α-Gluco-oligosaccharide in the research and development of a polymeric material for modified drug delivery

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ABSTRACT

This research aimed to analyse the influence of the incorporation of α-gluco-oligosaccharide (GOS-α) in the formation of isolated films of different combinations of polymethyl by applying physicochemical analyses such as Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), thermogravimetry (TG) and scanning electron microscopy (SEM). Polymer films were prepared by evaporation associating Eudragit® RS30D with α-GOS. FTIR results confirmed the incorporation of α-GOS. The intermolecular interaction involving carbonyl and hydroxyl groups of Eudragit® with α-GOS was not detected. By TG and DSC, it was possible to detect that there were no changes in the thermal properties between the proposed combinations and the standard film. Upon SEM analysis, the appearance of pores for the association 90:10 was evidenced. Possibly, these pores act as output ports for the drug. These results sharpen the perspective of applying this material to the coating of pharmaceutical formulations of modified drug delivery.

1. Introduction

The orally administrated systems for modified drug delivery focused on distal regions of the gastrointestinal tract (GIT) are generally based on the behavior of polymer materials in relation to time, pH and enzyme-dependency, which promote an interaction with some aspects of the particularities of GIT segments. They trigger expectations with a high specificity to the proposed therapeutic systems [1, 2].

For decades, natural and synthetic polymers have been used in the research and development of new polymeric materials for coating that are candidates for application in oral solid systems capable of delivering drugs only in specific regions of the gastrointestinal tract [3, 4, 5, 6, 7].

Many pathologies require the release of drugs in specific sites and at an exact dose. These pathologies, especially cancer, can be treated with the application of these systems. The colon-specific delivery could be considered the first choice for the treatment of some diseases, in particular when the material applied to the development of the therapeutic system is exclusively vulnerable to existing microbiota, ensuring the attack on the supporting framework of the formulation, generally consisting of oligo-polysaccharides, a substrate for bacteria [8].

Several oligo-polysaccharides are used. Due to their biodegradability characteristics, they offer an attractive and wide acceptance by the market due regarding low cost and high availability [9, 10].

A study coated pellets with the anti-inflammatory 5-ASA using a mixture of synthetic polymer ethylcellulose associated with Nutriose® polysaccharide, and used an in vivo model to demonstrate drug delivery. They observed the great advantage of using the proposed polysaccharide-based coating resulting from the sensitivity to microbiota, triggering a colonic-target-site delivery for the anti-inflammatory tested [11].

In this context, BIOECOLLANS® Alpha-Glucan Oligosaccharides, which are oligosaccharides obtained from natural sugars (sucrose and maltose), using an enzymatic synthesis process with transferase (Solabia®), has been highlighted. In this study, we proposed the formation of a film-forming polymeric material and analyzed the influence of the incorporation of α-gluco-oligosaccharide (α-GOS) in the formation of isolated poly(methyl methacrylate) films from different combinations, analyzing...
their physical and chemical characteristics, applying FTIR, calorimeter testing (DSC and TGA) and scanning electron microscopy (SEM).

2. Materials and methods

2.1. Materials

Eudragit® RS30D (Evonik®– Germany) and triethyl citrate (TEC) (Morflex®, Solabia – France) and other reagents of analytical grade were used in the study.

2.2. Preparation of the films

In the preparation of films containing α-GOS, the evaporation method was used as previously described [12, 13]. Polymethacrylate Eudragit® RS30D, a water-based pseudolatex, was associated to the oligosaccharide at four different concentrations, varying the concentration of the polymer and/or α-GOS, but keeping unchanged the final polymeric mass at 4% (w/v). The compositions of Eudragit® RS30D:oligosaccharide were EU 100:0 GO, EU 0:100 GO, EU 95:05 GO and EU 90:10 GO. Eudragit® requires adding a plasticizer; therefore, triethyl citrate (TEC) was added at a concentration of 20% related to the weight of the synthetic polymer. Then, the plasticized dispersions were left stirring for 30 min at room temperature until an effective homogenization. After elapsed this time, a concentration of 20% related to the weight of the synthetic polymer. A 10.0 mL sample was placed in Teflon® plates, allocated in an oven at 45 °C and left for 24 h for the complete and proper formation of films.

