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Drug diffusion from disperse systems with a hydrophobically modified polysaccharide: Enhancer® vs Franz cells

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ABSTRACT

This study assesses the capacity of a new hydrophobically modified polysaccharide –hydroxypropyl cellulose–methyl methacrylate – to control drug release in semisolid formulations. The dispersed systems contain the new polymer, Igepal® CO520 as surfactant and theophylline as model drug at three concentrations (0.5, 1 and 1.5%, w/w). Drug release study shows that the systems containing 0.5% (w/w) of drug have faster release and higher diffusion coefficient than the other two concentrations. These results can be explained by two different structures ("relaxed" and "structured") found from a rheological point of view. Also, this paper compares two different devices for testing drug release and diffusion. It has been obtained more reliable and reproducible results with Enhancer Cell® respect to Franz diffusion cell. In both cases, Fickian diffusion was the mechanism predominant for all systems. Finally, the utility of this polymer has been demonstrated to make three-dimensional gel structure and control theophylline release from systems in topical application.

1. Introduction

Hydrophilic dispersions are very useful as platforms in drug delivery applications since they can resist the physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of the applied area, and controlling drug release (Deshpande & Shirolkar, 1989; Ding, 1998; Yonese, 2001). Some of these systems have a gel-like behavior with high fluidity during the administration, and later they undergo a phase transition forming a viscoelastic gel (Ding, 1998; Kumar, Haglund, & Himmelstein, 1994).

Drug diffusion rates in aqueous dispersions of polymer are basically governed by the restrictive effects of the polymer on drug mobility, whether due to a reduction in free water volume or an increase in medium viscosity (Álvarez-Lorenzo, Gómez-Amoza, Martínez-Pacheco, Souto, & Concheiro, 1999). In general, systems of this type generally show an inverse relationship between release rate and gel viscosity (Wan & Lai, 1992). However, studies performed with dispersions of hydrophilic cellulosic and non-cellulosic polymers have indicated that drug diffusion rate scarcely changes over wide polymer concentration ranges that show considerable variation in apparent viscosity (Álvarez-Lorenzo et al., 1999).

On the other hand, the addition of a small amount of surfactant can modify the polymer conformation and the dispersion viscosity (Philippova, Chtcheglova, Karybiants, & Khokhlov, 1998). So, the cellulosic polymers show an appropriate structure to interact with amphyphilic molecules. Also, the interactions polymer–surfactant could affect the drug diffusion, and consequently the drug release (Amsden, Cheng, Peloquin, & Nafziger, 1998). In this sense, Paulsson and Edsman (2001) indicated three kinds of interactions affecting the drug release in a gel consisting of polymer, surfactant, and drug.

Flynn et al. (1999) and Shah, Elkins, and Williams (1999) suggest that the in vitro drug release study of semisolid preparations is an important tool to initial screening and optimization of the formulations, bioequivalence and quality control. Although dissolution devices exist (USP XXXIV, Apparatus V, VI and VII) to evaluate final transdermal dosage forms, specialized diffusion cells like Franz diffusion cell, recommended by FDA (SUPAC-SS, 1997), are still popular during the developmental stages to study transfer kinetics through membranes. However, the number of variables (stirring, temperature, dosage, manual sampling) of these cells means a high degree of variability between replicate experiments (Chattaraj & Kanfer, 1995). Also, it cannot be obtained results in the first times of the experiments (Addicks, Flynn, Weiner, & Chiang, 1988). So, different authors modified these cells in order to have higher reproducibility (Chattaraj & Kanfer, 1995; Kierstan et al., 2001; Solich, Sklenárova, Huclová, Satinsky, & Schaefer, 2003).

Vankel Industries, Inc., (Collins, Sanghvi, Little, Hofer, & Stevenson, 1995) developed the Enhancer Cell®, a new device for in vitro transdermal drug diffusion studies which can be used

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with existing dissolution equipment (USP XXXIV, Apparatus II). Sanghvi and Collins (1993) concluded that Enhancer Cell® has certain advantages when compared to the Franz diffusion cell such as reduced investment, loading the cells and set up of the equipment and sampling techniques, especially with automation. Also, Rege, Vilivalam, and Collins (1998) indicated that this method is simple, reliable and reproducible and has the ability to distinguish between formulations. Moreover, this device has been recently used for dissolution and diffusion studies (Murphy et al., 2012; Parojcic, Vasiljevic, Ibric, & Djuric, 2008).

Hydroxypropyl cellulose–methyl methacrylate (HCMMA) is a new hydrophobically modified polymer (HMP) synthesized and characterized by Castellano, Gurruchaga, and Goñi (1997). It has multiple advantages, in comparison with the hydrophilic cellulose ethers, such as surfactant properties and certain hydrophobic character (Claro, Muñoz, de la Fuente, Jiménez-Castellanos & Lucero, 2008). Used in tablets, we have demonstrated that HCMMA does not swell and controls drug release by weak bonds (Ferrero, Bravo, & Jiménez-Castellanos, 2003). Later, we have applied HCMMA to obtain hydrophilic dispersed systems for semisolid preparations. In the first study, we chose Igepal® CO520 as the best surfactant to obtain stable hydrophilic disperse systems (Claro et al., 2008). On the second one, we prepared different formulations with Igepal® CO520 and HCMMA with the aim to characterize them from a rheological and mechanical point of view. These systems were gels with properties to be base excipients for topical drug administration (Lucero, Claro, Casas, & Jiménez-Castellanos, 2011).

