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Eudragit® L100 Post-Modification via Ugi Multicomponent Reaction

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This work investigated the post-modification of commercial poly(methyl mechacrylate-*co*-acrylic acid) using the versatile multicomponent Ugi reaction. This reaction introduces diverse functionalities to tailor the polymer properties effectively. The commercial copolymer which is known for biocompatibility and drug delivery application was subjected to the Ugi reaction, altering its chemical structure. The structure of the modified polymer was checked by Fourier transform infrared spectroscopic and nuclear magnetic resonance and thermal characterizations, confirming successful Ugi component integration. Additionally, gel permeation chromatography assessed molecular weight changes. Results revealed enhanced thermal stability of the modified polymers compared to unmodified polymer, potentially advantageous in high-temperature applications. In summary, the study demonstrates efficient poly(methyl mechacrylate-*co*-acrylic acid) post-modification through a multicomponent Ugi reaction, yielding tailored polymers. Comprehensive spectroscopic, thermal, and gel permeation analyses shed light on structural changes and improved stability, pivotal for innovative applications like drug delivery.

Keywords: poly(methyl mechacrylate-*co*-acrylic acid), post-modification, Ugi multicomponent reaction, spectroscopic characterization

Introduction

One promising approach for obtaining diverse functional materials in a single system is the use of multicomponent reactions (MCRs). These reactions are synthetic tools that involve the coupling of more than two starting materials to form multifunctional compounds, reducing the number of synthetic steps required and making them highly economical.[1]

One well-known multicomponent reaction is the Ugi reaction, which was first described by Ivar Ugi in 1959.[2-4] This transformation belongs to the class of isocyanide-based MCRs and involves the use of four components: aldehyde, amine, isocyanide and carboxylic acid. The Ugi reaction leads to the formation of α-acetoamido carboxamide derivatives.[2-4]

By incorporating these organic reactions into polymer chemistry, it becomes possible to prepare new monomers, discover novel polymerization approaches and modify the ends or side chains of polymer chains through post-polymerization modification (PPM). This has led to the development of new polymers with a wide range of applications, including in the field of medicine for the treatment of cancer. These reactions enable the creation of polymers with controllable structures and multiple functions, allowing for the integration of collective properties from all the materials used.[5,6]

An extremely promising strategy using the Ugi MCR is the structural modification of polymer systems. This approach offers the potential to covalently incorporate various compounds into the polymer structure, including therapeutic agents, hydrolytically or enzymatically cleavable spacers and carbohydrates specific to tumor cell communication.[7-13]

By using carbohydrates specific to the communication of undifferentiated cells, targeting groups have been developed for directing drugs, ensuring the endocytosis of drug carriers and their internalization in the tumor.[7-10,13-17] These targeting groups facilitate the selective delivery of

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therapeutic agents to the desired site, improving the efficacy and minimizing off-target effects.

The combination of the Ugi MCR with structural polymer modification techniques has opened up new avenues in the field of drug delivery and targeted therapy.[6] By harnessing the power of MCR and specific cellular interactions, researchers are able to develop polymer systems with enhanced functionality and precise targeting capabilities, thus contributing to advancements in the treatment of diseases such as cancer.[2,18]

The possibility of synthesizing polymers with pH responsiveness from the Ugi reaction can allow the controlled release of drugs at specific target sites, such as the acidic environment of tumors or the slightly acidic conditions of the gastrointestinal tract. This situation can be achieved by incorporating acrylic-based polymers like Eudragit® materials into drug delivery systems, allowing the design of new formulations with enhanced drug release selectivity, optimized therapeutic outcomes and minimized potential side effects.[19,20]

In this regard, the aim of this study was to modify the commercial copolymer of methyl methacrylate and acrylic acid Eudragit® L100 (EL100) by the Ugi reaction using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. This modification is part of an ongoing work that aims, in the future, to test the development of polymeric systems with targeting capability and enhanced functionality that contribute to the advancement of disease treatment, such as cancer.

Experimental

Materials

Reagents were commercially available and were used without additional purification. Eudragit® L100 was manufactured by Evonik (South San Francisco, USA) (methacrylic acid-methyl methacrylate copolymer 1:1; methacrylic acid units: 46.0-50.6%; molecular weight = 125.000 g mol^{-1}); 2-iodobenzoic acid (Sigma-Aldrich, São Paulo, Brazil); Oxone® monopersulfate (Sigma-Aldrich, São Paulo, Brazil); 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (Galac) (Sigma-Aldrich, São Paulo, Brazil); 4-chloro-aniline (Sigma-Aldrich, São Paulo, Brazil); *tert*-butyl isocyanide (Sigma-Aldrich, São Paulo, Brazil); formaldehyde solution 37% (Quimex, Minas Gerais, Brazil); ethyl acetate (EtOAc) (QHemis, Espírito Santo, Brazil); acetone P.A. (Isofar, Rio de Janeiro, Brazil); methanol (Rio de Janeiro, Brazil, BHerzog); ethanol (Vetec, Santa Catarina, Brazil); membra-cel MD34 14 X 100 CLR (Viskase, Lombard Illinois, USA); deuterated dimethylsulfoxide (DMSO-d_6) and chloroform ($CDCl_3$) (Sigma-Aldrich, São Paulo, Brazil). The synthesis of the oxidizing agent iodoxybenzoic acid (IBX) was carried out following the methodology described by Frigerio *et al.*,[21] weighed 58%.

Aldehyde functionalization of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (Galac-COH)

Aldehyde functionalization of Galac (Galac-COH) occurred as described by Suri *et al.*[22] Commercially available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2.5 g, 0.137 mol L^{-1}) was weighed in a glove bag under nitrogen atmosphere and dissolved in EtOAc (70 mL), and IBX (8.1 g, 0.411 mol L^{-1}) was carefully added. The suspension was heated to reflux (70 °C) for 8 h, and then the precipitate was filtered through a medium porosity sintered-glass funnel. EtOAc was removed under vacuum at room temperature. The aldehyde functionalization yield was 40-50%.

Multicomponent reactions of Ugi

Reaction of Ugi with formaldehyde (Ugi-1)

In a 100 mL flask, 2.1 g of formaldehyde was dissolved in 30 mL of methanol. Subsequently, 3 g (0.67 mol L^{-1}) of 4-chloro-aniline was added over the solution and the reaction was processed for 20 h at room temperature and under constant stirring (aldehyde/amine molar ratio = 1:1). Formed imine center was then reacted with polymeric solution of Eudragit® L100 (0.7 g in 7 mL, 0.57 mol L^{-1}) and 0.3 g (8.89 mol L^{-1}; 0.45 mL) of *tert*butyl isocyanide for 72 h (polymer/isocyanide molar ratio = 1:1). For purification, resulting solution was precipitated in distilled water (pH = 7), liquid phase volume was reduced by vacuum and concentrated solution dialysised in ethanol for 1 week. The product was dried at 60 °C for 24 h.

