Thermoresponsive systems composed of poloxamer 407 and HPMC or NaCMC: mechanical, rheological and sol-gel transition analysis

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ABSTRACT

Poloxamer 407 (polox407) is widely studied as thermogelling polymer, transitioning to a gel state when warmed. Polox407 has the limitation that it forms weak hydrogels, with rapid dissolution in excess solvent. This study reports the development of new binary polymeric systems composed of polox407 and hydroxypropyl methylcellulose (HPMC) or sodium carboxymethylcellulose (NaCMC) with an aim to improve the rheological and mechanical properties of the hydrogel. The interaction between polox407 and cellulose derivatives was studied, and their interaction with biological surfaces predicted. The carbohydrates affected the mechanical and rheological behavior of polox407 in different ways, dependent on polymer type, concentration, and temperature. $T_{sol/gel}$ and rheological interaction parameters were useful to select the most suitable formulations for topical or local application, ensuring *in situ* gelation and the formation of a strong gel. Most of the binary systems exhibited plastic behavior, with thixotropic and viscoelastic properties. Appropriate formulations were identified for local application, such as 17.5/3; 17.5/4; 20/3 and 20/4 (%, w/w) for polox407/HPMC; and 17.5/1; 17.5/1.5; 20/1 and 20/1.5 (%, w/w) for polox407/NaCMC.

Keywords: hydrogel; cellulose derivatives; poloxamer 407; rheology; mechanical characterization.

1. Introduction

Polymer blends provide a simple approach to combine the advantages of different polymers, for example adhesiveness and environmental responsiveness (Barbosa et al., 2017; Borghi-Pangoni et al., 2015; Bruschi et al., 2007; Jones et al., 2009; Liu, Lin, Li, & Liu, 2005). Thermoresponsive gelling systems have been widely studied over the years for drug delivery, mainly due to their ease of application, spreadability and retention at the application site (de Francisco et al., 2019; Ramírez Barragán et al., 2018). Moreover, where these thermoresponsive materials are composed of nanostructured micelles derived from amphiphilic block copolymers they may improve solubilization, stabilization and control of drug delivery (Jindal & Mehta, 2015).

Poloxamer 407 (polox407), a non-ionic triblock copolymers composed of poly(ethylene oxide)$_{101}$-b-poly(propylene oxide)$_{56}$-b-poly(ethylene oxide)$_{101}$ (PEO-PPO-PEO), is the most commonly used thermogelling material. It is able to form a nanostructured gel system when the temperature is increased (Nie, Hsiao, Pan, & Yang, 2011). Polox407 aqueous dispersions above 15 % (w/v) behave as low viscosity fluids at room or fridge temperature, while at body temperature they increase in viscosity due to the formation of a gel mesophase. Raising the environmental temperature triggers a hierarchical process whereby the polymer macromolecules aggregate into micelles with a PPO-hydrophobic core and PEO-hydrophilic shell (Almeida, Amaral, Lobão, & Lobo, 2014; Dumortier, Grossiord, Agnely, & Chaumeil, 2006). When the volume fraction of the micelles is sufficiently high, the micelles pack into a face-centered cubic gel (Abou-Shamat, Calvo-Castro, Stair, & Cook, 2019). The presence of micelles also allows the solubilization of a wide range of pharmaceutic actives, since hydrophilic molecules can be kept in the shell or aqueous phase, while hydrophobics can remain into the core (De Souza Ferreira, Bassi da Silva, Borghi-Pangoni, Junqueira, & Bruschi, 2015).

In spite of its positive characteristics, polox407 forms weak hydrogels, usually with rapid dissolution (Wu et al., 2011). To improve its properties as a hydrogel former, many polymers have been included in binary mixtures containing polox407, including poly(acrylic acid) derivatives (Andrews, Laverty, & Jones, 2009; Bassi da Silva, Khutoryanskiy, Bruschi, & Cook, 2017; De Souza Ferreira, Bassi da Silva, et al., 2015; De Souza Ferreira, Moço, Borghi-Pangoni, Junqueira, & Bruschi, 2015), polycarbophil (Barbosa et al., 2017), polyvinylpyrrolidone and chitosan (Gratieri et al., 2010; Pagano, Giovagnoli, Perioli, Tiralti, & Ricci, 2020). This approach of mixing polymeric additives with polox407 is attractive as the resultant materials would not require the regulatory burden that a chemical modification would impart (Abou-Shamat et al., 2019).

Cellulose is the most abundant polymeric polysaccharide in nature, and one of the most widely used excipients in pharmaceutical industry. It is composed of $\beta(1 \rightarrow 4)$ linear chains linked to D-glucose units. Common cellulose derivatives include methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose and carboxymethylcellulose, which are good gel formers (Sosnik, Das Neves, & Sarmento, 2014). They do not present toxicity and are generally preferred for topical or mucosal application as they are also non-irritating polymers (Sosnik et al., 2014). Hydrogels containing polox407 and cellulose derivatives have already been described in the literature, for example combining polox407 with hydroxyethylcellulose (Jones, Woolfson, & Djokic, 1996) or carboxymethylcellulose (Hägerström & Edsman, 2001; Pagano et al., 2020; Wang et al., 2016). The addition of cellulose derivatives to hydrogels with polox407-content aims not only to contribute to the optimization of physical structures, but also to modulate the gelation temperature and rheological and mechanical properties of poloxamer hydrogels (Wang et al., 2016).

Polymeric blends containing polox407 and hydroxypropyl methylcellulose (HPMC) or sodium carboxymethylcellulose (NaCMC) have been poorly investigated (Barse, Kokare, & Tagalpallewar, 2016; Pagano et al., 2020; Pandey, Cabot, Wallwork, Panizza, & Parekh, 2017; Wang et al., 2016). Pandey and collaborators, for example, studied polox407 and HPMC in ternary blends with chitosan (Pandey et al., 2017), while Pagano and collaborators explored binary systems containing polox407 and NaCMC, exploring gelation temperature and time, with a single measure of overall viscosity (Pagano et al., 2020). Although there are some studies describing systems composed of these polymers for specific applications in the literature, none of them have conducted a systematic investigation into their rheological and mechanical characteristics (e.g. flow, viscoelasticity, texture and softness profile). There is also no study on synergisms and interactions between these polymers, or on the correlation between these properties over a range of polymer concentration and temperature.

Therefore, the aim of this work was to support the use of these systems as thermoresponsive materials with improved retention properties for biomedical applications, mainly as topical pharmaceutical systems. This work describes the rheological and mechanical characterization of polymeric systems composed of polox407 and HPMC or NaCMC and their correlation, in order to understand them fundamentally, including their interaction with biological surfaces, and select the best formulations for biomedical and pharmaceutical applications.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC; type K100, Methocel®, with hydroxypropoxyl content 8.1% and methoxyl content 22%) was donated from Colorcon Dow Chemical Company™ (United Kingdom), with a molecular weight of 29.905 KDa with a polydispersity index (PD) of 1.558 (information described in detail in the supplementary material). Sodium carboxymethylcellulose with a degree of substitution between 0.8 and 0.95, molecular weight of 29.567 KDa and PD=2.094 (supplementary material) was purchased from Synth (Brazil). The cellulose derivatives were also evaluated by ^{1}H NMR as described in the supplementary information. Poloxamer 407 (polox407) was purchased from Sigma-Aldrich (Brazil). Dimethyl formamide HPLC grade was purchased by Fisher Scientific (United Kingdom). Unless specified, all reagents were used without further purification. Purified water was obtained in-house using a Millipore Milli-Q water purification system (Germany).

2.2. Preparation of samples

The thermogelling systems were prepared by dispersion of HPMC (2, 3 or 4 %, w/w) or NaCMC (0.5, 1.0 or 1.5%, w/w) in purified water with stirring at room temperature. After complete dispersion of the cellulose derivatives, an appropriate amount of polox407 (15.0, 17.5 or 20 %, w/w) was added to the preparations, and the mixtures were stored at 4 °C for 48 h to ensure complete polymer wetting. Afterwards, the polymeric systems were stirred again to complete dissolution, and kept at 4 °C for at least 24 h before analysis (Bassi da Silva et al., 2017; De Souza Ferreira, Bassi da Silva, et al., 2015; Schmolka, 1972).

2.3. Rheology

The rheometry of formulations was performed using a controlled stress rheometer (MARS II, Haake Thermo Fisher Scientific Inc., Germany) with parallel steel cone-plate geometry (35 mm, separated by a fixed distance: 0.052 mm). All the analysis was performed at three temperatures: 5, 25 and 37 °C. The samples were carefully placed to the inferior plate, and allowed to resume their equilibrium for at least one minute before starting the analysis. At least three replicates of each sample were analyzed.

2.3.1. Continuous shear (flow) analysis

Two curves were obtained in flow mode over shear rates ranging from 0 to 2000 s^{-1} and 2000 to 0 s^{-1}. The up curve was measured over 150 s, kept at the high limit for 10 s and, then decreased over 150 s (Barbosa et al., 2017; Bassi da Silva et al., 2017; de Francisco et al., 2019). The up curve was fitted by Oswald-de-Waele equation as shown below Eq. (1):

$$\sigma = k\dot{\gamma}^{n} \tag{1}$$

where σ is the shear stress (Pa), k is the consistency index $(Pa.s)^n$, $\dot{\gamma}$ is the rate of shear (s^{-1}), and n is the flow behavior index (dimensionless). The yield stress values were investigated by the Casson model Eq. (2) (Hemphill, Campos, & Pilehvari, 1993):

$$\tau = \sqrt[n]{\left(\tau_0^n + \left(\dot{\gamma} n_p\right)\right)}^{n} \tag{2}$$

where τ represents the shear stress (Pa), n is the flow behavior index (dimensionless), τ_0 is yield stress (Pa), $\dot{\gamma}$ is the rate of shear (s^{-1}) and n_p is Casson plastic viscosity.

Additionally, the hysteresis area of each formulation was calculated using RheoWin 4.10.0000 (Haakes®) software.

2.3.2. Oscillatory measurements

The viscoelastic properties were assessed in oscillatory mode. Firstly, the linear viscoelastic region (LVR) of each sample was determined at each temperature studied. The frequency sweep analysis was then conducted from 0.1 to 10.0 Hz (Barbosa et al., 2017; Bassi da Silva et al., 2017; de Francisco et al., 2019). The storage modulus (G'), the loss modulus (G"), dynamic viscosity (η') and loss tangent (tan δ) were obtained using the RheoWin 4.10.0000 (Haakes®) software.

