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In vitro drug release mechanism and drug loading studies of cubic phase gels

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Abstract

Glyceryl monooleate/water cubic phase systems were investigated as drug delivery systems, using salicylic acid as a model drug. The liquid crystalline phases formed by the glyceryl monooleate (GMO)/water systems were characterized by polarizing microscopy. In vitro drug release studies were performed and the influences of initial water content, swelling and drug loading on the drug release properties were evaluated. Water uptake followed second-order swelling kinetics. In vitro release profiles showed Fickian diffusion control and were independent on the initial water content and drug loading, suggesting GMO cubic phase gels suitability for use as drug delivery system.

Keywords: Glyceryl monooleate; Drug delivery systems; Cubic phase; Swelling studies

1. Introduction

Glyceryl monooleate (GMO) is a polar lipid that forms several liquid crystalline phases in the presence of water (Larsson, 1989). This amphiphilic molecule can arrange itself into different ordered arrays and the formation of liquid crystalline phases depends on the water content, temperature and the presence of solutes. GMO/water systems can incorporate drugs with different solubilities and molecular weights (Wyatt and Dorschel, 1992) and have been studied as sustained drug delivery systems for several drugs, including peptidic and proteic ones (Chang and Bodmeier, 1997a; Engström and Engström, 1992; Geraghty et al., 1996; Lee and Kellaway, 2000; Sadhale and Shah, 1999). Recently Turchiello et al. (2003) investigated a potential of GMO/water cubic phase systems to deliver pro-drugs and a photosensitizer for topical application in photodynamic therapy. Cubic phase gels can be formed at defined conditions and have been considered as potential drug carrier to be used in several routes of administration (Dash et al., 1999; Mallone

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et al., 2000; Norling et al., 1992; Sallam et al., 2002; Shah et al., 2001). Cubic phase gels of GMO/water are formed at body temperature, are physically stable upon contact with excess of water, as physiologic conditions and have interesting characteristics for drug delivery (Chang and Bodmeier, 1997a). For pharmaceutical applications, some aspects should be considered such as the presence of drugs, which can modify the cubic phase structure and alter the drug release profile of the system. Additional factors such as initial water content, the type of liquid crystalline phase formed, swelling upon contact with water, drug loading and its solubility in the system, as well as possible interactions of the drug with the lipid phase may also influence the drug release (Burrows et al., 1994; Chang and Bodmeier, 1997a; Carr et al., 1997; Sallam et al., 2002).

The aim of this work was to investigate the potential of GMO/water gels as drug delivery systems characterizing the liquid crystalline phases formed in the presence of a model drug (salicylic acid) as well as to study the effect of swelling and drug loading on the release mechanism.

Further studies will be addressed to develop cubic phase GMO/water systems for delivering drugs with different physico-chemical characteristics and therapeutic use.

2. Materials and methods

The following reagents were used as received: a commercial grade of GMO, Myverol 18–99® distilled monoglycerides (Eastman Chemical Company) and salicylic acid from Sigma Chemical Co., reagent grade.

2.1. Preparation of GMO/water systems

GMO/water systems were prepared at several water contents by melting Myverol 18–99® at 42 °C followed by the addition of the required amount of water at the same temperature. Drug loaded systems were prepared by mixing the salicylic acid in the molten Myverol 18–99® prior to the addition of water. The systems were maintained in well-closed containers at room temperature for 7 days for equilibration.

2.2. Polarizing light microscopy

Polarizing light microscopy, using an Axiolab microscope (Carl Zeiss) fitted with a hot stage plate Linkan, identified the liquid crystalline phases. GMO/water systems with known amounts of water within the range of 5.0–40.0% (w/w) were observed by polarizing light microscopy between 20 and 90 °C at a heating rate of 1 °C/min and a binary phase diagram was constructed. A partial ternary phase diagram was also constructed to determine the influence of the presence of drug and it's loading on the phase properties. For this purpose, GMO/water systems with known amounts of water within the range of 5.0–40.0% (w/w) and salicylic acid content of 0–20.0% (w/w) were observed by polarizing light microscopy at 37 °C. An indication of the salicylic acid solubility in the systems was determinated by the presence of suspended drug crystals in the systems when observed microscopically.

