BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902022e20803

Article

Influence of additives on swelling and mucoadhesion properties of glyceryl monooleate liquid crystals

Ana Beatriz Cintra[1], Lariani Aparecida Delboni[1], Marilisa Guimarães Lara[1]*

[1]School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, SP, Brazil

Liquid crystalline systems of glyceryl monooleate/water are used as drug delivery systems due to their complex structure that controls drug diffusion. Mucoadhesive properties of glyceryl monooleate suggest it can be used for buccal delivery. Using additives is a strategy to modify physical and chemical properties of liquid crystalline systems and optimize their performance as a drug delivery system. However, the presence of additives can significantly alter properties such as phase behavior, swelling and mucoadhesion. Our aim is to investigate the influence of additives on swelling and mucoadhesion of glyceryl monooleate-based liquid crystals, intending them to be used as buccal drug delivery systems. The systems were characterized regarding their mesophases, swelling rate, and mucoadhesion. All the systems studied were able to absorb water and presented mucoadhesion, which is interesting for the development of buccal drug delivery systems. Additives induced phase transitions and affected the swelling performance, while mucoadhesive properties were poorly affected. Propylene glycol increased water uptake, while oleic acid induced the phase transition to the hexagonal phase and reduced the swelling rate. The association of oleic acid (5%) and propylene glycol (10%) resulted in a cubic phase system with strong mucoadhesive properties that can be a potential drug carrier for buccal delivery.

Keywords: Glyceryl monooleate. Liquid crystals. Drug delivery. Swelling. Mucoadhesion. Buccal drug delivery.

INTRODUCTION

Liquid crystalline systems of glyceryl monooleate (GMO) have been proposed as delivery systems for several drugs and routes of administration. Their complex matrix structure can control drug delivery and their amphiphilic nature allows the incorporation of both hydrophilic and lipophilic drugs. Moreover, these systems present mucoadhesion that increases the contact time at the application site. These properties suggest liquid crystalline systems as interesting candidates for drug delivery technology (Shah, Sadhale, Chilukuri, 2001; Boyd *et al*., 2006; Guo *et al*., 2010; Phan *et al*., 2011; Zabara, Mezzenga, 2014; Bisset, Boyd, Dong, 2015; Milak, Zimmer, 2015; Rajabalaya *et al*., 2017; Esposito *et al*., 2018; Wang *et al*., 2018).

Using additives is a strategy to modify physical and chemical properties of liquid crystalline systems, which consequently optimize their performance as a delivery system for a particular drug or route of administration. Thus, incorporating additives with different polarities into liquid crystalline systems can affect the packing parameters of self-assembled lipid systems and alter their phase behavior. These changes can be expressed as phase transitions or variations in the lattice diameter or channel size of liquid crystalline systems and affect properties such as viscosity, spreadability, thermal stability, drug release or drug permeation and mucoadhesion. Therefore, these changes influence the performance of a liquid crystalline system. In general, hydrophilic additives induce phase transitions to lamellar phases while lipophilic compounds are inserted among lipid tails, disturb mesophase packing, increase the apparent hydrophobic chain volume of lipids,

***Correspondence:** M. G. Lara. Faculdade de Ciências Farmacêuticas de Ribeirão Preto. Universidade de São Paulo. Av do café S/N, Monte Alegre. 14.040-903, Ribeirão Preto, SP, Brazil. Phone: 55-16-33154885. E-mail: mlara@fcfrp.usp.br. ORCID: https://orcid.org/0000-0002-7411-5762

and reduce the lattice parameter. These changes induce the formation of cubic and hexagonal phases (Chang, Bodmeier, 1997; Lee, Kellaway, 2000; Sallam *et al*., 2002; Shah, Paradkar, 2007; Libster, Aserin, Garti, 2011; Phan *et al*., 2011; Madheswaran *et al*., 2013; Bisset, Boyd, Dong, 2015; Wang *et al*., 2018; Li *et al*., 2018).

We previously studied GMO/water systems containing propylene glycol (PG) and oleic acid (OA) additives, either alone or in combination, for skin delivery of the anti-inflammatory drug celecoxib (Dante *et al*., 2018). An association of these additives has resulted in a very interesting skin delivery system to modulate celecoxib release and permeation (Dante *et al*., 2018). Considering this, we propose to study their potential as a drug delivery system for other routes of administration, such as buccal drug delivery.

The development of buccal drug delivery systems requires evaluating of the swelling and mucoadhesive properties, as well as the phase behavior and drug delivery. Swellable systems may absorb water upon contact with saliva in the oral cavity and mucoadhesion can increase the contact time between formulation and oral mucosa. GMO presents good mucoadhesive properties (Dash *et al*., 1999; Lee, Young, Kellaway, 2001) and therefore GMO based liquid crystalline systems are good candidates for vehicle drugs for buccal delivery. Furthermore, these systems are nontoxic, biodegradable and they can be easily applied at the buccal mucosa (Lee, Kellaway, 2000; Norling *et al*., 1992; Esposito *et al*., 1996; Nielsen, Schubert, Hansen, 1998; Okonogi, 2004; Souza *et al*., 2014; Nunes *et al*., 2016). However, the presence of additives can significantly alter the phase behavior and system properties, including swelling and mucoadhesion. Consequently, these properties must always be evaluated whenever polar and nonpolar compounds are added.