2.3.3. Interaction parameter

Interaction between polox407 and HPMC or NaCMC was investigated by determining the difference between the absolute value of the dynamic moduli (G') of the polymeric blends and the theoretical value of the G' obtained by summation of the individual parts (Hemphill et al., 1993; Jones et al., 2009). This interaction parameter was determined using the G' values at 10.0 Hz of oscillatory frequency, as shown in Eq. (3).

$$\Delta G' = G'_{\text{mixture}} - (G'_{\text{poloxamer 407}} + G'_{\text{HPMC or NaCMC}}) \qquad (3)$$

2.3.4. Measurement of solution-gel transition temperature ($T_{sol/gel}$)

Determination of $T_{sol/gel}$ was performed in oscillatory mode using a temperature ramp with the geometry described above. Once the LVR each formulation had been determined at 5 and 60 ºC, a temperature sweep analysis was performed over the temperature range of 5-60 ºC, at 1.0 Hz frequency, and a heating rate of 10 °C/min using a controlled stress within the LVR. G', G″, η' and tan δ were calculated using the RheoWin 4.10.0000 (Haakes®) software. The temperature at which the elastic modulus (G') was halfway between the values for the solution and for the gel was defined as $T_{sol/gel}$, based on the significant increase of dynamic viscosity (η') with increasing temperature (Barbosa et al., 2017; Bassi da Silva et al., 2017; Bruschi et al., 2007; de Francisco et al., 2019).

2.4. Texture profile analysis (TPA)

The evaluation of compressional flow was achieved using a TA-XTplus texture analyzer (Stable Micro Systems, Surrey, England) in TPA mode, at 5, 25 and 37 °C. Firstly, ca 16 g of sample was added to glass vials whilst avoiding the introduction of air. Then, the formulations were compressed twice by an analytical probe (10 mm diameter). The compressions were performed at 2 mm/s, to a depth of 15 mm. A delay period of 15 s was allowed between the end of the first compression, and the beginning of the second step. Hardness (maximum force during the compression), compressibility (the work required to deform the formulation during the first pass of the probe), adhesiveness (work required to overcome the attractive forces between the surfaces of the probe/sample), elasticity (ability to stretch and return to its original size and shape), and cohesiveness (work necessary to become united the surface of the sample and the surface of the probe) were calculated from the force-time and force-distance graphs, as demonstrated in Fig. S3 (Barbosa et al., 2017; Bassi da Silva et al., 2017; Bruschi et al., 2007; de Francisco et al., 2019).

2.5. Determination of softness

The softness of formulations was assessed by the texture analyzer in compression mode at 37 °C using a perspex conic probe (P/45C). Beakers (50 mL) were filled with the samples avoiding the formation of bubbles. The analytical probe was then compressed into each formulation at 1 mm/s, and to a depth of 10 mm. The maximum required force for the probe to penetrate each sample was calculated as the maximum value in a force-distance graph (Fig. S4), which was designated the softness index (Barbosa et al., 2017; Bruschi et al., 2007; de Francisco et al., 2019).

2.6. Statistical analysis

The effects of cellulose derivative type, polymer content and temperature on textural (hardness, compressibility, adhesiveness, elasticity and cohesiveness) and rheological properties (consistency index, flow index, yield stress and hysteresis area) were statistically compared using three-way analysis of variance (ANOVA). Similarly, the effects of polymer concentration and polymer type on softness index were statistically evaluated using two-way ANOVA. In all cases, individual differences between means were identified using Tukey's honestly significant difference test. Additionally, the linear correlation between consistency index and hardness, yield value and hardness, flow behavior index and adhesiveness, as well as, softness at 37°C and hardness or consistency index at 37 °C were determined by linear regression analysis. Statistical comparison of the moduli of polymeric blends and the theoretical modulus following addition of the individual moduli was performed using an unpaired *t*-test.

Finally, the paired Student's *t*-test was used to determine if the dynamic viscosity (η') of the formulations increased with rising temperature ($T_{sol/gel}$). Significant differences were accepted when $p<0.05$ and Statistica 8.0 software (StatSoft Company, Tulsa, Oklahoma) was used throughout.

3. Results and discussion

3.1. Continuous shear (flow) rheology

The study of rheological properties in polymeric systems can allow understanding of possible interactions among polymers which constitute the systems. This in turn may guide the selection of formulations considered most suitable for a given clinical application. Including the effect of stress variation to which formulations are exposed during the manufacturing process, bottling, storage, unpacking of the product until their behavior at the application site. All this knowledge allows us to predict and avoid the disruption of polymer system structure, improving product stability and therapeutic efficacy (Baloglu, Karavana, Senyigit, & Guneri, 2011; Barbosa et al., 2017).

Appropriate flow properties of thermoresponsive bioadhesive polymeric systems ensure ease of administration. In the relaxed mode, the polymer chains are tangled, which gives to the system greater viscosity. During administration, the stress increases in the system, and polymer chains become aligned following the direction of shear, which reduces their apparent viscosity. After application, polymeric systems regain their initial rheological profile. In this sense, formulations exhibiting pseudoplastic flow have better distribution on the applied surface (De Souza Ferreira, Moço, et al., 2015; Jones et al., 2009). Mono-polymeric formulations of polox407 exhibited Newtonian flow behavior at 5 and 25 °C. At 37 °C, and at all concentrations, non-Newtonian pseudoplastic behavior was demonstrated due to the formulations' thermoresponsive properties (Table 1) (Barbosa et al., 2017; Dumortier et al., 2006). Mono-polymeric formulations of HPMC showed pseudo-plastic flow behavior at all the evaluated temperatures and concentrations, i.e. the samples exhibited shear-thinning without yield observed on the flow curve. However, for all binary polymeric systems containing polox407 and HPMC, plastic behavior was observed, i.e. the samples exhibited shear-thinning with a yield observed on the flow curve. The addition of polox407 in HPMC mono-polymeric formulations led to a reduction in the flow behavior index (*n*), but this reduction did not show statistical significance ($p>0.05$). Starting from polox407 mono-polymeric formulations, the addition of HPMC also led to reduced flow behavior index, which were not statistically different as observed for polox407. Overall, an increase in temperature (5, 25 and 37 °C) reduced the value of n significantly, which is attributed to the gel mesophase exhibiting shear-induced structural rearrangements. A statistical difference was observed between 5 °C and 25 or 37 °C ($p<0.05$), but not between 25 and 37 °C ($p>0.05$). The contraction of n is directly related to the structure of the polymeric system. The smaller amount of free water in the system leads to a reduced Newtonian behavior, moving the value further from unity.

Table 1

The effects of concentration of poloxamer 407 (polox407), hydroxypropyl methycellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) on the consistency index (*k*) and rheological exponent (*n*) of binary polymeric systems at different temperatures.

Polymer (%, w/w)			*k* (Pa.s)^n			*n* (dimensionless)		
P407	HPMC	NaCMC	5 °C	25 °C	37 °C	5 °C	25 °C	37 °C
15	-	-	0.018 ± 0.001	0.026 ± 0.001	0.2698 ± 0.019	1.031 ± 0.009	1.049 ± 0.006	0.859 ± 0.006
17.5	-	-	0.024 ± 0.001	0.088 ± 0.003	97.793 ± 2.699	1.014 ± 0.002	1.038 ± 0.014	0.173 ± 0.002
20	-	-	0.039 ± 0.000	1.667 ± 0.188	163.900 ± 4.574	1.014 ± 0.002	0.762 ± 0.016	0.157 ± 0.007
-	2	-	0.876 ± 0.001	0.239 ± 0.001	0.111 ± 0.001	0.735 ± 0.001	0.615 ± 0.001	0.471 ± 0.005
-	3	-	4.898 ± 0.012	1.438 ± 0.001	0.598 ± 0.021	0.842 ± 0.003	0.724 ± 0.002	0.619 ± 0.004
-	4	-	25.653 ± 1.087	6.538 ± 0.046	3.178 ± 0.012	0.907 ± 0.002	0.811 ± 0.002	0.686 ± 0.001
15	2	-	0.341 ± 0.001	0.603 ± 0.048	130.232 ± 3.610	0.861 ± 0.001	0.603 ± 0.048	0.179 ± 0.002
15	3	-	1.087 ± 0.042	0.903 ± 0.071	66.360 ± 0.384	0.759 ± 0.047	0.829 ± 0.017	0.376 ± 0.012
15	4	-	19.431 ± 1.018	24.661 ± 3.801	115.731 ± 12.689	0.277 ± 0.026	0.425 ± 0.010	0.322 ± 0.031
17.5	2	-	0.205 ± 0.010	16.663 ± 0.402	130.302 ± 7.349	0.895 ± 0.001	0.505 ± 0.013	0.246 ± 0.013
17.5	3	-	0.705 ± 0.002	64.357 ± 4.022	138.570 ± 8.345	0.995 ± 0.001	0.299 ± 0.002	0.283 ± 0.012
17.5	4	-	0.314 ± 0.009	43.601 ± 2.867	257.800 ± 6.920	0.893 ± 0.000	0.461 ± 0.001	0.194 ± 0.001
20	2	-	0.092 ± 0.001	255.902 ± 8.787	380.481 ± 11.931	0.990 ± 0.001	0.128 ± 0.001	0.082 ± 0.001
20	3	-	0.093 ± 0.001	298.372 ± 6.012	318.601 ± 11.312	0.999 ± 0.002	0.122 ± 0.000	0.118 ± 0.002
20	4	-	0.121 ± 0.000	346.771 ± 8.670	441.771 ± 13.208	0.986 ± 0.003	0.107 ± 0.002	0.077 ± 0.003
-	-	0.5	1.832 ± 0.027	1.166 ± 0.011	0.911 ± 0.019	0.469 ± 0.012	0.498 ± 0.004	0.525 ± 0.011
-	-	1.0	14.260 ± 0.235	9.377 ± 0.052	6.596 ± 0.078	0.323 ± 0.001	0.358 ± 0.002	0.387 ± 0.002
-	-	1.5	43.947 ± 0.817	30.253 ± 0.516	22.431 ± 0.432	0.246 ± 0.001	0.278 ± 0.001	0.305 ± 0.001
15	-	0.5	3.205 ± 0.031	1.388 ± 0.071	2.734 ± 0.060	0.549 ± 0.001	0.729 ± 0.001	0.656 ± 0,001
15	-	1.0	17.870 ± 0.520	8.377 ± 0.452	18.597 ± 1.001	0.411 ± 0.001	0.578 ± 0.001	0.459 ± 0.003