2.3. Swelling studies

GMO/water systems containing 0, 20.0 and 35.0% (w/w) of water were moulded as matrices of 1.7 cm of diameter and 0.8 cm height. The matrices were prepared as described by Geraghty et al. (1996), weighed and placed in 300.0 ml of isotonic phosphate buffer pH 7.4 maintained at 37 °C. At fixed time intervals, the samples were removed and re-weighed. The water uptake data were analyzed with the first-order kinetics (1) and second-order kinetics (2) equation:

$$\ln \frac{W_\infty}{W_\infty - W} = kt \tag{1}$$

$$\frac{t}{W} = \frac{1}{kW_\infty^2} + \frac{t}{W_\infty} \tag{2}$$

where W_∞ is the maximum water uptake, W the water uptake at a time t, $(W_\infty - W)$ the unrealized water uptake and k is the proportionality constant. For the second-order kinetics, the initial rate of swelling is the reciprocal of the y-intercept in the plot of t/W versus t. The reciprocal of the slope indicates W_∞, which is the maximum or equilibrium water uptake. The units of W_∞ are grams of buffer absorbed per gram of matrix and the units of the initial swelling rate are grams of buffer absorbed per gram of dry matrix per hour (Chang and Bodmeier, 1997a; Schott, 1992; Lee et al., 2003).

2.4. In vitro drug release

Drug release was assessed by dissolution studies performed in triplicate based on the USP rotating-basket method. The samples evaluated were GMO/water systems, containing 35.0% (w/w) of water, moulded with the same dimensions described before. Drug loads in the range of 2.0–8.0% (w/w) were studied.

The influence of initial water content on drug release was also investigated with samples of 20.0% (w/w) initial water content and similar drug loads. The dissolution media was 300.0 ml of isotonic phosphate buffer, pH 7.4, maintained at 37 °C and 100 rpm agitation. Samples of the dissolution media were taken at specified time intervals and salicylic acid released amounts were assayed spectrophotometrically at 296 nm.

2.5. Evaluation of the release mechanism

The release data were analyzed to describe the release mechanism (Table 1) and could be fitted to both Higuchi and first-order models. In order to distinguish between diffusion control and first-order models, the data were analyzed by the method proposed by Schwartz et al. (1968). According to this method, plots of the ratio of release as function of the amount of drug released are linear in first-order kinetics models, whereas plots of the ratio of release as function of the reciprocal of the amount of drug released are linear in diffusion control release.

The influence of swelling on salicylic acid release was characterized using (Rigter and Peppas, 1987):

$$\frac{M_t}{M_\infty} = Kt^n \tag{3}$$

where M_t/M_∞ is the fraction of drug released, K a constant dependent on the system, t the release period and n is the diffusional exponent, indicative of the release mechanism for matrices of varying shape and swelling or non-swelling systems. For moderately swelling systems (equilibrium swelling ratio not greater than 1.33 equivalent to an increase in volume of 25.0%) of cylinder shape, a value of 0.45 indicates Fickian diffusion, where drug is released by the usual molecular diffusion through the system. A value between 0.45 and 0.89 is indicative of anomalous transport in which there must be some influence of swelling and/or erosion. A value of 0.89 indicates Case II relaxational mechanism, associated with the stresses and state-transitions that occur in the swelling.

The salicylic acid release mechanism was also characterized by Peppas and Sahlin (1989), which explores the relationship between Fickian diffusional release and Case II transport. The two mechanisms were considered to be additive and follow the equation:

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

where the first term of the right side is the Fickian contribution and the second term being Case II relaxational contribution and K_a and K_b are the Fickian and relaxational kinetic constant, respectively. The coefficient m is the Fickian diffusion exponent for a device of any

Table 1
Kinetics parameters of the salicylic acid release profiles from GMO/water systems with selected drug loads

Formulations	Higuchi model[a]		First-order model[b]	
	Gradient	Correlation coefficient	Gradient	Correlation coefficient
GMO/water systems with 35.0% (w/w) of water				
2.0% (w/w) of salicylic acid	5.2	0.99	−0.04	0.98
4.0% (w/w) of salicylic acid	10.8	0.99	−0.04	0.98
8.0% (w/w) of salicylic acid	21.5	0.99	−0.04	0.98
GMO/water systems with 20.0% (w/w) of water				
2.0% (w/w) of salicylic acid	4.4	0.99	−0.03	0.98
4.0% (w/w) of salicylic acid	9.3	0.99	−0.03	0.98
8.0% (w/w) of salicylic acid	18.3	0.98	−0.03	0.96

[a] Milligrams of drug released as a function of square root of time.
[b] Log of the amount of drug remaining in the samples as a function of time.

geometrical shape exhibiting controlled release and is dependent of the aspect ratio of the device.