2.3. Fourier transform infrared (FTIR)

The infrared spectrum was analyzed in a FTIR spectrometer (Bomen-MB-100-Michelson) using photoacoustics for samples that could not be sprayed. Considering sprayed samples, potassium bromide pellets were prepared (KBr) containing 1% of the sample. In both techniques, wave-lengths between 4,000 and 400 cm⁻¹ were used [14].

2.4. Thermal analysis (DSC and TGA)

The analysis of thermo-analytical parameters have been applied as excellent tools to study filmigenic formulations involving polymers and plasticizers destined to the development of systems for modified drug delivery [15]. DSC is a valuable and reliable method to determine possible interactions that may occur during the formation of films. With it, evidence can be derived from the appearance, alteration or disappearance of energy peaks or changes in enthalpy (∆H) [16]. In the DSC analysis, 6 mg from samples of isolated films were placed in a Shimadzu calorimeter (DSC-50) using an aluminum sample holder in an atmosphere with nitrogen flow at 20 mL min⁻¹. The temperature range was 0–500 °C, at 10 °C increase rate per minute.

Mass loss of polymeric compounds events were evaluated by TGA. A Shimadzu theromobalance (TGA-50) was used to analyze 10 mg samples placed in a platinum sample holder. The temperature range was 25–900 °C, with a nitrogen flow and a heating rate of 10 mL min⁻¹ and 10 °C min⁻¹, respectively [13].

2.5. Scanning electron microscopy (SEM) of isolated films

Polymeric materials that are candidates for the coating of solid oral forms for modified drug delivery can be analyzed by this assay, which is considered an excellent morphologic assessment tool. We analyzed possible changes in the structure and the surface of developed isolated films and submitted to different conditions of contact with physiological simulation of GIT fluids. Initially, prior to the immersion in simulated GIT fluids, we chose physically intact samples of polymer formulations, which showed no fractures and/or pores and were homogeneous, translucent and shiny [14].

Samples of films representative of each polymer composition (control, 95:05 and 90:10) were previously immersed in FSG (pH 1.2) and FSI (pH 7.5) for 2 h. Then, they were frozen in liquid nitrogen and lyophilized at -55 °C seeking to preserve their morphological characteristics under both test conditions. Micrographs of isolated films were obtained by scanning electron microscope using a Shimadzu SS-550 Superscan® microscope operated at 12 kV. All micrographs were obtained from fractured surfaces coated with gold, following an adapted technique [9].

Figure 1. FTIR spectra of isolated film components separated or in combination. (a) α-GOS, (b) isolated Standard Film (Eudragit® RS30D + 20% TEC), (c) isolated Film 95:05 (Standard +5% of α-GOS) and (d) isolated Film 90:10 (Standard +10% of α-GOS).

Figure 2. DSC curves of isolated film components separated or in combination. (a) α-GOS, (b) isolated Standard Film (Eudragit® RS30D + 20% TEC), (c) isolated Film 95:05 (Standard +5% of α-GOS) and (d) isolated Film 90:10 (Standard +10% of α-GOS).
3. Results and discussion