15	-	1.5	37.970 ± 4.132	29.043 ± 1.236	62.821 ± 9.873	0.352 ± 0.012	0.456 ± 0.022	0.371 ± 0.023
17.5	-	0.5	3.187 ± 0.066	3.202 ± 0.138	106.131 ± 2.861	0.574 ± 0.002	0.704 ± 0.003	0.218 ± 0.002
17.5	-	1.0	12.578 ± 0.254	43.851 ± 5.149	362.002 ± 25.402	0.479 ± 0.014	0.396 ± 0.032	0.075 ± 0.001
17.5	-	1.5	124.231 ± 11.325	370.601 ± 15.385	441.030 ± 4.292	0.256 ± 0.025	0.064 ± 0.002	0.039 ± 0.001
20	-	0.5	3.903 ± 0.093	249.772 ± 12.243	298.001 ± 6.154	0.573 ± 0.003	0.121 ± 0.011	0.110 ± 0.013
20	-	1.0	18.001 ± 0.467	470.633 ± 11.541	490.501 ± 7.425	0.435 ± 0.001	0.086 ± 0.010	0.063 ± 0.014
20	-	1.5	13.681 ± 1.887	475.232 ± 22.673	560.932 ± 49.692	0.554 ± 0.043	0.037 ± 0.001	0.001 ± 0.012

The consistency index (*k*) is related to the viscosity of a power law fluid at low shear. Thus, high values demonstrate great resistance to deformation due to the entanglement of polymer chains. As shown in Table 1, an increase in polox407 and HPMC concentration and an increase in temperature resulted in higher *k* values. The addition of polox407 into formulations containing only HPMC showed a significant increase in *k* value when 17.5 or 20% polox407 ($p<0.05$) were added. The addition of 15% (w/w) polox407 did not cause a statistically significant change in *k*, but the increased consistency value obtained by the addition of 20% polox407 was statistically different compared to the 15 or 17.5% polox407. Similarly, the addition of HPMC in the system gave an increase in the value of *k*. However, the increase in the consistency of the systems was not significant when compared polox407 solutions to any studied concentration of HPMC (2, 3 or 4%, w/w). Regarding the temperature, its increase led to a significant increase of the consistency index, since at high temperatures the gelation of the formulations occurs. Thus, polymer chains are better organized into packed micellar mesophases, leading a consequent increase in the consistency and/or viscosity of the system. As observed for *n* value, statistical difference was observed between 5 °C and 25 or 37 °C ($p<0.05$), but not between 25 and 37 °C ($p>0.05$).

The yield value represents the minimum stress required for the material starts flowing, and is characteristic for physically crosslinked materials since once the yield value is exceeded, the physical interactions are overcome and the material begins to flow (Barbosa et al., 2017). The temperature and concentration of polox407 and HPMC polymers influenced the yield value of the studied formulations (Table 2). HPMC mono-polymeric formulations at all observed temperatures demonstrated pseudoplastic behavior, with no yield. However, the other binary systems showed plastic flow, increasing their yield value when increasing polymer concentration. This behavior is attributed to the presence of polox407. Pharmaceutical systems that demonstrate higher yield value are more favorable for retention of the formulation at the applied site and may resist to different *in vivo* movements, such as chewing, mucociliary movement or clearance (De Souza Ferreira, Moço, et al., 2015). The temperature displayed a statistically significant influence on the yield value of systems composed of polox407 and HPMC, with the main difference observed between 5 °C and 25 or 37 °C ($p<0.05$).

When subjected to shear stress, some the materials undergo a reversible loss of viscosity which may exhibit hysteresis. The hysteresis area usually reveals the reversibility of the formulations' response to shear, showing two different profiles: thixotropic (positive hysteresis area) or rheopectic (negative hysteresis area) (Barbosa et al., 2017; Jones et al., 2009). The addition and increase of polox407 to HPMC mono-polymeric formulations changed the hysteresis area found, however no statistical difference was observed. The addition of HPMC changed the hysteresis area of polox407 formulations from rheopectic to thixotropic in most cases, except 15 % polox407 with 2 and 3 % HPMC. Rheopexy has been already reported in colloidal dispersions, as a reversible phenomenon with time-dependent increase in viscosity when exposed to a determined shear rate. Thixotropic systems, on the other hand, become more fluid when stress is applied, as during stirring, pumping or spread; returning gradually to their initial structure after removal of shear stress. Thixotropic behavior was observed mainly at 5 and 37 °C, without statistical difference between them.

Table 2

The effects of concentration of poloxamer 407 (polox407), hydroxypropylmethycellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) on the yield value and hysteresis area of binary polymeric systems at different temperatures.

Polymer (%, w/w)			Yield value (Pa)			Hysteresis area		
P407	HPMC	NaCMC	5 °C	25 °C	37 °C	5 °C	25 °C	37 °C
15	-	-	0.329 ± 0.019	5.143 ± 1.520	7.702 ± 0.772	2319.001 ± 51.391	-5953.323 ± 447.411	-34260.00 ± 4143.621
17.5	-	-	0.000 ± 0.014	1.732 ± 0.148	200.870 ± 8.503	1863.332 ± 15.308	-17673.323 ± 198.578	-18350.00 ± 1083.461
20	-	-	0.000 ± 0.048	79.053 ± 9.980	337.978 ± 18.505	452.833 ± 58.115	-5763.323 ± 340.193	-217.167 ± 12.432
-	2	-	0.000 ± 0.650	0.000 ± 0.226	0.000 ± 0.169	2405.667 ± 263.365	-2955.020 ± 144.441	-6718.670 ± 472.500
-	3	-	0.000 ± 0.338	0.000 ± 0.233	0.000 ± 0.188	3311.500 ± 99.702	-9155.667 ± 714.394	-17493.33 ± 1475.481
-	4	-	0.000 ± 0.370	0.000 ± 1.185	0.000 ± 1.168	21520.001 ± 533.948	-24786.667 ± 1033.554	-39463.33 ± 4248.580
15	2	-	0.000 ± 0.237	31.4567 ± 2.253	123.963 ± 4.265	303.333 ± 39.249	-33803.333 ± 2695.187	-18460.00 ± 690.217
15	3	-	0.000 ± 0.491	54.8067 ± 0.340	443.833 ± 37.508	4397.667 ± 388.647	-50290.000 ± 1479.864	-12510.00 ± 1132.607
15	4	-	0.000 ± 0.774	430.733 ± 11.609	647.633 ± 5.604	738066.66 ± 4841.830	-94525.000 ± 7.071	174133.33 ± 8581.569
17.5	2	-	0.000 ± 0.151	260.867 ± 14.319	185.200 ± 25.460	3924.500 ± 248.194	-53613.333 ± 4097.443	100246.67 ± 11667.413
17.5	3	-	0.000 ± 0.065	285.033 ± 3.121	398.800 ± 21.579	1183.000 ± 72.753	-2927.667 ± 269.786	370966.67 ± 8240.348
17.5	4	-	0.000 ± 0.123	388.366 ± 4.821	722.467 ± 32.178	4254.667 ± 239.863	-25346.667 ± 3015.317	160733.33 ± 15938.737
20	2	-	0.000 ± 0.037	410.833 ± 4.606	402.002 ± 23.539	462.867 ± 33.012	114916.667 ± 14179.59	148233.33 ± 21696.159
20	3	-	0.000 ± 0.019	458.967 ± 35.739	466.400 ± 18.780	-310.233 ± 32.010	13850.000 ± 1885.948	5552.33 ± 630.347
20	4	-	0.000 ± 0.056	460.092 ± 15.627	492.667 ± 20.175	755.767 ± 77.528	2985.000 ± 87.681	25530.00 ± 2940.272
-	-	0.5	1.169 ± 0.100	0.928 ± 0.097	0.582 ± 0.369	901.625 ± 85.082	-669.833 ± 67.861	-2237.001 ± 226.122
-	-	1.0	6.418 ± 1.801	0.178 ± 0.013	2.391 ± 0.408	5064.333 ± 453.632	-1293.667 ± 135.079	-430.333 ± 388.931
-	-	1.5	9.328 ± 0.922	45.067 ± 2.524	9.479 ± 0.397	15463.333 ± 609.289	4459.667 ± 38.070	-5116.001 ± 421.576

15	-	0.5	7.299 ± 0.531	12.487 ± 0.540	50.273 ± 0.092	5140.000 ± 391.559	-18626.667 ± 2015.746	-17963.33 ± 1955.081
15	-	1.0	18.570 ± 1.870	43.873 ± 4.721	142.267 ± 1.191	20000.00 ± 2115.390	9401.667 ± 1063.185	24566.662 ± 2795.790
15	-	1.5	87.770 ± 8.531	90.920 ± 5.467	247.567 ± 38.822	9286.667 ± 687.278	22426.667 ± 2687.979	36333.332 ± 905.232
17.5	-	0.5	9.222 ± 0.552	54.04 ± 3.001	106.838 ± 12.712	4734.333 ± 529.392	64813.330 ± 7606.720	54640.000 ± 6047.567
17.5	-	1.0	35.301 ± 3.952	245.507 ± 20.352	183.422 ± 22.090	5621.667 ± 650.079	15900.000 ± 1560.002	244466.67 ± 5024.277
17.5	-	1.5	64.001 ± 2.302	248.060 ± 71.751	245.669 ± 37.259	-8452.363 ± 107.740	22083.333 ± 1537.281	43973.332 ± 1801.011
20	-	0.5	13.621 ± 0.543	317.967 ± 32.004	190.814 ± 21.120	552.667 ± 60.511	18946.667 ± 1692.380	26170.001 ± 2507.858
20	-	1.0	34.951 ± 3.570	493.670 ± 30.435	1430.01 ± 16.206	868.133 ± 48.423	51183.337 ± 3773.292	69210.001 ± 7732.152
20	-	1.5	72.123 ± 6.021	526.800 ± 675.57	216.200 ± 17.253	-7008.000 ± 751.243	71200.000 ± 3917.891	48946.667 ± 2532.384

For systems containing NaCMC, all parameters evaluated had an effect on *k*, *n*, yield value and thixotropy. Mono-polymeric NaCMC systems, as well as binary polymeric systems composed of NaCMC and polox407 had *n* values less than one at all temperatures analyzed (Table 1) (Benchabane & Bekkour, 2008). Therefore, shear-thinning behavior was observed for all NaCMC systems, as well as for those containing HPMC. The increase in NaCMC concentration led to a significant reduction in the *n* values, but this reduction was only statistically significant between formulations without NaCMC and the two highest NaCMC concentrations studied – 1.0 and 1.5% (w/w). The addition of polox407 also resulted in a lower *n* value, with significant reduction only between formulations containing 15% (w/w) polox407 and those with 20% (w/w) polox407. Regarding *n* values, formulations without polox407 were not statistically different; nor were those composed of 17.5% (w/w) polox407. For a thermoresponsive system raising the temperature also reduces the values of *n*, since it results in a Newtonian to non-Newtonian transition.