Our objective is to study the influence of additives on swelling and mucoadhesion of GMO liquid crystals, aiming to use them as buccal drug delivery systems. Here we examined the behavior of GMO/water liquid crystalline systems containing OA and PG by focusing on the determination of swelling and mucoadhesion that are relevant properties for buccal delivery to investigate the influence of the additives on these properties.

MATERIAL AND METHODS

The glyceryl monooleate (GMO) used was a commercial preparation of monoglycerides derived from canola oil (Myverol 18-99) provided by Kerry do Brasil (Campinas, São Paulo, Brazil). Propylene glycol (PG) was obtained from Labsynth® (Diadema, SP, Brazil) and oleic acid (OA) was acquired from Sigma-Aldrich (St. Louis, MO, USA). All the other chemicals were of analytical grade.

Preparation of liquid crystalline systems of GMO and water

The systems were prepared by melting GMO at 40 ºC followed by adding water at the same temperature. For the systems containing additives, OA was added to molten GMO while PG was added to the aqueous phase due to their solubility. The systems were maintained at room temperature for 24 hours to reach equilibrium. The lamellar phase was obtained at the GMO/water ratio of 90:10 (**GMO-W (90:10)**), while the cubic phase was obtained at a 70:30 ratio (**GMO-W (70:30)**). PG and OA were added to the cubic phase (Table I) while the GMO/water ratio was kept constant.

The phase behavior was analyzed by polarizing light microscopy using the Eclipse E200 light microscope (Nikon) fitted to polarizing filters. Photomicrographs were acquired using a Moticam 2000 digital camera and the automatic image acquisition system called Motic Image Plus 2.0.

TABLE I – Composition of liquid crystalline systems containing additives

System	Composition (%, w/w)		
	GMO/water (70:30)	OA	PG
GMO-W (70:30)	100%	0	0
GMO-W (70:30)/OA	95%	5%	0
GMO-W (70:30)/PG(5)	95%	0	5%
GMO-W (70:30)/PG(10)	90%	0	10%

TABLE I – Composition of liquid crystalline systems containing additives

System	Composition (%, w/w)		
	GMO/water (70:30)	OA	PG
GMO-W (70:30)/OA/PG(5)	90%	5%	5%
GMO-W (70:30)/OA/PG(10)	85%	5%	10%

GMO-W: glyceryl monooleate/water system; OA: oleic acid; PG: propylene glycol.

Swelling studies

Water uptake by the liquid crystalline systems was determined gravimetrically after immersion in excess of liquid. The immersion media used was artificial saliva that is a solution of salts to mimic saliva containing potassium chloride (0.625g), sodium chloride (0.865g), magnesium chloride (0.058g), calcium chloride (0.166g), potassium hydrogenphosphate (0.803g), potassium dihydrogenphosphate (0.326g), sorbitol 70.0% (42.75g) and methylparaben (2.0g) to 1000.0mL of water (adapted from Nakamoto, 1979). No flavors, dyes and thickeners were added. Samples of the liquid crystalline systems (1.0 g) were placed on cylindrical supports fitted to cellulose acetate membranes and immersed in artificial saliva, at 37°C. At defined time intervals (1, 2, 3, 4, 5, 6 and 24 hours) the samples were removed from the immersion media and weighed. Water uptake was determined as the increase in weight of the sample over time normalized to the initial weight of the dry systems. All the measurements were recorded under ambient conditions (n=3).

The water uptake data were subjected to mathematical models in order to characterize the kinetic of swelling (Schott, 1992). Swelling data were plotted according to first and second-order kinetics equations 1 and 2, respectively:

$$\ln \frac{W_\infty}{W_\infty - W} = kt \quad \text{(Equation 1),}$$

$$\frac{t}{W} = \frac{1}{kW_\infty{}^2} + \frac{t}{W_\infty} \quad \text{(Equation 2),}$$

where $W\infty$ is the maximum water uptake, W is the water uptake at a time t, ($W\infty$–W) is the unrealized water uptake, and k is the proportionality constant. For the second-order kinetics, the reciprocal of the slope indicates $W\infty$, which is the maximum or equilibrium water uptake (Souza *et al*., 2014; Schott, 1992).

Mucoadhesion studies

Mucoadhesive properties were evaluated by determining the maximum detachment force (F_{max}) using a Texture Analyser TA.XT Plus (Stable Micro Systems) and natural mucosa (pig buccal cheek). Mucosa from freshly slaughtered healthy pigs was purchased from the *Frigoríficos Olhos D'agua Indústria e Comércio de Carnes Ltda* slaughterhouse (Ipuã, São Paulo, Brazil), cut into small strips, immediately frozen (−22°C), and stored for up to one month prior to use. Samples of the systems (0.4 g) were placed into a cylindrical probe for semisolid analysis (upper probe). Segments of mucosa were fixed on plexiglass discs using cyanoacrylate adhesive, which were attached to the lower platform of the equipment. The mucosa was hydrated with 300 µL of artificial saliva prior to the mucoadhesion testing. Then, the upper probe was lowered at a defined speed (0.1 mm/s) until the contact between samples and mucosa was established. A contact force of 1.0 N was applied for 5 minutes to ensure close contact between the systems and the mucosa. Next, the probe was withdrawn at a constant speed of 1 mm.s^{-1} and the force required for detachment was determined from the resulting force-distance plot. Sample systems and mucosa were used once, and the analysis was performed in triplicate. F_{max} (N) was automatically recorded by the software Exponent for XT Plus from the force-distance plot.