3.1. Fourier transform infrared (FTIR)

This technique allowed us to analyze bonds and characteristic functional groups of polymers and other constituents of formed isolated films, as shown in Figure 1. A author found significant peaks in the spectrum of Eudragit® RS without additive at 1,145 cm⁻¹ (C–O), 1,390 cm⁻¹ (CH₃), 1,450 cm⁻¹ (CH₂) and 1,735 cm⁻¹ (C=O) [17]. In the standard isolated film spectrum (Eudragit® RS30D + TEC plasticizer), the main absorptions occurred at 1,380, 1,470, 2,987 and 2,951 cm⁻¹. They were attributed to methylene (CH₂) and methyl (CH₃) carbons present in Eudragit® and in TEC. The 1,734 cm⁻¹ peak referred to carbonyl (C=O) also present in Eudragit®, characterizing saturated aliphatic esters, and in small quantities in TEC. Still in this same spectrum we found a peak at 1,220 cm⁻¹, referring possibly to an aliphatic amine bond (C–N) present in quaternary ammonium groups, which are aplenty in Eudragit® RS30D, as they have ammonium quaternary groups in their structure [17]. The bands at 3,400 cm⁻¹ were attributed to the hydroxyl (OH) present in the TEC. In the α-GOS spectrum (Bioecolians®), the main absorptions were in the range 3,500–3,200 cm⁻¹. They were attributed to the presence of hydroxyl (OH). In the combinations (95:05 and 90:10), the highest noted absorptions were at 1,734 cm⁻¹ due to esters present in the Eudragit® structure, and the increase in intensity in the range 3,500–3,200 cm⁻¹ due to hydroxyl groups present in the α-GOS structure (signals were proportional to the increased quantity of α-GOS). The results of FTIR analyses confirmed the incorporation of the α-GOS. The intermolecular interaction involving the carbonyl groups of Eudragit® and hydroxyl of α-GOS was detected, also evidenced by other manuscript, working with Eudragit associated with oligo-polysaccharides [18].

3.2. Thermal analyses: differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)

The thermal properties of the polymethacrylate (Eudragit® RS30D) and α-gluco-oligosaccharide, individually, and combinations thereof were analyzed by DSC and TGA. In the DSC curve of α-GOS, Figure 2, we observed a broad endothermic event centered at 76 °C attributed to water loss. Above 190 °C, other endothermic and exothermic processes were visible, which primarily corresponded to the thermal decomposition of the constituents of films isolated at 192, 206 and 217 °C, respectively.

On the DSC curve of polymethyl methacrylate and combinations thereof, an inclination at 47 °C (glass temperature) and an endothermic
event at 376 °C were observed, which might be attributed to the melting point of the new polymeric material. In addition, there is no interaction of α-GOS with the density of polymeric mesh (constant melting temperature of polymethacrylate and α-GOS combinations). Evaluation a study, DSC spectra showed the decomposition of the polymer Eudragit® RS30D above 180 °C and found an inclination in the graph between 55 and 60 °C related to the glass temperature (Tg) of Eudragit® RS30D [17]. A study found the glass temperature of the polymethacrylate (Eudragit® RS30D) at 49 °C and the melting temperature at 395 °C [19].

The breakdown presented by the TGA (Figure 3) of the three Eudragit® RS30D and α-GOS combinations (control, 95:05 and 90:10) showed the same characteristic peak at 376 °C, which is in line with DSC curves (Figure 2). In addition, no significant interference of the additive α-GOS was verified in the organizational structure of polymethylmethacrylate. Brief thermogram variations of the standard polymethyl formulation, as well as those containing the additive α-GOS (5 and 10 %), are due to the variation of methacrylate groups, which are randomly distributed along the copolymer chain, and may reduce interchain interactions. Therefore, the reduction of interchain interactions may affect the disposition of polymethacrylate chains and consequently change the melting point. It is also worth stressing, as mentioned by some authors, that sometimes these structural changes may affect the mechanical and permeability properties of the membrane formed [20].