The consistency index was affected by temperature and polymer concentration (Table 1). The addition and increase of polox407 content increased *k* values, as did the addition and increase of NaCMC content. Significant increase in *k* was observed between all formulations with low concentrations of polox407 (15 and 17. % (w/w)) and those containing 20% (w/w) polox407. Significant increases were not observed between formulations without polox407 and those with 15% (w/w) polox407, or between those composed of 15 and 17.5% (w/w) polox407. On the other hand, with the increase of NaCMC, there was a significant increase of *k* value only among 1.5% (w/w) NaCMC and formulations without or with 0.5% (w/w) NaCMC. A significant increase of *k* was observed between all analyzed temperatures. Conversely, NaCMC-containing mono-polymeric systems have been shown to reduce in *k* value with increasing temperature, suggesting the polox407 leads to structuring of the fluid at elevated temperatures.

Frequently a higher yield value at high temperature supports the clinical use of the pharmaceutical systems. At low temperatures they flow easily, as low or no stress is enough to remove them, when exposed at body temperature these formulations can remain longer in the desired site. Most NaCMC-containing polymeric systems had plastic behavior, with most mono-polymeric and binary NaCMC samples displaying a yield value at the three temperatures evaluated, except binary systems containing 17.5 and 20% (w/w) polox407 at 25 and 37 °C, which demonstrated pseudoplastic behavior, without yield (Table 2).

Regarding the hysteresis area, although a thixotropic profile of high concentrated NaCMC dispersions (4-7%) at 20 °C is reported, most of mono-polymeric systems (0.5-1.5%) had thixotropic behavior at 5 °C, and a rheopectic behavior at 25 and 37 °C (Table 2) (Benchabane & Bekkour, 2008). When in a binary polymeric system, most NaCMC/poloxamer mixtures showed a thixotropic profile at three temperatures. Formulations containing a higher concentration of polox407 and NaCMC had superior properties as pharmaceutical systems, since at 25 and 37 °C they exhibited thixotropy.

3.2. Oscillatory analysis

Oscillatory rheometry allows evaluation of the viscoelastic properties of the preparations. Oscillatory measurements allow to simulate the behavior of the systems when they are at low shear, probing the native properties of the semisolids at shears relevant to physiological environments. The elastic (G’) and viscous (G”) moduli obtained by oscillatory rheometry relate to the stored and recovered energy in each deformation cycle at a given frequency. Additionally, the division of G’’ by G’ determines the loss tangent (tan δ), with possible values greater or lower than one unit. Value above one characterizes elastoviscous systems, which have higher values of G” than G’. Conversely, when tan δ values are less than one the systems have viscoelastic properties, that means G’ is greater than G” (Baloglu et al., 2011; de Francisco et al., 2019; De Souza Ferreira, Moço, et al., 2015).

The oscillatory frequency and polymer concentration affected the viscoelastic properties of the formulations containing polox407 and HPMC or NaCMC (Fig. 1). An increase of oscillatory frequency resulted in the increase of G’ and G”, as well as a decrease of dynamic viscosity (η’). Most polymeric systems showed viscoelastic profiles at 5, 25 and 37 °C, except binary systems at 5 °C, which presented elastoviscous property at low frequencies (Table S1-S6).

As displayed in Tables S1-S6, formulations containing polox407 and HPMC were shown to be temperature, oscillatory frequency and polymer concentration dependent. Increasing the temperature, polymer concentration and frequency typically resulted in an increase of G’ and G”, while the values found for tan δ were reduced. An increase of η’ was observed with increasing polymer concentration and temperature; however the values were reduced with increasing oscillatory frequency. In addition, most binary polymeric systems demonstrated similar rheological values (G’, G”, η’ and tan δ) when analyzed at 25 and 37 °C, showing a better interaction between cellulose derivatives and thermoresponsive polymer, with an improved system structuring, at temperatures above 25 °C.

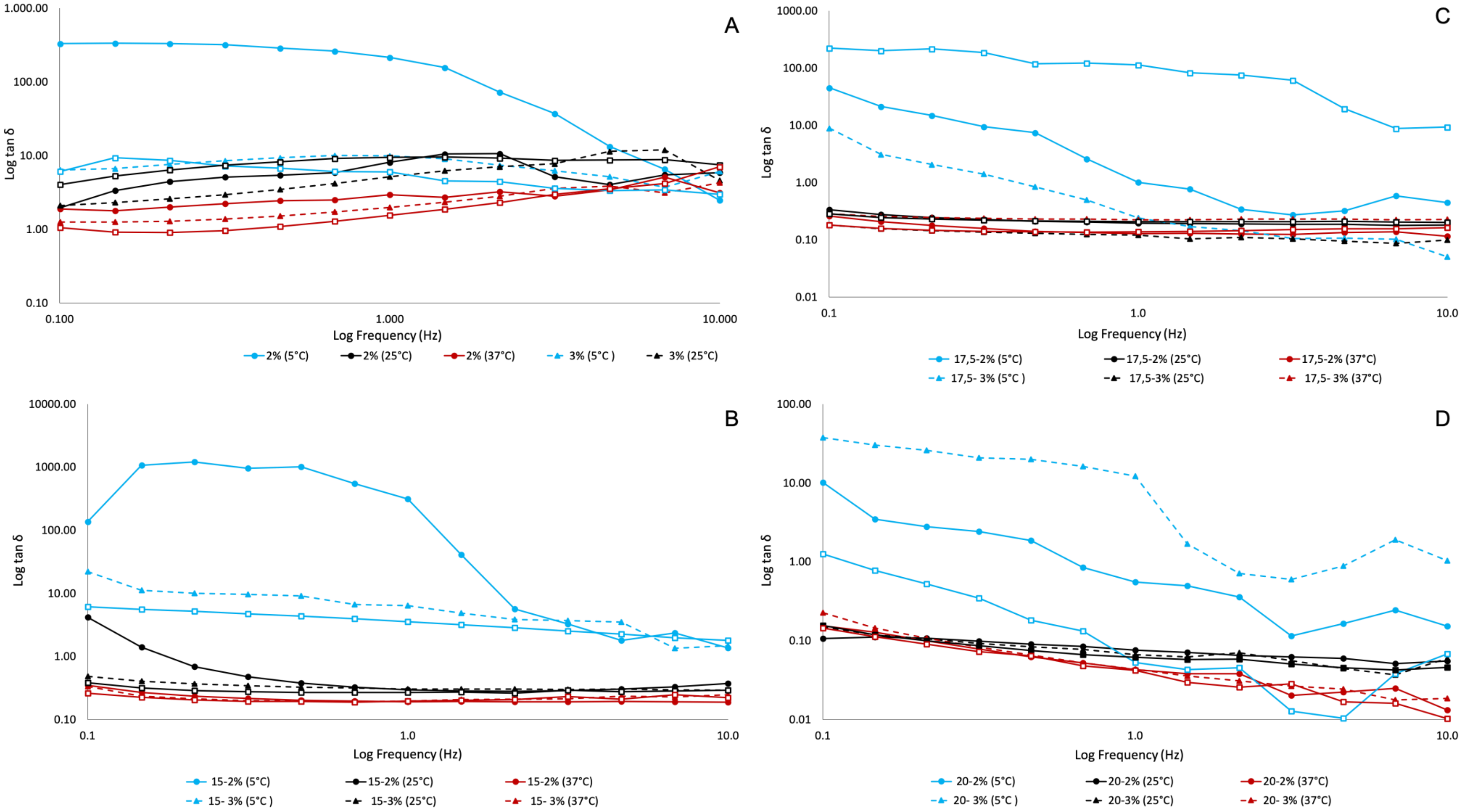

Fig. 1. Loss tangent (tan δ) as function of frequency at temperatures of 5 (blue), 25 (black) and 37 °C (red) for: (A) monopolymeric formulations containing 2 (●), 3 (▲) and 4 () (%, w/w) hydroxypropyl methylcellulose; (B) binary polymeric formulations containing 15% (w/w) poloxamer 407

and hydroxypropyl methylcellulose; (C) 17.5% (w/w) poloxamer 407 and hydroxypropyl methylcellulose; (D) 20% (w/w) poloxamer 407 and hydroxypropyl methylcellulose. Each point of the rheogram represents the mean of at least three replicates. Standard deviations have been omitted for clarity; however, in all cases, the relative standard deviation was lower than 12%.

For monopolymeric systems containing NaCMC (Fig. 2), an elastoviscous profile was observed for most formulations, and viscoelastic character was more evident at higher polymer concentration, as well as at higher frequencies, in accordance with the literature (Benchabane & Bekkour, 2008). The increase in oscillatory frequency resulted in an increase of G’ and G”, while η’and tan δ had their values reduced. Typically, binary polymeric systems containing 15, 17.5 and 20% (w/w) polox407 demonstrated similar behavior. This was not the case in systems with high polymer concentration, such as those containing 17.5 and 20% (w/w) polox407 with 1.5% (w/w) NaCMC, which showed an increased G’ but decreased G” with increasing oscillatory frequency at 25 and 37 °C. Furthermore, for most systems, the increase in the temperature and polymer content led to the increase of G’, G” and η’, while the values found for tan δ were reduced.

Viscoelastic behavior is often required in pharmaceutical systems as it gives to the formulation better application and retention properties at the desired site, which contributes to their therapeutic effectiveness. Therefore, systems containing 15, 17.5 and 20% (w/w) polox407 showed viscoelastic behavior for most polymer systems at 25 and 37 °C, especially for formulations containing 3 and 4% (w/w) HPMC and 1.0 and 1.5% (w/w) of NaCMC, and thus may be preferable for clinical application.

