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Rheological and mechanical properties of hydrophilic dispersions using a new hydrophobically modified polymer and Igepal® CO520

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ABSTRACT

Hydroxypropyl cellulose-methyl methacrylate and non-ionic surfactant Igepal® CO520 (20–25% (w/w)) have been characterized in aqueous-based dispersions for topical application systems. The systems have similar viscosity curves independent of the surfactant's concentration, showing shear-thinning fluids. Also, the elastic and viscous moduli are constant and independent of critical stress values applied; however, the storage modulus was always higher than the loss modulus. Both parameters showed a slightly dependence on the applied frequency, indicating a gel-like behavior. The complex dynamic viscosity increases until 23% (w/w) of surfactant, keeps then constant. The hardness, compressibility and adhesiveness parameters increase when increase the Igepal® CO520 concentration. The adhesiveness properties are 18–47% higher than the compressibility ones, with low values for hardness (~0.4 N). While fracture and Hencky's strain values increase when increase the surfactant concentration, fracture work decreased, and no relation is found to deformability modulus. Also, the dispersed system with 20% (w/w) of Igepal® CO520 has less stiffness than with 25% (w/w).

1. Introduction

In the development of pharmaceutical semisolid preparations for topical application, several desirable product characteristics may be defined in order to satisfy patient needs and reach the maximum clinical efficacy (Bruschi et al., 2007; Jones, Woolfson, & Djokic, 1996). These include among others mechanical properties and acceptable viscosity (Davis, 1971), because provides essential information related to these preparations.

So, rheological properties affected to all steps of manufacture and manipulate processes, and its topical application (Talukdar, Vinckier, Moldenaers, & Kinget, 1996). Moreover, these measures are important tools in quality control of components and final product. The rheological behavior of the formulations (preparations) used in pharmaceutical and cosmetics industries are characterized by flow and dynamic oscillatory shear (Niraula, King, & Misran, 2003). The last one, so-called 'fingerprint' provides information of intermolecular and interparticle forces under non-destructive conditions (Lippacher, Müller, & Mäder, 2001).

Texture profile analysis (TPA) is a technique that has been extensively employed to mechanically and geometrically characterize food (Jones, Woolfson, Djokic, & Coulter, 1996). Later, it has emerged also as a useful technique in the field of pharmaceutical gel analysis (Coviello et al., 2003). From the resulting force–distance and force–time plots, the hardness (the force required to attain a given deformation), compressibility (the work required to deform the product during the first pass of the probe), and adhesiveness (the work necessary to overcome the attractive forces between the surface of the sample and the surface of the probe) are derived (Bruschi et al., 2007). Also, from force–distance plots its can been obtained others mechanical parameters related to stiffness or fracture of the disperse system, that allow know its structure (Kaletunc, Normand, Nussinovitch, & Peleg, 1991; Kampf & Nussinovitch, 1997; Moya-Ortega, Álvarez-Lorenzo, Sigurdsson, Concheiro, & Loftsson, 2010). These mechanical properties are related with in vivo sensorial parameters, being applied to design of topical pharmaceutical preparations (Jones, Woolfson, & Djokic, 1996).

A hydrophobically modified polymer (HMP) is a water soluble polymer, onto which short hydrophobic side-chains have been grafted (Piculell, Guillemet, Thuresson, Shubin, & Ericsson, 1996). In a previous paper we determined the possible interaction between a new hydrophobically modified polymer (HMP), hydroxypropyl cellulose-methyl methacrylate (HCMMA) with different surfactants. Also, we explored the possibility to obtain stable dispersed system which could be used as topical dosage form in pharmaceutical applications. This work demonstrated that the copolymer studied, which exhibits predominant hydrophobic properties can be used to formulate long-term aqueous-based dispersions by choosing the right surfactant as well as suitable batch processing conditions. So, the best results were found with HCMMA/Igepal®

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CO520 system which presented a region of long term foam-like stable dispersions (Claro, Muñoz, de la Fuente, Jiménez-Castellanos, & Lucero, 2008).