3. Results and discussion

3.1. Polarizing light microscopy

The liquid crystalline phases of GMO/water systems were identified according to Rosevear (1954). Lamellar, cubic, L2 and reversed hexagonal phases were found in the systems. Binary phase diagrams of GMO and water prepared with systems containing several water contents as a function of increased temperature were prepared and is presented in Fig. 1A. A lamellar phase is found at low water contents in systems prepared at 20 °C. It consists of planar lipid bilayers stacked in a one-dimensional lattice separated by layers of water. This bilayer conformation is formed when layers of water interpenetrate polar heads groups. On heating these lamellar phase systems became isotropic and fluid, indicative of L2 structure. With increased hydrocarbon chain disorder due heating or increasing the water content, there is a transition from lamellar to cubic phase and finally into reverse hexagonal phase (Shah et al., 2001). An increase in water content produces gels with cubic phase structure which are transparent, optically isotropic and very stiff, consisting of two congruent networks of water channels surrounded by curved lipid bilayers extending in three dimensions. The GMO/water systems reach their maximum hydratation at water content of 40.0% (w/w), showing a cubic phase, which is stable in the presence of excess of water. At temperatures greater than 75 °C, samples became anisotropic with characteristic of reversed hexagonal phase structure at the microscope. This mesophase consists of water cylinders arranged in a two-dimensional lattice separated by lipid bilayers (Tate et al., 1991). Several authors reported phase diagrams of glyceryl monooleate/water systems (Clogston et al., 2000; Geraghty et al., 1996; Qiu and Caffrey, 2000; Shah et al., 2001).

In order to verify if salicylic acid has any influence in the mesophases of the GMO/water systems a ternary phase diagram was constructed (Fig. 1B). Drug crystals were observed in the samples loaded with more than 10% (w/w) of salicylic acid indicating that saturation concentration of the drug had been reached. Lamellar phase was found in samples with 10.0% (w/w) of water, while in the samples with 15.0% (w/w) of water both lamellar and cubic phase were observed that is indicative of a phase transition region. A cubic phase was found in the samples containing 20.0, 25.0, 30.0 and 35.0% (w/w) of water. These results were found for all the drug loads evaluated and they are in agreement with the expected liquid crystalline phases for GMO/water systems without drugs, indicating that the presence of salicylic acid had no effect on the phase behavior of the systems at the conditions studied.

Several authors have found modifications on the liquid crystalline phase of GMO/water systems as well as changes on the systems properties due the addition of drugs and solvents (Alfons and Engström, 1998; Caboi et al., 2001; Chang and Bodmeier, 1998; D'Antona et al., 2000; Geraghty et al., 1996; Mallone et al., 2000; Nielsen et al., 1998; Norling et al., 1992; Sallam et al., 2002). The polarity and molecular structure of the additive determines whether it is located at the polar interface or in the apolar region of the lipid bilayer, which led to different effects on the mesophase presented by the system. Generally hydrophilic drugs favored lamellar phases, while non-polar solutes which partition strongly into the lipid phase will tend to favor the formation of inverted non-lamellar phases (Seddon, 1990). It was demonstrated by Chang and Bodmeier (1997b) that the addition of oleic acid, which dissolved in the lipid bilayer, increases the apparent hydrophobic volume of lipid transforming the mesophase. Electrostatic interactions due the presence of oleic acid or the pH of dissolution media can affect the curvature of the lipid bilayer and change the average area of the lipid headgroup thereby changing the monoglyceride molecular packing and favoring a transition from cubic to hexagonal phase (Aota-Nakano et al., 1999; Caboi et al., 2001; Chang and Bodmeier, 1997b).

