POs instead of PEG are water solubility, chain flexibility, non-toxicity and easier synthesis of low-polydispersity derivatives that bear diverse side functionalities, improving the complexation/conjugation capacity.

2.4. Polyurethanes (PUs)

PUs are among the most bio and blood-compatible biomaterials and show a tremendously versatile chemistry and thus, a wide range of physical and mechanical properties [130]. PUs combine hard segments made of alternating diisocyanate and chain-extenders with soft ones such as flexible linear diols. Depending on the nature of the chain extender employed for the synthesis, thermoplastic or thermosetting materials are produced. The former comprises bifunctional chain extenders, while the latter makes use of tri or tetrafunctional. The ability to tailor their composition and performance *in vivo* has led to the development of derivatives with a broad range of properties, from highly biostable and inert devices used in vascular catheters, vascular grafts and the total artificial heart to fully biodegradable matrices for drug delivery and tissue engineering [131,132]. The former are very hydrophobic and withstand hydrolysis for very long periods. Conversely, the latter are more hydrophilic, can absorb water and biological fluids to different extents and undergo controlled biodegradation *in vivo*, these phenomena depending on the hydrophilic/hydrophobic balance. For example, Parrag and Woodhouse have recently reported on the synthesis of PUs containing the glycine–leucine dipeptide sequence, the selective site of cleavage of several matrix metalloproteinases [133]. The authors envision these polymers as novel biodegradable scaffolds with remodellable features for soft tissue engineering. Another bioresorbable PUs synthesized using novel chain extenders were reported by Caracciolo et al. [134,135]. Compounds containing urea groups or an aromatic amino-acid derivative were incorporated into the segmented PU formulation to strengthen the hard segment associations through either bidentate hydrogen bonding or π-stacking interactions, respectively. These elastomeric segmented polyurethanes were used for the development of biomimetic highly-porous elastomeric nanofibrous scaffolds [136]. In spite of their key role, the application of MWs to synthesize and process PUs has been remarkably limited when compared to other biomaterials. Moreover, all the studies focused primarily on the chemical aspects of the synthetic pathway and the molecular features attained. Even though these investigations did not envisage the potential implications of these novel developments in biomedicine, we briefly describe the most relevant findings. These studies will probably constitute a platform for further developments.

The first work addressing the reactivity of PUs under MW irradiation investigated the crosslinking of PU resins using diisocyanate and polyethertriol prepolymers [137]. More recently, by means of the diisocyanate route, Mal-

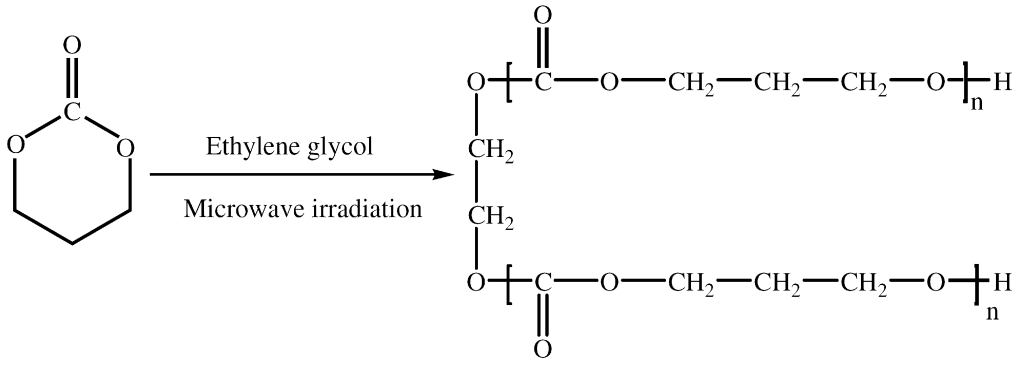
lakpour and Rafiemanzelat investigated the synthesis of different PU derivatives displaying unique features, such as optical activity [138], and containing azobenzene-based diacid chromophoric segments useful in the dye industry [139]. Azobenzene-containing materials are photochromic, and when exposed to light they display a photo-responsive behavior switch between two different spectroscopic forms. The solvent was 4% *N*-methyl pyrrolidone (NMP, $\tan\delta = 0.275$) and reactions were conducted in the presence of pyridine, dibutyltin dilaurate or no catalyst, in a domestic oven (maximum operating power of 900 W; effective power = 100%) [139]. Reaction times, usually <10–15 min, were substantially shorter and reaction yields greater than those often observed in classical reactions that under solvent conditions usually give unsatisfactory yields [139]. Data of the dielectric properties of the reactants were not reported, though the advantageous dielectric features of diisocyanates have been reported (see below). This a crucial issue that is often not well-investigated; most studies are more focused on the outcomes rather than in the fundamentals that support them. The same research group synthesized chromophoric urazole-containing poly(urea-urethane)s using the same domestic equipment (maximum operating power = 900 W; effective power = 60–100%) [140]. The innovative aspect of this work stemmed from the use of an ionic liquid instead of an organic solvent as the reaction medium. The performance of the MW technology was compared to that of conventional heating. The main outcomes of MAPS were that reaction times were significantly shortened from 6–12 h to less than 2 min, the yields were increased, and the use of toxic catalysts and organic solvents was avoided. It is remarkable that conventional reactions employed greater ionic liquid concentrations and even under such conditions longer reaction times were required. As usual, the authors did not explain the essential issues behind this improvement. Having expressed this, the presence of an ionic liquid that is especially sensitive to MWs probably played a fundamental role; this orientation–polarization phenomenon cannot be exploited under conventional heating.

A critical question that still needs to be answered is related to the potential impact that ionic liquid and any other additives may have on the biocompatibility and the clinical performance of the final product. Even if more toxic, the upper limits of volatile solvents are well defined by regulatory agencies and they can be eliminated more easily than ionic liquids, that usually have very high boiling points [141]. Another advantage of this technique pertains to the degree polymerization achieved. For example, Hiroki et al. increase the molecular weight 15- to 20-fold with respect to those obtained with the conventional treatment [142]. Reactions were conducted at 140–200 °C for 5–20 min in solvents of different dielectric properties. The non-polar decalin led to higher polymerization extents than polar solvents such as *N*,*N*-dimethylacetamide and chlorobenzene, probably due to the thermal degradation of the growing polymer chain, as shown for PCL–PEG–PCL triblocks in the high MW-absorbing DMSO [94]. Another interesting aspect of this work is that it also shed light into the beneficial role of diisocyanates as starting reactants. These precursors display relatively high ε'' values of approximately 4.2–4.8 [142].

Another limitation of PUs is their difficult solubilization due to the large amount of strong inter-chain hydrogen bonds generated [143]. MWs could contribute also to optimize this aspect by improving the rupture of these bonds in the presence of an appropriate solvent. Overall, these findings stress all the advantageous features of this technology.

2.5. Poly(alkyl carbonate)s (PACs)

PACs are a very versatile family of biomaterials, usually produced by the ROP of trimethylenecarbonate (TMC) and other 6-membered substituted ring derivatives in the presence of metallic catalysts [144]; conventional reactions are conducted at temperatures between 100 and 120 °C for at least 24 h [145]. Their main features are good biocompatibility, low inherent toxicity and tunable mechanical properties [146]. Regular PACs are highly hydrophobic and degrade very slowly. Remarkably, degradation products are non-acidic and the characteristic autocatalytic effect and tissue damage observed with poly(ester)s is prevented with PACs [147]. Depending on the chemical nature of the polymeric chain, PACs are also susceptible of enzymatic degradation [144]. To hasten the degradation rates, more hydrophilic derivatives that contain terminal PEG monomethylether blocks were developed [148]. For example, Kohn et al. have investigated the synthesis and biological performance of a broad spectrum of tyrosine-derived polycarbonates [149]. To expand their applicability, they copolymerized tyrosine diphenolic monomers with PEG blocks [150]. These products are softer, more hydrophilic and display slightly faster degradation rates than the standard counterparts, though still inappropriate for drug delivery in tissue engineering applications [151]. Others synthesized PACs highly functionalized with amine moieties for non-viral gene transfer [152]. In spite of their relevance, there are only a few reports describing the MW-assisted synthesis of polytrimethylenecarbonate (PTMC) [153–156]. Zhang et al. synthesized a high molecular weight derivative (80 kDa) with 83% in 10 min reaction, representing a 120-times faster reaction [153]. More recently, Liao et al. went even further, producing and investigating the synthesis of ethylene glycol-initiated symmetrical PTMC derivatives in the absence of any metallic catalyst in a single-mode MW oven employing an irradiation power between 5 and 30 W [154] (Scheme 2). The temperature–time profiles of the polymerization mixtures under MWs showed an initial moderate temperature increase (0–7 min) followed by a faster second temperature stage (7–13 min). This phenomenon could be related to the fact that molecular rotations are more restricted in the solid state of the precursors, making them less capable of responding to the MWs. Reactants irradiated at 10–30 W showed an exotherm before reaching a thermal equilibrium that relied on the rapid heat release in the ROP of TMC. The temperature profile depended on the power level and the EG relative concentration (Fig. 6). For the same effective MW power, the greater the ethylene glycol initiator concentration was, the earlier the appearance of the exothermic peak. In general,



Scheme 2. Rapid synthesis of poly(trimethylene carbonate) by microwave-assisted ring-opening polymerization. (Reproduced with permission of Elsevier from Ref. [154].)