Therefore, this study describes the rheological and mechanical characterization of ternary systems prepared from the hydrophobically modified polymer HCMMA, the surfactant Igepal® CO520 at different concentrations, and water with the aim of its study as platforms for topical application systems.

2. Materials and methods

2.1. Materials

The ternary system was constituted by the HMP, hydroxypropyl cellulose-methyl methacrylate (HCMMA), synthesized as detailed in a previous work (Castellano, Gurruchaga, & Goñi, 1997), a commercial non-ionic surfactant, the polyoxyethylene (EO = 5) nonylphenyl ether (Igepal® CO520, HLB 10, Mw 441, batch 17812LO, Sigma–Aldrich, Barcelona, Spain) and bidistilled water. The surfactant was used as received, without any further purification.

2.2. Methods

2.2.1. Preparation of dispersions

Concentrated aqueous dispersion of the HCMMA/Igepal® CO520 was prepared with an Ultra-Turrax T18 homogenizer equipped with an S-18 N-19G turbine (IKA, Staufen, Germany). Homogenization was carried out at 6000 rpm and the beaker containing the sample was kept in a circulator bath at 30 °C for the batch operation time (2 h). The detailed procedure consisted of adding the required amount of HCMMA on the previously prepared aqueous solution of surfactant. The dispersion compositions were: HCMMA (1.5% (w/w)) and Igepal® CO520 (20–25% (w/w)).

2.2.2. Rheological characterization

The systems were allowed to rest at room temperature for 24 h after their preparation before conducting any rheological test in order to ensure the same recent shear history for all the samples and to avoid mechanical memory effects. Multi-step flow curve measurements were run using a controlled-stress rheometer, RS-100 (Haake, Karlsruhe, Germany), using plate & plate sensor systems of 60 mm diameter with serrated surfaces. The experimental protocol consisted of applying every shear stress either until an approximation to the steady-state of 0.001 was reached or until a maximum time of 300 s per point.

Small amplitude oscillatory shear experiments were carried out in the RS-100 rheometer to determine the linear dynamic viscoelastic properties of samples. First of all, the linear viscoelastic region for the different systems was determined by stress sweeps at 1 Hz. A stress amplitude of 2 Pa was used to determine the mechanical spectra in a frequency range from 0.01 rad/s to 100 rad/s.

The analysis of results is based on the storage (G') and loss (G'') moduli, which are related to the elastic and viscous component, respectively. Also, the complex dynamic viscosity (η^*) are used as viscoelastic function (1):

$$\eta^* = \frac{G^*}{\varpi} \quad G^* = G' + IG'' \tag{1}$$

where ϖ is angular rate (rad/s) (Taylor, Tanna, Sahota, & Voermans, 2006).

All measurements were made at 25 ± 1 °C. Vaseline oil was used as sealing agent to prevent samples from drying-out. Each measurement was made in triplicate. The sensor systems used in this work were calibrated with SUA1 standard fluid (Hudson & Jones, 1993).

2.2.3. Mechanical characterization

Mechanical properties of the hydrophilic dispersions studies were determined by uniaxial compression with a load cell of 5 kg force. Texture analyzer (TA-XTA2, Stable Micro Systems, UK) was used controlled by a software. A standard extrusion disc with a 35 mm diameter (A/BE) was used as the sensor. Hardness, compressibility and adhesiveness were measured.

The force vs. time data was converted to a true stress (σ) and Hencky's strain (ε_{H}), relationship using the following substitutions (2) and (3) (Kampf & Nussinovitch, 1997; Ribeiro, Rodrigues, Sabadini, & Cunha, 2004).

$$\sigma = \frac{F(t)H(t)}{A_0 H_0} \tag{2}$$

$$\epsilon = \left| \ln\left(\frac{H(t)}{H_0}\right) \right| \tag{3}$$

where F is the momentary force at time t, H is the height at time t, A_0 is the cross-sectional area of the original gel (962.115 mm^2) and H_0 is the initial length when the compression starts (4 mm).