3.2. Swelling studies

GMO absorbs water until it reaches its equilibrium water content when it goes through an inverted micellar phase (L2), a lamellar phase (Lα) and a viscous isotropic phase, which was demonstrated to be cubic phase. Fig. 2 presents the plots of increase of weight of GMO/water gels with initial water contents of 0, 20.0 and 35.0% (w/w), expressed as a function of time. The samples with 35.0% (w/w) showed a minimal swelling

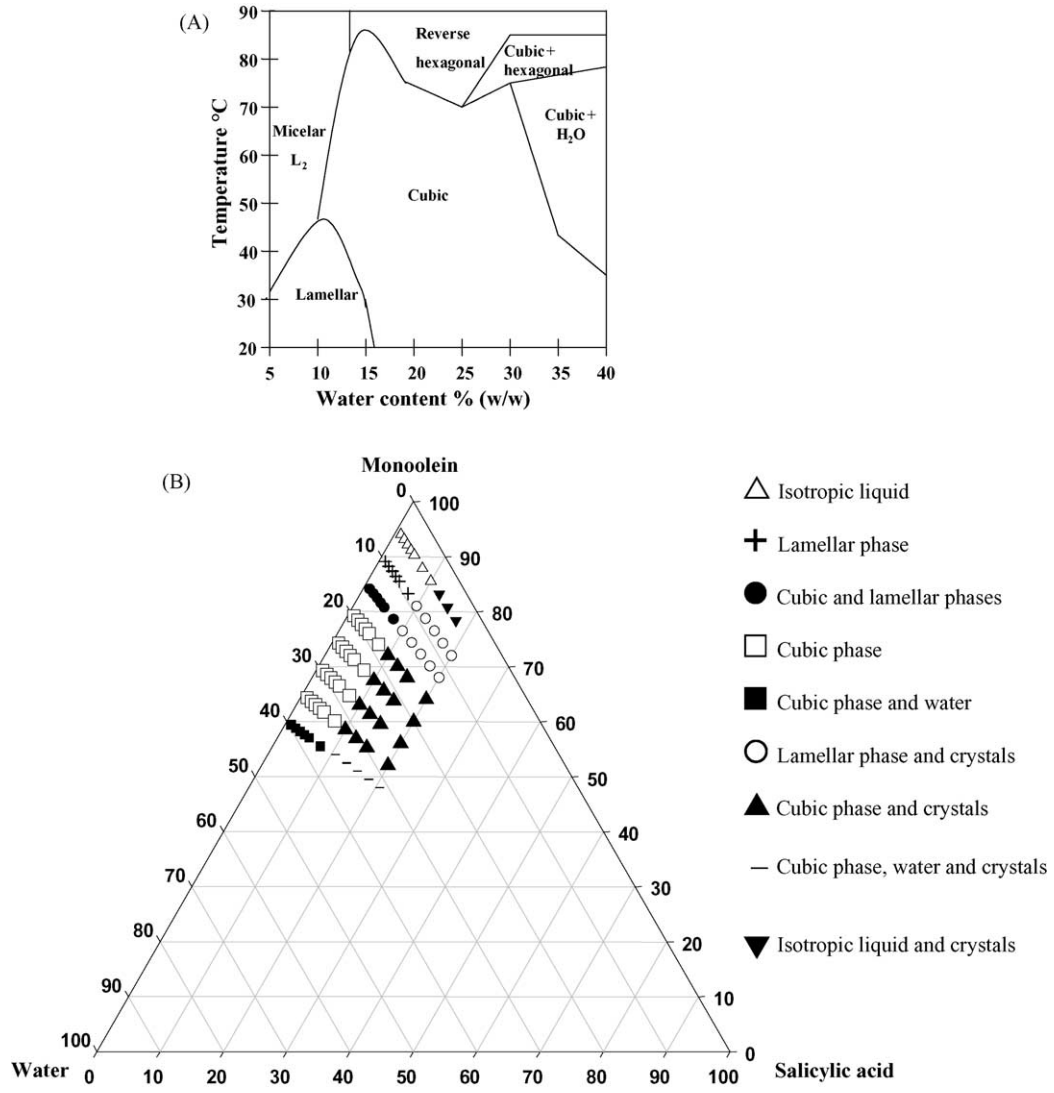

Fig. 1. Phase diagrams: (A) binary phase diagram of GMO/water systems with known water contents within the range of 5.0–40.0% (w/w) observed between 20 and 90 °C at a heating rate of 1 °C/min. (B) Partial ternary phase diagram showing the lyotropic liquid crystalline phases formed by GMO/water/salicylic acid mixtures at 37 °C.

because they are almost fully hydrated. Samples with lower water content presented a rapid absorption of water to reach this water content equilibrium. Samples prepared in the absence of water reached the expected equilibrium water content of 40.0% (w/w). Samples with an initial water content of 20.0% (w/w) increased their weight by 12%, which is lower than the expected water uptake necessary to reach a fully hydrated system. An explanation for this finding can be related to the dimensions of the matrix used, since smaller matrices with the same initial water content reached the water content of 40.0% (w/w) in similar studies (Geraghty et al., 1996). The water uptake initially increased rapidly and approached the equilibrium, where the systems present cubic phase structure (Chang and Bodmeier, 1997a; Geraghty et al., 1996).