For the above reasons, the novelties of this paper are: (1) to evaluate, for the first time, the capacity of HCMMA to control drug release in semisolid formulations and (2) to compare two different devices Enhancer Cell® and Franz diffusion cell for testing drug release and diffusion, since the information about the suitability of Enhancer Cell® is still limited. So, the ternary systems were prepared with HCMM, the Igepal® CO520 surfactant, water and theophylline at 0.5, 1 and 1.5% (w/w) as model drug (Álvarez-Lorenzo et al., 1999; Heard, Johnson, Moss, & Thomas, 2006; Klimentová, Kosák, Vávrová, Holas, & Hrabálek, 2006; Sloan et al., 1998; Vávrová, Hrabálek, Dolezal, Holas, & Klimentová, 2005).

2. Materials and methods

2.1. Materials

For the synthesis: Hydroxypropyl cellulose (HC) (Aldrich, 32.306-3) was used as received. The methyl methacrylate monomer (MMA) (Merck) was purified by distillation under previously described conditions (Goñi, Gurruchaga, Valero, & Guzman, 1983). The initiator was ceric ammonium nitrate (Fluka). All the other products were reagent grade or the equivalent.

For the disperse system: A dispersed system was constituted by the HMP, hydroxypropyl cellulose–methyl methacrylate (HCMMA) synthesized and characterized as detailed in a previous work (Castellano et al., 1997), a commercial non-ionic surfactant (SF), the polyoxyethylene (EO = 5) nonylphenyl ether (Igepal® CO520, HLB 10, Mw 441, batch 17812LO, Sigma–Aldrich, Barcelona, Spain) and distilled water. All products were used as received. Also, anhydrous theophylline (TH) was used as model drug (batch 99H0870, Sigma–Aldrich, Germany).

2.2. Methods

2.2.1. Synthesis of hydroxypropyl cellulose–methyl methacrylate

The synthesis was made following the procedure described by Castellano et al., 1997. Hydroxypropyl cellulose (40 g) was dispersed in 550 ml of bidistilled water. The medium was purged with purified nitrogen and the bath temperature was maintained at 30 °C. 100 ml of (MMA) was added and, 15 min later, 50 ml of the initiator solution (0.1 M ceric ammonium nitrate in 1 N nitric acid) were added. Grafting was allowed to proceed for 4 h under a constant light source (100 W). The product obtained was filtered off and washed with diluted nitric acid (1 N) and bidistilled water until neutral pH was reached. A noteworthy aspect to mention is that the use of water as reaction solvent guarantees, not only an effective dispersion of all the reactants and reagents, but also the absence of toxic substances in the final product (Echeverría, Silva, Goñi, & Gurruchaga, 2005). The product was dried in an oven until constant weight under vacuum (Vacucell 22, Gräfelting, Germany) at 50 °C (0.5 Pa).

2.2.2. Characterization of hydroxypropyl cellulose–methyl methacrylate

In order to study the efficiency of the graft copolymerization reaction, the poly-methyl methacrylate (PMMA) homopolymer was removed from the total reaction product, with tetrahydrofuran (THF), by soxhlet extraction for 72 h. So, the pure graft copolymer was obtained. Afterwards, the grafted PMMA was isolated from carbohydrate chains by acid hydrolysis with perchloric acid (60%) in a glacial acetic acid medium (Gurruchaga, Goñi, Valero, & Guzmán, 1992). The results are shown as the mean values of two replicates. The quantification of the PMMA homopolymer and the grafted PMMA was recorded by the following parameters (Gurruchaga et al., 1992):

- Percent grafting efficiency (% GE) (Eq. (1)) was used to quantify the % ratio between grafted copolymer after removal of PMMA (purified copolymer) and the crude product mixture of PMMA and grafted polymer:

$$\%GE = \frac{\text{Graft copolymer weight}}{\text{Total product}} \times 100 \quad (1)$$

- Percentage grafting (%*G*) (Eq. (2)) was used to assess the grafted methacrylic polymer–carbohydrate (HC) ratio in the copolymer:

$$\%G = \frac{\text{Grafted methacrylic polymer weight}}{\text{Grafted carbohydrate weight}} \times 100 \quad (2)$$

Also, the powder has been characterized by particle size and apparent particle density. Particle size analysis was carried out on a vibratory sieve shaker (Retsch Vibro, Haan, Germany) using 500, 355, 250, 180, 125, 90, 63, 45, 38 μm calibrated sieves (Cisa, Barcelona, Spain). From plots of powder weight (%) versus size (μm), typical parameters from a particle size distribution were determined: mean particle diameter, relative standard deviation (RSD) and skewness and kurtosis coefficients (SPSS® 14.0). The apparent particle density of the product was determined, in triplicated, by means of an air comparison pycnometer (Ultrapycnometer 1000, Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas, according to European Pharmacopoeia (2012). The morphology of particles was studied by means of a scanning electron microscope (Philips XL-30, Eindhoven, Holland), after coating the samples with a thin layer of gold on a sputter coater (Edwards Pirani 501 Scan-Coat Six, Crawley, West Sussex, UK).