Stress (σ_{f}) and strain (ε_{f}) fractures were determined as the maximum point of the true stress–Hencky strain curve and the fracture work (W_{f}) was the area under curve of the fracture sone (Wium & Qvist, 1997). Since gels are viscoelastic rather than elastic and are usually subjected to large compression during testing, the strict definition of Young's modulus as an expression of a food's stress–strain ratio was replaced by the 'modulus of deformability' (M_{D}), (Kampf & Nussinovitch, 1997; Moya-Ortega et al., 2010) defined as the slope of the linear portion of the stress–strain relationship. M_{D} was determined taking into consideration between 47 and 80 data. This deformability module is a stiffness index and is widely used to characterized gels and soft materials (Konstance, 1993).

Force relaxation curves were normalized and linearized by the following equation (4) (Kampf & Nussinovitch, 1997).

$$\frac{F_0 t}{F_0 - F(t)} = k_1 + K_2 t \tag{4}$$

where F_0 and $F(t)$ are the initial and momentary forces and k_1 (min) and k_2 are constants. The constant k_2 derived from Eq. (5), was used to calculate an asymptotic residual modulus, E_A, that serves as a measure of gel solidity (Peleg & Pollak, 1982).

$$E_A = \frac{(F_0[1 - 1/K_2])}{A(\varepsilon)\varepsilon} \tag{5}$$

where ε is the imposed strain and $A(\varepsilon)$ is the corresponding calculated cross-sectional area of the deforming sample.

Measures were made after 24 h kept at 25 ± 1 °C. 60 g of sample were put in a standard recipient of 50 mm diameter. Before assay, the distance initial measure (70 mm from the recipient base) and the penetration deep (4 mm since the sensor contact the sample) were determined. Speed before, during and after assay was 2 mm/s. Each measurement was made in triplicate.

3. Results and discussions

3.1. Rheological characterization

Viscosity curves of dispersions at 25 °C are shown in Fig. 1. All systems have similar viscosity curves independent of the surfactant's concentration. Also, all of them show shear-thinning fluids which means that their viscosity decreases as the shear rate increases. The shear-thinning behavior may be regarded as arising from modifications in macromolecular organization in the solution as the shear rate changes. At low shear rates, the disruption of entanglements by the imposed shear is balanced by the formation of new ones, so that no net change in entanglements occurs;

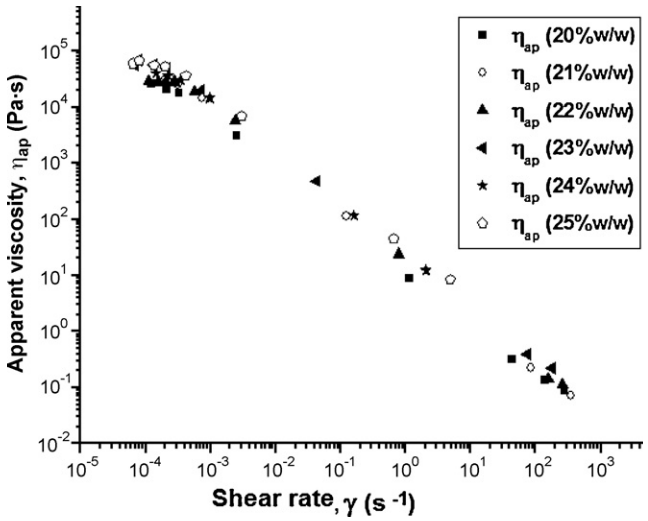

Fig. 1. Viscosity curves of different systems HCMMA–Igepal® CO520 (% w/w)-water at 25 °C.

it is the Newtonian plateau region, where the viscosity has a constant value. For higher shear rates, disruption predominates over formation of new entanglements, molecules align in the direction of flow and the apparent viscosity decreases with increasing shear rate. As a consequence, the shear rate corresponding to the transition from Newtonian to shear-thinning behavior moves to lower values as the concentration increases (Badiger, Lutz, & Wolf, 2000; Rudraraju & Wyandt, 2005; Sittikijyothin, Torres, & Gonçalves, 2005).