Swelling kinetics of the samples presenting initial water content of 0 and 20.0% (w/w) were identified

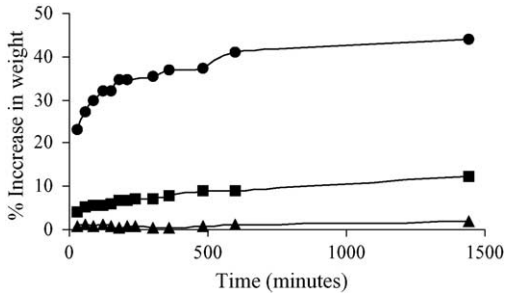

Fig. 2. Plots of the percentage increase in the weight of GMO/water gels with initial water content of: (●) 0% (w/w), (■) 20% (w/w) and (▲) 35% (w/w), as a function of time when placed in excess isotonic phosphate buffer (pH 7.4, $n = 3$).

as following the second-order model, since a linear relationship was obtained by plotting the swelling data according to Equation (2), which describes this kinetic model (Fig. 3A). Linear correlation coefficients were 0.99 and 0.98 for the samples with initial water contents of 0 and 20.0% (w/w), respectively. These results are in accordance with other data reported (Chang and Bodmeier, 1997a; Lee et al., 2003; Schott, 1992). The initial rate of swelling could be calculated by second-order swelling kinetics and values of 0.64 and 0.08 g/(g h) were obtained for samples with initial water contents of 0 and 20.0% (w/w), respectively. The maximum water uptake was calculated as 0.42 and 0.10 g/g for samples containing initial water contents of 0 and 20% (w/w), respectively. Both the initial rate of swelling and the maximum water uptake increased with decreasing initial water content of the liquid crystalline systems. Similar results were reported (Lee et al., 2003).

3.3. In vitro drug release studies

3.3.1. Influence of initial water content

In vitro drug release from GMO/water systems with specified water contents and drug loadings were studied. Fig. 4 presents the plots of the salicylic acid percentage released as a function of time from GMO/water systems containing 20.0 and 35.0% water content, at drug loadings of 2.0, 4.0 and 8.0% (w/w). Samples with 35.0% (w/w) water content are almost completely hydrated, while samples with 20.0% (w/w) were not fully hydrated. There was no evidence of erosion of the matrices in the drug release studies, as no parti-

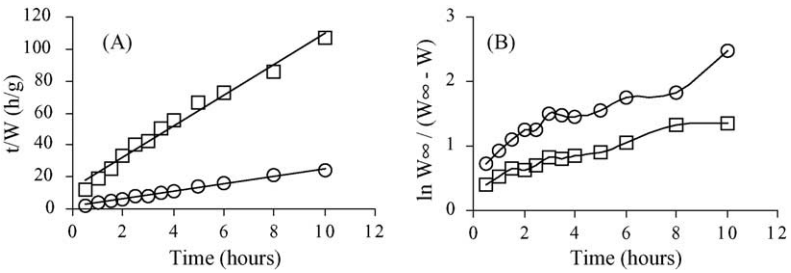

Fig. 3. Swelling isotherms of GMO water systems non-hydrated (◯) and 20% (w/w) initial water content (□) according to: (A) the second-order kinetics (Equation (2)) and (B) the first-order kinetics swelling (Equation (1)). Swelling data were obtained from Fig. 2 ($n = 3$).