RESULTS AND DISCUSSION

Additives such as solubilizers and permeation enhancers can be used to modulate drug release and permeation through natural membranes and optimize drug delivery. Their presence can affect the phase behavior and properties such as drug release, swelling and mucoadhesion. In this study, we investigated the

influence of OA and PG on GMO/water liquid crystalline system properties.

GMO-W (70:30) was isotropic at polarizing light microscopy and exhibited the macroscopic aspect of the cubic phase, as expected**. GMO-W (90:10)**, **GMO-W (70:30)/PG(5)** and **GMO-W (70:30)/PG(10)** presented the texture of the lamellar phase, while **GMO-W (70:30)/OA** presented the hexagonal phase. Representative photomicrographs of the phases of the liquid crystalline systems, identified by polarizing light microscopy, are depicted in Figure 1. These results corroborate reported data that indicate that hydrophilic additives such as PG favor the formation of lamellar phases while lipophilic additives, such as OA favor the formation of cubic and hexagonal phases (Milak, Zimmer, 2015; Rajabalaya *et al*., 2017; Wang *et al*., 2018; Chang, Bodmeier, 1997; Shah, Paradkar, 2007; Lopes *et al*., 2006; Alfons, Engström, 1998; Merclin *et al*., 2004; Bender *et al*., 2005; Bender *et al*., 2008; Peng *et al*., 2010).

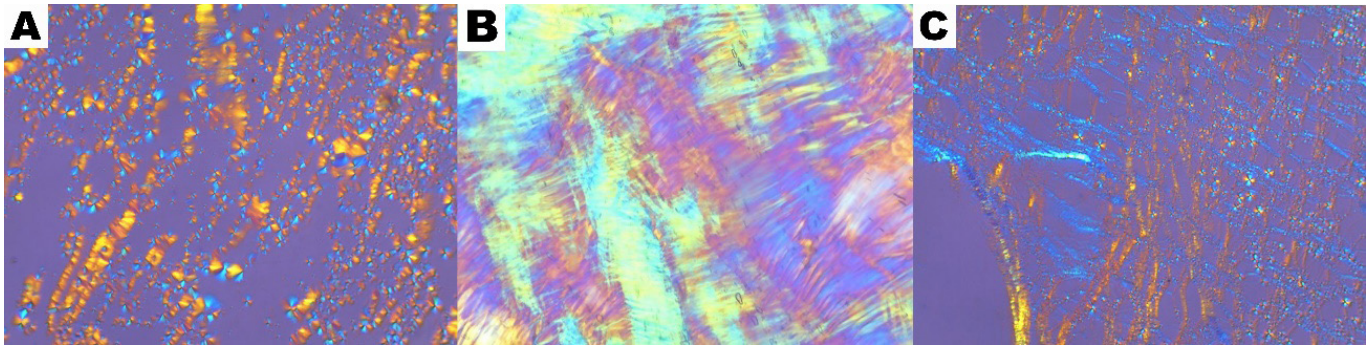

FIGURE 1 - Representative photomicrographs of the liquid crystalline systems containing or not additives, after 24 hours of equilibrium: A-) **GMO-W (90:10),** B-) **GMO-W (70:30)/OA,** C-) **GMO-W (70:30)/PG(10**). Glyceryl monooleate (GMO), water (W), oleic acid (OA), propylene glycol at 10% (PG10).

PG is a hydrophilic compound that can be added to GMO/water systems to act as a solubilizer or to partition into water channels and widen their size. PG induces phase transitions to the lamellar phase in a concentration-dependent manner and to the sponge phase at high loads (Li *et al*., 2018; Alfons, Engström, 1998; Merclin *et al*., 2004; Bender *et al*., 2005; Bender *et al*., 2008; Peng *et al*., 2010). OA is a lipophilic additive widely used as a permeation enhancer for natural membranes. Adding OA to GMO/water systems induces phase transitions from cubic to hexagonal phases (Wang *et al*., 2018; Chang, Bodmeier, 1997; Shah, Paradkar, 2007; Lopes *et al*., 2006). Incorporating different triglycerides induce a phase transition to the hexagonal phase in GMO/water liquid crystals (Libster, Aserin, Garti, 2011). A delicate interplay between lipid packing and the presence of salts has been reported with changes in the mesophases and lattice parameter of liquid crystals (Brasnett *et al*., 2017). Adding OA has changed molecular packing and phase behavior of phytantriol cubic phases, while the association of OA and sucrose stearate affects the lattice parameter and the size of water channels in a pH-dependent manner (Bisset, Boyd, Dong, 2015). The effect of a guest molecule on the microstructure of liquid crystalline systems seems to be dependent on the polar or nonpolar nature of the molecule. Our results corroborate the effects of lipophilic OA and hydrophilic PG on the studied systems, and therefore we have investigated the association of these additives.