The shear thinning behavior can be fitted to well within experimental error by the Ostwald–de Waele or "Power Law" model (Medina-Torres, Brito-De La Fuente, Torrestiana-Sanchez, & Katthain, 2000) given by (6):

$$\eta = k\dot{\gamma}^{n-1} \tag{6}$$

where k is the consistency index (Pa s), $\dot{\gamma}$ is the shear rate (s^{-1}) and n the fluid behavior index. The parameters n and k are obtained by linear regression analysis. To Newtonian fluids $n = 1$, to pseudoplastic fluids $n < 1$ and to dilatants fluids $n > 1$.

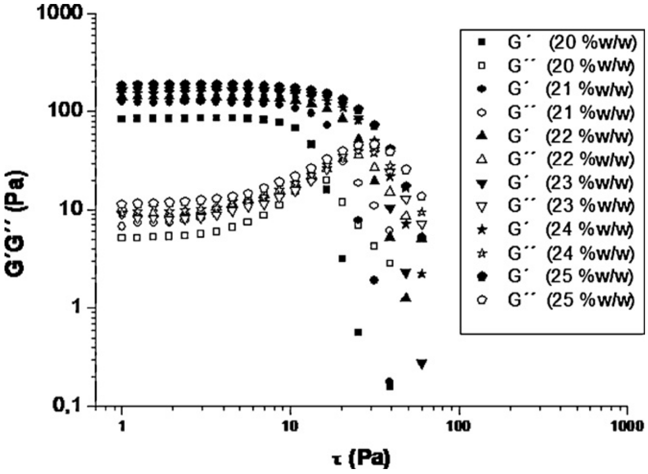

Fig. 2. Storage (G') and loss (G'') moduli values of different systems HCMMA–Igepal® CO520 (% w/w)-water at 25 °C.

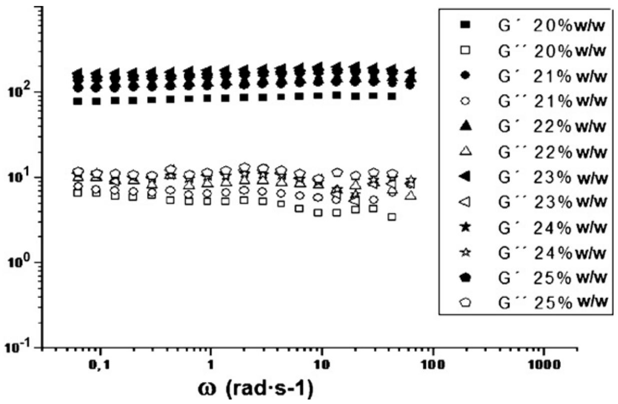

Fig. 3. Storage (G') and loss (G'') moduli vs. frequency sweep of different systems HCMMA–Igepal® CO520 (% w/w)-water at 25 °C.

Also, Cross flow model (Medina-Torres et al., 2000) has been used to describe the shear-thinning or pseudoplastic behavior by Eq. (7):

$$\eta(\dot{\gamma}) = \frac{\eta_0}{1 + (\lambda\dot{\gamma})^m} \tag{7}$$

where η_0 is the zero-shear rate viscosity (Pa s), λ is a structural relaxation time or time constant (s) and m is a shear index dimensionless which indicated the degree of shear thinning ($m = 1 - n$). When m approaches zero the liquid is Newtonian, while the most shear thinning liquids have a value of m approaching unity (Álvarez-Manceñido et al., 2006; Rudraraju & Wyandt, 2005).

Therefore, both models are vinculated since the dimensionless constant m of Cross model is related to the exponent n of Power Law (Medina-Torres et al., 2000).