Reaction of Ugi with Galac-COH (Ugi-2)

In a 50 mL flask, 2 g (0.75 mol L^{-1}) of Galac-COH were dissolved in 4 mL of methanol. Subsequently, 0.4 g (0.75 mol L^{-1}) of 4-chloro-aniline was added and the reaction carried out for 20 h at room temperature and under constant stirring (aldehyde/amine molar ratio = 1:1). Formed imine center was then reacted with polymeric solution of Eudragit® L100 (0.2 g in 2 mL; 0.3 mol L^{-1}) and 0.05 g (8.57 mol L^{-1}, 0.07 mL) of *tert*-butyl isocyanide for 72 h (polymer/isocyanide molar ratio = 1:1). For purification, solution was precipitated in distilled water (pH = 7), centrifuged and taken for dialysis for 1 week in ethanol. The product was dried at room temperature for 24 h.

Characterization of Galac-COH

The structure of Galac-COH was investigated by proton nuclear magnetic resonance (^{1}H NMR) using a Varian Mercury VX-300 spectrometer (California, USA) (^{1}H frequency 300 MHz) under the following conditions: pulse width of pw(90) = 11; delay d1 = 20; number of transients nt = 16 s; temperature = 30 °C; and solvent $CDCl_3$.

Fourier transformed infrared (FTIR)

Fourier transformed infrared (FTIR) was also used to confirm the structure of Galac-COH. The analysis was performed in a PerkinElmer spectrometer model Frontier FTIR/FIR version 10.4.2, (Norwalk, Connecticut, USA), using attenuated total reflectance (ATR) mode, number of scans = 60 and resolution = 4 cm^{-1}.

Characterization of multicomponent reactions of Ugi

Products of Ugi MCR were analyzed by nuclear magnetic resonance (^{1}H NMR; ^{13}C NMR; correlated spectroscopy (COSY); attached proton test (APT) and heteronuclear single quantum coherence (HSQC)) using a Varian Mercury VX-300 spectrometer (^{1}H frequency: 300 MHz; ^{13}C frequency 75 MHz).

The bisamide formed via the Ugi reaction was analyzed under the following conditions.

(*i*) Ugi-1: ^{1}H NMR pulse width of pw(90) = 62; delay d1 = 10 s; number of transients nt = 64; ^{13}C NMR delay of d1 = 1s; pulse width pw(90) = 13; number of transients nt = 25000; COSY pulse width of pw(90) = 62; number of transients nt = 16; number of increments ni = 200; delay d1 = 2 s; APT pulse width of pw(90) = 13; delay d1 = 1 s; number transients nt = 32000; HSQC delay of d1 = 1 s; number of increments ni = 200; number of transients nt = 20; pulse width pw(90) = 62; value of the heteronuclear coupling constant j1xh = 146; arrayed spectra experiments acquire a series of free-induction decay (FID) mult = 2. The analyses were performed at 60 °C and in DMSO-d_6.

(*ii*) Ugi-2: ^{1}H NMR pulse width of pw(90) = 62; delay d1=10s; number of transients nt = 16. APT pulse width of pw(90) = 11.4; delay d1 = 1 s; number transients nt = 32000; HSQC delay of d1 = 1 s; number of increments ni = 200; number of transients nt = 20; pulse width pw(90) = 13.2; value of the heteronuclear coupling constant j1xh = 146; arrayed spectra experiments acquire a series of FID's mult = 2. The technique was performed at a temperature of 55 °C and in DMSO-d_6.

The structures of the Ugi-1 and Ugi-2 were also analyzed by FTIR using KBr disk (number of scans = 20 and 60 and resolution = 1 and 4 cm^{-1}).

Differences in the thermal stability of the polymers were analyzed by thermogravimetric analysis (TGA) in a TA TGA Q500 instrument (New Castle, USA) using a temperature range from 25 to 700 °C, heating rate of 10 °C min^{-1} under nitrogen atmosphere.

Glass transition temperatures of the polymers were investigated by differential scanning calorimetric (DSC) using a TA Q1000 Calorimeter (New Castle, USA) under a nitrogen flow rate of 50 mL min^{-1}, with a heating rate of 20 °C min in the range of 0 to 200 °C and about (7 mg ± 0.5 mg) of polymer as powder. Before performing the analyses, samples were kept for 10 min at 100 °C under an inert atmosphere in order to eliminate low molar mass compounds that could hinder the visualization of the glass transition.

The number-average molecular weight (M_n), and polydispersity (M_w/M_n) of Eudragit® L100 and modified polymers (Ugi 1 and Ugi 2) were measured by gel permeation chromatography (GPC) using a Shimadzu LC 20AD chromatograph equipped with CTO-20A oven, DGU-20A3R degasser, and RID-20A refractive index detector and Phenogel 5 μm, 300 × 7.8 mm, 00H-0445-K0 (range 5-500 K) and Phenogel 5 μm linear 300 × 7.8 mm, 0H-3259-K0 (range 100-10,000 K) columns (Oregon, USA). The analyses were performed using dimethylacetamide (DMAc) containing 0.01 M LiBr as eluent, flow rate of 1.0 mL min^{-1} and injection volume of 20 μL at 30 °C.

Results and Discussion

Synthesis of the Galac-COH

In order to confirm the obtained reaction mixture composition, the structure and percentage yield of the functionalized galactopiranose were determined by FTIR and ^{1}H NMR spectroscopy. To identify which signals belonged to the starting material and which to the functionalized product, subtraction of the ^{1}H NMR spectrum of the starting material (Galac) from the ^{1}H NMR spectrum of the reaction mixture was performed using the arithmetic software MestreNova version 12.01- MestreLab 2018,[23] as observed in Figure 1. In this figure, the signal at δ 5.67 ppm corresponds to the Hc hydrogen of the functionalized product, and the signal at δ 5.66 ppm corresponds to the Hc hydrogen of the starting material.

By summing up both signals to 100%, we can estimate a yield of 85.7% for the functionalization reaction, as shown in Figure 2. It is worth noting that all spectra were

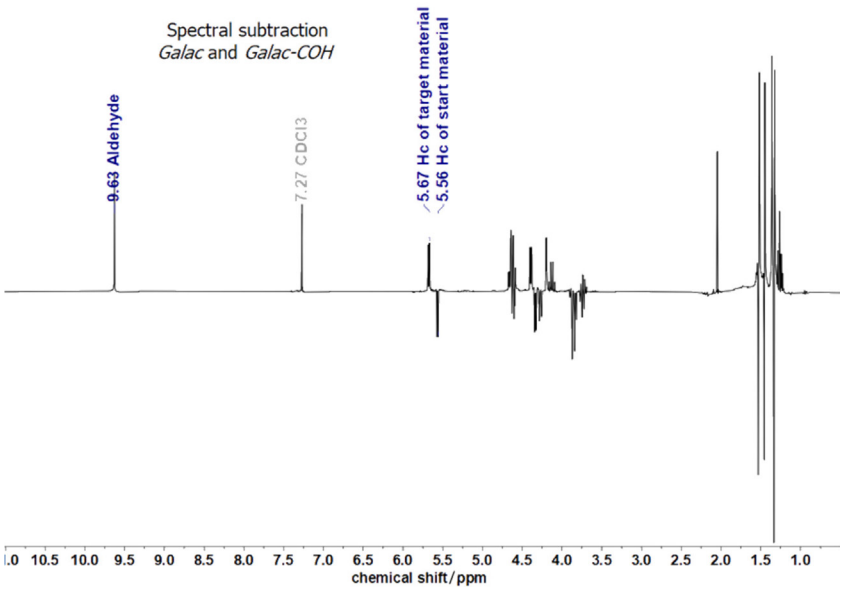


Figure 1. Spectral subtraction (^{1}H NMR, 300 MHz, $CDCl_3$, 25 °C) Galac and Galac-COH.

