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The importance of the relationship between mechanical analyses and rheometry of mucoadhesive thermoresponsive polymeric materials for biomedical applications

Sabrina Barbosa De Souza Ferreira[a], Jéssica Bassi Da Silva[a], Mariana Volpato Junqueira[a], Fernanda Belincanta Borghi-Pangoni[a], Raquel Guttierres Gomes[b], Marcos Luciano Bruschi[a,*]

[a] Postgraduate Program in Pharmaceutical Sciences, Laboratory of Research and Development of Drug Delivery Systems, Department of Pharmacy, State University of Maringá, Maringá, Paraná, Brazil
[b] Department of Food Engineering, State University of Maringá, Maringá, Paraná, Brazil

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ABSTRACT

Pluronic F127® was associated with a carbomer homopolymer type B, as a model polymer blend to evidence the information provided by rheological and mechanical analyses on the development of bioadhesive thermoresponsive systems. The mechanical analysis enabled to observe that 20% (w/w) Pluronic F127®-polymer blends were harder, more adhesive, more mucoadhesive, more compressive and less soft. In addition, continuous flow rheometry demonstrated that the systems were plastic with rheopexy (15%, w/w, Pluronic F127®) or thixotropic (20%, w/w, Pluronic F127®). Oscillatory rheometry exhibited the increase of temperature, and the polymeric concentration increases the elasticity of the formulations. Moreover, correlation index showed that softness and textural analysis can be correlated and complementary, whereas adhesiveness cannot be correlated to mucoadhesion and is less specific. Rheological interaction parameter and gelation temperature showed that 15/0.25-polymer blend is suitable for pharmaceutical and biomedical application, since it can be administered in the liquid form and be gelled in the application site with proper mucoadhesion that can suggest an improved clinical efficacy. Therefore, the mechanical and rheological analyses are useful to characterize and select the best bioadhesive thermoresponsive formulation for the proposed treatment with improved performance.

1. Introduction

The association of two or more polymers, such as those with thermoresponsive and bioadhesive properties, can provide blends with improved and new functionalities for biomedical applications (Lefnaoui and Moulai-Mostefa, 2014; Liu et al., 2005; Muthuvinayagam and Gopinathan, 2015). These materials can be used for the development of new drug delivery systems with important advantages like easy administration, prolonged residence time, protection of drugs, improved in vitro and in vivo drug delivery performance and consequently, increased bioavailability (Almeida et al., 2013; Bhowmik et al., 2013; Chang et al., 2002; Han et al., 2006; Mayol et al., 2008). Moreover, these preparations can be utilized at different application sites, such as topical, vaginal, ocular, and oral cavity (Andrews et al., 2009; Bhowmik et al., 2013; Pereira and Bruschi, 2012; Mayol et al., 2008).

The smart polymers which exhibit the phenomenon of reverse thermal gelation are called thermally responsive or thermoresponsive. When dispersed in water, in a suitable concentration, these systems are viscous liquids at room temperature and above some certain concentrations and temperatures, shift to a gel phase (Almeida et al., 2013; Bhowmik et al., 2013; Matanović et al., 2014). Thermoresponsive polymeric systems have been extensively investigated due to its biodegradable properties, easy application, spreadability and retention on the application site (Dumortier et al., 2006; Matanović et al., 2014). The non-ionic triblock copolymers composed of poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (PEO-PPO-PEO), known as poloxamer or Pluronic®, have been widely used as thermally responsive polymers. In special, Pluronic F127® (poloxamer 407; F127), a copolymer with a 12,000 Da molecular weight and PEO:PPO ratio of 2:1, has been broadly applied in drug delivery systems (Almeida et al., 2013; Dumortier et al., 2006; Matanović et al., 2014). In this way, the temperature increase leads to physicochemical changes and, then, F127

Abbreviations: ANOVA, analysis of variance; CHB, carbomer homopolymer type B; LVR, linear viscoelastic region; F127, poloxamer 407; TPA, texture profile analysis; TTA, triethanolamine; $T_{sol\text{-}gel}$, gelation temperature

[*] Correspondence to: Department of Pharmacy, State University of Maringá, Colombo Avenue, n. 5790, K68, S15a, CEP 87020-900 Maringá, Paraná, Brazil.
E-mail address: mlbruschi@uem.br (M. Luciano Bruschi).