GMO-W (70:30)/OA/PG(10) was isotropic with a macroscopic aspect of the cubic phase. Adding both OA (5.0% w/w) and PG (5.0 and 10.0% w/w) to **GMO-W (70:30)** was carefully studied by Small Angle X-ray Scattering (SAXS) and the results were reported in a

previous study (Dante *et al*., 2018). Briefly, **GMO-W (70:30)/OA/PG(5)** comprised both the hexagonal and cubic phases (2 diamond-type cubic phase); adding of 10.0% (w/w) of PG to form the **GMO-W (70:30)/OA/PG(10)** system induced a total phase transition to the cubic phase (2 diamond-type cubic phase (Pn3, space group) (Dante *et al*., 2018).

Swelling studies are important to characterize liquid crystalline systems because water uptake can affect their self-assembly and *in situ* gelling properties, which can impact their drug release and mucoadhesive properties (Shah, Paradkar, 2007; Nunes *et al*., 2016). The results from the swelling studies were expressed as a percentage of water uptake as a function of time (Figure 2). The liquid crystalline systems studied presented a rapid water uptake followed by an equilibrium state in agreement with similar results reported (Nunes *et al*., 2016; Rizwan *et al*., 2009). The lamellar phase system **GMO-W (90:10)** presented higher water uptake than the cubic phase system **GMO-W (70:30)**, as expected. Lamellar phases usually absorb more water than cubic phases: in contact with an excess of water, GMO/water systems absorb water until the water content equilibrium is reached; then, they undergo phase transitions to the cubic phase, which is stable in an excess of water. In general, systems with low water content such as lamellar phases uptake water and reach equilibrium quickly; in contrast, cubic phases are almost fully hydrated due to their high initial water content and present high viscosity, which are limiting factors for water uptake (Chang, Bodmeier, 1997; Rizwan *et al*., 2009).

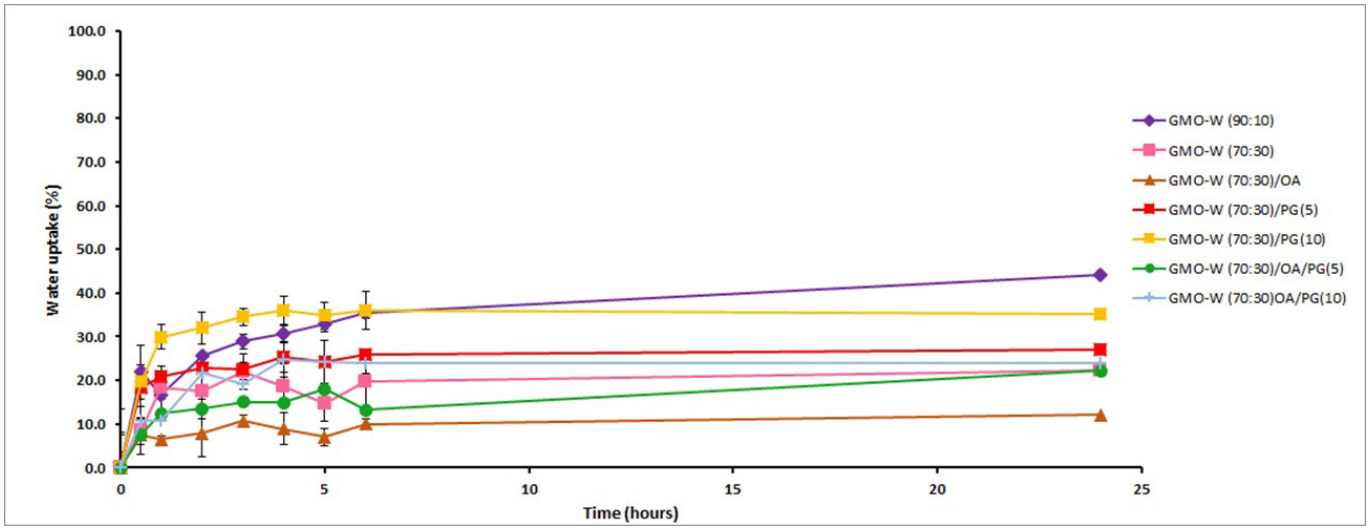

FIGURE 2 – Water uptake (%) by liquid crystalline systems immersed in artificial saliva (n = 4). Water uptake was determined gravimetrically after immersion in excess of artificial saliva and expressed as the increase in weight of the sample over time normalized to the initial weight of the dry systems. Glyceryl monooleate (GMO), water (W), oleic acid (OA), propylene glycol at 5% (PG5), propylene glycol at 10% (PG10).

To examine how additives affected the swelling performance of liquid crystalline systems, PG and OA were added to a selected cubic phase system: **GMO-W (70:30)**. Compared with the PG-free system, an addition of PG increased water uptake probably due to its hydrophilic nature and its ability to induce the phase transition to the lamellar phase. It was also observed that the water uptake rate increased with the PG content.

The swelling performance of pure GMO matrices in the presence of drugs and/or additives has already been investigated (Shah, Paradkar, 2007; Kumar *et al*., 2004). It is known that the swelling rate increases linearly with the hydrophilicity of drugs and/or additives (Shah, Paradkar, 2007). Therefore, the load of polar drugs enhances water uptake while the load of non-polar drugs impairs water uptake, probably due to the mesophases formed in the presence of such drugs. In general, the addition

of hydrophilic drugs to GMO favors the formation of lamellar phases and increases water uptake, while adding lipophilic drugs favors the formation of cubic and hexagonal phases. When the formation of the cubic phase is induced by the presence of lipophilic additives, the liquid crystalline system absorbs less water, and consequently it has a weak swelling performance (Shah, Paradkar, 2007; Kumar *et al.*, 2004).

