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Research Paper

Rheological, mucoadhesive and textural properties of thermoresponsive polymer blends for biomedical applications

Sabrina Barbosa De Souza Ferreira[a,b], *Talita Dias Moço*[b], *Fernanda Belincanta Borghi-Pangoni*[a,b], *Mariana Volpato Junqueira*[a,b], *Marcos Luciano Bruschi*[a,b,c,*]

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

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ABSTRACT

The development of binary polymeric mixtures (polymer blends) containing bioadhesive and thermoresponsive polymers can provide new materials for biomedical applications, with higher contact, increased adhesion, prolonged residence time, protection, and in determined cases, secured absorption of an active agent from the site of application. Mixtures were prepared using a wide range of poloxamer 407 and Carbopol 971P® amounts. The rheological (flow and oscillatory), sol–gel transition temperature, mechanical (hardness, compressibility, adhesiveness, cohesiveness and elasticity), softness, and mucoadhesive properties of formulations were investigated. Moreover, the interaction between the different proportions of polymers was also analyzed. Continuous shear and oscillatory rheometry identified the plastic flow with various degrees of thixotropy, besides the viscoelastic behavior of formulations. The determination of gelation temperature displayed values ranged from 27.17 to 41.09 °C. It was also found that low carbomer concentrations were enough to provide positive interaction parameter. However, the highest values were obtained for the polymeric blends with higher concentration of poloxamer 407. The mucoadhesion and softness index were greater in preparations containing 20% (w/w) poloxamer 407. The rheological, mechanical and mucoadhesive properties of the polymeric blends can be manipulated by changing the concentrations of the polymers and they suggest the blends are worthy of biomedical applications.

Abbreviations: ANOVA, analysis of variance; Carb971P, Carbopol 971P®; PEO, polyethylene oxide; Polox407, poloxamer 407; PPO, polypropylene oxide; TPA, texture profile analysis; $T_{sol/gel}$, sol–gel transition temperature.

*Corresponding author at: Department of Pharmacy, State University of Maringá, Maringá, Paraná, Brazil. Tel.:+55 44 3011 5998; fax: +55 44 3011 4999.
E-mail address: mlbruschi@uem.br (M.L. Bruschi).

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1. Introduction

Polymer blending is a simple approach that can combine the advantages of different polymers, like bioadhesive and thermoresponsive polymers (Douglas et al., 2015; Liu et al., 2005; Mayol et al., 2008). It is usually cheaper and faster than the development of new monomers and/or new polymerization routes. Polymeric materials can be obtained with new and improved funcionalities as those of individual composing, including new release mechanisms, biocompatibility, improved mechanical properties for drug delivery systems (He et al., 2004; Lefnaoui and Moulai-Mostefa, 2014; Liu et al., 2005). Furthermore, the incorporation of bioadhesive polymers in thermoresponsive polymeric systems has improved the adhesion and the *in vitro* and *in vivo* drug delivery performance on the mucosal surfaces (Bhowmik et al., 2013; Chang et al., 2002; Han et al., 2006).

Bioadhesive materials present the ability to get into close contact with the biological substrate and also increase the residence time of a dosage form at application site (Bruschi et al., 2007; Fabri et al., 2011; Pereira et al., 2013). They can increase the drug permeation and bioavailability as well as promote local or systemic effects and protect drugs from mucociliary clearance (Andrews et al., 2009; Carvalho et al., 2010; Hägerström and Edsman, 2003). The selection of the components can modify the bioadhesive properties of the formulation due to the importance on the adhesive interaction (Carvalho et al., 2010; Jones et al., 2009). Various materials have been used for developing of such systems (*e.g.* polymers derived from poly (acrylic acid) or cellulose, alginates, and chitosan) (Andrews et al., 2009; Carvalho et al., 2014, 2010). According to the manufacturing conditions and crosslinking degree, poly (acrylic acid) derivatives have demonstrated different mechanical and rheological characteristics (Jones et al., 2010, 2009). Hence, these polymers have been employed in biomedical application for wound healing as well as, remineralization dentin (Chen et al., 2014; Smith et al., 2009).