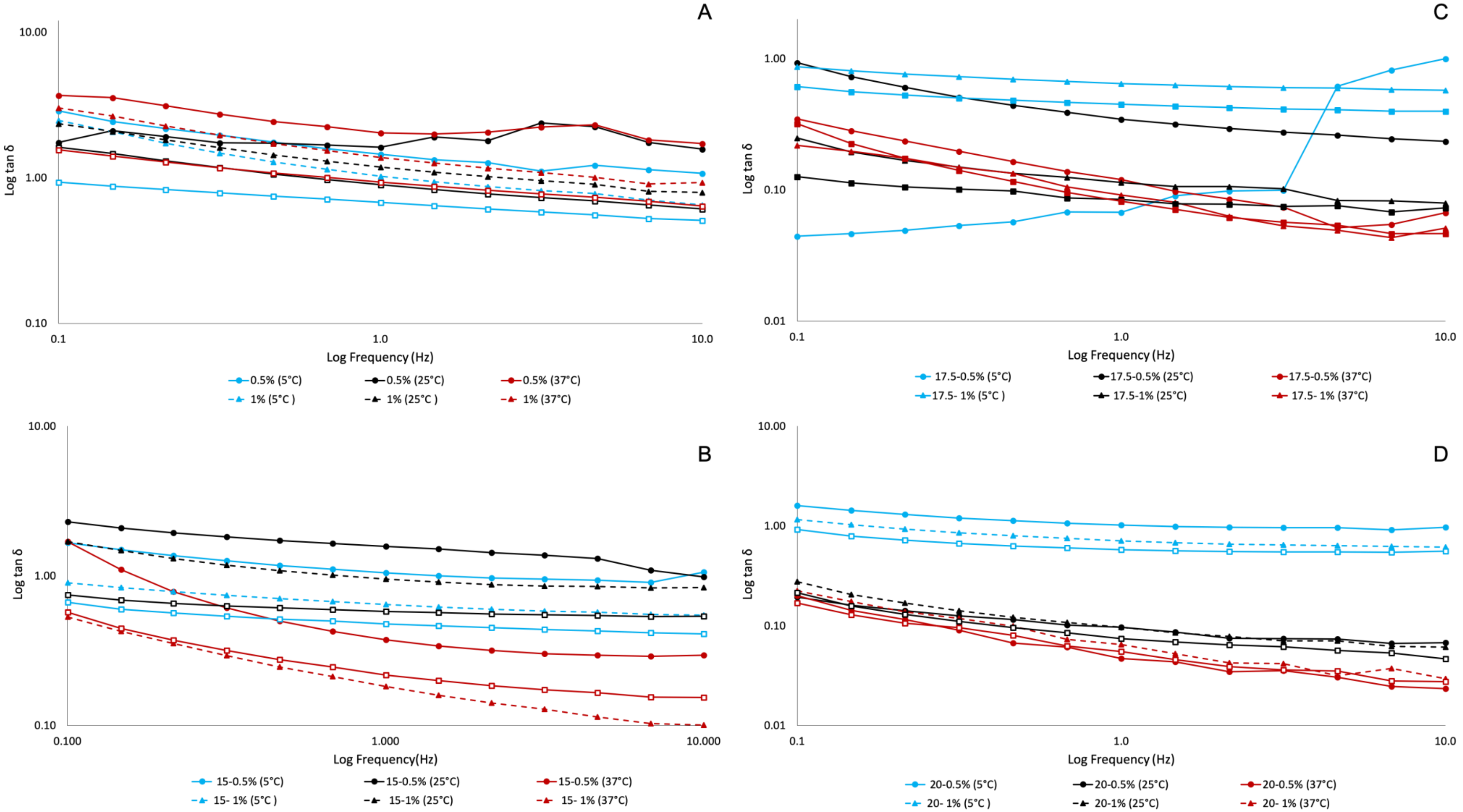

Fig. 2. Loss tangent (tan δ) as a function of frequency at temperatures of 5 (blue), 25 (black) and 37 °C (red) for: (A) monopolymeric formulations containing 0.5 (●), 1.0 (▲) and 1.5 () (%, w/w) sodium carboxymethylcellulose; (B) binary polymeric formulations containing 15% (w/w) poloxamer

407 and sodium carboxymethylcellulose; (C) 17.5% (w/w) poloxamer 407 and sodium carboxymethylcellulose; (D) 20% (w/w) poloxamer 407 and sodium carboxymethylcellulose. Each point of the rheogram represents the mean of at least three replicates. Standard deviations have been omitted for clarity; however, in all cases, the relative standard deviation was lower than 12%.

3.3. Interaction parameter

The strength of interactions between cellulose derivatives and polox407 may be investigated by measurement of G’. A rheological synergism is observed when G’ of a polymer mixture is greater than the sum of G’ of the constituent polymers in solutions of equivalent concentration. Synergism was assessed using G’ values obtained at 10.0 Hz, in order to intensively force the polymeric systems as a function of the oscillatory frequency (Barbosa et al., 2017; Jones et al., 2009). $G'_{observed}$ was the G’ of the formulation at this frequency, and $G'_{calculated}$ was the sum of the G’ at 10 Hz for the constituent mono-polymeric solutions at the same concentrations.

Table 3 shows $G'_{observed}$ and $G'_{calculated}$ for each binary polymeric system composed of polox407 and HPMC, as well as their interaction parameter, which was calculated at each temperature studied (5, 25 and 37 °C). The temperature increase was followed by an increase in G’ for all HPMC systems. However, the $G'_{calculated}$ did not increase proportionally, with 15% (w/w) polox407 formulations, exhibiting a reduction of its value as a function of the evaluated temperatures. Systems containing 17.5% (w/w) polox407, in turn, showed similar values between $G'_{calculated}$ at 5 and 25 °C, with values almost ten times higher at 37 °C than those observed at the lowest temperatures. Additionally, formulations composed of 20% (w/w) polox407 demonstrated a decrease in calculated G’ at 5 °C and increasing values at other temperatures. Thus, at 5 °C only systems containing 20% (w/w) polox407 showed low rheological synergism, the other systems presented rheological antagonism. At 25 and 37 °C, by contrast, a synergic profile was observed for all systems containing HPMC.

Table 3

Observed and calculated values for elastic modulus (G') of binary polymeric formulations containing poloxamer 407 (polox407) and hydroxypropyl methylcellulose (HPMC) or sodium carboxymethylcellulose (NaCMC).

Polox407 (%. w/w)	HPMC (%. w/w)	NaCMC (%. w/w)	Temperature (°C)	G'_{observed} (Pa)[a]	$G'_{\text{calculated}}$ (Pa)[a]	Interaction parameter (Pa)
15	2.0	-	5	22.46 ± 1.10	129.53 ± 8.85	-107.07 ± 9.24
15	2.0	-	25	44.68 ± 5.28	153.43 ± 2.77	-108.75 ± 6.34
15	2.0	-	37	1057.67 ± 57.42	67.56 ± 7.12	990.10 ± 55.55
15	3.0	-	5	101.93 ± 2.51	177.62 ± 8.39	-75.68 ± 10.90
15	3.0	-	25	75.02 ± 2.33	151.23 ± 4.76	-76.21 ± 2.97
15	3.0	-	37	6665.33 ± 162.21	82.98 ± 6.30	6582.35 ± 115.93
15	4.0	-	5	238.70 ± 20.32	263.10 ± 7.41	-33.55 ± 6.29
15	4.0	-	25	252.73 ± 26.42	211.45 ± 2.58	25.15 ± 4.70
15	4.0	-	37	3799.33 ± 384.71	137.20 ± 6.29	3662.14 ± 382.68
17.5	2.0	-	5	25.73 ± 0.83	131.13 ± 0.88	-105.40 ± 1.03
17.5	2.0	-	25	4288.67 ± 224.28	135.87 ± 6.03	4152.80 ± 224.23
17.5	2.0	-	37	8900.67 ± 234.61	9424.87 ± 498.99	-340.92 ± 150.86
17.5	3.0	-	5	89.92 ± 3.07	179.22 ± 1.02	-89.30 ± 2.98
17.5	3.0	-	25	9582.00 ± 523.64	133.67 ± 6.73	9448.33 ± 529.69
17.5	3.0	-	37	10930.00 ± 670.22	9138.96 ± 49.43	2159.58 ± 452.05
17.5	4.0	-	5	223.90 ± 7.21	264.70 ± 2.76	-42.35 ± 6.29
17.5	4.0	-	25	10603.33 ± 361.16	193.88 ± 6.45	10409.45 ± 365.92
17.5	4.0	-	37	11750.00 ± 1090.00	9659.62 ± 577.24	1545.38 ± 193.50
20	2.0	-	5	29.05 ± 0.33	37.88 ± 6.09	-8.83 ± 5.85
20	2.0	-	25	12442.33 ± 827.61	9517.73 ± 495.34	2924.60 ± 333.28
20	2.0	-	37	11663.33 ± 445.57	14908.54 ± 293.79	-3245.207 ± 382.47
20	3.0	-	5	93.47 ± 1.43	85.97 ± 5.65	7.51 ± 6.99
20	3.0	-	25	13200.00 ± 312.25	9515.53 ± 497.16	3684.47 ± 788.09
20	3.0	-	37	14165.0 ± 487.90	14923.96 ± 295.34	-588.55 ± 50.27
20	4.0	-	5	130.25 ± 11.24	171.45 ± 4.66	-39.49 ± 6.16
20	4.0	-	25	13980.00 ± 482.80	9575.75 ± 995.38	4404.25 ± 671.84

20	4.0	-	37	17385.00 ± 1308.48	14978.17 ± 294.69	2316.96 ± 954.25
15	-	0.5	5	14.28 ± 1.62	134.99 ± 9.33	-120.11 ± 10.34
15	-	0.5	25	550.37 ± 32.33	128.62 ± 5.15	421.75 ± 36.57
15	-	0.5	37	1163.67 ± 25.38	68.78 ± 6.14	1094.88 ± 29.49
15	-	1.0	5	8.32 ± 0.48	135.33 ± 9.22	-127.01 ± 9.67
15	-	1.0	25	5931.33 ± 455.62	124.06 ± 4.69	5807.28 ± 458.67
15	-	1.0	37	8708.33 ± 499.34	64.71 ± 6.82	8643.62 ± 492.72
15	-	1.5	5	135.73 ± 9.96	173.83 ± 5.31	-38.09 ± 15.26
15	-	1.5	25	8339.33 ± 1025.06	127.55 ± 4.54	8211.78 ± 1025.00
15	-	1.5	37	5117.33 ± 645.02	85.32 ± 6.77	5032.01 ± 638.90
17.5	-	0.5	5	84.96 ± 128.44	135.99 ± 1.02	-51.03 ± 6.88
17.5	-	0.5	25	8724.33 ± 128.44	111.06 ± 5.04	8613.27 ± 131.90
17.5	-	0.5	37	9723.67 ± 744.12	9426.09 ± 498.49	297.57 ± 449.11
17.5	-	1.0	5	122.97 ± 3.16	136.93 ± 0.18	-13.96 ± 3.01
17.5	-	1.0	25	12396.67 ± 140.48	106.50 ± 5.89	12290.17 ± 144.36
17.5	-	1.0	37	12646.67 ± 473.43	9135.23 ± 60.97	3784.77± 60.97
17.5	-	1.5	5	6.99 ± 0.37	175.43 ± 4.29	-168.43 ± 4.48
17.5	-	1.5	25	1402.33 ± 81.28	109.99 ± 6.61	1292.34 ± 86.85
17.5	-	1.5	37	14166.67 ± 3.69	9442.63 ± 498.44	4724.03 ± 441.43
20	-	0.5	5	98.51 ± 3.69	42.74 ± 6.57	55.774 ± 3.89
20	-	0.5	25	15130.00 ± 1263.61	9492.92 ± 496.24	6369.01 ± 807.30
20	-	0.5	37	23360.00 ± 3095.11	14909.76 ± 295.24	6585.14 ± 163.50
20	-	1.0	5	47.49 ± 6.07	43.68 ± 6.49	7.8305 ± 12.27
20	-	1.0	25	17466.00 ± 1590.37	9488.35 ± 496.62	8590.69 ± 837.87
20	-	1.0	37	22663.33 ± 1249.97	14905.69 ± 294.57	7757.64 ± 968.38
20	-	1.5	5	115.27 ± 4.90	82.18 ± 2.89	33.09 ± 2.75
20	-	1.5	25	18266.67 ± 1528.93	9491.85 ± 496.95	7621.88 ± 122.83
20	-	1.5	37	22746.67 ± 741.44	14926.30 ± 293.87	7820.37 ± 961.59

[a]Storage modulus (G’) determined at10 Hz.