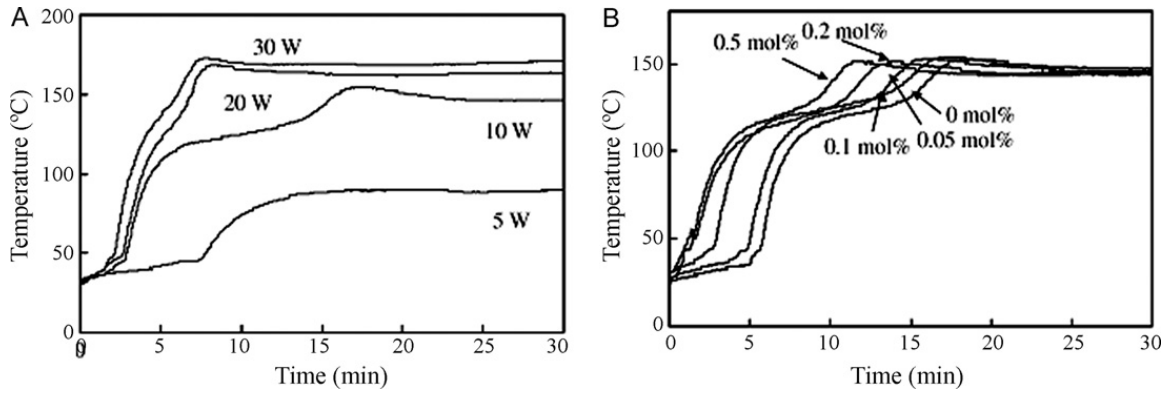


Fig. 6. Temperature profile versus power level and ethylene glycol content. (A) Temperature–time profiles of the TMC/EG reaction mixtures at different power levels (0.1 mol% EG, 30 min). (B) Temperature–time profiles of the TMC/EG reaction mixtures with different EG concentrations (10 W, 30 min). (Reproduced with permission of Elsevier from Ref. [154].)

the number-average molar mass and the monomer conversion by the MW method were substantially greater than those under conventional heating [154]. High conversions, usually above 95%, were obtained after 30 min irradiation [155], average molecular weights (GPC) being up to 15 kDa. When the reaction was conducted in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (an ionic liquid), a higher molecular weight of 36.4 kDa was attained, after 60 min [155]. PTMC–PEG–PTMC triblocks were produced under MW radiation employing PEG initiators of molecular weights between 0.6 and 2 kDa and reaction temperature of 120 °C [156]. A short irradiation time of 10 min led to copolymers with a number-average molecular weight (GPC) of 6.8 kDa, the conversion being only 21%. Then, the gradual increase of the irradiation time from 10 to 30 min, resulted in a clear molecular weight growth from 6.8 to 16.4 kDa (Fig. 7). Conversions showed a similar trend with a steady growth from 21% to 93%. Longer exposure times of 60 and 120 min led to a decrease of the molecular weight to 14.9 and 13.0 kDa, respectively, with no or slight

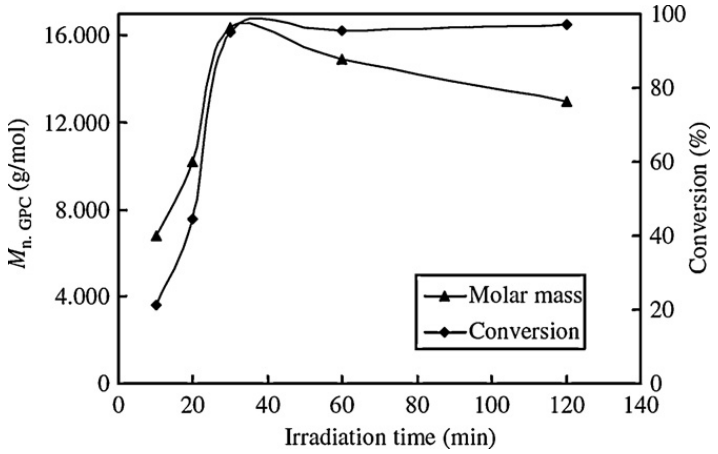


Fig. 7. Effect of irradiation time on the polymerization extent of a TMC/PEG2000 reaction mixture (1000 molar ratio), at 120 °C. (Reproduced with permission of Elsevier from Ref. [156].)

changes in the conversion extent (93–97%). These results indicated that the polymerization was completed within 30 min and that MW over-exposure caused random thermal degradation of the PTMC segment. This detrimental effect has been reported for different copolymers. Conversions were extremely low (3–14%) and molecular weights smaller than 2.7 kDa for similar TMC/PEG mixtures reacted by the conventional method (120 °C, 60 min). Noticeably, when four different types of zinc lactate catalyst were used to homopolymerize TMC, polymers of molecular weights up to 75.4 kDa were produced, within 30 min [157]; the temperature of the reaction was again 120 °C. In addition, conversions remained high, between 85 and 98%. When the conventional heating method was employed (120 °C, 30 min), reactions were significantly slower and only oligomers with molecular weights of approximately 1.2 kDa were obtained, these results corresponding to 2–3% TMC conversion. The MW-synthesized counterparts displayed remarlably greater molecular weights. These findings support the implementation of MW in an industrial setting.

2.6. Polypeptides

Polypeptides displaying different architectures have found multiple biomedical applications, not only due to their biological activity but also as drug and gene carriers and tissue engineering scaffolds (see below). The synthesis usually comprises the sequential reaction of protected aminoacids for the formation of the peptidic bond. A main drawback in this process is the strong aggregation tendency of the peptidic sequences due to strong inter- and intra-molecular hydrogen bonding that results in incomplete acylation/deprotection reactions and hinders the reaction progress [158]. Considerable research dealing with the synthesis of biologically active oligo and polypeptides and peptidomimetic molecules by means of MWs is available, mainly aiming to improve the synthesis of "difficult" peptide sequences [159]. A pioneering (and isolated) work by Ito at al. investigated the MW-assisted synthesis of polypeptides by exposing an equimolar mixture (each 0.1 M) of glycinamide, L-alaninamide, L-valinamide, L-aspartic acid α-amide, and L-histidinamide, to repeated hydration-dehydration cycles [160]. Muthusamy et al. reported the MW-supported solid phase polypeptide synthesis (SPPS) of amylin, a 37-Aa amyeloid polypeptide that forms aggregates in the islets of Langerhans of type II diabetes patients [161]. Amylin is secreted by the pancreas together with insulin and serves in the metabolism of carbohydrates. In this case, there was no need for pseudoproline derivatives, which enable faster and more complete couplings [162]. In general, reactions were faster than the conventional synthetic method due to the ability of MWs to disrupt the inter- and intra-chain bonds. In addition, the preventable use of further additives led to products containing lesser impurities [161]. However, the goal of this review is to focus on peptides employed as a platform for the delivery of drugs and in cell culture and regenerative medicine. Only a few groups introduced this technology to produce polypetidic biomaterials. Tantry and collaborators synthesized oligopeptides employing 9-fluorenylmethyloxycarbonyl (Fmoc)-aminoacid hydrochlorides as precursors, and zinc dust, 1-(t-butyldimethylsilyloxy)benzotriazole, bismuth and indium as coupling additives [163]; a comparative study between conventional and MW methods was conducted. Zinc was the most effective coupling agent of all those investigated. Using a domestic MW oven (maximum operating power = 1200 W; effective power = 720 W), the formation of the peptide bond was completed in 30–45 s, yields being greater than 90%. Conversely, under the conventional thermal treatment 15–30 min were required for each coupling step. It is worth mentioning that, regardless the impressive data, the authors did not explain the mechanism responsible for this improvement. One might surmise that the fast MW-mediated heating commonly observed could explain, at least partially, the faster reaction rate. After a series of sequential couplings and a final deprotection, the enantiopure pentapetide Fmoc-Val-Pro-Gly-Val-Gly-OBzl, a repeating sequence present in the protein elastin, was obtained with a 67% yield. Interestingly, no racemization was observed. Moreover, the reaction was efficiently scaled up. The authors of this study did not discuss the potential reasons for the non-racemization though one might speculate that the conservation of the enantiomeric purity relied on the employment of substantially shorter heating times.