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aggregates into micelles, with a PPO-hydrophobic core and PEO-hydrophilic shell. Moreover, this polymer can improve the solubility of drugs (Almeida et al., 2013; Bhowmik et al., 2013; Dumortier et al., 2006; Gratieri et al., 2010; Matanović et al., 2014; Parmar et al., 2014).

Furthermore, the use of bioadhesive molecules enables to increase the retention time of formulation at the biological substrate, as well as, increase bioavailability and promote improved local or systemic effects (Andrews et al., 2009; Bruschi et al., 2015; Carvalho et al., 2010; Dupuy et al., 1994; Madrigal-Carballo et al., 2008). Among them, carbomers have been extensively studied due to their high bioadhesive property and low toxicity (Andrews et al., 2009; Bonacucina et al., 2004; Carvalho et al., 2014, 2010; Hosmani et al., 2006). Due to their wide range of molecular weight and cross-linking level, these materials have demonstrated diverse mechanical and rheological characteristics (Jones et al., 2010, 2009). Carbomer homopolymer type A (Carbopol 971P®) are commonly used as thickening, suspending, emulsion-stabilizing to low viscous systems, because of their lightly cross-linked chain. On the other side, carbomer homopolymer type B (e.g. Carbopol 974P® and Carbopol 934P®) provide highly viscous gels, since they have demonstrated a high cross-linked structure (Bonacucina et al., 2004; Carvalho et al., 2014; Hosmani et al., 2006; Lubrizol, 2013a).

Recently, some polymer blends or interpenetrating polymer networks containing F127 and derived of polyacrilic acid (such as Carbopol 934P®, Carbopol 971P® or polycarbophil) have been developed and characterized for a range of biomedical and pharmaceutical applications (Baskan et al., 2013; Bruschi et al., 2007; De Souza Ferreira et al., 2015, 2017; Jones et al., 2010, 2009; Pereira et al., 2013). However, the Carbopol 974P®, a mucoadhesive polymer with important rheological properties, has not studied yet as polymeric blend with poloxamer 407. Moreover, the suitable characterization of these systems has been shown to be fundamental. Particularly, the mechanical, mucoadhesive and rheological characterization can help to tailor the formulation for the suit application site and, then ensuring the biomedical and pharmaceutical performance (Andrews et al., 2009; Jones et al., 1996). In this sense, the aim of this work was to evaluate the performance of mechanical, mucoadhesive and rheological analysis using different polymer blends composed of poloxamer 407 and carbomer homopolymer type B 974P.

2. Materials and methods

2.1. Materials

Carbomer homopolymer type B (Carbopol 974P®; CHB) was kindly donated by Lubrizol (São Paulo, SP, Brazil). Poloxamer 407 (Pluronic F127®; F127) and mucin (from porcine stomach type II) were purchased from Sigma (St. Louis, MO, USA). Triethanolamine (TTA), used as neutralizing agent, was purchased from Synth (Diadema, SP, Brazil).

2.2. Preparation of systems

Monopolymeric systems were prepared using CHB (0.10, 0.15, 0.20, 0.25 or 0.50%, w/w) or F127 (15 or 20%, w/w). CHB dispersions were prepared by gradually dispersing the required amount of polymer in purified water, using mechanical stirring, and the pH was adjusted to 7.0 with TTA. F127 formulations were prepared by dispersing the required mass in purified water at 5 °C, under gentle agitation (500 rpm) using mechanical stirrer (De Souza Ferreira et al., 2017, 2015; Schmolka, 1972).