Moreover, thermoresponsive materials are environmental-sensitive polymers, which can change their conformational structure in response to temperature, resulting *in situ* gelling systems (Almeida et al., 2013a; Gupta et al., 2010; Qiu and Park, 2001). They offer advantages like easy administration, spreadability on the application site, as well as slow clearance due to the sol–gel transition (Dumortier et al., 2006; Liu et al., 2009; Qiu and Park, 2001; Smith et al., 2009). The thermoresponsive polymers most widely used are poloxamers, xyloglucan and poly(N-isopropylacrylamide). Poloxamers, specially poloxamer 407 (Polox407), are non-ionic block of copolymers that consists of polyethylene oxide (PEO) and polypropylene oxide (PPO) units and are temperature sensitive. When temperature increases, the poloxamer molecules in aqueous solutions aggregate into micelles due to dehydration of PPO chains in the core with an outer surface of hydrated PEO chains, which provides the solubility of hydrophilic and hydrophobic drugs (Almeida et al., 2013b; Bhowmik et al., 2013; Gratieri et al., 2010; Jones et al., 2010; Kehoe et al., 2012; Liu et al., 2009; Mayol et al., 2008; Zaki et al., 2007). These properties provides some applications such as, permeation enhancer, wound and burn healing and periferic nerve regeneration (Djekic et al., 2015; Kehoe et al., 2012; Täuber and Müller-Goymann, 2015).

In this sense, the association of bioadhesive and thermoresponsive polymers, such as Polox407 and Carbopol 934P® (Bruschi et al., 2007; Fabri et al., 2011; Jones et al., 2009; Pereira et al., 2013), chitosan (Gratieri et al., 2010) or carragenaan (Liu et al., 2009) can provide new platforms for drug delivery. These polymeric blends can offer easy administration, as well as improved retention at the application site (Fabri et al., 2011; Liu et al., 2009). In addition, binary mixtures containing Polox407 and Carbopol 934P® have shown suitable mechanical, mucoadhesive and rheological characteristics to be used for vaginal, periodontal, buccal, rectal and topical routes (Bruschi et al., 2007; Fabri et al., 2011; Jones et al., 2009; Pereira et al., 2013). Carbopol 934P® is a bioadhesive polymer highly crosslinked with allyl sucrose, presents good bioadhesive properties and lower amount of free carboxyl groups. Although, the residual benzene present in this type of carbomer decreases the acceptance by regulatory agencies. The "P" term refers to the low residual benzene content (approximately 0.1%), which is acceptable and allows the use by *per oral* route (Bonacucina et al., 2004; Hosmani et al., 2006; Técnica, 1998).

Therefore, the obtainment of a polymeric platform containing Polox407 and a carbomer without residual benzene, like Carbopol 971P® (Carb971P), provides increased safety. Since this material is polymerized with ethyl acetate and is well accepted by regulatory agencies. Carb971P is a lightly crosslinked polymer with allyl penta erythritol and display a large amount of free carboxyl groups available to perform the interaction between poloxamer polymeric chain and biological substrate. These properties provide increased swelling and consequently, greater deformability and low viscosity to Carb971P gels (Bonacucina et al., 2004; Carvalho et al., 2013; Hosmani et al., 2006; Lubrizol, 2013; Mezreb et al., 2004).

Moreover, these blends could be employed for mechanical protection, drug delivery, and wound or burn healing, for example. Since, wound healing is a dynamic process and dressings that afford warm and moist environment provide rapid healing, as well as, demonstrate ease administration and removal and proper adherence (Smith et al., 2009). Furthermore, poly (acrylic acid) derivatives have been applied in drug release system as a strategy for dentin remineralization (Chen et al., 2014). So these systems could facilitate the administration, improve the retention and probably to control the drug release (Pereira et al., 2013). Moreover, polymeric systems composed of Polox407 and other poly (acrylic acid) derivative were developed to deliver propolis extract or sildenafil citrate for dental pulp protection (Fabri et al., 2011).

In this context, a comprehensive investigation of rheological, mechanical and mucoadhesive properties of these systems enable to get a greater understanding about the interaction between these polymers, to evaluate the behavior against of a wide range of stresses, and the mucoadhesive performance of these systems (Baloglu et al., 2011; Jones et al., 2009; Tamburic and Craig, 1995). Moreover, such information allows to identify the potential applications and routes of administration. To our knowledge, no studies on the characterization of these blends were performed,