Our finding that adding the hydrophilic PG additive to GMO/water systems increased water uptake agrees with the data in the literature that was mentioned previously. In addition, after adding OA, the decreased water uptake can be related to the phase transition to the hexagonal phase that it induced, as well as to its hydrophobic nature.

Compared with liquid crystalline systems containing only PG, systems containing both PG and OA exhibited weaker water uptake because the association of these additives induced the phase transition to the cubic phase, which usually presents a low water uptake rate. However, when compared to the system containing only OA, the presence of hydrophilic PG increased water uptake. These results suggest that the impact of additives on water uptake by liquid crystalline systems was closely related to the way that they interfered with the system mesophase.

The kinetic analysis of swelling data (Figure 3 and Table II) showed evidence that all the systems presented second-order linearity, as the plots of t/W versus t resulted in a linear relationship, according to Equation 2. Correlation coefficients and calculated maximum water uptake (W_∞) are presented in Table II. These results indicate that the presence of the PG and OA additives did not alter the swelling kinetics of the liquid crystalline systems. Several authors have reported that GMO/water liquid crystalline systems usually follow second-order kinetics (Souza *et al.*, 2014; Rizwan *et al.*, 2009; Lee *et al.*, 2003; Lara, Bentley, Collett, 2005). According to this model, stress relaxation forces during swelling are relevant to the overall process of water uptake, as swelling initially occurs due to diffusion and stress relaxation, but relaxation becomes the dominant mechanism when swelling progresses (Souza *et al.*, 2014; Schott, 1992).

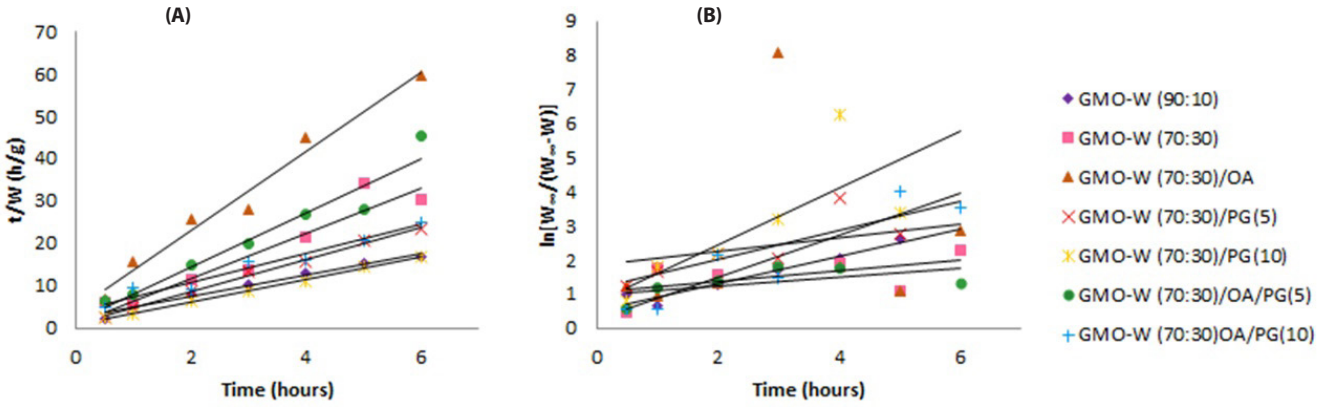

FIGURE 3 – Swelling isotherms of liquid crystalline systems according to: (A) the second-order kinetics (Equation 2) and (B) the first-order kinetics (Equation 1). Swelling data were obtained from Figure 1. $W\infty$ is the maximum water uptake, W is the water uptake at a time t, ($W\infty$–W) is the unrealized water uptake (Schoot, 1992). Glyceryl monooleate (GMO), water (W), oleic acid (OA), propylene glycol at 5% (PG5), propylene glycol at 10% (PG10).

TABLE II - Kinetic parameters from swelling studies

System	Linear correlation coefficient		Maximum water uptake W∞ (g/g)
	First-order model	Second-order model	
GMO-W (90:10)	0.9390	0.9759	0.3966
GMO-W (70:30)	0.2919	0.9134	0.1873
GMO-W (70:30)/OA	0.9402	0.9961	0.9016
GMO-W (70:30)/PG(5)	0.6600	0.9952	0.2649
GMO-W (70:30)/PG(10)	0.5921	0.998	0.3814
GMO-W (70:30)/OA/PG(5)	0.3183	0.9400	0.1570
GMO-W (70:30)/OA/PG(10)	0.8567	0.9605	0.2938

Linear correlation coefficients were calculated according to first- and second-order kinetic models.

The maximum water uptake was expressed as *g* of immersion media absorbed per *g* of the liquid crystalline system.