Synthetic self-assembly elastin oligopeptides are becoming increasingly appealing as non-thrombogenic coatings [164] and matrices for tissue engineering [165]. Polyaspartic acid (PAsp) [166] and polyglutamic acid (PGlut) [167] are biodegradable synthetic homopolypeptides that have found application as drug and gene carriers [168,169]. In water, they form pH-sensitive gels [170,171]. PAsp and PGlut and their benzyl derivatives have been also combined with PEG, PEO or other hydrophilic blocks to produce amphiphiles that self-aggregate in water forming polymeric micelles [172–175] and vesicles [176]. The synthesis of homo and heteropolymers usually encompasses the ROP of β-benzyl-L-aspartate or β-benzyl-L-glutamate *N*-carboxyanhydride initiated by different initiators (e.g., amine-terminated PEG). Reactions were conducted at room temperature over several days [175]. Deprotection of the benzyl moiety is carried out in NaOH [177]. They have also been copolymerized with PLA to adjust the degradation rate, the hydrolysis being accelerated by the presence of aspartic acid units [178]. In another work, PAsp was used as surface modifier to improve cell adhesion and function of osteoblasts when seeded in PDLLA scaffolds [179]. Surprisingly, studies on the potential of MW irradiation for the synthesis of polypetides are scarce. Huang et al. recently assessed the feasibility of the synthesis of PAsp from maleic acid and ammonia under bulk conditions and in the absence of catalyst [180]. Reactions were completed within less than 5 min. Similarly, Piatkowski et al. studied the polycondensation of D,L-aspartic acid without catalyst at 160–230 °C for 41 min [181]. The cyclic form primarily generated was then exposed to mild alkaline hydrolysis to generate the linear derivative. Zhang et al. synthesized PAsp–PGlut copolymers in DMF, using ortophosphoric acid as the catalyst [182]; a domestic oven was employed. Conversion was almost 100%, though the

molecular weight was relatively low (2.7 kDa). The copolymerization yield was mainly influenced by the effective MW power, while the final molecular weight was affected by both the effective power and the amount of organic solvent. This study did not comprise any comparison with the conventional heating procedure. More recently, Cavallaro et al. described the MW-assisted synthesis of α,β-poly-(N-2-hydroxyethyl)-D,L-aspartamide (PHEA) bearing pendant oligoamine groups such as diethylenetriamine as non-viral vectors for gene delivery [183]. MWs were employed as the heat source in the activation of PHEA with *bis*-(4-nitrophenyl)carbonate (4-NPBC) and the coupling of diethylenetriamine (DETA), the reaction being conducted in DMF. Reaction mixtures were irradiated for 30, 60 or 90 min using an irradiation power of 10 W and a temperature of 40 °C, yields being between 80 and 95%. These conditions were selected because the conventional activation of hydroxyl groups of PHEA with 4-NPBC is usually performed at 40 °C. The use of professional equipment constitutes a remarkable advantage. When the same reaction was conducted under conventional heating employing the same temperature and time, no derivatization with DETA was detected at the same reaction times of 30 and 60 min, and only 10% derivatization was found after 90 min. These findings confirm that a more homogeneous, fast and effective heating is attained with MWs. In agreement with a previous study [94], the volume of irradiated solvent affected the performance of the reaction; heat dissipation is more limited with smaller solvent contents and the heat is more efficiently adsorbed by the solute. The second step of the synthesis (nucleophylic addition of the amine to activated PHEA) does not require heating and was conducted at 25 °C for 4 h.

Copolymers complexed DNA, the efficiency depending on the aspartamide derivatization degree. In addition, they showed good blood compatibility and DNA/copolymer polyplexes were cytocompatible when tested with mouse melanoma (B16F10) and neuroblastoma (N2A) cell lines [183]. New automated and dedicated microwave peptide synthesizers are commercially available, facilitating the entire solid-phase peptide synthesis process, including deprotection, coupling, and cleavage reactions.

2.7. Polyethers

Poly(ethylene glycol) (PEG) is one of the most biocompatible polyethers and one of the most well investigated biomaterials [129,184]. The main features of interest are high solubility in both aqueous and organic solvents and limited toxicity and immunogenicity. Even though PEG does not undergo chemical hydrolysis *in vivo*, it is cleared by renal filtration, this process being dependent of the molecular weight. Due to this performance, different mono and bifunctional PEGs have been extensively used to modify surfaces, particles and biologically active molecules [185]. Pristine and PEG-containing biomaterials have also been employed to develop polymeric micelles and physical and chemical hydrogels. The synthesis of PEG comprises the polycondensation of ethylene glycol in the presence of acid or basic catalysis; this polymerization process is not very efficient and it results in derivatives of relatively low molecular weight, usually below 6 kDa [186]. Conversely, the high molecular weight counterpart, poly(ethylene oxide) (PEO), is produced by the polymerization of ethylene oxide. This synthetic pathway is more efficient than the polycondensation and leads to high molecular weight molecules (up to 1000 kDa). The MW-assisted synthesis of PEG or PEO homopolymers has not been investigated yet. Having expressed this, the original copolymerization of ETO with CO_2 to produce a poly(ether carbonate) using double metal cyanide catalysts under MW radiation has been preliminarily investigated by Dharman et al. [187]. The equipment employed enabled the convenient adjustment of the effective power between 100 and 500 W, the reactions demanding 3.5–11.5 min for conversion extents above 99%. However, the amount of CO_2 incorporated was low (~1%). The irradiation power influenced the reaction time, which decreased with the power. Conversely, the power did not strongly affect the molecular weight. MW irradiation led to shorter reactions and narrower molecular weight distributions than those obtained by the conventional thermal method (36 h), probably due to a faster and more homogenous heating. However, the conventional method resulted in significantly greater amounts of incorporated CO_2. Thus, the benefits of this technology are doubtful and additional studies to evaluate its use are demanded.

Even though the hydrolysis of these copolymers was not investigated, the presence of hydrophilic PEG segments is expected to confer greater water affinity and biodegradability. In a similar way, cyclohexene oxide was copolymerized with CO_2 to produce a highly hydrophobic counterpart [188]. It is worth stressing though, that the use of highly toxic catalysts remains a main hurdle towards any biomedical application. Chatti et al. explored the synthesis of other linear polyethers of isosorbide and isoidide [189,190]. Small toluene amounts (1 mL per 5 g reactants) were used to (i) control the reaction temperature due to heat dissipation owing to its low ε'' and (ii) diminish the viscosity of the medium [189]. Yields were similar to those observed with the thermal method but the times required to obtain a similar degree of polymerization (measured as the high-molecular weigh fraction soluble in methanol) decreased dramatically from 1–30 days to 0.5–1 h. Even though these studies are quite far from the biomaterials arena, they represent a valuable technological basis for further investigations leading to the faster and more efficient synthesis of PEG and PEO homo and heteropolymers.