2.2.3. Preparation of dispersions

The required amount of TH (0.5, 1 or 1.5%, w/w) was added on a previously prepared aqueous solution of SF (Igepal® CO520: 20–25%, w/w). Later, HCMMA (1.5%, w/w) was added to the systems. To prepare the dispersions, an Ultra-Turrax T18 homogeniser equipped with an S-18 N-19G turbine (IKA, Staufen, Germany) was

used. Homogenization was carried out at 6000 rpm for 2 h. The beaker containing the sample was kept in a circulator bath at 30 °C.

2.2.4. Rheological characterization

The systems were allowed to rest at room temperature for 24 h after its 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 selected samples. First of all, the linear viscoelastic region for the different systems was determined by stress sweeps at 1 Hz. 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. All measurements were made at 37 ± 0.1 °C. Each measurement was made in triplicate. The sensor systems used in this work were calibrated with SUA1 standard fluid (Hudson & Jones, 1993).

2.2.5. Studies of the theophylline release

The Enhancer Cell® device (2 cm diameter) (Vankel Industries, Barcelona, Spain), and cellulose nitrate membrane (25 mm diameter, 0.0145 cm thickness and 0.45 μm pore size) (Whatman® International Ltd, Maidstone, England) were used to the drug release study. Previously, the membrane was wetted with the dissolution medium for 24 h. The effective area was 1.77 cm^2. Samples of different dispersions (1.5 g) were put in the device. The Enhancer Cell® was introduced into the vessels of the USP XXXIV, Apparatus II (Aidec, Barcelona, Spain) and tested for 24 h (three replicates). Phosphate buffer (pH 6.8) (900 ml) maintained at 37 ± 0.5 °C was used as dissolution medium. Paddle rotation speed was 100 rpm. The space between the device and paddle was 3 cm.

Filtered samples (2.8 ml) were withdrawn at determined time intervals via a peristaltic pump (Hewlett-Packard 8452a diode-array UV-vis spectrophotometer, Waldbronn, Germany). TH release was monitored continuously at λ = 272 nm.

Drug release data ($M_t/M_\infty \leq 0.6$) were analyzed according to Korsmeyer, Gurny, Doelker, Buri, and Peppas (1983) (Eq. (3)) and Peppas and Sahlin (1989) (Eq. (4)) equations:

$$\frac{M_t}{M_\infty} = k' t^n \tag{3}$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \tag{4}$$

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k' is the kinetic constant characteristic of the drug/polymer system, t is the release time, n is the release exponent that depends on the release mechanism and the shape of the matrix tested (Ritger & Peppas, 1987), k_d, k_r are the diffusion and relaxation rate constants respectively, from Peppas and Sahlin equation; m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

2.2.6. Studies of the theophylline diffusion

The diffusion studies were made using the traditional Franz diffusion cell (VidraFoc, Barcelona, Spain) (three replicates). Hydrophilic artificial membranes of cellulose nitrate (pore size: 0.45 μm and thickness: 0.0145 cm) (Whatman® International Ltd, Maidstone, England) were put between the two compartments (donor and receptor). Previously, the membranes were wetted with the receptor medium during 24 h. Samples of different dispersions (2 g) were put in the donor compartment. Phosphate buffer (pH 6.8) (15 ml) maintained at 37 ± 0.5 °C was used as diffusion medium, stirring with a magnetic bar at 300 rpm, to obtain sink conditions (Vucinic-Milankovic, Savic, & Vuleta, 2007). The effective area was 3.14 cm^2. At determined time intervals, samples (0.2 ml) were removed and replaced with an equal volume from receptor compartment. TH release was determined by spectrophotometry at λ = 272 nm (Hewlett-Packard 8452a diode-array UV-vis spectrophotometer, Waldbronn, Germany).

The diffusion coefficient was estimated by fit to Higuchi equation (1960, 1961) (Eq. (5)):

$$\frac{Q}{A} = 2C_o \cdot \left(\frac{D_t}{\pi}\right)^{1/2} \tag{5}$$

where Q is the drug release amount (μg) at t time (s); A is the diffusion area (cm^2); C_o is the TH initial concentration in the samples (μg/ml); D is the diffusion coefficient (cm^2/s).

The optimum values for the release or diffusion parameters in each equation were determined by linear or non-linear least-squares fitting methods with SPSS 17.0 software. The corrected determination coefficient (r^2_{corr}) was used to test the applicability of the release/diffusion models.

Release and diffusion profiles were compared using similarity factor, f_2, calculated by the following equation (Eq. (6)):

$$f_2 = 50 \cdot \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0,5} \cdot 100\right\} \tag{6}$$

where R_t and T_t are the percentages released at each time point. An f_2 value between 50 and 100 implies similarity between two release profiles (Guidance for Industry, 1997).