The results from mucoadhesion studies expressed as maximum detachment force (F_{max}) are presented in Figure 4. **GMO-W (90:10)** (lamellar phase) and **GMO-W (70:30)** (cubic phase) displayed the highest and the lowest F_{max} values, indicating that they had the strongest and the weakest mucoadhesion, respectively. Our findings corroborate the reports that mucoadhesion of GMO-based liquid crystalline systems can be related to their mesophase and water uptake capacity (Dash *et al*., 1999; Lee, Young, Kellaway, 2001; Souza *et al*., 2014). GMO absorbs water and undergoes phase transitions from the lamellar to the cubic phase (Dash *et al*., 1999) when in contact with an excess of water. Lamellar phases with low initial water content have better mucoadhesive properties than fully swollen cubic phases and can be used as precursors for *in situ* formation of cubic phases (Lee, Young, Kellaway, 2001; Nielsen, Schubert, Hansen, 1998). These systems are preferred for mucosal drug delivery and can therefore be used as a reference. There is a quantitative relationship between the maximum detachment force and initial water content that drives water uptake in GMO/water systems (Lee, Young, Kellaway, 2001). It is reported that GMO mucoadhesion depends on water uptake and this process probably occurs through the substrate dehydration (Dash *et al*., 1999; Lee, Young, Kellaway, 2001; Nielsen, Schubert, Hansen, 1998; Souza *et al*., 2014). According to this theory, materials that absorb water and gelify in an aqueous environment can dehydrate mucous membranes; the resulting water movement consolidates the adhesive bond instead of causing interpenetration of macromolecular chains such as polymeric systems. The GMO/water systems presenting cubic phases had poor mucoadhesive properties due to their fully swollen state and consequent poor water uptake capacity (Dash *et al*., 1999; Lee, Young, Kellaway, 2001; Nielsen, Schubert, Hansen, 1998; Smart, 2005; Carvalho *et al*., 2010).

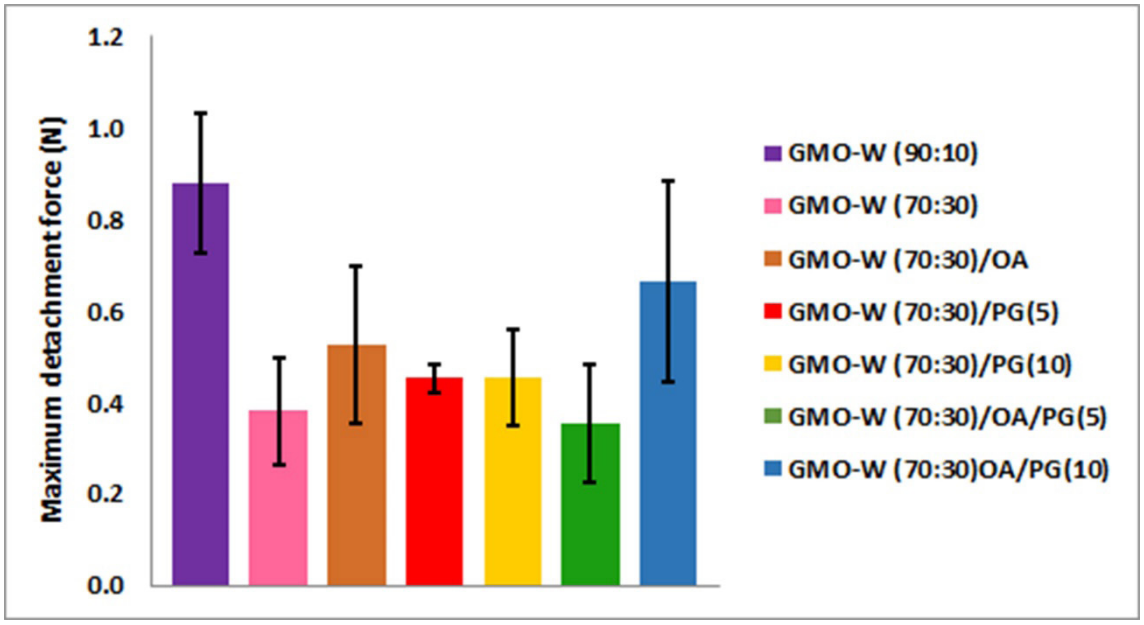

FIGURE 4 – Maximum detachment force (F_{max}) of liquid crystalline systems obtained using a Texture Analyser TA.XT Plus (Stable Micro Systems) and pig buccal cheek (n=3). Glyceryl monooleate (GMO), water (W), oleic acid (OA), propylene glycol at 5% (PG5), propylene glycol at 10% (PG10).

We investigated if the presence of additives would modify swelling and mucoadhesive properties of liquid crystalline systems. A comparison between F_{max} values of the system without additives (**GMO-W 70:30)** and systems containing additives suggests that mucoadhesion was little affected by the presence of these compounds despite changes in the mesophase and water uptake. In the presence of additives, the relation between water uptake and mucoadhesion was not so clear. This influence was more significant in the **GMO-W (70:30)/OA/PG10,** which presented an intermediate value of F_{max} between the lamellar and the cubic phase. This finding is relevant because this association yielded a cubic phase system, as confirmed by SAXS analysis (Dante *et al*., 2018), but it had stronger mucoadhesion than the cubic phase system formed without additives.