acquired under the same quantitative conditions, with the pulses calibrated to 90°. Figure 2 also provides a complete assignment of the hydrogen signals of the functionalized product. The peak at δ 9.66 ppm (1H, s) related to the aldehyde; δ 5.68 ppm (1H, d), δ 4.63 ppm (2H, ddd), δ 4.39 ppm (1H, q), δ 4.20 ppm (1H, d), δ 1.52 ppm (3H, s) correspond to the CH groups of the galactopyranose main chain, and δ 1.47 ppm (3H, s), δ 1.39 ppm (3H, s), δ 1.33 ppm (3H, s) correspond to the CH_3 groups. Regarding the IR spectrum (Figure S1, Supplementary Information (SI) section), peaks were observed at 1737 cm^{-1} (C=O, aldehyde) and at 2980-2900 cm^{-1} (CH_3, CH_2, primary and secondary carbon).[22,24]

Reactions of Ugi multicomponent

In the present study, the Ugi mechanism was employed to modify the anionic copolymer of methacrylic acid with methyl methacrylate (1:1), Eudragit® L100, which is a commercial copolymer widely employed in enteric coating. This modification aims to reduce potential stomach irritation and enable targeted drug release in the colon for the localized treatment of intestinal disorders such as Crohn's disease, ulcerative colitis, or intestinal cancer.[20,25] Therefore, these reactions were carried out with the aim of assessing the feasibility of using this reactional platform for the development of multifunctional systems in the future.

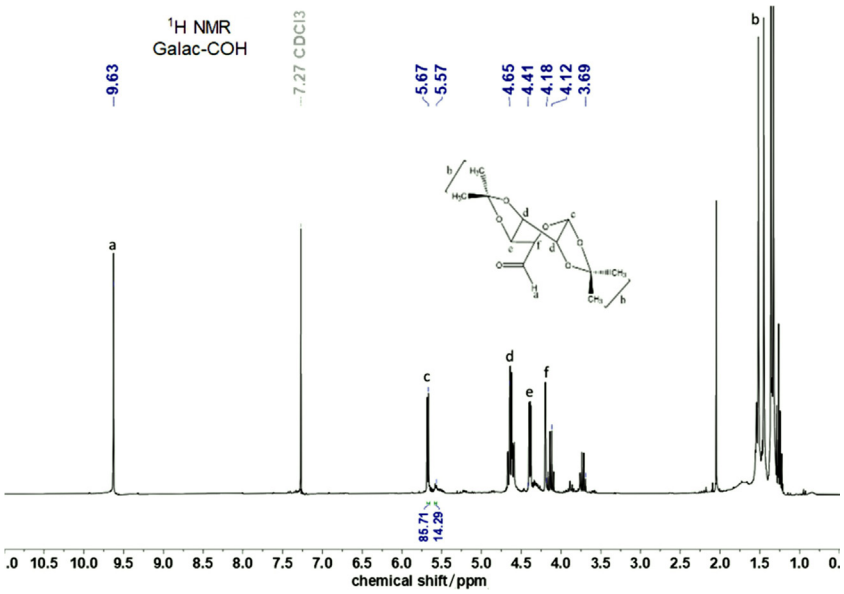


Figure 2. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) spectrum of galactopyranose modified with aldehyde group.

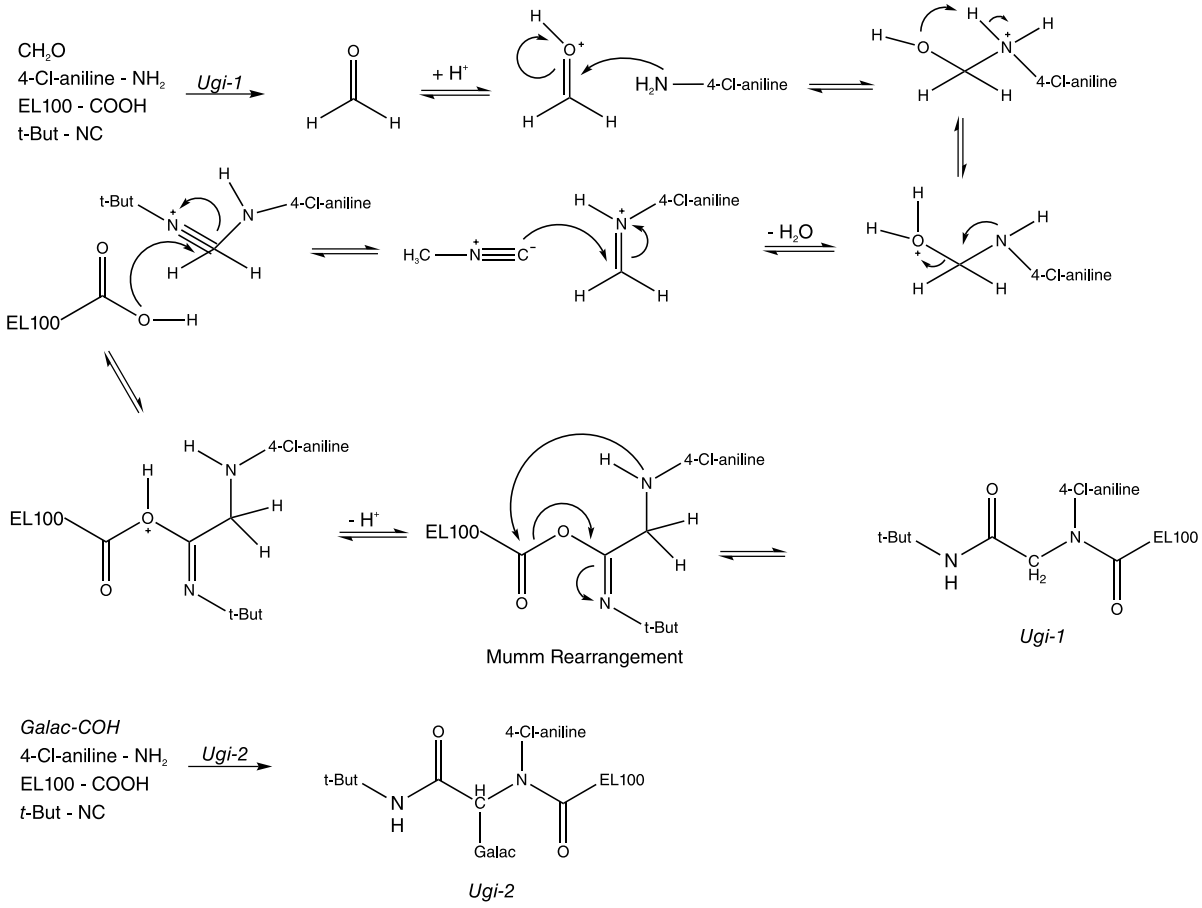
In this study, we will discuss the synthesis of two different Eudragit® L100-based modified acrylic copolymers (Ugi-1 and Ugi-2) obtained according to the proposed mechanism illustrated in Scheme 1.

