EXPLOITING RAFT POLYMERIZATION TO TAILOR VEHICLES FOR UPTAKE AND RELEASE OF POLYPHENOLS

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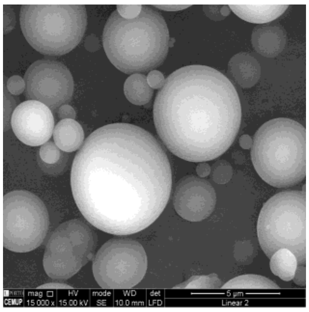
Introduction

Polyphenols have been attracting a growing interest by pharmaceutical, biomedical, cosmetic and food industries due to their proven beneficial effects on human health (e.g. antioxidant and anti-inflammatory effects with positive impact on protection of the cardiovascular system, cancer prevention or anti-aging actions). However, an effective bioavailability is an important practical issue. Failing to achieve it leads to no visible benefits of their use. Indeed, fast degradation in common conditions (owing to high sensitivity to temperature, pH and light), poor solubility in biological fluids and high metabolic and secretion rates are some well-known processes limiting polyphenols impact [1]. Thus, the development of vehicles aiming at stabilizing and protecting polyphenols from degradation, also allowing their sustained release, is a key issue to improve the effectiveness of such compounds.

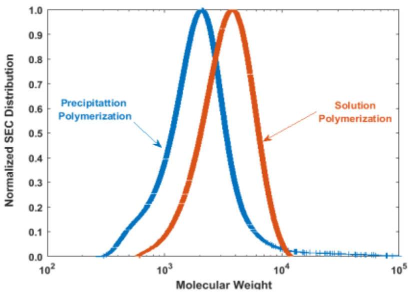
In this research, we explore RAFT polymerization to develop tailored materials useful as vehicles for the uptake and release of polyphenols. The preparation and testing of polymersomes based on RAFT-synthetized amphiphilic block copolymers and the generation of hybrid natural/synthetic materials, namely through the RAFT-mediated grafting of synthetic polymers on cellulose, are two different approaches here reported.

Results and Discussion

Preparation of spherical polymer compartments (polymer vesicles) can be achieved by self-assembly of amphiphilic block copolymers (e.g. diblock AB or triblock ABA). These kinds of architectures are being widely considered in therapeutic and biotechnological applications [2] but their performance is dependent on the structure and properties of the constituent block copolymers. RAFT polymerization offers the possibility to design the block copolymers (as also does ATRP, another good alternative) to be used as precursors of the polymersomes, namely concerning the size of the different chains and their possible sensitivity to external stimulation (e.g. through the incorporation of pH/temperature sensitive polymers). Following this line of thought, our research explores the RAFT for the synthesis of different kinds of amphiphilic block copolymers, considering hydrophilic monomers, such as acrylic acid (AA) or methacrylic acid (MAA), and styrene (S) to generate hydrophobic moieties.



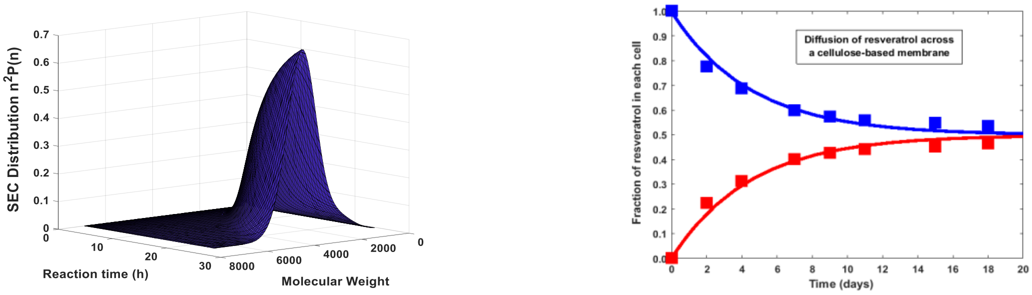
(a)



(b)

Figure 1. (a) SEM micrograph of RAFT-synthetized MAA homopolymer particles obtained through precipitation polymerization in ACN/MeOH 10/1. (b) Measured SEC distributions for RAFT-synthetized polystyrene homopolymers obtained alternatively in a DMF solution or by precipitation polymerization in ethanol.

Different RAFT agents have been tested (e.g. dithiobenzoates as 4-cyano-4-(thiobenzoylthio)pentanoic acid or trithiocarbonates as 2-cyano-2-propyl dodecyl trithiocarbonate). Different polymerization conditions (e.g. initial proportion monomer/RAFT agent/initiator) have also been used as a potential tool to tailor the copolymers and the final polymersomes. The effect of the use of solution and precipitation polymerization is likewise assessed. Produced homopolymers and copolymers are characterized using different techniques, namely GPC, FTIR and SEM (see Fig. 1(a) and 1(b)). Our experimental work is accompanied by modeling studies concerning solution/precipitation RAFT polymerization, aiming at the development of polymer reaction engineering tools to design such kind of products (see Fig 2(a)).