For systems containing polox407 and NaCMC, the observed and calculated G’, as well as the interaction parameter values are shown in Table 3. A temperature increase led to an increase in the observed G’ values, while for calculated G’ the same decrease was observed as seen for HPMC systems. At 5 °C rheological antagonism was observed for all systems, and only those with greater polymer concentration showed synergism at 25 °C. However, at 37 °C synergism was observed in most binary systems, except for the 17.5/0.5, 20/0.5 and 20/1.0 formulations.

Both HPMC and NaCMC systems demonstrated antagonism at 5 °C, showing no interaction between the cellulose derivatives and the thermoresponsive polymer, as also observed in the accelerated centrifuge stability results performed at this temperature for binary polymeric systems containing 17.5 or 20% (w/w) polox407 and HPMC (3 and 4%, w/w) or NaCMC (1.0 and 1.5%, w/w) (Fig. S5). Nonetheless, at room and body temperature, these polymers demonstrated strong interaction. The lowest studied polymer concentrations have already demonstrated their ability to establish interactions at 37 °C, where non-covalent interactions may occur between the cellulose derivatives and polox407 in its micellar state. However, using higher polymer concentrations, the systems demonstrated better interaction parameters at both temperatures, since the potential for chain overlap to occur is greater.

3.4. Solution-gel transition temperature ($T_{sol/gel}$)

$T_{sol/gel}$ is characterized by the temperature at which the formulation ceases to be liquid and becomes a gel. This parameter is essentially important for systems containing thermoresponsive polymers, such as polox407. For pharmaceutical and biomedical applications, polymeric systems with $T_{sol/gel}$ at around 25-37 °C allow gel formation to occur when the formulation is warmed from room temperature to body temperature

(Pund, Rasve, & Borade, 2013; Yun Chang et al., 2002). $T_{sol/gel}$ study allows the selection of the most appropriate formulations according to the intended use, with topical sites having slightly lower temperatures than parenteral administration, for instance.

Most formulations containing 15, 17.5 and 20% (w/w) polox407 showed a significant increase in viscosity (η’) during temperature sweep, presenting a $T_{sol/gel}$. When in the liquid state, the systems presented low G’ values, while at higher temperatures, when they became a gel with greater elasticity. The value of G’ increased significantly with temperature, except for the formulation composed of 17.5% (w/w) polox407 and 2% (w/w) HPMC. The $T_{sol/gel}$ results obtained by rheology for binary polymeric systems composed of polox407 and HPMC or NaCMC are shown in Table 4.

Table 4

Sol-gel transition temperature ($T_{sol/gel}$) of binary polymeric systems containing poloxamer 407 (polox407) and hydroxypropyl methylcellulose (HPMC) or sodium carboxymethylcellulose (NaCMC)[a].

Formulations	Polymer % (w/w)			$T_{sol/gel}$ (°C)
	Polox407	HPMC	NaCMC	
15 / 2	15	2	-	33.760 ± 0.078
15 / 3	15	3	-	32.863 ± 0.081
15 / 4	15	4	-	28.708 ± 0.045
17.5 / 2	17.5	2	-	30.545 ± 0.076
17.5 / 3	17.5	3	-	28.788 ± 0.033
17.5 / 4	17.5	4	-	25.993 ± 0.059
20 / 2	20	2	-	24.120 ± 0.065
20 / 3	20	3	-	22.792 ± 0.098
20 / 4	20	4	-	22.280 ± 0.084
15 / 0.5	15	-	0.5	43.860 ± 0.018
15 / 1.0	15	-	1.0	39.240 ± 0.077
15 / 1.5	15	-	1.5	36.505 ± 0.064
17.5 / 0.5	17.5	-	0.5	36.460 ± 0.066
17.5 / 1.0	17.5	-	1.0	29.647 ± 0.029
17.5 / 1.5	17.5	-	1.5	30.900 ± 0.038
20 / 0.5	20	-	0.5	28.240 ± 0.060
20 / 1.0	20	-	1.0	30.528 ± 0.045
20 / 1.5	20	-	1.5	29.577 ± 0.053

[a] Each mean represents the mean (± standard deviation) of at least three replicates.

As previously observed, 15 and 20% (w/w) polox407 mono-polymeric systems have a $T_{sol/gel}$ of 31.5 and 25.4 °C, respectively (Barbosa et al., 2017). The addition of HPMC to the systems did not generate major changes in polox407 $T_{sol/gel}$. However, it can be observed that the increase of HPMC concentration, as well as the increase of polox407 concentration, reduced $T_{sol/gel}$, since at higher concentrations the polymeric chains are more likely to overlap as there are a greater quantity in the same dispersion volume. Critical volume fractions for gelation may be reached at lower temperatures, and the polymer chains may experience less water solvation overall (Weaver, Stockmann, Postma, & Thang, 2016). Considering the $T_{sol/gel}$ values obtained for the polymeric systems, most of the formulations will undergo gelation when warmed from room to body temperature. All HPMC systems were considered suitable, but 15/0.5 and 15/1 (%/%) NaCMC systems did not show $T_{sol/gel}$ below 37 °C. In good agreement, Barse and collaborators showed that a combination between polox407 and lower concentrations of HPMC (0.5-1%), also displayed a $T_{sol/gel,}$ ranging from 25 and 39 °C (Barse et al., 2016).

Gelation occurring below 25 °C makes the formulation difficult to manufacture, handle and administer as pharmaceutical dosage form, while systems with gelation temperatures above 37 °C will not exhibit the required increase in viscosity after administration to the body. Considering the gelation temperature alongside the rheological interaction parameter, the most suitable HPMC formulations for pharmaceutical use are 17.5/3; 17.5/4; 20/3 and 20/4, particularly for topical sites such as the mouth and eyes.

The literature provides some suggestions on how polymeric additives may mechanistically alter the $T_{sol/gel}$ of polox407. It is suggested that substances which are able to establish strong non-covalent bonds with polox407 decrease its $T_{sol/gel}$ since, in this case, polox407 interaction with water is reduced, favoring its dehydration and micellization (Baloglu et al., 2011; Choi, Lee, Kim, & Kim, 1999; Dumortier et al., 2006). It is also possible that reductions in $T_{sol/gel}$ occur due to preferential interaction of the additive with water, reducing the overall fraction of water able to hydrate the poloxamer chains. Some studies suggest that elevation of $T_{sol/gel}$ may be a result of disturbing the micellar packing of polox407, requiring greater temperatures and micelle volume fraction to be achieved prior to gelation occurring (Kim, Gao, Park, Li, & Han, 2002). It is also possible that critical micelle concentrations of polox407 may be altered by additives, in turn affecting $T_{sol/gel.}$

In general, formulations containing NaCMC or HPMC demonstrated an increase of polox407 $T_{sol/gel}$, which may be attributed to a disruption of the micelle packing mechanism. However, NaCMC systems displayed higher gelation temperature values comparing to those containing HPMC. This may be attributed to the greater interaction of NaCMC with water, providing a large steric bulk to interfere with micelle packing. The higher hydrophobicity of HPMC, compared with NaCMC, may also provide reductions in the solvation degree of the polox407 chains in the dispersion, which is consequently seen as a relatively retarded $T_{sol/gel}$ (Weaver et al., 2016).

The $T_{sol/gel}$ values obtained for NaCMC and polox407 systems were further reduced as the concentration of those polymers increased. Systems containing 15% (w/w) polox407 demonstrated high values of $T_{sol/gel,}$ inappropriate for topical application. However, they may still be viable for use in some febrile regions, for example, where the temperature is higher. Additionally, the $T_{sol/gel}$ of 17% (w/w) polox407 and 1% (w/w) NaCMC polymeric system has already been described in the literature with $T_{sol/gel}$ of approximately 33 °C, slightly above that found by rheology measurement for formulations containing 17.5% (w/w) polox407 and 1% (w/w)

NaCMC, which was 29.6 °C (Pund et al., 2013). Therefore, considering gelation temperature and others rheological parameters, the most promising systems to be investigated as topical pharmaceutical systems are 17.5/1; 17.5/1.5; 20/1 and 20/1.5 polox407/NaCMC.

3.5. Texture profile analysis (TPA)

TPA is a useful tool for the evaluation of mechanical properties in pharmaceutical systems like semi-solids. It can provide information about the mechanical structure of hydrogels, predicting interactions between the polymers that constitute them. Additionally, it allows the evaluation of systems under different temperature conditions, simulating a physiological environment, for example. The data obtained by texture analysis in this study allowed for the calculation of five parameters: hardness, elasticity, adhesiveness, cohesiveness and compressibility, as described in the material and methods section (De Souza Ferreira, Bassi da Silva, et al., 2015; Jones et al., 1996).

Considering topical semi-solid pharmaceutical systems, properties such as easy removal from packaging material, adequate spreadability, adhesiveness and viscosity are important parameters to be investigated in order to support patient adherence to the treatment. For systems applied on the skin, eye or mouth, it is also necessary to consider the natural process of the clearance from mucosal membranes in the presence of natural fluids (such as saliva or tears), and shear forces occurring during speech, chewing and blinking, for instance. For pharmaceutical dosage forms, low hardness and compressibility values are expected, in order to ensure ease of application and removal of the product. Also, low elasticity values, high cohesiveness and high adhesion are better in terms of formulations performance at the intended location, mainly for those exposed to movements which can make their retention difficult (De Souza Ferreira, Bassi da Silva, et al., 2015).

Texture profile analysis was conducted in order to evaluate the mechanical properties of binary polymeric systems as possible candidates for topical application, shown in Table 5 and 6. Both HPMC and NaCMC platforms showed significant differences for all texture profile parameters evaluated, with changes observed when varying polox407 concentration, cellulose-derivative concentration, and temperature. Regarding the polymeric systems containing HPMC (Table 5), significant increases in hardness, compressibility and adhesiveness parameters were observed with the increase of polox407 content. Elasticity and cohesiveness, despite having their values reduced with increasing concentration of polox407, did not show significant change. The increase of HPMC led to a significant increase in hardness and compressibility. Adhesiveness showed a significant increase between 4% (w/w) and the lowest tested HPMC concentration. Between 2 and 3% (w/w) HPMC the increase in adhesiveness was not significant ($p>0.05$). The elasticity did not change when increasing HPMC concentration. Although the cohesiveness did not show a huge variation, it had its values slightly reduced with increasing concentrations of HPMC, being statistically significant only between 2 and 4% (w/w) of HPMC ($p<0.05$). These polymeric systems demonstrated significant increase in hardness and compressibility with temperature. Although the adhesiveness of formulations increased with temperature, there was not a significant difference between 25 and 37 °C ($p<0.05$). The elasticity of the systems remained unchanged with temperature variation. The cohesiveness varied being significant only between temperatures of 5 and 25 °C ($p<0.05$), as well as 5 and 37 °C ($p<0.05$).