Ugi-1

The reaction of formaldehyde, 4-chloro-aniline, Eudragit® L100 and *tert*-butyl isocyanide produced a solid material (Ugi-1) with a yield of approximately 12%. Figure 3a presents the ^{1}H NMR spectra of Ugi-1. Signals at δ 7.15 ppm (2H; dd) and δ 6.98 ppm (2H; d), attributed to the aromatic aniline, were observed. The spectrum also showed signals at δ 4.88 and δ 4.86 ppm (2H; d) related to the isolated CH_2 formed after the Mumm rearrangement and at δ 3.53 ppm (3H; s) corresponding to the CH_3 group of methyl methacrylate ester. Signals at δ 1.82-0.72 ppm are also present, with the latter being ascribed to the methyl groups of *tert*-butyl isocyanide and the polymer chain overlapping. In Figure S2 (SI section), 2D NMR-COSY spectrum confirms the aforementioned spectra, also showing the peak related to the isolated CH_2, formed after the Mumm rearrangement.

Knowing that in the Ugi reaction, a bisamide is formed as a product, and that the signal corresponding to the CH_2 of formaldehyde, after the Mumm rearrangement, would produce a more isolated peak in the spectrum, a ^{13}C NMR analysis was also performed to verify the presence of these peaks (Figure 3b). Signals were observed at δ 179.18 ppm (ester C=O); δ 169.89 and δ 167.42 ppm (amide C=O); δ 129.33 ppm (CH near Cl); δ 119.06 ppm (aromatic C–CH); δ 67.34 and δ 65.87 ppm (isolated CH_2); δ 54.27 ppm (polymer chain C–CH); δ 51.95 ppm (OCH_3); δ 44.41 ppm (polymer chain CH_2); δ 29.00 ppm (*tert*-butyl isocyanide CH_3); δ 18.97-16.92 ppm (polymer chain CH_3).[27]

In the spectrum of ^{1}H NMR (500 MHz) obtained at 60 °C, it was observed that the signal attributed to the CH_2 of formaldehyde exhibited splitting, yielding two signals at δ 4.88 and 4.86 ppm. Spectra taken at 80 and 90 °C showed a tendency for these signals to coalesce, indicating the possibility that two conformers were generated in the synthetic process, as shown in Figure 4. Polymers in solution always change their conformation due to internal rotations around single bonds. The discrete nature of the rotational potential of polymeric chains is a recognized fact,



Scheme 1. Proposed mechanism of synthesis of Ugi-1 and Ugi-2 (adapted from Icart *et al.*[26]).

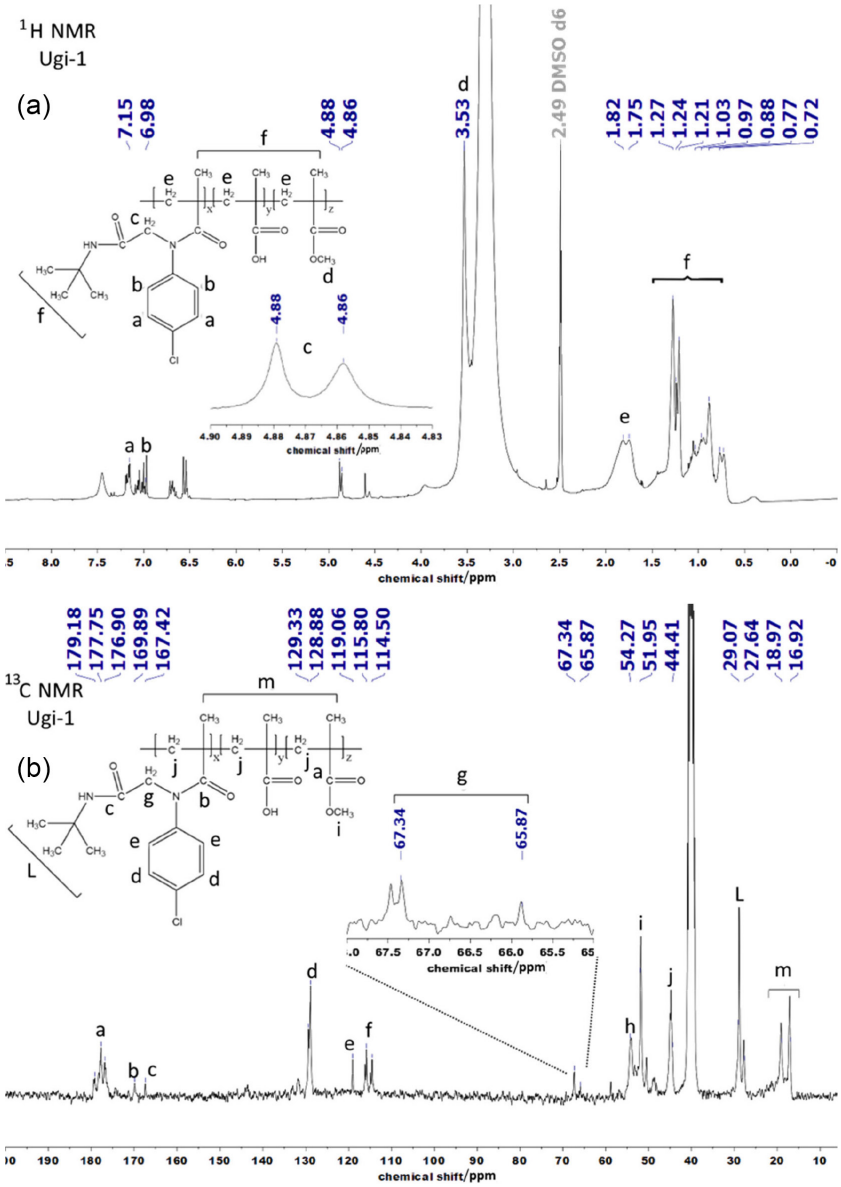


Figure 3. NMR spectra of Ugi-1 with formaldehyde: (a) ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C), (b) ^{13}C NMR (75 MHz, DMSO-d_6).

as it is presumed that a small number of discrete rotations occur at each bond in the polymer chain.[28] Not only are the bonds in the polymeric chain typically restricted to a few movements, but there is also the possibility of any rotational state of closely connected neighboring groups. This rotational interdependence of conformations can be attributed to the steric interactions of substituent 4-chloro-aniline in chain Eudragit® L100.[29] Another possibility for conformational changes arises from the fact that nitrogen, being trivalent, serves as a center of pseudoasymmetry. Amines possess a unique property known as nitrogen inversion,[30] which can alter the positions of a substituent group and the unpaired electron pair of the nitrogen atom. If the substituent group is bulky, inversion can occur at room temperature. Nitrogen inversion always leads to conformational changes, and with an approximately 4 kcal difference in free energy between different conformations, during the transition state, the unpaired electron pair tends to behave like a p orbital, which can cause the hydrogen atoms to appear coplanar.[31] In 2D NMR-HSQC spectrum (Figure S3, SI section), this phenomenon attributed to the formaldehyde CH_2 signal is also observed, displaying splitting, producing two signals at δ 4.87 and 4.90 ppm, which relate to carbon shifts at δ 65.70 and 67.36 ppm, respectively. Furthermore, the NMR-APT (Figure S4, SI section) analysis indicates in-phase peaks, confirming it is a CH_2.