(a) (b)

Figure 2. (a) Predicted time-evolution of the SEC distribution for the RAFT polymerization of styrene in DMF solution. (b) Measured and predicted profiles for the diffusion of resveratrol across a cellulose-based membrane separating a two-compartment cell.

The purified copolymers were used to prepare polyphenol-loaded/non-loaded polymersomes through their dissolution in an organic solvent in the presence/absence of the selected bioactive molecule (e.g. resveratrol, quercetin, oleuropein), followed by its dropwise addition to a selected aqueous media (e.g. at a specified pH value). After stirring, the resulting solution was dialyzed in a cellulose membrane bag against the same/other aqueous media, which was replaced along the time. The loading efficiency and the release of the different polyphenols in the polymersomes were evaluated through HPLC/UV measurements of samples collected in the successive dialysis processes performed.
On the other hand, RAFT polymerization can also be used to graft synthetic polymers on cellulose leading to hybrid materials with modified features (e.g. elasticity, hydrophobicity/hydrophilicity, stimulation ability, etc.) [3]. Crosslinking of cellulose is another possible strategy to modify the physicochemical properties of native cellulose (e.g. water absorption) [4]. These possibilities were also explored in this work to design hybrid cellulose-based carriers for uptake/release of polyphenols, namely concerning the sizes of the RAFT-grafted chains (see also see Fig 2(a)) or the development of membranes with tuned rates of polyphenols diffusion (see Fig. 2(b)).
Results obtained up to now shown that RAFT polymerization is a valuable tool for designing carriers of polyphenols. Ongoing studies explore the specific relations between the polyphenol structure (e.g. their size/functionality) and the design of the carrier structure (e.g. polymersome size/functionality).

Acknowledgments

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9:00-9:45	**PL3**	**Marc A. Hillmyer.** Harnessing disorder in self-assembled block polymers for functional nanostructures.		
9:45-10:15	**KN9**	**Annette M. Schmidt.** Exploiting Particle-Matrix Interactions in Complex Soft Matter		
10:15-10:40	**IL7**	**Eric Drockenmuller.** Poly (1, 2, 3-triazolium)s: functional and dynamic polymer electrolytes.		
10:40-11:05	**IL8**	**Christophe Detrembleur.** A robust and versatile process for converting CO_2 into new families of regioregular and functional polymers		
11:05-11:40		**COFFEE BREAK** **Rooms Madera+Música+Blanco.**		
		Session Nano- Materials (II) **Room J. C. Baroja.**		**Session Nanobiomaterials** **Room Comedor Real**
11:40-12:00	**OR17**	**F. Barroso-Bujans**. Synthesis of cyclic polyethers with orientation of the dipolar moment along the chain contour	**OR21**	**Marcelo Calderón.** Protease degradable nanogels with fluorogenic reporter for theranostic applications
12:00-12:20	**OR18**	**Leire Ruiz-Rubio.** Hybrid polymer-polyoxometalate assemblies as precursors of advanced materials	**OR22**	**Thomas Defize.** Coumarin-based poly(ε-caprolactone) for light-controlled design and remodeling of shape-memory networks
12:20-12:40	**OR19**	**Catarina P. Gomes**.Exploiting RAFT polymerization to tailor vehicles for uptake and release of polyphenols	**OR23**	**Luciano F. Boesel.** Nanophase-separated, functional APCNS for biomedical applications
12:40-13:00	**OR20**	**Martin Steinhart.** Non-classical Surface patterning with (sacrificial) spongy block copolymer monoliths	**OR24**	**Aitor Larrañaga.** Fabrication of nanostructured polymer films based on bioresorbable polyesters and graphene oxide to promote neurodifferentiation of stem cells
13:00-13:30				**Special Session Short talks** **ST23**. B. Robles-Hernández **ST24** D.E. Martinez-Tong **ST25** O. Ofoegbu
13:30-15:00		**LUNCH** **Rooms Madera+Música+Blanco.**		
		Room J. C. Baroja. Session Nanostructured Materials (III)		
15:00-15:20	**OR56**	**Lars Berglund.** Chitin fibrils in organisms and man-made materials		
15:20-15:40	**OR26**	**Florent Dalmas.** Self-repairing silicone materials: links between supramolecular interactions, microstructure and thermomechanical behavior		
15:40-16:00	**OR27**	**Nikolaos Politakos.** 3D-Porous graphene and graphen-polymer composite materials for selective CO2 capture		
16:00-16:20	**OR28**	**Juan M. Giussi.** Responsive soft-nanopillars with tunable induced changes		
16:20-16:45	**IL9**	**Beata Luszczynska.** Organic photodetectors and photovoltaics – influence of space charge limited current and unbalanced mobilities on device parameters		
16:45-17:00		**CLOSING REMARKS**		