Ten polymer blends were prepared comprising F127 (15 or 20%, w/w) and CHB (0.10, 0.15, 0.20, 0.25 or 0.50%, w/w). The required mass of CHB was dispersed in purified water using a mechanical stirrer. Then, F127 was added to the preparation and it was reserved at 5 °C for 12 h, to ensure complete hydration. In order to provide the complete mixing of both polymers, formulations were stirred. Subsequently, the resultant systems were neutralized with TTA and centrifuged (3000 rpm) to remove entrapped air. Preparations were reserved at 4 °C for at least 24 h before further analysis (Bruschi et al., 2007; De Souza Ferreira et al., 2017).

2.3. Texture profile analysis

This determination was performed in TA-XTplus Texture Analyzer (Stable Micro Systems, Surrey, England) at 5 °C, 25 °C, 37 °C. The sample (16 g) was carefully transferred to bottles, preventing the introduction of air. In TPA mode, an analytical probe (10 mm diameter) compressed the samples two times at 2 mm/s, at a defined depth (15 mm), with a 15 s of the delay period between the end of the first and the beginning of the second pass. The parameters, hardness, compressibility, adhesiveness, elasticity and cohesiveness were derived from the force-time and force-distance plots (Borghi-Pangoni et al., 2015; Bruschi et al., 2007; De Souza Ferreira et al., 2017; Mazia et al., 2016). The analyses were performed, at least, in five replicates.

2.4. Softness determination

The analysis was carried out using the same texture analyzer previously described, at 37 °C. The formulations (22.5 g) were packed into 5-mL beakers, in order to prevent the formation of air bubbles. In compression mode, the perspex conic probe (P/45 C) compressed into the sample at 1 mm/s and to a defined depth (10 mm) for 25 s. From the relationship force and distance, the softness index was calculated and at, least, three replicates were analyzed for each system (De Souza Ferreira et al., 2017, 2015).

2.5. *In vitro* assessment of mucodhesive properties

The mucoadhesive properties of the formulations were assessed by the force required to detach the samples from the partially hydrated mucin discs, using the same equipment and probe described previously. The mucin discs were prepared by compression of crude porcine mucin (300–400 mg) and then, horizontally attached to the lower end of the probe using a double-sided adhesive tape. These discs were hydrated by submersion at 5% (w/w) mucin solution for 30 s and the excess of surface liquid was removed, by gentle bottling. Prior the mucoadhesive test, the samples of each preparation were filled into shallow vessels, stored at 37 °C and placed under the analytical probe. Subsequently, the system was lowered until the mucin disc touched the sample surface, a downward force of 0.1 N was applied for 30 s, to ensure the intimate contact between both. The probe was moved upward in a constantly speed of 1 mm/s. The force necessary to separate the mucin disc and the formulation was calculated from the resulting force-time plot (Borghi-Pangoni et al., 2015; De Souza Ferreira et al., 2017; Mazia et al., 2016). The analyses were performed, at least, in five replicates.

2.6. Continuous shear rheometry

Flow analysis of preparations were carried out at 5 °C, 25 °C and 37 °C using a controlled stress rheometer (MARS II, Hacke Thermo Fisher Scientific Inc., Newington, Germany) with parallel steel cone-plate geometry (60 mm, separated by a fixed distance of 0.052 mm). Samples were carefully applied to the lower plate, making sure that the shear of the formulations was minimized, and at least 1 min rest to equilibrate before the analysis. In flow mode, the downward and upward curves were calculated over shear rates ranged from 0 to 2000 s^{-1}, increasing over a period of 150 s, held at the high limit for 10 s, and after decreasing over a period of 150 s. The flow properties of at least five replicate samples were determined. The upward flow curves were modelled using Oswald-de-Waele equation (Power Law) (Eq. (1)) (Bruschi et al., 2007; De Souza Ferreira et al., 2015; Jones et al., 2009):