FTIR spectrum of Ugi 1 (Figure 5) showed the presence of bands that indicate the success of the Ugi reaction when the spectrum of commercial Eudragit® L100 (EL100) is

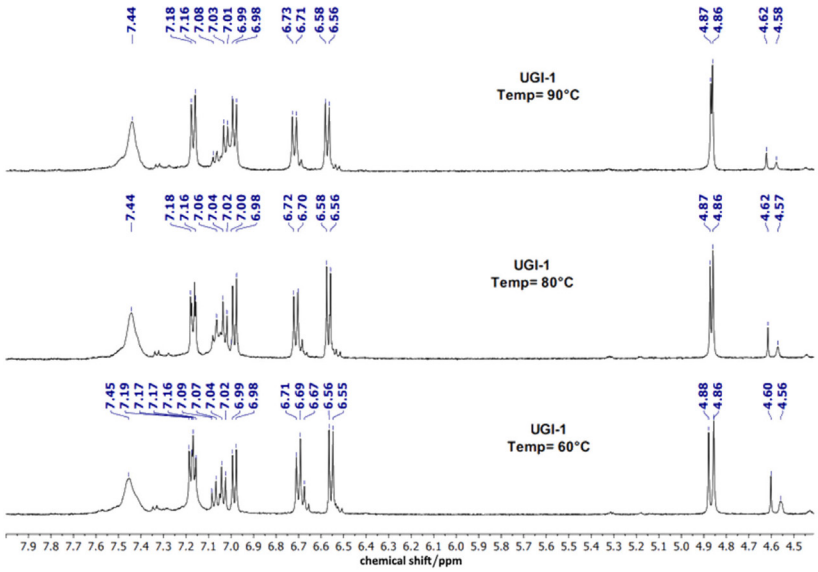


Figure 4. ^{1}H NMR spectra (500 MHz, DMSO-d_6, 60, 80 and 90 °C) of Ugi-1 with formaldehyde.

compared. Figure 5a presents both spectra in the complete range of FTIR wavenumber, 400-4000 cm^{-1}. In the EL100 spectrum, bands at 3000-2850, 1728, 1195, and 1165 cm^{-1} were observed. These bands are attributed to the CH_x vibration, ester C=O vibration, and C–O bonds of the ester and carboxylic acid, respectively.[32] In regards to the spectrum of the Ugi-modified EL100, it was possible to assign the following bands at 1640 cm^{-1} (C=O of the simple open-chain secondary amide), at 1599 cm^{-1} (characteristic C=C band of the aromatic ring), at 1093 cm^{-1} (C–N band of the amide group), and at 808 cm^{-1} (symmetric out-of-plane angular deformation of the N–H group).[27] For better resolution, analyses were also carried out at 1 cm^{-1} intervals (Figure 5b) where these absorption bands can be clearly seen.

In order to assess the thermal stability and glass transition (Tg) of the materials, TGA and DSC analyses were performed on the commercial EL100 and the Ugi-1 copolymer. Regarding the TGA of Ugi-1 (Figure 6a), a change in the amount of water loss was observed when compared with the commercial copolymer, with a variation from 6% (EL100) to 1% (Ugi-1). Ugi-1 seems to be more hydrophobic due to the introduction of *tert*-butyl and aromatic ring moieties.[33] Furthermore, four mass loss events were observed for Ugi-1 differently from the commercial unmodified polymer. These events may be related to the cleavage of the new bonds formed during the Ugi MCR, which corroborates the results of NMR and FTIR.[26] Regarding the DSC analysis (Figure 6b), a decrease in Tg (156 to 133 °C) was observed in the material obtained after the reaction compared to the commercial one. This result was expected since the introduction of aromatic rings at pendant acid groups of the copolymer reduced the hydrogen bonding between these groups. At the same time, it allowed the polymer chains to exhibit greater flexibility in their arrangement, thus requiring less energy to induce the transition.[26,34]

The influence of the chemical reaction on the molecular weight was investigated by GPC. Figure 6c shows the GPC

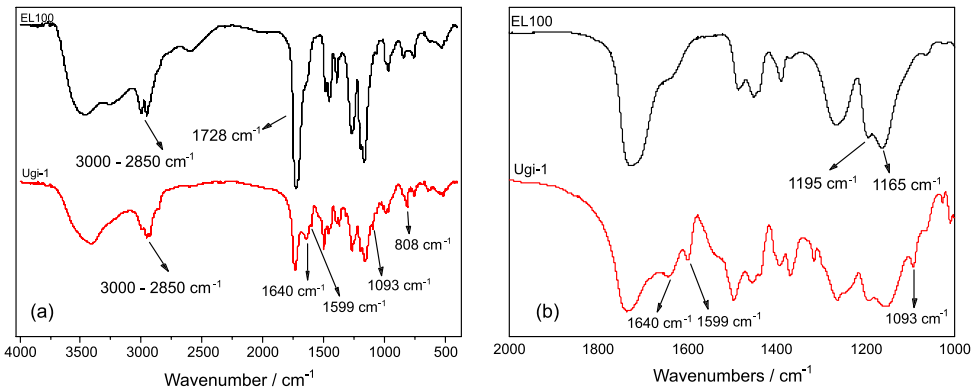


Figure 5. FTIR (KBr) spectra of EL100 and Ugi-1: (a) 4000-400 cm^{-1} with 4 cm^{-1} resolution and (b) region of 2000-1000 cm^{-1} with 1 cm^{-1} resolution.