3. Results and discussion

3.1. Synthesis and characterization

The polymer was synthesized by free radical copolymerization of methyl methacrylate (MMA) and hydroxypropyl cellulose (—HC—). It is constituted by two main subunits in the copolymer: one of them due to the hydroxypropyl cellulose and the other one due to the incorporation of methyl methacrylate into the sugar unit, with the cleavage of the C2—C3 bond in the glucose moiety (Fig. 1) (Mansour & Nagaty, 1985; Tosh & Routray, 2011). In this study we have used the total product, this means a mixture between HCMMA and PMMA (homopolymer). The reproducibility of the synthetic and drying processes were demonstrated by comparison of three batches of each product (data not shown). Once the reproducibility of the synthesis was established, the preparation in high extension of the copolymers was carried out.

The yields obtained for HCMMA are the following: %GE = 58.1 ± 0.4; %G = 126.3 ± 6.6. The low relative standard deviation values reported confirm the reproducibility of the synthesis and the high %G values in the final product indicate the hydrophobic character of the synthesized copolymer. Respect to the particle size characterization of polymer reveals a size of 154 μm (102), with leptokurtic and low symmetric distribution (Kurtosis coefficient 1.50 and skewness coefficient 1.25) in agree with its broad size dispersion. Moreover, microphotographs of individual particles show prismatic particles with smooth faces. Also, the polysaccharide has an apparent particle density of 1.223 g/cm^3 (0.0002), lower than values of commercial polymers.

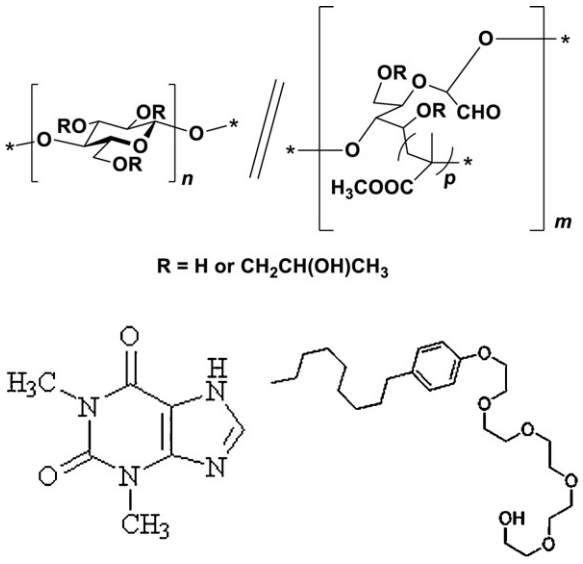

Fig. 1. Chemical structure of HCMMA, theophylline and Igepal® CO520.

3.2. Rheological characterization

Rheological properties of HCMMA-Igepal® CO520 were determined at 25 °C in a previous paper (Lucero et al., 2011). Due to the influence of temperature on the semisolid preparations with viscoelastic behavior and three-dimensional structure, now, we make these measures at 37 °C in order to correlate them with release and diffusion data at physiological conditions. Also, we can determine the influence of drug in the rheological structure of these systems. An example of viscosity curves of dispersions with and without TH at 37 °C is shown in Fig. 2a. All systems show shear-thinning fluids which means that viscosity decreases as the shear rate increases. The drug incorporation does not modify this behavior. In spite of this, in the systems with theophylline the plasticity grade slightly increases at deformation rates lower than 0.01 s^{-1} respect to the systems without the drug.

The shear-thinning behavior can be fitted to well within experimental error to Cross flow model (Medina-Torres, Brito-De La Fuente, Torrestiana-Sanchez, & Katthain, 2000) given by Eq. (7), taking into account that $\eta_0 \gg \eta_\infty$:

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

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. When m approaches zero, the liquid has Newtonian behavior. However, the majority shear-thinning liquids have a value of m approaching unity (Álvarez-Manceñido et al., 2006; Lucero et al., 2011; Rudraraju & Wyandt, 2005).

Table 1 shows the principal parameters of Cross model to the systems with and without TH. Both cases show good fit to this model ($r^2_{corr} = 0.910–0.997$). Also, all systems are shear-thinning fluids because displays m values near 1. In addition, it is possible to appreciate that η_0 increases when the SF concentration increases, only for the systems containing 1.5% (w/w) of TH. In the other three cases (0%, 0.5 and 1%, w/w TH), η_0 shows a decrease, that was at 22% of SF to 0 and 1% (w/w) of TH, and 23% (w/w) to 0.5% (w/w) of TH. However, the η_0 values from the systems with drug are, in general, lower than the corresponding values without TH. This indicates that TH promotes a different cross-linking of the three components which depends on SF concentration.

Fig. 2b shows an example of sweep frequency at 2 Pa. As both moduli (storage, G', and loss, G'') are practically independent of frequency applied and G' is higher than G'', our systems behave as gel (Alfaro, Guerrero, & Muñoz, 2000). Moreover, tan δ values corroborate the elastic predominant behavior of systems (tan $\delta < 1$), which can be explained by the higher cross-linking in the disperse systems (Lippacher, Müller, & Mäder, 2001; Torres, Iturbe, Snowden, Chowdhry, & Lehane, 2007).

However, the η^* values indicate very low viscosity (Table 2), especially with the preparations with drug. Also, G'' values were, in general, for the systems with TH lower than the corresponding with systems without drug. So, our preparations, in lineal viscoelastic conditions, are structured fluid disperse systems.