Characteristic parameters of Power Law and Cross models are illustrated in Table 1. Power Law model show a good fit, with r^2 values between 0.920 and 0.990. In all cases n values were lower than 1, which indicates that they are pseudoplastic systems (Bonacucina, Martelli, & Palmieri, 2004), characterized by an apparent viscosity decrease when the shear rate increase. A slightly increase of n and k values can be appreciated from systems when increase surfactant concentration. Medina-Torres et al. (2000) also observed an increase of n and k when the polysaccharides concentration increases in a vegetal gum.

Cross model also shows good fit with r^2 values between 0.898 and 0.991. In agreement with Rudraraju and Wyandt (2005) and Sittikijyothin et al. (2005), the viscosity (η_0) increases when increase the surfactant concentration (Table 1). Taking into account that the magnitude of zero-shear rate viscosity is a macroscopic representation of microstructural nature of systems, these results

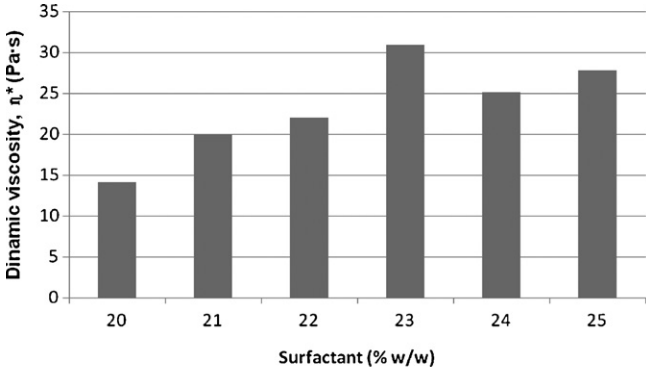

Fig. 4. Dinamic viscosity (η^*) vs. surfactant's concentration of the different systems of HCMMA–Igepal® CO520-water at 25 °C.

Table 1
Characteristic parameters of Ostwald-de Waele or Power Law and Cross model for the systems HCMMA–Igepal® CO520-water studied at 25 °C.

Igepal® CO520 (% w/w)	Power Law model			Cross model			
	k (Pa s)	n	r^2	η_0 (Pa s)	λ (s)	m	r^2
20	7.30	0.06	0.970	27,175	1250	0.94	0.980
21	14.57	0.08	0.980	32,724	1250	0.96	0.951
22	16.72	0.07	0.990	34,295	1429	0.95	0.977
23	22.05	0.12	0.950	53,302	2000	0.95	0.898
24	33.61	0.18	0.920	53,408	2041	0.98	0.991
25	47.16	0.20	0.930	61,370	2000	0.95	0.964

Table 2
Parameters obtained in mechanical characterization of different systems HCMMA–Igepal® CO520-water at 25 °C.

Parameters	Surfactant (% w/w)					
	20	21	22	23	24	25
Hardness (N)	0.321 ± 0.005	0.350 ± 0.008	0.392 ± 0.013	0.418 ± 0.005	0.504 ± 0.020	0.546 ± 0.008
Compressibility (N mm)	0.848 ± 0.048	0.897 ± 0.090	1.066 ± 0.049	1.019 ± 0.047	1.242 ± 0.118	1.263 ± 0.085
Adhessiveness (N mm)	1.038 ± 0.056	1.229 ± 0.068	1.256 ± 0.025	1.445 ± 0.039	1.678 ± 0.127	1.862 ± 0.076
Fracture strain (Pa)	2065	2247	2566	2497	3084	3000
Hencky's strain	0.3524	0.2678	0.2887	0.4700	0.5255	0.6867
Deformability modulus (Pa)	6850	6784	9767	2176	3174	1672
Fracture work (J/m^2)	232.02	154.59	185.26	98.92	101.48	80.32
k_1 (s)	0.001	0.001	0.001	0.002	0.002	0.003
k_2	1.006	1.007	1.008	1.008	1.010	1.012
E_a (Pa)	338.96	364.07	404.20	404.20	504.25	603.91

Table 3
Parameters obtained in mechanical characterization of different systems Igepal® CO520-water at 25 °C.