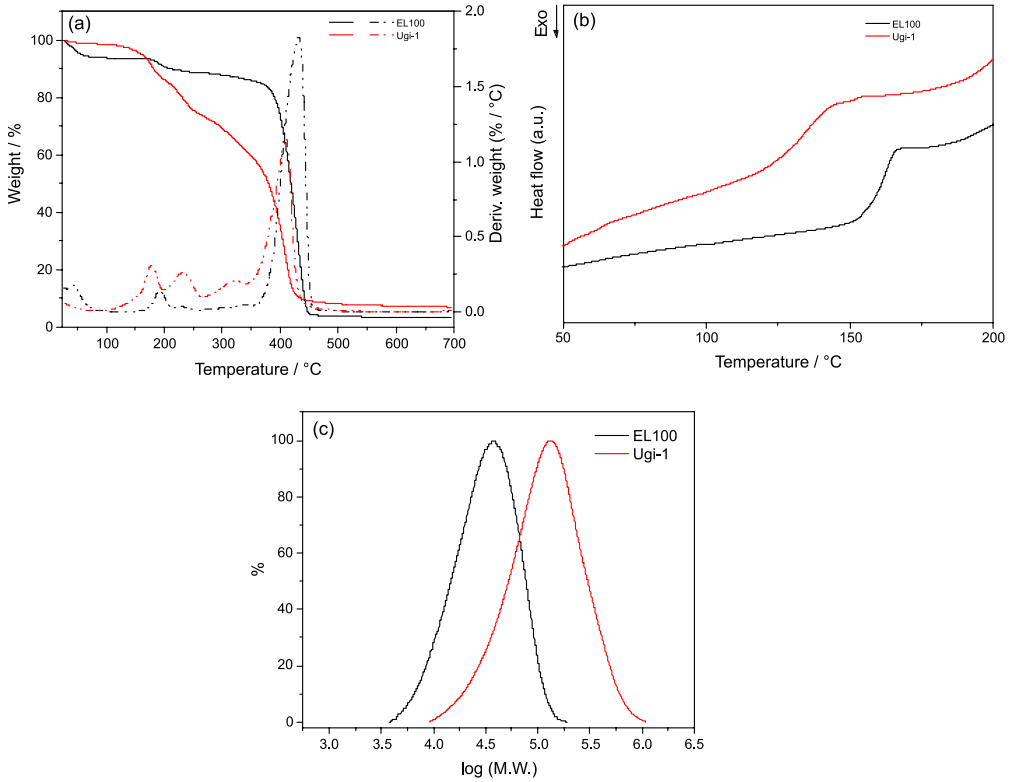


Figure 6. (a) Thermogravimetric (TG) and first order derivatives thermogravimetric (DTG) curves; (b) DSC curves (second heating run) showing the glass transitions temperatures, (c) GPC curves (eluent: DMAc) of and EL100 and Ugi-1.

curves of EL100 and the Ugi-1. The molecular weight values of Ugi-1 (136.015 g mol^{-1}) increased compared to EL100 (39.866 g mol^{-1}). Taking into account that the reaction occurs in the acid side groups of the copolymer structure, one would not expect a contribution to the increase in molecular weight. However, with the insertion of bulky groups, such as 4-chloroaniline, it can be inferred that there was an increase in the hydrodynamic volume which may increase the value obtained from GPC.[35]

Ugi-2

In the second multicomponent reaction described in this work, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose was used as the aldehyde component of Ugi reaction. To investigate the procedure, a ^{1}H NMR analysis was also conducted, as shown in Figure 7. Unlike the first reaction, the MCR of Ugi-2 exhibited lower incorporation of the initial components (yield < 10%). This can be attributed to the higher steric hindrance of the galactopyranose in addition to 4-chloroaniline, which contains an aromatic ring.

These conditions resulted in low-intensity signals in the spectrum, requiring amplification of the regions of interest. The following signals were observed: δ 12.40 ppm (1H; s), attributed to the hydroxyl groups of the acid groups from the commercial copolymer used, as there was low incorporation of the components into it; δ 7.20 and δ 4.00 ppm (5H; s), attributed to the hydrogens in the galactopyranose structure; δ 4.90 ppm (1H; d), an isolated CH group after the Mumm rearrangement; δ 3.52 ppm (2H; d); δ 3.52 ppm (3H; s), methyl group of the ester; δ 1.77 ppm (12H; s), methyl groups of the galactopyranose; δ 1.22 ppm (9H; s), methyl groups of the *tert*-butyl isocyanate; δ 0.84 ppm, the methyl groups of the polymer chain.[24] The HSQC and APT NMR techniques were also performed. With both, we were able to corroborate the findings of ^{1}H NMR regarding the signal of the isolated CH from the proposed structure, which arises from the Mumm rearrangement, as indicated in the spectrum (Figures S5 and S6, SI section).

FTIR spectra of Ugi-2 is presented in Figure 8. From the spectra, it was possible to highlight the emergence of typical bands in Ugi-2 spectrum, indicating the feasibility of the Ugi reaction. Figure 8a shows the spectra of Ugi-2 in the wavenumber from 400-4000 cm^{-1} and a resolution of 4 cm^{-1}. This spectrum shows absorption bands at 1646 cm^{-1} assigned to C=O, simple open-chain secondary amide, at 1600 cm^{-1} characteristic C=C band of the aromatic ring, and at 1550 cm^{-1} attributed to the angular deformation of N–H in the secondary amide group. These absorptions were originated from the interaction between the N–H angular deformation and the axial deformation of C–N

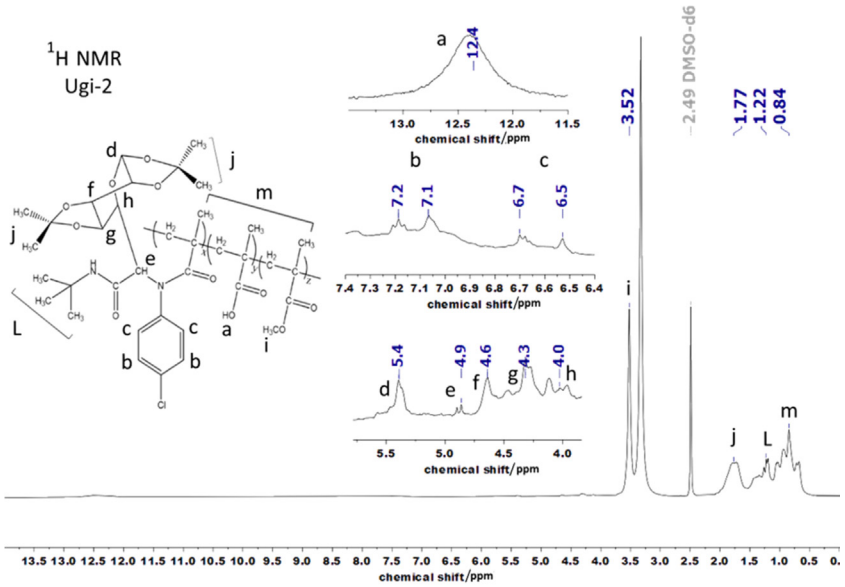


Figure 7. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) spectrum of Ugi-2 with Galac-COH.

in the C–N–H group.[27] Figure 8b shows the region of the spectrum related to carbonyl groups obtained with a higher resolution (1 cm^{-1} intervals) where the discussed absorption bands can be better identified.

To assess the effects of copolymer modification on the thermal stability and Tg, TGA and DSC analyses were also performed. Figure 9a presents the TGA curves of Ugi-2. There was no significant change in the amount of water loss when the Ugi-2 curve is compared with the EL100 curve. This material appeared to be equally hydrophilic, as there was low incorporation of side groups containing Galac-OH and aromatic rings due to the intrinsic steric hindrance of these Ugi reaction components. However, when Ugi-2 DTG curves is compared to EL100 one, new mass loss events were observed, which may indicate the insertion of new groups into the structure.