3.3. Scanning electron microscopy (SEM)

Figure 4 shows the scanning electron micrographs of tested isolated films representing the 100:00 control (Eudragit® RS30D + TEC), as well as the compositions 95:05 (Eudragit® + 5 % of α-GOS) and 90:10 (Eudragit® + 10 % of α-GOS). It was observed that the morphological characteristics are quite similar as to homogeneity for all samples. In a more detailed analysis, we found that the films immersed in FSG (pH 1.2) kept the homogeneity without the appearance of pores or any other physical changes that could be evidenced in these micrographs. However, for samples of films submitted to FSI conditions, the appearance of pores was clear, with an increase both in quantity and in the diameter depending on and proportional to the concentration of α-GOS, i.e., especially for the association 90:10. This morphological change may even justify previous results with hydration assays (Swelling Index) performed by Minard [19], where there was a greater swelling under a 7.5 pH, depending on and proportional to the highest concentration of the oligosaccharide. We can infer that the behavior presented herein, especially for the association 90:10, where samples were exposed to high pH values, triggered an increase of the ionized groups of the oligosaccharide, which may have contributed to the emergence of the electrostatic repulsion phenomenon, leading to an expansion of the polymer mesh of isolated films. The base polymer, polymethacrylate, has time-dependent properties, establishing material integrity to the distal regions of the GIT. Certainly, the incorporation of specific substrate for microbiota, that is, the α-GOS prebiotic, established a high expectation for the existence of the target-site-specificity of the formed material. These data suggest a greater vulnerability under colonic pH conditions in face of the loosening of the polymer mesh, increasing a possible attack by the microbiota on the material (substrate). In addition, this condition will trigger the full diffusion of the trapped active ingredient when it is applied in a system (store and/or matrix) destined to a modified delivery of active ingredients. However, additional tests focused on colon-specificity may confirm our initial evidence.

4. Conclusion

In conclusion, the results have been demonstrated through FTIR the incorporation of α-GOS, as well as it was not detected the intermolecular interaction involving carbonyl and hydroxyl groups of Eudragit® with α-GOS. By TG and DSC, it was possible to detect that there were no changes in the thermal properties between the proposed combinations and the standard film. These results sharpen the perspective of applying this material to the coating of pharmaceutical formulations of modified drug delivery.

Declarations

Author contribution statement

Frederico Minardi de Oliveira: Performed the experiments; Analyzed and interpreted the data.
Elio José Bunhak: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Leandro Freire dos Santos, Priscila Debastiani Barros: Analyzed and interpreted the data; Wrote the paper.
Osvaldo Albuquerque Cavalcanti: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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References

[1] A. Maroni, M.D. Del Curto, L. Zema, A. Foppoli, A. Gazzaniaga, Film coatings for oral colon delivery, Int. J. Pharm. 457 (2) (2013) 372–394.
[2] S. Amidon, J.E. Brown, V.S. Dave, Colon-targeted oral drug delivery systems: design trends and approaches, AAPS PharmSciTech 16 (4) (2015) 731–741.
[3] R.R.P. Cabral, P.M. de Oliveira, G.M. Gelfuso, T. de S. Cardoso Quintao, J.A. Chaker, E.J. Bunhak, E.S. Mendes, N.C. Pereira, E.A.G. Pineda, A.A.W. Hechenleitner, M.G.O. Karnikowski, E.F. Gris, Improving stability of antioxidant compounds from Plinia cauliflora (Jabuticaba) fruit peel extract by encapsulation in chitosan nanoparticles, J. Food Eng. 238 (2018) 195–201.
[4] S. Abbaspoor, A. Ashrafi, M. Salehi, Synthesis and characterization of ethyl cellulose micro/nanocapsules using solvent evaporation method, Colloids Polym. Sci. 296 (9) (2018) 1509–1514.
[5] J.F. S. Maior, A.V. Reis, E.C. Muniz, O.A. Cavalcanti, Reaction of pectin and glycidyl methacrylate and ultraformer formation of free films by reticulation, Int. J. Pharm. 355 (1–2) (2008) 184–194.
[6] A.B. Meneguin, B.S. Ferreira Cury, R.C. Evangelista, Films from resistant starch–pectin dispersions intended for colonic drug delivery, Carbohydr. Polym. 99 (2014) 140–149.
[7] E.J. Bunhak, E.S. Mendes, N.C. Pereira, A.A.G. Fineda, A.A.W. Hechenleitner, O.A. Cavalcanti, Physicochemical analyses of modified chondroitin sulfate biofilms, Quim. Nova 38 (3) (Mar. 2015) 316–320.
[8] K.M. Rao, S. Nagappan, D.J. See, C.S. Ha, pH sensitive halloysite-sodium hyaluronate/poly(hydroxyethyl methacrylate) nanocomposites for colon cancer drug delivery, Appl. Clay Sci. 97 (98) (2014) 33–42.
[9] J.F. S. Maior, A.V. Reis, L.N. Pedreiro, O.A. Cavalcanti, Phosphated crosslinked pectin as a potential excipient for specific drug delivery: preparation and physicochemical characterization, Polym. Int. 59 (1) (Jan. 2010) 127–135.
[10] R. Khurana, K. Singh, B. Supra, A.K. Tiwary, V. Rana, Tamarindus indica pectin blend film composition for coating tablets with enhanced adhesive force strength, Carbohydr. Polym. 102 (2014) 55–65.
[11] Y. Karrou, L. Dubauqoy, F. Pfeut, E. Siepmann, E. Mousso, D. Wils, T. Beghyn, C. Neuv, M.-P. Flament, L. Guerin-Deremaux, L. Dubreuil, B. Deprez, P. Bessemeaux,
J. Siepmann, In vivo efficacy of microbiota-sensitive coatings for colon targeting: a promising tool for IBD therapy, J. Control. Release 197 (Jan. 2015) 121–130.