Moreover, similar sequences are possible to see for viscosity at shear rate 0 (η_0) (Table 1) and elasticity (G') data (Table 2). So, the values decrease until 23% (w/w) of SF to 0.5% of TH, and 22% (w/w) of SF to 1% of TH, but no decrease is observed to 1.5% (w/w) of TH. Furthermore, since 23% of SF, the G' values display the following sequence: 0.5% < 1% < 1.5%. This indicates that the systems with 1.5% (w/w) of TH are more structured and less fluids systems than the other formulations. All these results make think that the concentrations of surfactant and theophylline have influence on the final structure of the hydrophilic disperse systems.

The results can be explained as follows. Certain theophylline and surfactant concentrations are necessary to obtain high cross linking density. On the other hand, depending on the systems one of the two following structures predominates: "relaxed" (low number of cross-linking) and "structured" (high number of cross-linking). This hypothesis is based on the chemical structure of HCMMA, Igepal® CO520 and TH (Fig. 1). In all of them, hydrophobic groups exist corresponding to methyl methacrylate (HCMMA), imidazole ring and methyl groups (theophylline) and nonylphenyl ether (Igepal® CO520). The "relaxed" structure is characterized by weak, random

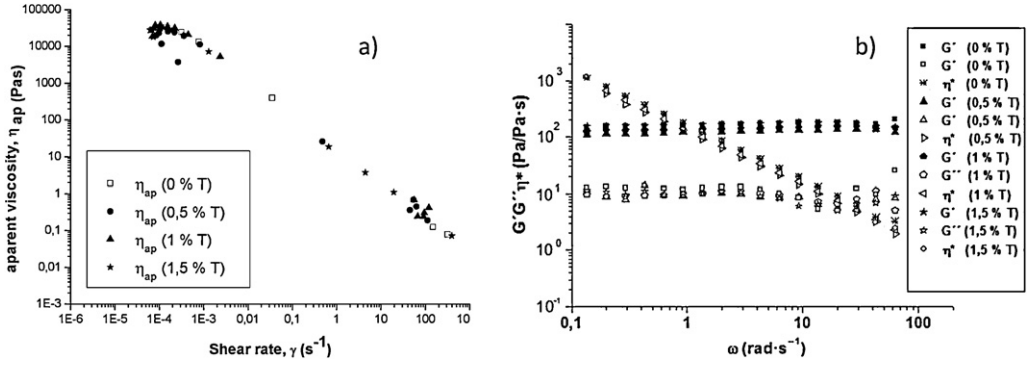

Fig. 2. Rheological properties of hydrophilic systems with HCMMA, Igepal® CO520 (22%, p/p) and theophylline (0, 0.5, 1 and 1.5%, w/w) at 37 °C: (a) viscosity curves, (b) storage modulus (G'), loss modulus (G'') and complex viscosity (η^*) in function of applied oscillatory frequency.

Table 1
Characteristic parameters of Cross model to different hydrophilic disperse systems with and without theophylline at 37 °C.

Igepal® CO520 (%)	0% theophylline		0.5% theophylline		1% theophylline		1.5% theophylline	
	η_0 (Pa s)	m	η_0 (Pa s)	m	η_0 (Pa s)	m	η_0 (Pa s)	m
20	56966	0.93	28511	0.95	40013	0.91	5862	0.98
21	75803	0.95	34395	0.95	44684	0.94	46995	0.91
22	61777	0.95	31100	0.95	18107	0.94	59944	0.99
23	60426	0.92	12780	0.97	18138	0.91	62529	0.91
24	157338	0.90	39973	0.95	35325	0.93	83845	0.81
25	98018	0.96	55816	0.91	66063	0.95	84816	0.99

Table 2
Elastic modulus (G'), viscous modulus (G'') and complex viscosity of the different hydrophilic disperse systems with and without theophylline at 37 °C and 1 Hz frequency.

Igepal® CO520 (%)	0% theophylline			0.5% theophylline			1% theophylline			1.5% theophylline		
	G' (Pa)	G'' (Pa)	η^* (Pa s)	G' (Pa)	G'' (Pa)	η^* (Pa s)	G' (Pa)	G'' (Pa)	η^* (Pa s)	G' (Pa)	G'' (Pa)	η^* (Pa s)
20	85.5	4.4	13.6	85.4	5.3	13.62	91.96	4.9	14.7	71.36	5.2	11.39
21	107.6	6.3	17.2	111.1	7.2	17.72	118	6.0	18.8	98.84	5.9	15.76
22	138.3	9.1	24.0	108.1	6.9	17.23	75.41	6.4	12.0	142.2	7.7	22.67
23	158.5	9.4	25.3	78.4	6.5	12.51	100.8	6.3	16.1	130	7.6	20.73
24	152.3	9.1	24.3	104	7.9	16.6	116	7.9	18.5	172.3	7.5	27.45
25	178.4	10.2	28.4	131.5	8.6	20.8	146.1	9.4	23.3	176.1	8.5	28.06

and temporary hydrophobic bonds between the three components. On the other hand, to obtain the structured systems is necessary the presence of high concentration of TH and/or surfactant that leads to a higher cross-linking on the gel. This is possible to see in Table 1 and 2 because the parameters η_0, G' and η^* are higher to the surfactant concentration 25% (w/w) than 20% (w/w), for all drug concentrations. However, the interaction polymer–surfactant has more influence in the viscosity of the preparation (Table 1). Moreover, the values for these three parameters increase following the sequence: 0.5% < 1% < 1.5% (w/w) TH, from 23% (w/w) of SF.