2.8. Polyamides

Poly(ε-caprolactam), commonly known as nylon 6, is a PCL counterpart that withstands hydrolysis for longer times. Water swelling can reach approximately 10% and hydrolysis due to enzymatic catalysis may result in surface erosion [191]. Another related polyamide, poly(hexamethylene adipamide) or nylon 6,6 lost 25% and 83% of the tensile strength after 89 and 726 days in dogs, respectively [192]. Nylon 6 was intended for the development of an intrauterine device though it was

abandoned because of stress cracking and pelvic inflammatory disease [193]. A profuse literature describing the synthesis of aliphatic and aromatic polyamides under different conditions has been published [194–196]. In general, data support the advantages of MWs in terms of reaction rate, monomer conversion and yield. However, these polymers are not intended to perform as biomaterials and thus, they are out of our scope. Fang and coworkers homopolymerized ε-caprolactam ($\tan\delta = 0.46$, $\varepsilon'' = 6.440$) in the presence of an ε-aminocaproic acid catalyst under 90–135 W irradiation (temperatures were from 250 to 280 °C) over 1–3 h [77]. The equipment was a variable-frequency oven. Yields after purification were greater than 80%. Due to their biostability, homo-polyamides have found a more limited application in the biopharmaceutical field, though we mention this work to emphasize the versatility of the MW technology. Aiming to hasten the biodegradation and extend their use to tissue engineering, copolymers such as poly(ester amide)s have been developed [197]. For example, Borriello et al. polycondensed sebacic acid and ω-amino alcohols under MW irradiation to obtain poly(amide ester)s [198]. Biomaterials displaying pendant amide groups such as polyacrylamide and poly(N-isopropylamide) will be described below.

2.9. Poly(anhydride)s

Poly(anhydride)s were first investigated in drug delivery by Langer et al. in the early 1980s [199]. Their uniqueness stems from the ability to adjust the uniform surface bioerosion process from a few days to several years [200] and this versatility has paved the way to implement them in localized drug delivery [201]. The conventional synthesis is the melt polycondensation of acetylated dicarboxylic acid prepolymers over 1.5–3 h. In general, high molecular weight polymers are obtained with high yield. However, the complete synthetic process may take several working days. To hasten the synthesis of polyanhydrides, Vogel et al. studied for the first time the polycondensation of sebacic and 1,6-bis-(paraphenoxy) hexane diacids under MW irradiation without vacuum [202]. The most outstanding data are the significantly shorter reaction times, reduced to 6–20 min, probably owing to the fast and homogeneous heating. Due to the unavailability of dielectric properties data, the beneficial effect of any of the reactants cannot be established. Having expressed this, it is apparent that the reactants display good MW-absorbing properties that favor the reaction progress. Further studies of this research group are not available yet.

2.10. Other polymeric biomaterials

Other key biomaterials under extensive preclinical and clinical evaluation such as poly(alkylcyanoacrylates) and poly(ortho ester)s have not been synthesized employing MW. However, as extensively exemplified above, the potential of this technology indicates that the method to be further expanded and evaluated.

3. Graft polymerization

The chemical modification of natural and synthetic multifunctional macromolecular templates (e.g., carbohydrates, polyvinyl alcohol, etc.) by graft polymerization is a research area of great interest; it enables the combination of several polymers in one single molecule and, thus provides the final product novel and unique molecular architectures and physicochemical, mechanical and biological features. For example, Abraham et al. grafted PCL blocks onto acrylic backbones using dimethylacrylamide and/or methylmethacrylate as precursors [203]. The combination of dissimilar structures led to the control of the hydrophobic/hydrophilic balance and the biodegradation rate of the grafted polyester moieties. Thus, the ratio of the components tailored the swelling and degradation rate and modulated the release of an antitumoral drug from the matrix to the tumor bed. The present section will discuss the different MW-assisted chemistries used in graft polymerization.

3.1. Free radical polymerization

The linear free radical polymerization comprises two steps: (i) the generation of free radicals derived from primary alcohol groups and (ii) the reaction of the free radical with monomers bearing allyl groups. Singh et al. published the first report describing the MW-assisted free radical polymerization of acrylamide monomers onto guar gum [41]. While under MWs the reaction was efficiently conducted in the absence of any catalyst or radical initiator in aqueous medium, a redox pair of ascorbic acid/potassium persulfate (with $AgNO_3$ as the catalyst) was used to initiate the reaction under conventional heating. In addition, reaction rates and yields under MW irradiation were substantially greater than those under thermal conditions (Table 3); e.g., the grafting efficiency (the fraction of the monomer grafted) was 66.66% and the % grafting (the percentage increase in weight of the backbone) 190% after 0.22 min irradiation, as opposed to 49.1% efficiency and 140% grafting after 80 min with the conventional method. When the MW-assisted polymerization was carried out in the absence of the initiator/catalyst, the reaction indeed proceeded; the efficiency was 42.1% and the grafting 120% after 0.33 min. It is worth mentioning that since the reactions were conducted with a domestic oven, the MW

$$\mathrm{GOH} + \mathrm{M} \overset{\mathrm{MW}}{\rightarrow} \mathrm{GO}^{\cdot} + \mathrm{M}^{\cdot} \quad (1)$$

$$\mathrm{GO}^{\cdot} + \mathrm{M} \rightarrow \mathrm{GOM}^{\cdot} \quad (2)$$

$$\mathrm{GOM}^{\cdot} + \mathrm{M} \rightarrow \mathrm{GOMM}^{\cdot} \quad (3)$$

$$\mathrm{GOMM}^{\cdot}_{n-1} + \mathrm{M} \rightarrow \mathrm{GOM}^{\cdot}_{n} \quad (4)$$

$$\mathrm{GOM}^{\cdot}_{n} + \mathrm{GOM}^{\cdot}_{n} \rightarrow \text{Grafted polymer} \quad (5)$$

$$\mathrm{M}^{\cdot} + \mathrm{M} \rightarrow \mathrm{MM}^{\cdot} \quad (6)$$

$$\mathrm{M}^{\cdot}_{n-1} + \mathrm{M} \rightarrow \mathrm{M}^{\cdot}_{n} \quad (7)$$

$$\mathrm{M}^{\cdot}_{n} + \mathrm{GOH} \rightarrow \mathrm{GO}^{\cdot} + \mathrm{M}_{n}\mathrm{H}\ (\text{homopolymer}) \quad (8)$$

Scheme 3. Mechanism proposed for the MW-assisted grafting of acrylamide on guar templates. (Reproduced with permission of Elsevier from Ref. [41].)

Table 3
Conditions employed to graft poly(acrylamide) chains onto guar templates (adapted from Ref. [41] with permission of Elsevier).

	Conventional thermal method (with redox system and catalyst)	Under MW (with redox system and catalyst)	Under MW (without redox system and catalyst)
Grafting (%)	140	190	120
Efficiency (%)	49.12	66.66	42.10
Microwave power (80%)[a]	–	80	70
Temperature (°C)	60	60	63
Time (min)	80	0.22	0.33
% N	4.98	3.26	2.47

[a] MW power expressed as the percentage of the maximum MW potency (1200 W); the oven employed was a domestic one.

effective power is estimated as a percentage of the maximum power (1200 W).

The mechanism proposed by the authors involves the enhanced generation of free radicals by the MWs (Scheme 3). Because guar gum is a relatively rigid molecule, pendant –OH groups could behave as anchored to an immobile template. This phenomenon would favor their preferential fast dielectric heating when the system is irradiated. Since carbohydrate molecules cannot store the thermal energy, it is transferred to neighboring molecules (e.g., water, acrylamide). This overall evidence would suggest that MWs induce the formation of free radicals along the carbohydrate chain due to a localized overheating of –OH groups and the generation of O• reactive moieties that attack the reactive monomer, initiating the polymerization. An additional effect would rely on the lowering the Gibbs energy of activation of the reactions by the MWs. The same research group grafted polyacrylonitrile (PAN) and polyacrylamide (PAA) onto chitosan templates [204,205]. The thermal reaction with the potassium persulfate/ascorbic acid redox system resulted in 105% PAN grafting, while under MW 170% grafting was achieved within 1.5 min [204]. Moreover, with PAA, the MW-assisted grafting increased from 82% to 169% and in a dramatically shorter time, 1.2 min instead of 60 min. The hybrid lost the fibrilar nature of chitosan (Fig. 8). A similar trend was observed with the chitosan grafting of poly(methylmethacrylate) [206].

Other studies employed templates like starch [207] and xyloglucan [208]. Regardless of the usefulness of this synthetic approach and the substantial contribution of MWs to optimize the reactions, most of the research focused on the chemical aspects and did not fully exploit the results for biopharmaceutical applications. On the other hand, there exists an increasing interest in using this synthetic approach to produce hydrogels. These studies will be discussed in more detailed in Section 4.