[12] B.B. V Alves, A.L. Reis, A.A.W. Hechenleitner, E.A.G. Pineda, A.E. Job, O.A. Cavalcanti, Formulation additives on formation of films isolated from ethylcellulose. Physicochemical and morphological studies, Lat. Am. J. Pharm. 28 (6) (2009) 685–691.

[13] M.F. Rabito, A.V. Reis, A. dos R. Freitas, E.B. Tambourgi, O.A. Cavalcanti, A pH/enzyme-responsive polymer film consisting of Eudragit (R) FS 30 D and arabinoyxylane as a potential material formulation for colon-specific drug delivery system, Pharm. Dev. Technol. 17 (4) (2012) 429–436.

[14] X. Huang, F. Xie, X. Xiong, Surface-modified microcrystalline cellulose for reinforcement of chitosan film, Carbohydr. Polym. 201 (2018) 367–373.

[15] G. Regdon Jr., D. Hegyesi, K. Pintye Hodi, Thermal study of ethyl cellulose coating films used for modified release (MR) dosage forms, J. Therm. Anal. Calorim. 108 (1) (2012) 347–352.

[16] W.C. Wei, S. Feng, Q.H. Zhou, H.Q. Liang, Y.J. Long, Q. Wu, H.Y. Gao, G.D. Liang, F.M. Zhu, Study on glass transition and physical aging of polystyrene nanowires by differential scanning calorimetry, J. Polym. Res. 24 (3) (2017).

[17] S. Azarmi, F. Ghaffari, R. Lobenberg, A. Nokhodchi, Mechanistic evaluation of the effect of thermal-treating on Eudragit RS matrices, Il Farm 60 (11–12) (2005) 925–930.

[18] O.A. Cavalcanti, G. Van den Mooter, I. Caramico-Soares, R. Kinget, Polysaccharides as excipients for colon-specific coatings. Permeability and swelling properties of casted films, Drug Dev. Ind. Pharm. 28 (2) (2002) 157–164.

[19] L.F. dos Santos, E.A.G. Pineda, M.A.P.C. Celligui, O.A. Cavalcanti, Levan as a new additive for colon-specific films: a new approach in the use of exopolysaccharides in time-dependent free films (Aminomethacrylate Copolymer RS), Pak. J. Pharm. Sci. 26 (5) (2013) 943–948.

[20] L.A. Kanis, M. Generoso, M.M. Meier, A.T.N. Pires, V. Soldi, Poly(ethylene-co-methyl acrylate) membranes as rate-controlling barriers for drug delivery systems: characterization, mechanical properties and permeability, Eur. J. Pharm. Biopharm. 60 (3) (2005) 383–390.