Table 5

Mechanical properties obtained by texture profile analysis (TPA) of binary polymeric systems containing poloxamer 407 (polox407) and hydroxypropyl methylcellulose (HPMC)[a].

Polox407 (% w/w)	HPMC (% w/w)	Temperature (°C)	Hardness (N)	Compressibility (N.mm)	Adhesiveness (N.mm)	Elasticity (mm)	Cohesiveness (dimensionless)
15	2.0	5	0.052 ± 0.001	0.135 ± 0.006	0.000 ± 0.000	0.987 ± 0.037	0.781 ± 0.017
15	2.0	25	0.521 ± 0.005	2.617 ± 0.034	2.711 ± 0.044	1.000 ± 0.007	0.944 ± 0.006
15	2.0	37	0.660 ± 0.028	3.367 ± 0.118	2.930 ± 0.102	0.996 ± 0.005	0.949 ± 0.017
15	3.0	5	0.058 ± 0.002	0.168 ± 0.008	0.000 ± 0.000	0.997 ± 0.037	0.855 ± 0.012
15	3.0	25	0.694 ± 0.030	3.554 ± 0.172	3.130 ± 0.150	0.997 ± 0.003	0.959 ± 0.006
15	3.0	37	0.831 ± 0.024	4.121 ± 0.077	3.546 ± 0.118	0.996 ± 0.005	0.949 ± 0.007
15	4.0	5	0.067 ± 0.003	0.182 ± 0.008	0.000 ± 0.000	0.992 ± 0.007	0.816 ± 0.028
15	4.0	25	0.819 ± 0.009	4.076 ± 0.138	3.810 ± 0.109	0.995 ± 0.009	0.941 ± 0.015
15	4.0	37	0.964 ± 0.046	4.811 ± 0.177	3.915 ± 0.106	1.000 ± 0.006	0.933 ± 0.008
17.5	2.0	5	0.058 ± 0.003	0.148 ± 0.007	0.000 ± 0.000	1.000 ± 0.053	0.978 ± 0.038
17.5	2.0	25	0.893 ± 0.033	4.644 ± 0.197	4.203 ± 0.203	0.997 ± 0.001	0.917 ± 0.027
17.5	2.0	37	0.938 ± 0.046	4.757 ± 0.195	4.098 ± 0.187	1.001 ± 0.007	0.957 ± 0.007
17.5	3.0	5	0.064 ± 0.002	0.199 ± 0.009	0.000 ± 0.000	1.003 ± 0.025	0.794 ± 0.039
17.5	3.0	25	0.978 ± 0.045	4.705 ± 0.498	4.003 ± 0.158	0.999 ± 0.007	0.906 ± 0.024
17.5	3.0	37	1.171 ± 0.048	6.072 ± 0.289	4.853 ± 0.116	0.999 ± 0.008	0.889 ± 0.012
17.5	4.0	5	0.079 ± 0.003	0.293 ± 0.014	0.000 ± 0.000	0.990 ± 0.002	0.834 ± 0.039
17.5	4.0	25	1.354 ± 0.026	6.673 ± 0.203	5.239 ± 0.201	0.992 ± 0.009	0.858 ± 0.013
17.5	4.0	37	1.528 ± 0.051	8.109 ± 0.373	5.927 0.193	0.999 ± 0.006	0.843 ± 0.034
20	2.0	5	0.063 ± 0.003	0.176 ± 0.007	0.000 ± 0.000	0.971 ± 0.038	0.602 ± 0.023
20	2.0	25	1.048 ± 0.057	5.340 ± 0.268	5.749 ± 0.240	0.997 ± 0.005	1.135 ± 0.042
20	2.0	37	1.267 ± 0.026	6.340 ± 0.155	5.423 ± 0.072	0.997 ± 0.007	0.948 ± 0.014
20	3.0	5	0.072 ± 0.003	0.234 ± 0.011	0.000 ± 0.000	1.010 ± 0.010	0.803 ± 0.029

20	3.0	25	1.340 ± 0.032	6.538 ± 0.184	5.548 ± 0.182	1.000 ± 0.007	0.926 ± 0.009
20	3.0	37	1.455 ± 0.061	7.730 ± 0.055	6.226 ± 0.139	0.996 ± 0.011	0.909 ± 0.018
20	4.0	5	0.124 ± 0.005	0.368 ± 0.016	0.049 ± 0.002	0.990 ± 0.012	0.755 ± 0.037
20	4.0	25	1.533 ± 0.061	7.413 ± 0.388	6.143 ± 0.246	0.999 ± 0.004	0.907 ± 0.020
20	4.0	37	1.629 ± 2.651	8.415 ± 0.197	6.479 ± 0.209	0.996 ± 0.004	0.882 ± 0.013

[a] Each mean represents the mean (± standard deviation) of at least three replicates.

For platforms containing NaCMC, changes in polox407 content also provided significant increase in hardness, compressibility and adhesion parameters. However, elasticity and cohesiveness showed differences only between the lowest and the highest polox407 concentrations studied. On the other hand, increasing the concentration of NaCMC cellulose derivative led to a significant increase in hardness and compressibility parameters. The progressive increase in adhesiveness as a function of the increase in NaCMC concentration was statistically significant only between systems containing 0.5 and 1.5% (w/w) NaCMC ($p<0.05$). Formulations containing 1 and 1.5% (w/w) NaCMC did not present statistical difference for adhesiveness. The elasticity was considered to be statistically equivalent between formulations containing different NaCMC concentrations; however, their cohesiveness was significantly reduced as concentration increased. A significant increase in hardness, compressibility and adhesiveness was observed when temperature was increased between 5, 25 and 37 °C. The elasticity did not change with NaCMC concentration, but cohesiveness was increased as the polymer concentration increased, and only the lowest concentration differed statistically from the others.

Overall, it was observed that an increase of polymer concentration, either for polox407, HPMC or NaCMC led to an increase of hardness and compressibility. Adhesiveness was mainly dependent on the concentration of cellulose derivative used, obtaining higher values for the highest concentrations of HPMC and NaCMC, with the greatest adhesive force observed for formulations containing 4% (w/w) HPMC. Formulations containing 1 or 1.5% (w/w) NaCMC were significantly more adhesive those containing 0.5% (w/w) NaCMC, however, no significant difference was observed between the concentrations of 1 and 1.5% (w/w) NaCMC. The elasticity of the systems did not change significantly with variation of the cellulose derivative or their concentration. Regarding cohesiveness, despite a tendency to decrease values when increasing polymer concentration, only small changes were observed, with the highest concentrations giving the greatest loss of cohesiveness.

Table 6

Mechanical parameters obtained by texture profile analysis (TPA) of binary polymeric systems containing poloxamer 407 (polox407) and sodium carboxymethylcellulose (NaCMC)[a].

Polox407 (%, w/w)	NaCMC (%, w/w)	Temperature (°C)	Hardness (N)	Compressibility (N.mm)	Adhesiveness (N.mm)	Elasticity (mm)	Cohesiveness (dimensionless)
15	0.5	5	0.064 ± 0.002	0.188 ± 0.007	0.000 ± 0.000	1.068 ± 0.029	0.848 ± 0.017
15	0.5	25	0.062 ± 0.002	0.165 ± 0.003	0.000 ± 0.000	1.082 ± 0.045	0.911 ± 0.032
15	0.5	37	0.314 ± 0.014	1.454 ± 0.063	1.307 ± 0.054	0.993 ± 0.024	0.996 ± 0.002
15	1.0	5	0.160 ± 0.004	0.666 ± 0.033	0.300 ± 0.011	1.005 ± 0.014	0.759 ± 0.011
15	1.0	25	0.138 ± 0.002	0.563 ± 0.028	0.244 ± 0.010	1.005 ± 0.025	0.743 ± 0.030
15	1.0	37	0.387 ± 0.008	1.772 ± 0.056	1.161 ± 0.031	1.009 ± 0.011	0.761 ± 0.024
15	1.5	5	0.572 ± 0.038	2.097 ± 0.091	0.711 ± 0.028	1.001 ± 0.009	0.771 ± 0.056
15	1.5	25	0.494 ± 0.010	2.484 ± 0.082	0.849 ± 0.045	1.008 ± 0.009	0.678 ± 0.020
15	1.5	37	0.819 ± 0.002	3.735 ± 0.192	2.202 ± 0.070	0.998 ± 0.009	0.757 ± 0.039
17.5	0.5	5	0.068 ± 0.003	0.201 ± 0.007	0.000 ± 0.000	0.976 ± 0.018	0.845 ± 0.022
17.5	0.5	25	0.529 ± 0.018	2.663 ± 0.112	2.458 ± 0.109	0.999 ± 0.007	0.980 ± 0.008
17.5	0.5	37	0.568 ± 0.007	2.750 ± 0.021	2.383 ± 0.017	1.001 ± 0.007	0.965 ± 0.003
17.5	1.0	5	0.192 ± 0.009	0.680 ± 0.030	0.199 ± 0.009	0.998 ± 0.013	0.838 ± 0.021
17.5	1.0	25	0.766 ± 0.031	2.977 ± 0.114	2.517 ± 0.077	1.000 ± 0.003	0.952 ± 0.029
17.5	1.0	37	1.013 ± 0.030	4.532 ± 0.187	3.665 ± 0.189	1.001 ± 0.007	0.889 ± 0.015
17.5	1.5	5	0.494 ± 0.005	2.033 ± 0.085	0.700 ± 0.028	1.003 ± 0.009	0.737 ± 0.0377
17.5	1.5	25	1.035 ± 0.022	3.822 ± 0.111	3.386 ± 0.166	0.999 ± 0.006	0.922 ± 0.019
17.5	1.5	37	1.100 ± 0.010	4.956 ± 0.091	4.009 ± 0.107	1.003 ± 0.004	0.899 ± 0.039
20	0.5	5	0.072 ± 0.002	0.224 ± 0.004	0.000 ± 0.000	0.988 ± 0.047	0.835 ± 0.027
20	0.5	25	0.733 ± 0.033	3.793 ± 0.129	3.939 ± 0.162	1.006 ± 0.004	0.977 ± 0.014

20	0.5	37	0.891 ± 0.019	4.450 ± 0.158	3.852 ± 0.109	1.004 ± 0.004	0.968 ± 0.010
20	1.0	5	0.268 ± 0.007	0.107 ± 0.006	0.033 ± 0.001	1.004 ± 0.003	0.739 ± 0.025
20	1.0	25	1.151 ± 0.015	4.626 ± 0.152	4.082 ± 0.143	1.002 ± 0.006	0.958 ± 0.038
20	1.0	37	1.314 ± 0.056	6.490 ± 0.125	5.639 ± 0.185	1.004 ± 0.004	0.952 ± 0.023
20	1.5	5	0.669 ± 0.033	2.812 ± 0.138	0.917 ± 0.031	1.006 ± 0.006	0.706 ± 0.036
20	1.5	25	1.515 ± 0.083	5.824 ± 0.273	4.107 ± 0.163	1.001 ± 0.002	0.847 ± 0.034
20	1.5	37	1.484 ± 0.050	6.814 ± 0.319	4.180 ± 0.182	1.006 ± 0.007	0.836 ± 0.038

[a] Each mean represents the mean (± standard deviation) of, at least, three replicates.