3.2. Ring opening polymerization (ROP)

This grafting mechanism relies on the use of polysaccharide initiators, inherently displaying various –OH initiation sites for the ROP of lactones such as CL. Since the initiator is multifunctional, for similar monomer/initiator weight ratios the length of the poly(ester) blocks produced is shorter than that of PCL copolymers synthesized with mono or bifunctional initiators (e.g., PEG). In addition, the final products are more hydrophilic. Often, this architectural alteration not only affects the thermal behavior (lower crystallinity) and the biodegradability, but also improves processability [209]. As with linear ROP (see above), the main drawback of thermal reactions is that they may demand several hours. Liu et al. used chitosan templates to polymerize CL using SnOct as catalyst under mild conditions [210]. Amphoteric chitosan-g-PCL copolymers with high grafting percentage (up to 232%) were obtained in remarkably short times (∼15 min). Amine groups were initially protected with phthaloyl moieties, generating phthaloyl-protected chitosan (PHCS) and constraining the initiation step only to the –OH groups. The amine groups were then regenerated after the ROP with hydrazine monohydrate in water at 100 °C. The grafting percentage increased with irradiation time up to a maxima after 12.5 min (at 450 W) (Fig. 9). Additional irra-

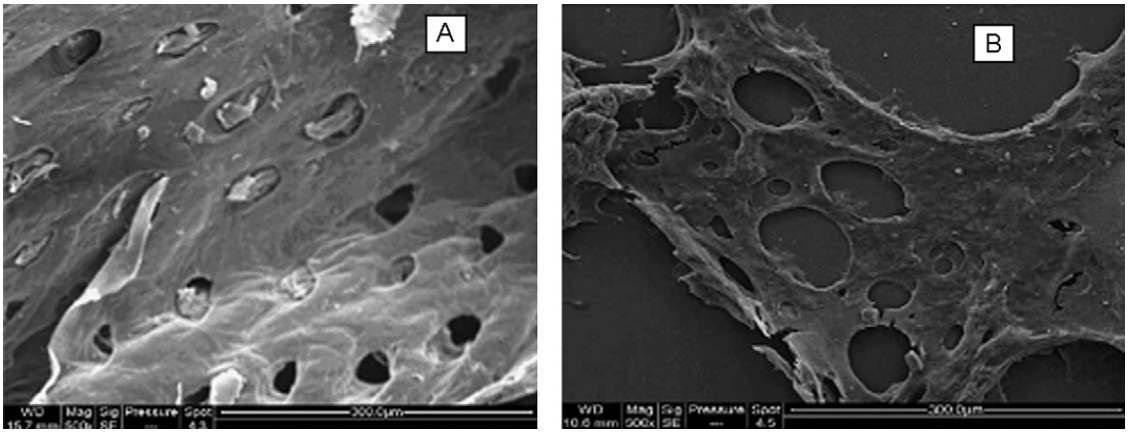


Fig. 8. SEM picture of chitosan (A) and PAA-grafted chitosan (B). (Reproduced with permission of Elsevier from Ref. [205].)

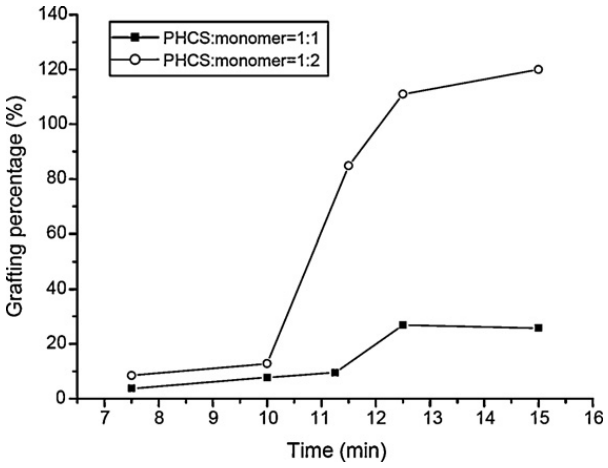


Fig. 9. Effect of irradiation time on the grafting percentage of chitosan-g-PCL (450 W). (Reproduced with permission of Elsevier from Ref. [210].)

diation did not improve the grafting extent, but either it did not provoke substantial chain scission and molecular weight decrease, as previously described for other polymerization reactions. This phenomenon may stem from the great number of relatively short PCL blocks grafted to the carbohydrate template. Even if chain scission takes place in several points and several PCL chain are lost, this would have only a slight impact on the overall molecular weight. Conversely, when a similar number of chain scissions takes place in a linear polymer result in a more pronounced molecular weight decrease. Chitosan was also evaluated to initiate the polymerization of D,L-LA [211]. Under MWs, grafting % between 323% and 632% were obtained for LA:chitosan feeding molar ratios of 20:1 and 40:1, respectively. Similarly, CL was polymerized using polyvinyl alcohol [212] and starch as initiators [213].

Following the same concept, surface-functionalized inorganic and organic micro and nanoparticle reinforcements were used to initiate the polymerization of CL and LA and to produce composites. These studies are the focus of Section 6.

4. Hydrogels

Hydrogels are water-swollen three-dimensional polymeric networks generated by the physical or chemical crosslinking of polymeric chains [214]. Owing to the high water content, natural and synthetic hydrogels are among the most appealing systems for the drug delivery of soluble and insoluble drugs and biologically active molecules (e.g., proteins) [215,216], and cell culture and tissue engineering [217]. For an introduction on hydrogels for biomedical applications, we invite the readers to consult reference [218]. The use of MWs in the synthesis of biomedical hydrogels is confined to the last 5–6 years. Prior to 2004, MW irradiation was only barely evaluated in the disinfection of hydrogel contact lenses [219]. Since the use of this means has been relatively limited, we chronologically describe the most relevant investigations in a single section. The first work expressly envisaging the use these chemically modified polysaccharides in the biomedical field described the synthesis of gel-forming polyvinylpyrrolidone (PVP)-grafted agar and κ-carragenan blends [39]; the synthetic pathway used was the radical polymerization grafting depicted in Section 3.1. Reactions were completed within 2 min and owing to their crosslinked nature the products were not crystalline as the pristine carbohydrates. The dry copolymers displayed greater water-absorption capacity than the pristine derivatives; e.g., agar-g-PVP and carageenan-g-PVP absorbed 8.5 g and 9.6 g water per gram of copolymer, while the unmodified sugars only 5.0 and 4.1 g, respectively. In addition, the hydrogels exhibited enhanced water-holding capacity. On the other hand, smaller mechanical strengths were apparent. In this context, they could be more advantageous for the development of absorbent wound dressings [220,221], tissue engineering matrices [222] and topical drug delivery systems [223]; subcutaneous carrageenan induces an inflammatory response in animal models and cannot be administered by the parenteral route [224]. Following a similar rationale, they synthesized adhesive κ-carrageenan-g-PAA copolymers with different N contents [225]. Matrices made of the copolymer containing 6.35% N were soft gels, while with 11.05% they were more adhesive. Materials with intermediate N content of 10.56% displayed greater water-absorbing properties (up to 22-times). MW irradiation was also evaluated in the condensation of PAA with amine-bearing adamantyl groups [226]. The reaction was completed within 20 min without solvents and coupling agents. The incorporation of hydrophobic pendant groups improved the hydrophobic interchain interactions in water, generating physical networks. Lin-Gibson et al. reported for the first time on the implementation of MW irradiation in the context of the synthesis of crosslinked hydrogels [227]. Crosslinked PEG and PEG-rich hydrogels have been extensively investigated for drug delivery and cell culture [228–232]. However, in this work, MW irradiation was involved only in the primary synthesis of the photopolymerizable and biocompatible poly(ethylene glycol) dimethacrylate (PEGDMA) precursor [227]; PEGDMA was obtained by reacting PEG of different molecular weights (1–8 kDa) with methacrylic anhydride under solvent-free conditions; a domestic oven with operating power of 1100 W was used. Conversely, the conventional method involved the use of triethylamine. The conventional thermal reaction demanded 4 days, while the MW-assisted one only required 10 min. Even though the authors of this study did not address the mechanism that leads to this improvement, it may be related to the high MW-absorbing capacity of PEG; although PEG is expected to display a more limited absorbing capacity than its ethylene glycol monomer, ethylene glycol is among the materials displaying the highest tan δ and ε'', values being 1.350 and 49.95, respectively. [43].

Since the hydrogels were intended for the encapsulation of chondrocytes, performing the crosslinking of cell-containing systems under MW irradiation would lead to total cell death. This is a serious limitation when this technology is compared to other crosslinking methods that display good cytocompatibility (e.g., photoinitiated crosslinking) [228–231].