It is important to note that cubic phase systems present interesting properties to be used as drug delivery systems, such as stability in contact with water and ability to sustain drug release due to their particular internal structure. However, fully hydrated cubic systems present poor mucoadhesion, as discussed before. Adding OA and PG at the concentrations tested here was an effective strategy to obtain cubic phase systems with stronger mucoadhesion, which may help to develop drug delivery systems intended for mucosal delivery of drugs. The same formulation (**GMO-W (70:30)/OA/PG10**) effectively modulated the release and permeation of celecoxib through the skin (Dante *et al*., 2018). In the present study, this system presented a good performance as a mucoadhesive delivery system. Taken together these results indicate that **GMO-W (70:30)/OA/PG10**) is a potential carrier for buccal delivery of drugs, combining drug release, drug permeation and mucoadhesion properties.

This study characterized the swelling and mucoadhesive properties of GMO/water systems containing additives that can carry drugs to be used as buccal drug delivery systems. All the systems studied were able to absorb water and presented mucoadhesive properties. Addition of OA and PG induced phase transitions that affected the type of mesophases of the GMO/water systems and their swelling, while mucoadhesive properties were only slightly affected. PG increased water uptake, while OA induced the phase transition to the hexagonal phase and reduced water uptake. An association of OA (5.0% w/w) and PG (10.0% w/w) resulted in a cubic phase system with strong

mucoadhesive properties that could be a potential carrier for buccal drug delivery. In addition, the solubilizing effect of PG and the permeation enhancer effect of OA could improve drug release and permeation, and therefore contribute to the drug delivery performance of this liquid crystalline system.

ACKNOWLEDGMENTS

University of São Paulo (USP), National Council for Scientific and Technological Development (CNPq) for finantial support

REFERENCES

Alfons K, Engström S. Drug compatibility with the sponge phases formed in monoolein, water, and propylene glycol or poly(ethylene glycol). J Pharm Sci. 1998;87(12):1527–30.

Bender J, Ericson MB, Merclin N, Iani V, Rosén A, Engström S, et al. Lipid cubic phases for improved topical drug delivery in photodynamic therapy. J Controlled Release. 2005;106(3):350–60.

Bender J, Jarvoll P, Nydén M, Engström S. Structure and dynamics of a sponge phase in the methyl delta-aminolevulinate/monoolein/water/propylene glycol system. J Colloid Interface Sci. 2008;317(2):577–84.

Bisset NB, Boyd BJ, Dong Y. Tailoring liquid crystalline lipid nanomaterials for controlled release of macromolecules. Int J Pharm. 2015;495(1):241–8.

Boyd BJ, Whittaker DV, Khoo S-M, Davey G. Lyotropic liquid crystalline phases formed from glycerate surfactants as sustained release drug delivery systems. Int J Pharm. 2006;309(1-2):218–26.

Brasnett C, Longstaff G, Compton L, Seddon A. Effects of cations on the behaviour of lipid cubic phases. Sci Rep. 2017;7:8229.

Carvalho FC, Bruschi ML, Evangelista RC, Gremião MPD. Mucoadhesive drug delivery systems. Brazilian J Pharm Sci. 2010;46(1):1–17.

Chang C-M, Bodmeier R. Effect of dissolution media and additives on the drug release from cubic phase delivery systems. J Controlled Release. 1997;46(3):215–22.

Dante M de CL, Borgheti-Cardoso LN, Fantini MC de A, Praça FSG, Medina WSG, Pierre MBR, et al. Liquid crystalline systems based on glyceryl monooleate and penetration enhancers for skin delivery of celecoxib: characterization, in vitro drug release, and in vivo studies. J Pharm Sci. 2018;107(3):870–8.

Dash AK, Gong Z, Miller DW, Huai-Yan H, Laforet JP. Development of a rectal nicotine delivery system for the treatment of ulcerative colitis. Int J Pharm. 1999;190(1):21–34.

Esposito E, Carducci F, Mariani P, Huang N, Simelière F, Cortesi R, et al. Monoolein liquid crystalline phases for topical delivery of crocetin. Colloids Surf B. 2018;171:67–74.

Esposito E, Carotta V, Scabbia A, Trombelli L, D'Antona P, Menegatti E, et al. Comparative analysis of tetracycline-containing dental gels: Poloxamer- and monoglyceride-based formulations. Int J Pharm. 1996;142(1):9–23.

Guo C, Wang J, Cao F, Lee RJ, Zhai G. Lyotropic liquid crystal systems in drug delivery. Drug Discov Today. 2010;15(23-24):1032–40.

Kumar M. K, Shah MH, Ketkar A, Mahadik KR, Paradkar A. Effect of drug solubility and different excipients on floating behaviour and release from glyceryl monooleate matrices. Int J Pharm 2004;272(1-2):151–60.

Lara MG, Bentley MVLB, Collett JH. In vitro drug release mechanism and drug loading studies of cubic phase gels. Int J Pharm. 2005;293(1-2):241–50.

Lee J, Choi SU, Yoon MK, Choi YW. Kinetic characterization of swelling of liquid crystalline phases of glyceryl monooleate. Arch Pharm Res. 2003;26:880–5.

Lee J, Kellaway IW. Combined effect of oleic acid and polyethylene glycol 200 on buccal permeation of [D-Ala2, D-Leu5]enkephalin from a cubic phase of glyceryl monooleate. Int J Pharm. 2000;204(1-2):137–44.

Lee J, Young SA, Kellaway IW. Water quantitatively induces the mucoadhesion of liquid crystalline phases of glyceryl monooleate. J Pharm Pharmacol. 2001;53(5):629–36.