Parameters	Surfactant (% w/w)					
	20	21	22	23	24	25
Hardness (N)	0.128 ± 0.001	0.136 ± 0.002	0.168 ± 0.006	0.162 ± 0.003	0.205 ± 0.002	0.275 ± 0.003
Compressibility (N mm)	0.385 ± 0.004	0.398 ± 0.007	0.473 ± 0.004	0.459 ± 0.011	0.543 ± 0.015	0.698 ± 0.028
Adhessiveness (N mm)	0.313 ± 0.001	0.331 ± 0.007	0.423 ± 0.002	0.358 ± 0.020	0.444 ± 0.008	0.746 ± 0.006

indicate a higher number of entanglements (Álvarez-Manceñido et al., 2006). On the other hand, m values are closely to 1 (0.94–0.98), which indicates a shear-thinning behavior. Both parameters, m and λ, increase when increase Igepal® CO520.

It is possible to see in Fig. 2 linear viscoelastic behavior where elastic (G') and viscous (G'') moduli are constant and independent of critical stress values applied (Ferrari, Beferoni, & Caramella, 2001). Also, the viscoelastic area increases when the surfactant percentage increases.

Fig. 3 displays G' and G'' vs. frequency sweep. The storage modulus was always higher than the loss modulus in the frequency range investigated. Therefore, the dispersed systems were more elastic than viscous (Torres, Iturbe, Snowden, Chowdhry, & Leharne, 2007). Both parameters showed a slightly dependence on the applied frequency, as expected, indicating a gel-like behavior (Alfaro, Guerrero, & Muñoz, 2000). Also, tan δ values lower than 45° suggest the tendency of system to a shear elastic response (Torres et al., 2007), which can be explain by the more dense packing of the particles in the dispersion (Lippacher, Müller, & Mäder, 2000). Moreover, the complex dynamic viscosity (η^*) (Fig. 4) increases until 23% (w/w) of surfactant, keeps then constant. These results are justified by the increase of surfactant and polymer interactions of the systems, until 23% (w/w) of surfactant's concentration when the interactions or entanglements do not increase.

3.2. Mechanical characterization

Typical mechanical curves are shown in Fig. 5 as an example of the register obtained with the texture analyzer (force vs. time and force vs. distance).

The three parameters (hardness, compressibility and adhesiveness) increase when increase the Igepal® CO520 concentration

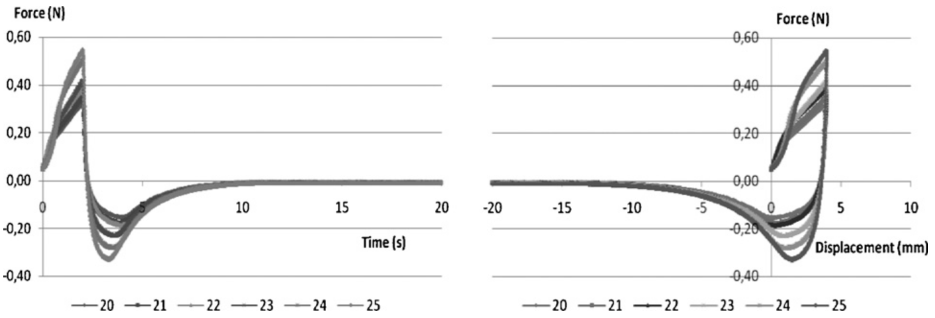

Fig. 5. Typical mechanical curves obtained with the texture analyzer (force vs. time and force vs. displacement) to the different systems of HCMMA–Igepal® CO520 (% w/w)-water at 25 °C.

(Table 2), in agreement with Ferrari, Bertoni, Caramella, and La Manna (1994) and Jones, Woolfson, and Brown (1997). From a point of view of application in the skin, it is interesting to mention that the adhesiveness properties are higher than the compressibility ones. Also, hardness values are very low. However, adhesiveness is a measure of the work required to remove the probe from the surface of sample, which may in some cases involve fracture of cohesive bonds within the sample, and therefore is partly dependent on sample tack (Jones et al., 1997).