3.3. Drug release study

Release profiles of TH from hydrophilic disperse systems, using Enhancer Cell® device are shown in Fig. 3. This figure illustrates a faster drug release for systems containing 0.5% (w/w) of drug compared with the other two TH concentrations. The percent drug release at 24 h for the different formulations was between: 36–51% to 0.5% (w/w), 27–40% to 1% (w/w) and 28–30% to 1.5% (w/w) of drug, with very small standard deviations (data not show in the figures). Although not biopharmaceutical differences were found for the different formulations containing similar amount of drug ($f_2 > 50$), the profile similarities were higher for the concentration 1.5% (w/w) (f_2: 50–97.6 to 0.5% (w/w) of TH; 59.6–97.4% to 1% and 84.9–99.1 to 1.5% (w/w) of TH).

In relation with the surfactant concentration, the formulation containing 21% (w/w) of SF and 0.5% (w/w) of TH shows biopharmaceutical differences ($f_2 < 50$) with practically all the formulations containing 1 or 1.5% (w/w) of TH.

These results agree with rheological studies. Therefore, the higher percent release to 0.5% (w/w) of TH is due to the predominant relaxed structure. Moreover, the predominance of this structure in the formulations containing 20–22% of SF explains the higher variations observed in the release percent at 24 h. On the contrary, the formulations containing 1.5% (w/w) of TH have a structure more structured, that difficult the release of the drug.

On the other hand, it can be contradictory the higher drug release observed to the formulations containing 25% (w/w) respect to 24% (w/w) of SF, since the first one shows higher viscosity (Table 1). This can be explained because when the surfactant concentration increases, this takes the place of TH in its bonds with the polymer, leaving the drug free, and at the same time increasing the viscosity of the system.

Release data ($M_t/M_\infty < 0.6$) were analyzed according to Korsmeyer et al. (1983) and Peppas and Sahlin (1989) equations. The main parameters are listed in Table 3. As the samples under study presented an aspect ratio (diameter/thickness) around 2, the m value was 0.44 (Peppas & Sahlin, 1989). The corrected determination coefficient (r^2_{corr}) was used to test the applicability of the release models.

In general, all formulations show good fit to the different models ($r^2_{corr} = 0.968–1$), indicating a Fickian diffusion mechanism as predominant for all systems (Table 3). Moreover, the k_r values reject relaxation. In relation with diffusion coefficients, it is important to mention that, although all formulations have the same magnitude order (10^{-5}), systems containing 0.5% (w/w) of drug exhibit higher values (4.53×10^{-5}–9.63×10^{-5} cm^2/s) than the formulations with

Table 3
Mathematical modeling and drug release kinetics from different hydrophilic disperse systems.

Igepal® CO520 (%)	0.5% theophylline				1% theophylline				1.5% theophylline			
	n'	k (min)	k_d (min$^{-0.4}$)	k_r (min$^{-0.8}$)	n	k' (min)	k_d (min$^{-0.4}$)	k_r (min$^{-0.8}$)	n	k' (min)	k_d (min$^{-0.4}$)	k_r (min$^{-0.8}$)
20	0.47	0.010	0.013	0.000	0.52	0.010	0.012	0.000	0.52	0.007	0.009	0.000
21	0.49	0.013	0.016	0.000	0.54	0.009	0.010	0.000	0.52	0.007	0.009	0.000
22	0.53	0.009	0.006	0.000	0.59	0.008	0.009	0.000	0.51	0.008	0.009	0.000
23	0.56	0.009	0.008	0.000	0.56	0.008	0.008	0.000	0.48	0.008	0.010	0.000
24	0.52	0.009	0.008	0.000	0.52	0.007	0.008	0.000	0.44	0.007	0.010	0.000
25	0.60	0.011	0.009	0.000	0.58	0.009	0.008	0.000	0.50	0.008	0.010	0.000

k': Korsmeyer constant; k_d: diffusion constant; k_r: relaxation constant.