Li Q, Cao J, Li Z, Chu X. Cubic Liquid Crystalline Gels Based on Glycerol Monooleate for Intra-articular Injection. AAPS Pharm Sci Tech. 2018;19(2):858–65.

Libster D, Aserin A, Garti N. Interactions of biomacromolecules with reverse hexagonal liquid crystals: Drug delivery and crystallization applications. J Colloid Interface Sci. 2011;356(2):375–86.

Lopes LB, Lopes JLC, Oliveira DCR, Thomazini JA, Garcia MTJ, Fantini MC de A, et al. Liquid crystalline phases of monoolein and water for topical delivery of cyclosporin A: Characterization and study of in vitro and in vivo delivery. Eur J Pharm Biopharm. 2006;63(2):146–55.

Madheswaran T, Baskaran R, Thapa RK, Rhyu JY, Choi HY, Kim JO, et al. Design and in vitro evaluation of finasteride-

loaded liquid crystalline nanoparticles for topical delivery. AAPS Pharm Sci Tech. 2013;14(1):45–52.

Merclin N, Bender J, Sparr E, Guy RH, Ehrsson H, Engström S. Transdermal delivery from a lipid sponge phase--iontophoretic and passive transport in vitro of 5-aminolevulinic acid and its methyl ester. J Controlled Release. 2004;100(2):191–8.

Milak S, Zimmer A. Glycerol monooleate liquid crystalline phases used in drug delivery systems. Int J Pharm. 2015;478(2):569–87.

Nakamoto, RY. Use of a saliva substitute in postradiation xerostomia. J of Prost Dent. 1979;42(5):539-542.

Nielsen LS, Schubert L, Hansen J. Bioadhesive drug delivery systems. I. Characterisation of mucoadhesive properties of systems based on glyceryl mono-oleate and glyceryl monolinoleate. Eur J Pharm Sci. 1998;6(3):231–9.

Norling T, Lading P, Engström S, Larsson K, Krog N, Nissen SS. Formulation of a drug delivery system based on a mixture of monoglycerides and triglycerides for use in the treatment of periodontal disease. J Clin Periodontol. 1992;19(9 Pt2):687–92.

Nunes KM, Teixeira CCC, Kaminski RCK, Sarmento VHV, Couto RO, Pulcinelli SH, et al. The monoglyceride content affects the self-assembly behavior, rheological properties, syringeability, and mucoadhesion of in situ–gelling liquid crystalline phase. J Pharm Sci. 2016;105(8):2355–64.

Okonogi S, Khongkhunthain S, Bunyaratavej P, Thusaphorn T, Umpriwan R. Development of local injectable dental gel: the influence of certain additives on physicochemical properties of glycerylmonooleate-based formulations. Drug Dev Ind Pharm. 2004;30(4):347–57.

Peng X, Wen X, Pan X, Wang R, Chen B, Wu C. Design and in vitro evaluation of capsaicin transdermal controlled release cubic phase gels. AAPS PharmSciTech. 2010;11(3):1405–10.

Phan S, Fong WK, Kirby N, Hanley T, Boyd BJ. Evaluating the link between self-assembled mesophase structure and drug release. Int J Pharm. 2011;421(1):176–82.

Rajabalaya R, Musa MN, Kifli N, David SR. Oral and transdermal drug delivery systems: Role of lipid-based lyotropic liquid crystals. Drug Des Devel Ther. 2017;11:393–406.

Rizwan SB, Hanley T, Boyd BJ, Rades T, Hook S. Liquid crystalline systems of phytantriol and glyceryl monooleate containing a hydrophilic protein: Characterisation, swelling and release kinetics. J Pharm Sci. 2009;98(11):4191–204.

Sallam AS, Khalil E, Ibrahim H, Freij I. Formulation of an oral dosage form utilizing the properties of cubic liquid crystalline phases of glyceryl monooleate. Eur J Pharm Biopharm. 2002;53(3):343–52.

Schott H. Kinetics of swelling of polymers and their gels. J Pharm Sci. 1992;81(5):467–70.

Shah MH, Paradkar A. Effect of HLB of additives on the properties and drug release from the glyceryl monooleate matrices. Eur J Pharm Biopharm. 2007;67(1):166–74.

Shah JC, Sadhale Y, Chilukuri DM. Cubic phase gels as drug delivery systems. Adv Drug Deliv Rev. 2001;47(2-3):229–50.

Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Ver. 2005;57(11):1556–68.

Souza C, Watanabe E, Borgheti-Cardoso LN, Fantini MC de A, Lara MG. Mucoadhesive system formed by liquid crystals for buccal administration of poly(hexamethylene biguanide) hydrochloride. J Pharm Sci 2014;103(12):3914–23.

Wang X, Zhang Y, Gui S, Huang J, Cao J, Li Z, et al. Characterization of lipid-based lyotropic liquid crystal and effects of guest molecules on its microstructure: a systematic review. AAPS Pharm Sci Tech. 2018;19(5):2023–40.

Zabara A, Mezzenga R. Controlling molecular transport and sustained drug release in lipid-based liquid crystalline mesophases. J Controlled Release. 2014;188:31–43.

Received for publication on 20th August 2020
Accepted for publication on 12nd January 2021