A lineal correlation ($p < 0.000$) is observed between these parameters and surfactant percentage, with higher r^2 values for hardness and adhesiveness (0.956 and 0.929, respectively). Moreover, a good correlation is found between adhesiveness-hardness ($r^2 = 0.963$) and between compressibility-hardness ($r^2 = 0.879$), in agreement with Jones et al. (1997).

With the end to check if these results are due to the surfactant percentage or the interactions surfactant–polymer, we made the same experiment without polymer. So, it is possible to see a pronounce decrease of the three mechanical parameter values (Table 3) and their lineal correlation ($r^2 = 0.846$, 0.005, 0.660 to hardness, compressibility and adhesiveness, respectively), indicating the important role of both factors: surfactant concentration and the interactions between Igepal® CO520 and HCMMA.

Fracture (ε_f) and Hencky's (ε_H) strain values increase when increase the surfactant concentration; however, fracture work decreased. No relation is found between deformability modulus (M_D) and Igepal® CO520 concentration (Table 2). So, two extremely different behaviors can be distinguished. One of them, corresponding to 25%, indicates that this system is slight deformable, but easily to break applying a big strain; this means that is a rigid system from a mechanical point of view. On another hand, to 20% of surfactant, the system is more deformable but it is difficult to break; so this system is less rigid. In general, there is no direct relation between Igepal® CO520 and these parameters, in agreement with Kaletunc et al. (1991) who observed that strength, deformability and stiffness are independent gel's properties.

After obtained a very good linearity ($r^2 = 1$) in Eq. (3), it has been calculated parameters corresponding to mechanical relaxation of dispersed systems (Table 2). k_1 values indicate that the different gels have a similar relaxation because we observed only a slightly increase from 20 to 25% (w/w) of surfactant (Kampf & Nussinovitch, 1997).

Generally, k_2 represents the degree of solidity and varies theoretically between 1 for a material that is truly a liquid (i.e. all the stress relaxes) and ∞ for an ideal elastic solid where the stress does not relax at all. In our study, k_2 values are closely to unity (1.006–1.012) that indicate soft or semi-solid systems (Kampf & Nussinovitch, 1997).

Regarding to E_A (asymptotic modulus), the values increase when the surfactant concentration increases, but without a lineal behavior. Taking into account that this parameter represents the internal structural changes occurring in the material, a lower value of E_A means more cracks developing in the structure and, consequently, the dispersed system with 20% (w/w) of Igepal® CO520 has less stiffness than with 25% (w/w) (Kampf & Nussinovitch, 1997).

4. Conclusions

Systems constituted with HCMMA–Igepal® CO520-water show similar flow curves, independent of the surfactant's concentration, with a shear-thinning behavior, confirmed by the mathematical models.

Frequency sweeps show a minimum dependence of storage and loss moduli (G' and G'') with the frequency applied, that indicates a clear tendency to the formation of macromolecular nets with a predominance of elastic properties, characteristic of gels. This behavior was confirmed, again, with independence of surfactant's concentration; since loss tangent values ($\tan\delta$) were lower than 0.1. G', G'' and the complex viscosity increase until 23% of Igepal® CO520 comparing values obtained at 1 Hz.

Mechanical properties show that systems studied are easily to deform due to the low hardness values, but having important adhesiveness properties. Fracture and solidity parameters indicate that system made with the higher surfactant's concentration is more rigid and solid than with 20% of Igepal® CO520. In fact implies that it breaks easier applying higher stress as it has a less cracked structure.

Mechanical (hardness, compressibility and adhesiveness), fracture (strain and Hencky deformability) and solidity parameters (k_1, k_2 and E_A) increase when surfactant's concentration increase. On the opposite, fracture work and deformability module does not increase with the concentration of Igepal® CO520.

Rotationally, oscillatory and mechanical studies demonstrate that, in general, dispersed systems constituted by the hydrophobically modified polymer, HCMMA, and Igepal® CO520 are gels with adapt rheological and mechanical properties to be base excipients for topical drug administration. For the above reason, drug release and absorption in these systems are being investigated.

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