3.6. Softness

Softness determination is a complementary measure to TPA. The use of a conical probe ensures that samples demonstrate their plastic behavior due to reduced viscosity during its penetration. Hence, softness analysis enables measurement of characteristics such as the spreadability (previously observed in glass plates), allowing for rigidity determination of semi-solid materials, that can be correlated with the sensorial evaluation and softness index of the formulations (Barbosa et al., 2017).

Softness analysis was performed only for formulations previously found to be suitable as topical pharmaceutical systems by rheology and TPA, with analysis at 37 °C. The objective was to evaluate the smoothness of these samples under body conditions, simulating their application appropriately. Softness is a very sensitive property, which can vary according the humidity and pH, for example. The softness index, determined as the force required for penetration of conical probe at a depth of 10 mm of the sample, is shown in Fig. 3.

The higher the softness index of the formulations, the harder and less soft they will be, since a greater strength will be required for the probe to penetrate the sample. Binary polymeric systems containing NaCMC or HPMC demonstrated similar softness profiles, suggesting that the polox407 is the major determinant of this property. Formulations containing HPMC demonstrated higher softness values when compared to formulations composed of NaCMC, likely due to the greater concentration of polymer in those systems.

Formulations containing 17.5% (w/w) polox407 displayed, in both cases, lower smoothness when compared to the highest concentration of the same polymer. The lowest concentration of HPMC, 3% (w/w), demonstrated the lowest softness index for monopolymeric systems, with similar results to 4% (w/w) HPMC. For binary polymeric systems containing NaCMC, the lowest softness index was found for the highest concentration of NaCMC - 1.5% (w/w), followed by 1.0% NaCMC. The most suitable systems for topicals with respect to softness index are those composed of 17.5% (w/w) polox407, suggesting that polox407 has the major contribution to this parameter.

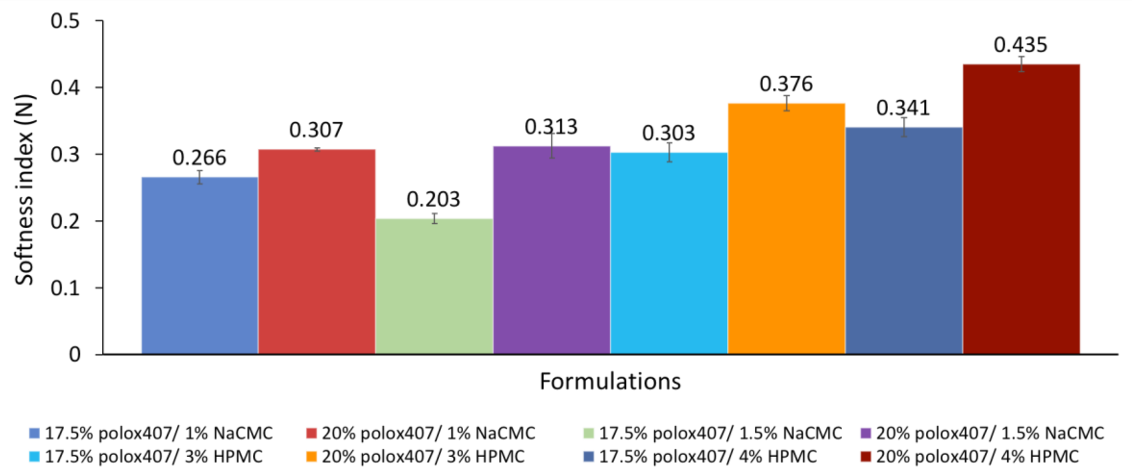

Fig. 3. Softness of binary systems composed of poloxamer 407 (polox407) and carboxymethylcellulose (NaCMC) or hydroxypropyl methylcellulose (HPMC) determined at 37 ° C. Each value represents the mean (± standard deviation) of at least three replicates.

3.7. Rheological-mechanical properties correlation

The linear regression is frequently used to assess the strength of linear relationships between two variables (Schober & Schwarte, 2018). Therefore, it was used to evaluate the linear correlation between mechanical and continuous shear properties with r^2-values ranging from 0.0072 to 0.9953 for HPMC systems and from 0.2407 to 0.9801 for NaCMC formulations. Moreover, softness index was also linearly correlated with hardness and consistency index at 37 ° C, and the results are all displayed in Table 7.

Table 7

Correlation between rheological (consistency index, yield value, flow behavior index) and mechanical properties (hardness, adhesiveness, compressibility and softness) of binary systems composed of poloxamer 407 (polox407) and hydroxypropyl methylcellulose (HPMC) or carboxymethylcellulose (NaCMC) at temperatures of 5, 25 and 37 ° C.

Mechanical or rheological parameter	Temperature (ºC)	Polymeric systems	
		polox407/HPMC	polox407/NaCMC
		r^2*-value*	
		Hardness	
Consistence index	5	0.0072	0.255
	25	0.5728	0.7953
	37	0.6936	0.9048
		Hardness	
Yield value	5	-	0.9301
	25	0.6527	0.8557
	37	0.0117	0.3911
		Adhesiveness	
Flow behavior index (n)	5	0.0489	0.2407
	25	0.7087	0.7128
	37	0.4492	0.7648
		Compressibility	
Hardness	5	0.8957	0.9018
	25	0.9951	0.9544
	37	0.9953	0.9801
		Softness	
Hardness	37	0.7169	0.5365
		Softness	
Consistency index	37	0.9871	0.3131

Generally, negative correlations were not observed. Rheological and mechanical parameters were not strongly correlated for systems composed of polox407 and cellulose derivatives, with a r^2 frequently lower than 0.90. However, formulations containing NaCMC demonstrated a better correlation when compared with HPMC, particularly at high temperatures.

The correlation between two mechanical responses (hardness and compressibility) was the best fitted by linear regression, resulting in r^2-values near 1, since they came from the same TPA assay. It may be possible to predict compressibility from hardness values by regression.

Consistency index and hardness are parameters which try to infer how structured the semi-solid systems were using two different approaches. It was seen that both systems are better correlated at 25 and 37 °C, where the formulations are in the gel state. The yield value infers the necessary stress for a sample start flowing, which is intuitively related to the hardness. Thus, a poor correlation was observed between those parameters for cellulose derivative formulations at 5 °C, mainly for HPMC samples, emphasizing the low interaction between polox407 and HPMC at this temperature. The systems showed a better correlation between those parameters at 25 °C, which decreased at 37 °C, demonstrating that yield value and hardness are more poorly correlated above gelation temperature. On the other hand, flow behavior index and adhesiveness demonstrated a good correlation at 25 and 37 °C. Therefore, adhesiveness is improved above gelation temperatures, where the micellization process makes them more structured.

Softness, hardness and consistency index are parameters able to evaluate similar properties, such as the ability of removing the formulation from the packaging material, application at a specific site and smoothness during administration (Tuğcu-Demiröz, Acartürk, & Erdoğan, 2013). Correlating softness with hardness and consistency index at 37 °C, HPMC systems showed good correlation values, with better predictability than NaCMC. Emphasizing the necessity of the softness assay as complementary to TPA, it was seen that hardness and softness were well correlated, with r^2-values of r^2=0.7169 for HPMC binary systems and r^2=0.5365 for NaCMC binary systems (Barbosa et al., 2017). Increasing hardness or consistency index linearly increased the softness response, but it is not possible to predict softness from hardness or consistency index, except for HPMC binary systems where softness was well correlated with consistency index values (r^2=0.9871).

While good correlations between rheological and mechanical properties were not demonstrated for most studied parameters, it is important to consider that rheological responses may be more sensitive and able to detect possible interactions between the components of the semi-solid systems more effectively, and better able to investigate the organization of the formulations in a nanoscale (de Francisco et al., 2019).

4. Conclusions

Binary polymeric systems composed of polox407 and HPMC or NaCMC were developed and characterized by mechanical and rheological analyses. It was possible to probe the interactions between polox407 and the cellulose derivatives through measurements of rheological synergisms, $T_{sol/gel}$, and changes in consistency, for example. All properties were valuable in the selection of suitable systems for biomedical and pharmaceutical applications. However, $T_{sol/gel}$ and rheological interaction parameters were especially useful to select the most suitable formulations for local application. The most appropriate formulations were those with higher polymer content, which then studied to investigate their softness profile. Through this process, the formulations composed of 17.5/1.5 polox407 and NaCMC, as well as those composed of 17.5/3 polox407 and HPMC were identified as potential materials for topical administration of drugs.

All mechanical and rheological properties were temperature and polymer concentration dependent. Most of the systems exhibited plastic behavior, with yield observed at high temperatures. The formulations also presented rheopectic and thixotropic properties, being most thixotropic at high polymer concentration and 37 °C. Oscillatory rheology predicts that they are able to be retained at the application site, improving drug delivery, since most of them were viscoelastic materials at 37 °C. Considering $T_{sol/gel}$, most formulations were considered appropriate to ensure ease of application and good retention, forming gels above 22 °C. The rheological interaction parameter demonstrated that at 5 °C the systems were not synergic, whereas the interaction between polox407 and HPMC or NaCMC was improved at 25 and 37 °C. Additionally, the linear correlation among mechanical and rheological properties was typically poor when compared to the correlation among mechanical properties, such as hardness and compressibility or softness.

Therefore, considering all the findings, it may be suggested that systems containing higher polymeric concentrations like 17.5/3; 17.5/4; 20/3 and 20/4 for HPMC and 17.5/1; 17.5/1.5; 20/1 and 20/1.5 for those containing NaCMC had advantageous properties for thermoresponsive gels. For local or topical administration in pharmaceutical or biomedical applications, systems containing 17.5 % (w/w) polox407, with 3% (w/w) HPMC and 1% (w/w) NaCMC were most appropriate.

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Appendix A. Supplementary data

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