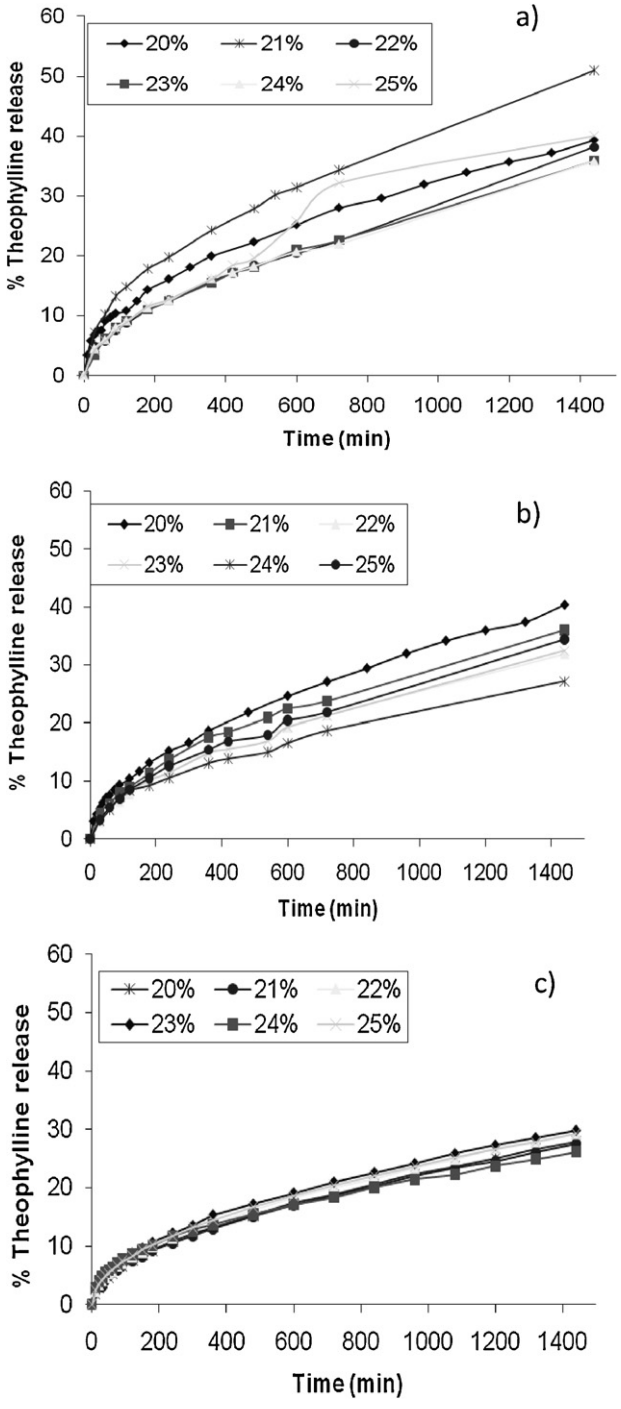

Fig. 3. Release profiles of theophylline from hydrophilic disperse systems containing HCMMA, Igepal® CO520 (20 and 25%, w/w) and the drug: (a) 0.5% (w/w), (b) 1% (w/w) and (c) 1.5% (w/w).

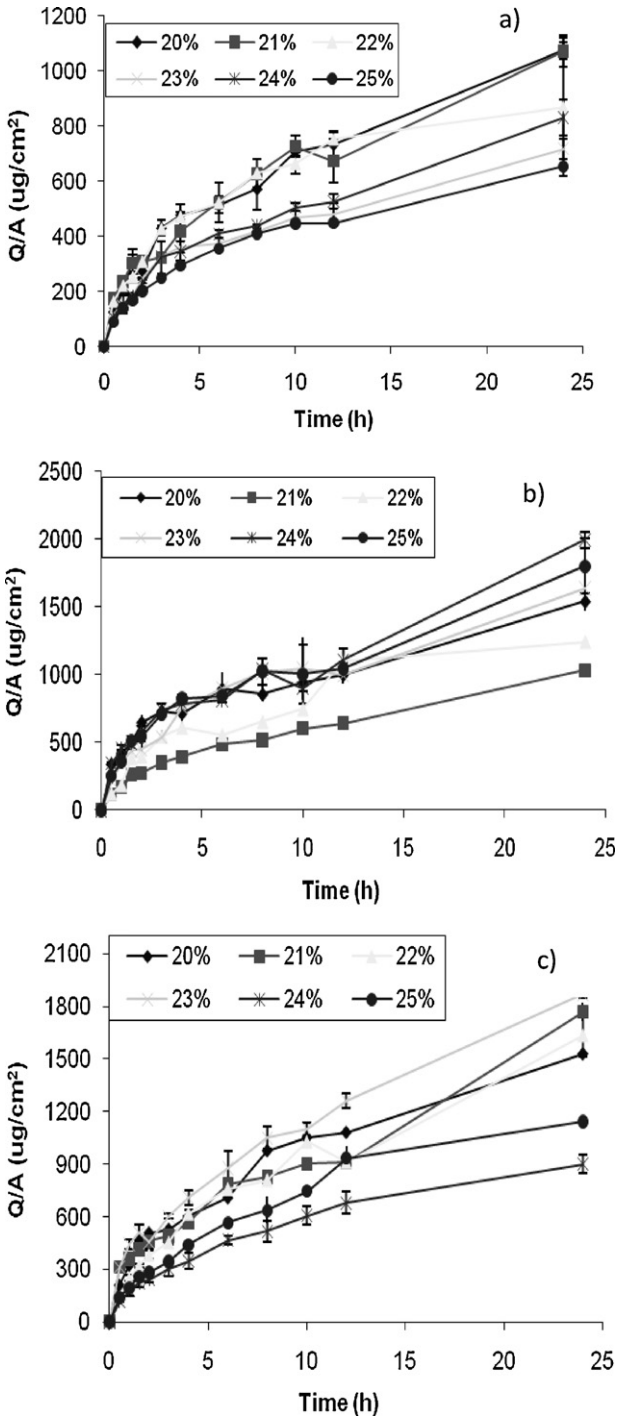

Fig. 4. Accumulate amount of theophylline by unity of surface from the different hydrophilic disperse systems containing HCMMA, Igepal® CO520 (20–25%, w/w) and the drug: (a) 0.5% (w/w), (b) 1% (w/w) and (c) 1.5% (w/w).

