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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