DSC curves of both materials are presented in Figure 9b. An increase in the glass transition temperature was observed for Ugi-2 (Tg = 169 °C) when comparison is done with EL100 (Tg = 156 °C). It can be inferred from this result that although a limited degree of modification was reached in the Ugi reaction, as already shown by ^{1}H NMR, the insertion of two bulky groups in the copolymer structure may have contributed to increase the stiffeness of polymer chains, thereby increasing the transition temperature.[36]

The influence of the chemical reaction on the molecular weight of Ugi-2 was investigated by GPC (Figure 9c). The molecular weight of the modified copolymer (130.153 g mol^{-1}) increased when compared with that determined for the commercial polymer EL100 (39.866 g mol^{-1}). Knowing that the reaction also occurs in the side acid groups of the copolymer structure, one would expect no contribution to increase in molecular weight. However, with the insertion of bulky groups, such as 4-chloroaniline and aldehyde-modified 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, an

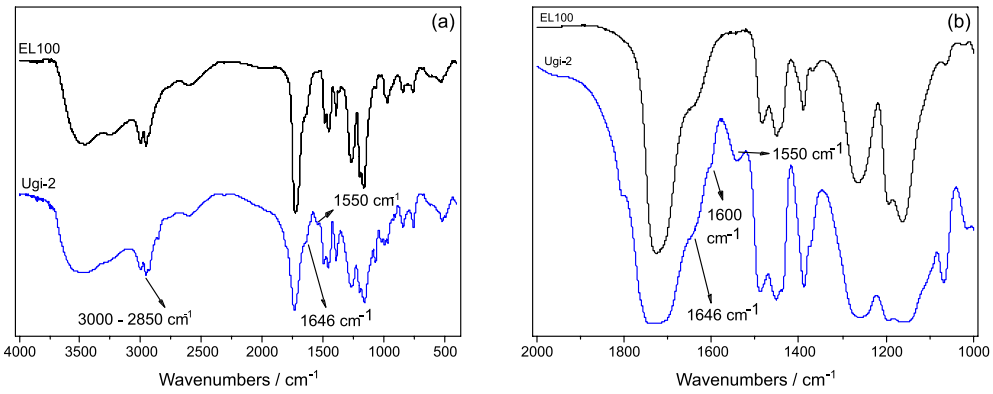


Figure 8. (a) FTIR (KBr) of EL100 and Ugi-2 (4000-400 cm^{-1} with 4 cm^{-1} resolution), (b) higher resolution of the FTIR spectrum of EL100 and Ugi-2 (1 cm^{-1}, in the region of 2000-1000 cm^{-1}).

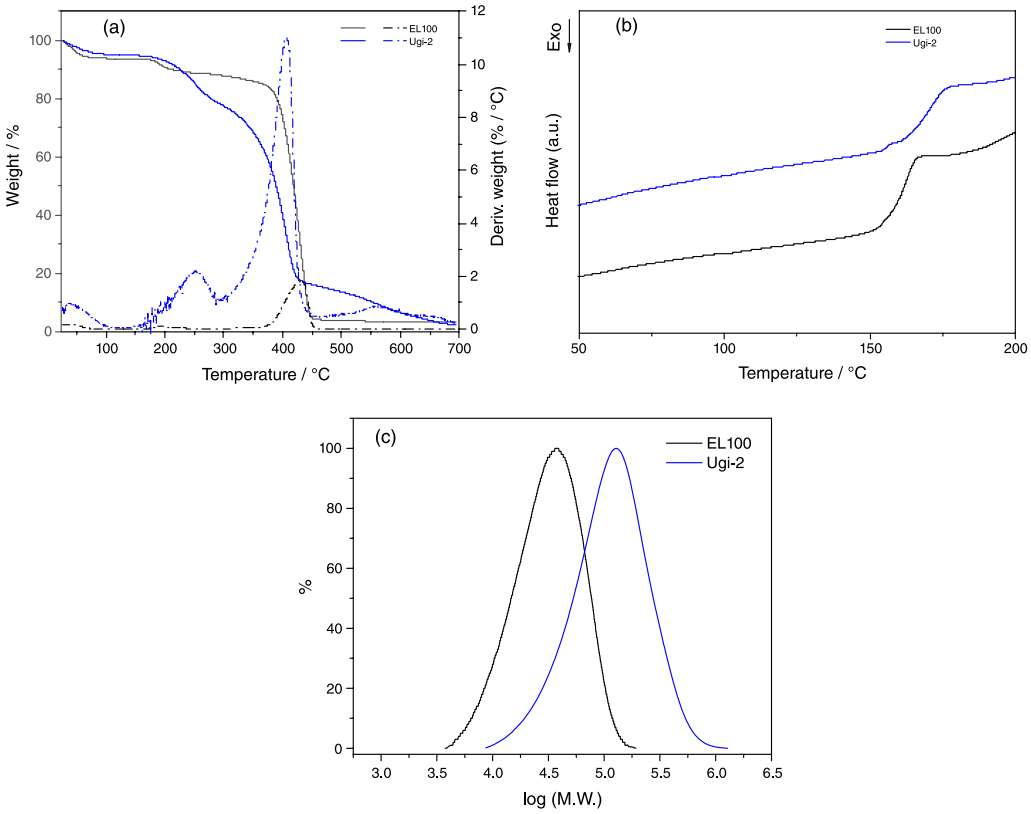


Figure 9. (a) Thermogravimetric (TG) and first order derivatives thermogravimetric (DTG) curves; (b) DSC curves (second heating run) showing the glass transitions temperatures; (c) GPC curves (eluent: DMAc) of and EL100 and Ugi-2.

increase in the hydrodynamic volume in the analysis solvent (DMAc) may have occurred, as in the case of Ugi-1.[35]

Conclusions

In this study, the synthesis and characterization of an aldehyde-functionalized carbohydrate based on galactopyranose (Galac-COH) was performed. By ^{1}H NMR, aldehyde-functionalization was quantified as 89%. This aldehyde was used in the modification of the commercial poly(methyl mechacrylate-*co*-acrylic acid) Eudragit® L100 by using the Ugi multicomponent reaction. The synthesis of two Ugi-Eudragit modified copolymer (Ugi-1 and Ugi-2) was successful, aiming at the feasibility of future multifunctional systems. ^{1}H and ^{13}C NMR analyses of Ugi-1 revealed typical peaks related to the introduction of functional groups, such as aniline and *tert*-butyl isocyanide, confirming the formation of new chemical bonds. Thermal analyses (TGA and DSC) demonstrated changes in the properties of the post-reaction material, including alterations in thermal stability and Tg. GPC analysis also indicated an increase in molecular weight due to the insertion of bulky groups. ^{1}H NMR analysis of Ugi-2 revealed lower incorporation of the initial components compared to Ugi-1, attributed to steric hindrance caused by galactopyranose and 4-chloroaniline, but FTIR analysis confirmed the formation of new functional groups. In both cases, the analytical techniques provided crucial information about the structure and properties of modified copopolymers, validating the effectiveness of Ugi reaction in producing polymers with different functionalities that are of interest for specific medical applications, contributing to advances in the fields of personalized medicine and targeted treatment of intestinal diseases.