Poly(*N*-isopropylacrylamide) (PNIPAM) generates thermo-responsive physical hydrogels that are liquid at

Table 4
Reaction temperature and reaction time of the polyNIPAM hydrogels (adapted from Ref. [234] with permission of Elsevier).

Method	Sample	T (°C)	Reaction time (min)	Yield (%)	Pore volume (cm^3/g)	Average pore size (nm)
Conventional thermal heating MW (300 W)	PN-70-24 h	70	1440	72.11	5.2×10^{-4}	2.10
	PN-80-24 h	80	1440	73.35	1.5×10^{-3}	2.37
	PN-90-24 h	90	1440	75.33	1.2×10^{-3}	2.55
	PN-70-20 min	70	20	97.69	5.4×10^{-3}	3.19
	PN-80-20 min	80	20	98.09	2.7×10^{-2}	2.91
	PN-90-20 min	90	20	99.43	4.4×10^{-3}	3.14

PN: PNIPAM.

room temperature and gels at 37 °C; the temperature of the sol–gel transition is defined as the lower critical solution temperature (LCST) and it is usually around 32 °C. Thus, PNIPAM derivatives are widely used as "smart" drug delivery matrices and tissue engineering scaffolds that can be injected by minimally invasive techniques [121]. Shi and Liu polymerized NIPAM using PEG of molecular weight 600 as the reaction medium, radiation absorbing agent and porogen [233]. By changing the NIPAM/PEG feeding ratio, controllable pore size and swelling/deswelling properties were attained. Similarly, Zhao and coworkers compared the synthesis of crosslinked PNIPAM by thermal and MW methods [234,235]; *N,N′*-methylenebisacrylamide and azobis (isobutyronitrile) were used as crosslinker and initiator, respectively. The former was conducted at 70, 80 and 90 °C and demanded 24 h (yield was ~73%), while the latter required only 5–30 min and the yield was 87–100% [234] (Table 4). MW-produced hydrogels showed a more porous structure that enabled more efficient water diffusion into or out of the network upon cooling/heating cycles [234,235] (Fig. 10). These findings were consistent with a more complete crosslinking process. Very recently, PAA hydrogels were rapidly produced and the kinetics of the network formation was thoroughly investigated [236]. The reaction rate increased between 32 and 43 times with MW. In addition, the MW-assisted process behaved as a first-order reaction, whereas the thermally driven as a second-order one.

"Click chemistry" is a synthetic rationale introduced approximately one decade ago that relies on the quick and reliable synthesis of compounds by reacting small functional groups [237]. Bardts and Ritter employed MWs for the first time to incorporate pendant cystamine groups into poly(methacrylic acid) (PMAA) chains by the formation of amide bonds [238]; the reaction was conducted at 80 W over 10 min. Then, this derivative was reacted with allyl-derivatized PMAA by thiol-ene reactions to form crosslinked gels. Surprisingly, MW irradiation was not evaluated in the crosslinking step and this reaction demanded 2 h.

Overall data converge to crown MW as the fastest and more efficient method for the production of water-containing matrices. Nevertheless, these incipient studies still appear as relatively isolated efforts and thus, the potential of this area remains unexploited.

5. Emulsion *in situ* polymerization for the production of latex micro and nanoparticles

Micro (MPs) and nanoparticles (NPs) are among the most attractive technological tools to encapsulate drugs and improve their aqueous solubility, stability and bioavailability as well as controlling their release, independently of the administration route [116]. A method extensively used to produce drug-loaded particles is the emulsion *in situ* polymerization of reactive vinyl derivatives (e.g., styrene and methacrylic acid) that results in the generation of the commonly named "latex particles" [239]. Since these materials are not biodegradable, they are mainly envisioned for administration by non-parenteral routes such as pulmonary and mucosal [240,241] and they can be also intended for *in vitro* diagnosis applications [242,243]. Owing to the faster radical polymerization rates and the more homogeneous heating, MW irradiation was

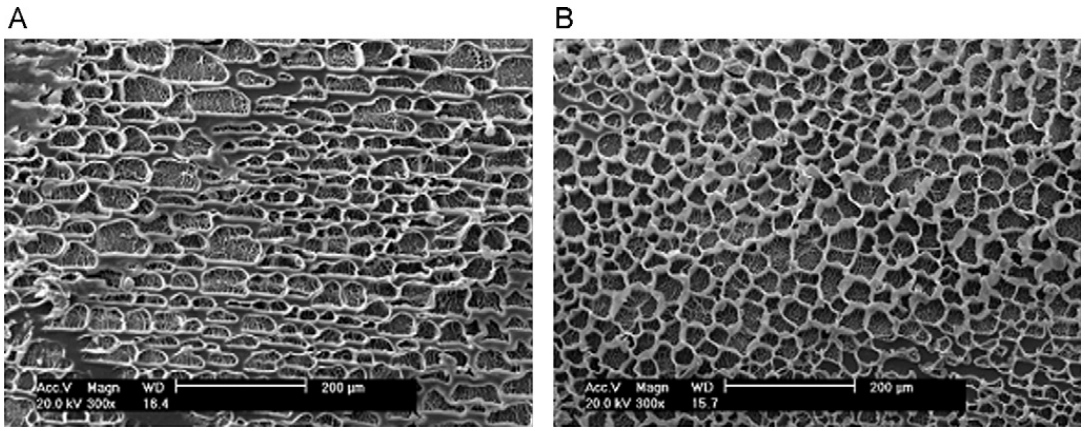


Fig. 10. SEM micrographs of PNIPAM hydrogels produced by (A) conventional thermal method (PN-80-24 h) and (B) MW (PN-80-20 min). Magnification is 300×. (Reproduced with permission of Elsevier from Ref. [234].)

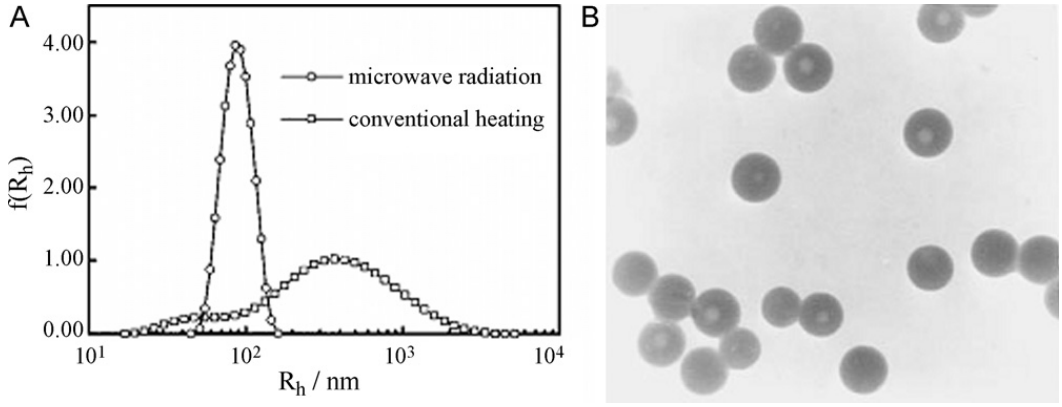


Fig. 11. (A) Comparison of the typical hydrodynamic radius distributions ($f(R_h)$) of the nanospheres prepared by microwave radiation (○) and by the conventional heating method (□). (B) Electron microscopy micrograph of surfactant-free polystyrene nanoparticles prepared by MW. Magnification = 50,000 times. (Reproduced with permission of the American Chemical Society from Ref. [244].)