1.5% (w/w) (1.92×10^{-5}–2.71×10^{-5} cm^2/s) (data not shown). This agrees with the release percents mentioned before.

3.4. Diffusion studies

Drug diffusion properties from the semisolid preparations are necessary to the development of a topical formulation, as the release rate is limited by the drug diffusion (Lu & Jun, 1998). Also, the effect of different excipients has been studied in the release and retention of drug by the skin to optimize the formulations (Chambin-Remoussenard, Treffel, Bechte, & Agache, 1993; Hilton et al., 1994). For this reason, we have made the diffusion study in the formulations with and without HCMMA. So, Fig. 4 illustrates the accumulate amount of TH by unity of surface from the different hydrophilic disperse systems.

Biopharmaceutical differences were found for all diffusion profiles ($f_2 < 50$), showing different behavior depending on the formulation. This result confirms the criticisms mentioned before made by different authors respect to the Franz diffusion cells (Addicks et al., 1988; Chattaraj & Kanfer, 1995). Also, worse fit to the kinetic model was obtained in the diffusion study with Franz

Table 4
Drug diffusion kinetics and diffusion coefficient values from different hydrophilic disperse systems with HCMMA.

Igepal® CO520 (%)	0.5% theophylline			1% theophylline			1.5% theophylline		
	k ($min^{-1/2}$)	D (cm^2/s)	r^2_{corr}	k ($min^{-1/2}$)	D (cm^2/s)	r^2_{corr}	k ($min^{-1/2}$)	D (cm^2/s)	r^2_{corr}
20	0.068	1.48×10^{-3}	0.988	0.044	6.08×10^{-4}	0.955	0.030	3.41×10^{-4}	0.987
21	0.067	1.41×10^{-3}	0.986	0.032	3.24×10^{-4}	0.990	0.033	3.52×10^{-4}	0.948
22	0.059	1.11×10^{-3}	0.967	0.041	5.4×10^{-4}	0.939	0.035	3.81×10^{-4}	0.978
23	0.044	6.28×10^{-4}	0.979	0.051	8.33×10^{-4}	0.979	0.038	4.66×10^{-4}	0.990
24	0.052	8.54×10^{-4}	0.989	0.055	9.7×10^{-4}	0.937	0.020	1.27×10^{-4}	0.996
25	0.042	5.67×10^{-4}	0.993	0.053	8.97×10^{-4}	0.969	0.026	2.17×10^{-4}	0.984

k: Higuchi constant.

diffusion cells ($r^2_{corr} = 0.937–0.996$) than in the release ones using Enhancer® cells. The predominant mechanism is Fickian diffusion (Table 4), although it is possible to see some relaxational contribution of gel structure (k_r). The diffusion coefficient values (Table 4) agree with the diffusion profiles observed in Fig. 4 for each TH concentration studied.

With the aim to compare, we calculated the diffused drug percentage at 8 h with and without HCMMA in the formulations (data not shown). TH percentage diffused was, in general, similar or a little higher for the formulations containing HCMMA (5.4–19.7%) than for systems without HCMMA (7.1–15.8%). Therefore, this could indicate that our polymer do not control the release of theophylline. However, our polymer is necessary to obtain the gel structure because the absence of HCMMA provides a liquid disperse system. So, the diffusion control in the formulation with HCMMA is made by a three-dimensional structure, whereas in the formulation without this polymer is by micelle structure (Claro et al., 2008).

4. Conclusions

This study confirms the utility of HCMMA in the hydrophilic disperse systems containing also Igepal® CO520 (20–25%, w/w) and theophylline (0.5, 1 and 1.5%, w/w) to make three-dimensional gel structure and to control theophylline release from these topical systems. From a rheological point of view, all systems are shear-thinning fluids. However, two different structures have been observed: "relaxed" (characterized by weak, random and temporary hydrophobic bonds between polymer–surfactant–drug) and "structured". The presence of high concentration of TH and/or surfactant is necessary to obtain structured systems. So, an inflexion point, detected to zero-shear rate viscosity, elasticity modulus and complex viscosity, determines the structure change from relaxed to structured. In agree with this, higher drug release and diffusion coefficient are obtained to 0.5% (w/w) than 1.5% (w/w) of the drug, due to the predominant relaxed structure of the first one. All formulations show Fickian diffusion as predominant mechanism.

Respect to the different devices used for drug release and diffusion, it has been obtained more reliable and reproducible results with Enhancer Cell® device than with Franz diffusion cell due to a better monitorization and control of the different variables. So, biopharmaceutical differences were found for all the diffusion profiles with HCMMA ($f_2 < 50$), showing different behavior depending on the formulation. Also, worse fit to the different kinetics models were found in Franz diffusion cell respect to Enhancer Cell®.

For further studies, correlating in vitro and in vivo results would be interesting in order to verify the ability of this new hydrophobically modified polysaccharide to control drug release in humans too.

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