Supplementary Information

Supplementary information (Figures S1-S6) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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References

1. Fouad, M. A.; Abdel-Hamid, H.; Ayoup, M. S.; *RSC Adv.* **2020**, *10*, 42644. [Crossref]
2. Rocha, R. O.; Rodrigues, M. O.; Neto, B. A. D.; *ACS Omega* **2020**, *5*, 972. [Crossref]
3. Marcaccini, S.; Torroba, T.; *Nat. Protoc.* **2007**, *2*, 632. [Crossref]
4. Gangloff, N.; Nahm, D.; Döring, L.; Kuckling, D.; Luxenhofer, R.; *J. Polym. Sci., Part A: Polym. Chem.* **2015**, *53*, 1680. [Crossref]
5. Hu, B.; Sun, D.; Sun, C.; Sun, Y. F.; Sun, H. X.; Zhu, Q. F.; Yang, X. R.; Gao, Y. B.; Tang, W. G.; Fan, J.; Maitra, A.; Anders, R. A.; Xu, Y.; *Biochem. Biophys. Res. Commun.* **2015**, *468*, 525. [Crossref]
6. Yu, G. T.; Rao, L.; Wu, H.; Yang, L.-L.; Bu, L.-L.; Deng, W.-W.; Wu, L.; Nan, X.; Zhang, W. F.; Zhao, X. Z.; Liu, W.; Sun, Z.-J.; *Adv. Funct. Mater.* **2018**, *28*, 1801389. [Crossref]
7. Ulbrich, K.; Etrych, T.; Chytil, P.; Pechar, M.; Jelinkova, M.; Rihova, B.; *Int. J. Pharm.* **2004**, *277*, 63. [Crossref]
8. Huang, J.; Habraken, G.; Audouin, F.; Heise, A.; *Macromolecules* **2010**, *43*, 6050. [Crossref]
9. Masood, F.; *Mater. Sci. Eng., C* **2016**, *60*, 569. [Crossref]
10. Hu, C. M. J.; Fang, R. H.; Luk, B. T.; Zhang, L.; *Nanoscale* **2014**, *6*, 65. [Crossref]
11. Yan, H.; Chen, X.; Bao, C.; Wu, S.; He, S.; Lin, Q.; *Polym. Bull.* **2020**, *77*, 73. [Crossref]
12. Yan, H.; Chen, X.; Li, J.; Feng, Y.; Shi, Z.; Wang, X.; Lin, Q.; *Carbohydr. Polym.* **2016**, *136*, 757. [Crossref]
13. Wen, Y.; Chen, X.; Liu, Z.; Zhu, Q.; Li, Z.; He, G.; Yan, H.; Lin, Q.; *ChemistrySelect* **2021**, *6*, 10965. [Crossref]
14. Kratz, F.; Müller, I. A.; Ryppa, C.; Warnecke, A.; *ChemMedChem* **2008**, *3*, 20. [Crossref]
15. Wicki, A.; Witzigmann, D.; Balasubramanian, V.; Huwyler, J.; *J. Controlled Release* **2015**, *200*, 138. [Crossref]
16. Shen, H.; Ma, H.; Liu, P.; Huang, W.; Han, L,; Li, C.; Li, Y.; *Macromol. Rapid. Commum.* **2017**, *38*, 1700353. [Crossref]
17. Zeng, G.; Qiu, L.; Li, X.; Wen, T.; *Polymer* **2022**, *239*, 124432. [Crossref]
18. Siddique, S.; Chow, J. C. L.; *Nanomaterials* **2020**, *10*, 1700. [Crossref]
19. Prasad, S.; Dangi, J. S.; *Artif. Cells, Nanomed., Biotechnol.* **2016**, *44*, 1824. [Crossref]
20. Sonje, A.; Chandra, A.; *Int. Res. J. Pharm.* **2013**, *4*, 71. [Crossref]
21. Frigerio, M.; Santagostino, M.; Sputore, S.; *J. Org. Chem.* **1999**, *64*, 4537. [Crossref]
22. Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F.; *J. Org. Chem.* **2006**, *71*, 3822. [Crossref]
23. *MestreNova*, version 14.0.0-23239; MestreLab Research Chemistry Software Solutions, Santiago de Compostela, Spain, 2019.
24. Xiao, N.; Liang, H.; Lu, J.; *Soft Matter* **2011**, *7*, 10834. [Crossref]
25. Guan, X.; *Acta Pharm. Sin. B* **2015**, *5*, 402. [Crossref]
26. Icart, L. P.; Fernandes, E.; Agüero, L.; Ramón, J.; Zaldivar, D.; Dias, M. L.; *J. Appl. Polym. Sci.* **2016**, *133*. [Crossref]
27. Wang, X.; Liu, C.; Xing, Z.; Suo, H.; Qu, R.; Li, Q.; Qin, Y.; *Macromolecules* **2022**, *55*, 8857. [Crossref]
28. Tonelli, A. E.; *NMR Spectroscopy and Polymer Microstructure-The Conformational Connection*; VCH: New York, 1989, ch. 5.
29. Flory, P. J.; Schimmel, P. R.; *J. Am. Chem. Soc*. **1967**, *89*, 6807. [Crossref]
30. Bushweller, C. H. In *Acyclic Organonitrogen Stereodynamics*; Lambert, J. B.;Takeuchi, Y., eds.; VCH Publishers: New York, USA, 1992, ch. 1.
31. Sasanuma, Y.; Hattori, S.; Imazu, S.; Ikeda, S.; Kaizuka, T.; Iijima, T.; Sawanobori, M.; Azam, M. A.; Law, R. V.; Steinke, J. H. G.; *Macromolecules* **2004**, *37*, 9169. [Crossref]
32. Santos, T. M. M.; Oliveira Jr., P. H.; Ribeiro, L. A. A.; de Oliveira, H. P.; *Asian J. Biochem. Pharm. Res.* **2014**, *4*, 63. [Link] accessed in April 2024
33. Guimarães, C. R. W.; *Rev. Virtual Quim.* **2012**, *4*, 348. [Crossref]
34. Icart, L. P.; dos Santos, E. R. F.; Pereira, E. D.; Ferreira, S. R.; Saez, V.; Ramon, J. A.; Nele, M.; Pinto, J. C. S.; Toledo, R. D.; Silva, D. Z.; Souza, F. G.; *Express Polym. Lett.* **2016**, *10*, 188. [Crossref]
35. Khor, S. Y.; Hu, J.; McLeod, V. M.; Quinn, J. F.; Williamson, M.; Porter, C. J. H.; Whittaker, M. R.; Kaminskas, L. M.; Davis, T. P.; *Nanomedicine* **2015**, *11*, 2099. [Crossref]
36. Zhu, X.; Zhou, Y.; Yan, D.; *J. Polym. Sci., Part B: Polym. Phys.* **2011**, *49*, 1277. [Crossref]

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