assessed to produce narrowly distributed latex MPs and NPs. In a pioneering work, Zhang et al. produced almost monodisperse polystyrene (PS) nanospheres by polymerizing a surfactant-free styrene nanoemulsion under mild MW irradiation (80 W) over 1 h [244]; the monomer conversion was completed within 40 min, while under conventional heating for 10 h was required. NPs with sizes between 60 and 120 nm were produced, the size being a linear function of the initial monomer concentration. Moreover, a dramatic decrease in the size polydispesity was observed (Fig. 11). Correa et al. also reported that MW irradiation hastens the emulsion polymerization more than 70-times when compared to a similar reaction under conventional heating. In addition, the molecular weight by MWs was increased 1.2-fold [245]. The main feature of MWs leading to a more uniform size distribution probably stems from the fast and homogeneous heating of the droplet in both the bulk and at the interface; homogeneity is an additional feature of MAPS that leads to narrower molecular weight distributions. However, the mechanism also depends on the monomer concentration and the monomer nature [245]. Palacios and coworkers observed that the MW-assisted polymerization of styrene is completed within 20 min, while the thermally driven polymerization requires more than 5 h [246]. This technique can be also used to emulsion-polymerize other monomers, such as methyl methacrylate (MMA) [247,248], *n*-butyl methacrylate (BMA) [249], NIPAM [250,251], silicone precursors [252] and monomer mixtures [253,254]; PMMA, PBMA and the thermo-responsive PNIPAM are hydrogel-forming polymers usually used in the sustained release of drugs. An et al. prepared functionalized NPs by polymerizing and crosslinking MMA together with ethylene glycol diacrylate, ethylene glycol dimethacrylate and *N*,*N*′-methylenebisacrylamide [255]. The size distribution was controlled very well by confining the cross-linking to intraparticle rather than interparticle cross-linking (Fig. 12). In addition, the incorporation of hydroxyethylmethacrylate into the reaction mixture enabled modification of the surface chemistry to improve the physical stability of the colloid. In a more recent study, the same research group produced double hydrophilic block copolymers and nanogels made of PNIPAM and poly(*N*-isopropylmethacrylamide) (PNIPMAM) by reversible addition-fragmentation chain transfer (RAFT) polymerization [256]. Since RAFT is a living polymerization, NPs displayed reactive groups on the surface that can be capitalized to modify the surface chemistry with recognition ligands. Remarkably, the size of the particles can be elegantly adjusted by varying compositional parameters of the reactive system such as monomer, emulsion stabilizer and dispersant chemistry and concentration, initiator concentration and ionic strength [257,258] and the parameters of the oven (e.g., irradiation power) [259].

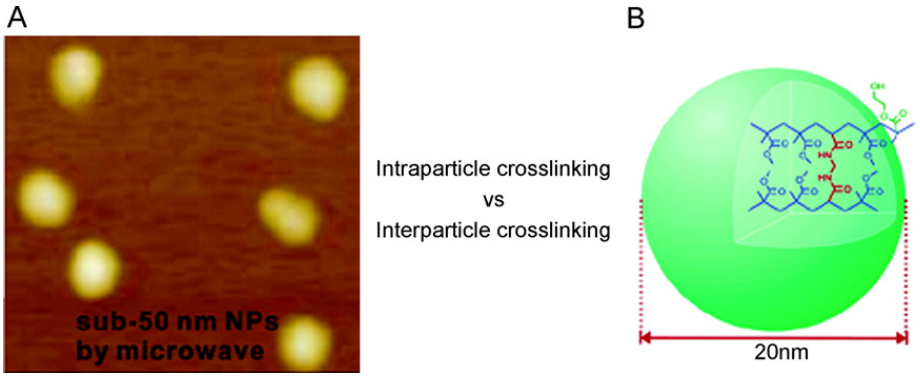


Fig. 12. AFM image of cross-linked poly(methyl methacrylate) sub-50 nm NPs obtained under MW irradiation (A). The intraparticle crosslinking was favored over the interparticle one (B). (Reproduced with permission of the American Chemical Society from Ref. [255].)

In summary, the findings strongly support the versatility of MW technology for the development of particles made of polymers usually used in drug delivery, such as poly(alkylcyanoacrylate)s and the pH-responsive PMAA and poly(acrylic acid) (PAA) can also be envisioned.

6. Synthesis of inorganic biomedical polymers

Inorganic polymers are defined as structures displaying a main chain built of repeating units that do not contain carbon [260]. The most common in the biomedical field are polydimethylsiloxane (PDMS, $-[O-Si(CH_3)_2]_n-$) and other Si-containing polymers. Polyphosphazenes, a phosphorous-based polymer ($-RR'P{=}N-$) [261], also belong to this peculiar group. In general, their properties can be tailored by changing the pendant side groups. The advantages of MW-assisted synthesis and sintering of osteoactive calcium phosphate ceramics have been extensively investigated [262,263]. However, we will focus only on those inorganic materials of polymeric nature. On the other hand, in the next section, the use of ceramic materials as polymerization substrates for the production of hybrid composites will be reviewed. The application of MW in this niche has been very limited and exclusively assessed of the production of silica materials by the sol–gel process; sol–gel involves the initial hydrolysis of a siloxane precursor to silanol and the later condensation to form a 3D $-(-Si-O-)_n-$ crosslinked network [264].

Geppi and collaborators polymerized tetraethoxysilane and a triethoxysilane-terminated polyethylene-*b*-PEG copolymer to produce inorganic–organic hybrids [265]. The molecular structure of the material formed under conventional heating was compared to that of MW. In full agreement with previous studies showing the acceleration of the reaction rates, the extent of condensation that demanded several hours under the standard conditions, was attained within 1 min with MW. When this approach was employed for the production of silica particles, reactions were more efficient and narrower size distributions were obtained [266,267]. These results were in agreement with previous studies [235]. In a different application of MW, Steinberg et al. used liposomes made of L-α-dipalmitoylphosphatidylcholine and the PEGylated phospholipid N-(carbonylmethoxypoly(ethylene glycol 2000))-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine as templates for the production of silica and alkylated silica nanocapsules (100 nm) [268]. The nanocarriers entrapped anionic dyes water solutions that were released from the reservoir under MW irradiation. MWs apparently produce very small fissures that are visually undetectable.

7. Synthesis of polymer-based biomedical composites

Composites are materials comprised of two or more constituents of similar or different chemical nature, separated by an interface; the dispersed or non-continuous component, namely the reinforcement, is embedded in the continuous matrix [269]. The reinforcement can be polymer and carbon fibers and particles and glass or ceramic fillers, while the matrix is usually of polymeric nature. The ability of the matrix to transfer an applied stress to the reinforcement renders these materials with especially improved mechanical characteristics, appropriate for fulfilling structural and mechanical roles in hard tissue repair and dentistry. The energy transfer process relies on intimate reinforcement/matrix interaction. Thus, the better the interaction attained, the greater the mechanical properties of the material. For example, Papargyris et al. compared the mechanical properties of carbon fiber/epoxy composites produced by the conventional method and MW [270]. When exposed to four-point bending and interlaminar shear testing, samples produced by the conventional method showed poorer interfacial bonding and more extensive fiber pullout than the composites produced by MW irradiation (Fig. 13). This improvement of the interlaminar shear strength for MW-produced samples was attributed to the lowering of the resin (matrix) viscosity at the initial stages of the curing process due to more effective heating, this phenomenon facilitating resin flow and interfacial resin-fiber bonding.

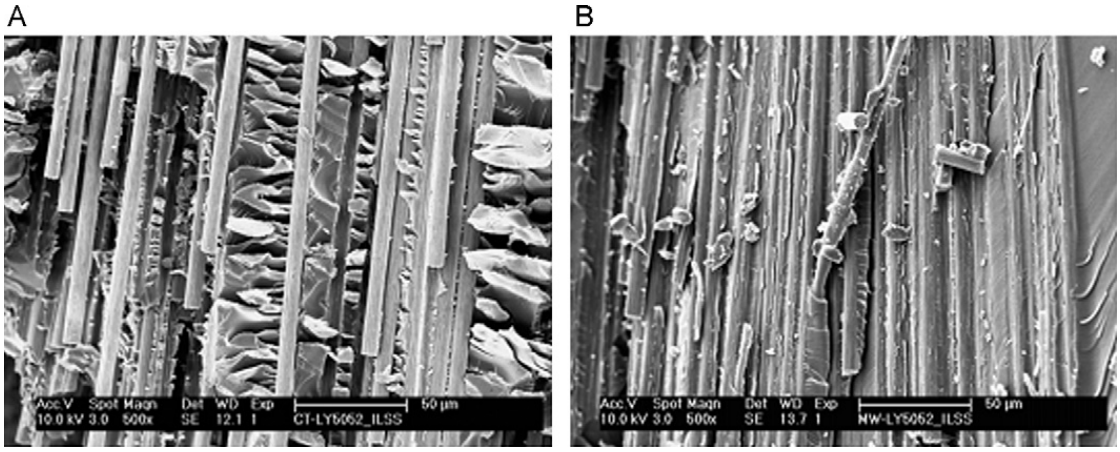


Fig. 13. SEM micrographs of carbon fiber/epoxy composites after interlaminar shear test showing: (A) clean fibers in conventionally cured specimen and (B) fibers coated with resin in microwave cured specimen. (Reproduced with permission of Elsevier from Ref. [270].)

In this framework, few research groups capitalized on MWs for the *in situ* polymerization of the matrix in presence of the reinforcement that also plays the role of an initiator. In general, better interfacial integration and greater mechanical performances were observed. The ROP of lactones (e.g., CL and LA) employing surface-functionalized inorganic and organic reinforcing agents such as hydroxyapatite [271], carbon nanotubes [272–274], clays [275,276] and nanocrystalline starch [277] has probably been a common synthetic approach to produce biomedical composites. In spite of the proven synthetic capabilities of MWs, only a few studies describing the *in situ* MW-assisted synthesis of biomedical composites have been published. For example, biodegradable β-tricalcium phosphate/PLGA composites for bone tissue engineering were produced by the *in situ* polymerization of LA and GA [40]. Tang et al. synthesized organic–inorganic polyacrylamide–calcium phosphate nanocomposites from calcium chloride, ammonium phosphate and acrylamide monomer in aqueous solution by a single-step microwave-assisted method [278]. Hexagonal hydroxyapatite nanorods were homogeneously distributed in the polyacrylamide matrix. However, these studies did not compare the mechanical properties attained by both methodologies. Kajiwara et al. prepared a poly(2-hydroxyethyl methacrylate) (PHEMA)/silica hybrid by polymerizing HEMA together with the sol–gel process of methyltrimethoxysilane [279]. The reaction rate and the HEMA degree of polymerization were increased by MWs, while the thermal properties remained almost unchanged with respect to the same material produced under conventional heating. Additional studies explored the effect of a post-synthesis MW-heating on the mechanical properties of the material. Data consistently indicated that the post treatment results in greater strength and modulus [280,281]. The lack of substantial contributions, as apparent from the very small number of articles available, stresses the unexplored character of this field and the immense potential that research in these avenues encompasses.

8. Microwave processing of polymeric scaffolds and particles

Three-dimensional (3D) structures have been recognized since the mid-1970s as key components for the development of engineered tissues and organs. The development of artificial extracellular matrices to serve as templates for cell attachment/suspension, proliferation, growing, and delivery, has progressed at a tremendous rate in recent years. Many methods are available for developing 3D porous scaffolds using polymeric materials for tissue-engineering applications, each showing advantages and disadvantages [282]. Among them, solvent casting and particulate leaching, membrane lamination, fiber bonding, phase separation/inversion, melt-based technologies, microparticle aggregation, and MW baking and expansion, just to cite some examples. Highly reproducible 3D scaffolds have been also obtained using rapid prototyping technologies such as fused deposition modeling and 3D printing [283,284]. Many of these technologies fail to provide the scaffolds with basic requirements such as pore interconnectivity and suitable mechanical properties, and most of them are only able to produce scaffolds with specific requirements for a limited number of applications. MW processing of polymer scaffolds has been reported by Reis et al. [285,286] as an innovative methodology for producing porous biodegradable starch-based tridimensional structures for tissue engineering. MW-based techniques allowed the preparation of porous scaffolds exhibiting an interesting combination of morphological and mechanical properties that matched the compressive behavior of human cancellous bone. It was possible to produce starch-based degradable scaffolds with interconnecting pores and density in the 0.40–0.50 g/cm^3 range that may find use in tissue engineering or drug delivery applications. Formulations containing 10% blowing-agent (corn starch, sodium pyrophosphate and sodium bicarbonate) in the presence of hydrogen peroxide, exhibited a compression modulus of 530 MPa and a compressive strength of 60 MPa, values close to those of the native cancellous bone. To improve the mechanical properties and to introduce bioactive components into the porous structures, composite porous structures using hydroxyapatite as filler by means of a similar MW technique were also investigated [286]. This processing route was also used to obtain loaded drug delivery porous carriers, incorporating meclofenamic sodium salt, a non-steroid anti-inflammatory agent, as model drug. It was expected that the developed methodology might be used for other drugs and growth factors that play a crucial role in tissue engineering. MW was also used to produce biodegradable scaffolds from different types of starch-based polymers using water and glycerol as plasticizers [287]. Compressive mechanical properties were assessed by indentation tests, and a strong dependence of the indentation stress on the average pore size was found. Studies in simulated body fluid studied the *in vitro* bioactivity, degradability, and surface topology evolution in the scaffolds. MW radiation under vacuum was another methodology reported for the fabrication of 3D porous scaffolds [288].

MW treatment also alters the structure of polymeric matrices and thus, the release profile of encapsulated drugs. For example, Vandelli et al. crosslinked diclofenac-containing gelatin microparticles by exposing them to MW radiation for 10 min [289]; no chemical crosslinker was used. Treatments at increasingly higher temperatures between 150 and 250 °C reduced the water-soluble fraction from 85% (untreated) to 16%. These findings suggested that the condensation of free amine and carboxylic groups and formation of amide moieties takes place on MW exposure. In addition, the microparticles remained biodegradable and biocompatible. A drawback of the approach was that owing to the need to avoid diclofenac degradation under these extreme temperature conditions, the drug was loaded by means of the "unelegant" soaking method. Similarly, diclofenac-loaded pectinate and pectinate–chitosan beads were exposed to 80 W for 5, 10, 21 and 40 min and the release kinetics investigated [290]. The drug stability was not affected by the radiation. In the case of pure pectin beads, an increase in the extent and rate of drug released was observed upon expo-

sure to MW, this phenomenon probably stemming from the reduced pectin–pectin interactions. Simple coacervation of pectinate matrix with chitosan did not reduce the release and the MW treatment was essential to increase the drug–matrix and the pectin–chitosan interaction that moderates the release. Treatment of chitosan beads at 80 W for 5 min reduced the rate and extent of release though to a smaller extent than that observed in pectin–chitosan systems that appeared as the most appropriate. Finally, MW-assisted plasma has been also intended for the post-treatment surface modification of scaffolds with greater efficiency than the standard plasma technique [291]; MW applies higher frequency radiation. The benefits of this approach have already been apparent for improving the chondrogenic response of porous silk fibroin scaffolds [292]. Having expressed this, these studies are beyond the boundaries of the present review.

9. Conclusions and perspectives

The different applications of MW irradiation for the fast, reproducible and scalable synthesis of polymeric materials have been thoroughly (and critically) discussed. Independently of the biomaterial, data consistently point out MW as a novel and powerful tool in this field. As opposed to the extremely extensive work done in organic synthesis, where MW irradiation is an undeniable and key player, the potential of this platform in biomaterials science remains uncapitalized. This phenomenon is evidenced by the relatively few contributions available in the scientific literature and the still few industrial ventures that embraced it. A main obstacle that needs to be overcome to expand the applicability of MW irradiation in the pharmaceutical and biotechnology industry pertains to the design and commercial availability of professional ovens that enable precise control of the reaction conditions, on one hand, and the mass production in one single reaction process, on the other. A crucial difference between drugs and biomaterials is that while the former are often required in a relatively low concentration per dose unit, the latter are used in larger amounts. In this context, their massive production under high-quality standards is still difficult due to the lack of appropriate MW equipment. Until now, trials aiming to design batch, semi-continuous and continuous flow MW reactors have been relatively independent and they employed home-designed equipment. Another interesting perspective relates to the potential application of this technology in fine polymer chemistry to carry out specific chemical modifications. For example, we are investigating the mild MW-assisted oxidation of the terminal –OH groups of linear and branched PEO–PPO block copolymers to produce reactive aldehyde precursors; preliminary results suggest that the reaction times can be shortened from 8–30 h to 5 min. As mentioned in the introduction, the establishment of the first industrial plant for the synthesis of PLA in Japan represents a turning point in the perspectives of the field. MW irradiation has shown many advantageous features over the conventional methods and, even if the experimental conditions to implement and expand its applications in industry remain to be optimized, it is crystal-clear that MW irradiation represents one the most versatile and promising synthetic and processing technologies available today. We certainly envision MW irradiation as a key player to make biomaterials more accessible pharmaceutical excipients and the products that involve them more affordable to patients. The pace of these progresses will be probably dictated by the ability to design and produce professional ovens that combine great versatility of applications and working conditions at reasonable costs.

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