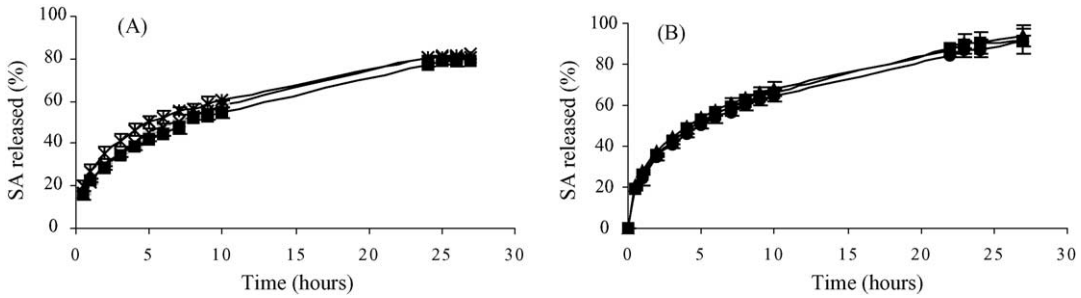

Fig. 4. Plots of the cumulative amount of salicylic acid (SA) released from GMO/water systems with water content of 20.0% (w/w) (A) and 35.0% (w/w) (B) at the drug loadings: (●) 2.0% (w/w); (■) 4.0% (w/w) and (▲) 8.0% (w/w) ($n = 3$, ±S.D.).

cles of the matrices were observed in the dissolution media.

The fraction of salicylic acid released after 27 h and its rate of release from the samples containing 20.0% (w/w) of water were slightly lower (around 80.0% of drug released) when compared with the samples with 35.0% of water content (around 90% of drug released after 27 h). An explanation for these findings can be related to the swelling of the samples with lower initial water content that may have increased the diffusional path of the drug thereby retarding its release slightly. An increased hydrophilic domain, which is achieved at higher water contents, can also influence drug release, as observed by Chang and Bodmeier (1997a).

Several authors have studied the influence of initial water content on the drug release from GMO/water matrices: Lee and Kellaway (2000) found a greater drug release in samples initially fully hydrated probably because hydrophilic channels available during the drug release increased with increasing initial water content; Chang and Bodmeier (1997a) also reported an increased drug release with increasing initial water content due to an increased hydrophilic domain in these samples and the difference occurred within the initial release period. However, no significant difference in the drug release characteristics has been reported from GMO/water matrices as a function of several initial water contents (Burrows et al., 1994; Geraghty et al., 1996), due to the rapid water uptake of the samples. These contrasting findings on the influence of the initial water content on the release profile for different drugs studied could be related to the drug partitioning between the GMO and aqueous phase. Carr et al. (1997) reported that increasing the water content of the vehicle increased the apparent diffusion coefficient of drugs, which show a significant partitioning in the GMO phase, whereas for drugs, which do not partition in to this phase, the apparent diffusion coefficient usually decreased. In the first case, the increase in the initial water content would decrease the concentration in the GMO phase, and hence increase drug release. For drugs with no affinity for the GMO phase the increase in water content simply reduced the concentration of the drug, and hence resulted in a reduced release.

3.3.2. *Influence of drug loading*

Fig. 4 presents drug release data expressed as a percentage base. The salicylic acid fraction released as a function of time from a GMO/water cubic phase system containing 35.0% (w/w) of water content and initial drug loadings between 2 and 8% (w/w) were similar for all the samples studied (Fig. 4A), indicating that the drug release was independent of the initial drug loading. The fraction of drug released from GMO/water systems with lower water content (20.0%, w/w) was also independent of the initial drug loading (Fig. 4B). Similar results were found for oxibutinin (Geraghty et al., 1996) and pseudoephedrine hydrochloride (Chang and Bodmeier, 1997a) in vitro release. The solubility and concentration of the incorporated drug influences the release profile from the GMO/water system according to Norling et al. (1992) and Burrows et al. (1994).

Location of the drug is an important parameter affecting release and kinetics. For example, lipophilic drugs become incorporated in the lipid bilayers, and thus partition into the aqueous channels becomes the rate-limitating step. Therefore, the effect of drug loading on the drug release profile depends also on the drug partitioning between the GMO and aqueous phase (Kumar et al., 2004; Shah et al., 2001).

Other workers using GMO/water systems reported that drug release followed square root of time dependence, indicative of a diffusion controlled release mechanism (Chang and Bodmeier, 1997a; Geraghty et al., 1996). However, depending on the drug studied, its solubility becomes the rate-limitating step of the release. In this case, the systems presented zero-order release (Allababidi and Shah, 1998; Burrows et al., 1994).

3.3.3. *Evaluation of the drug release mechanism*

The release data obtained in the present work were analyzed to describe the release mechanism (Table 1). The amount of salicylic acid released was found to be linear with the square root of time, indicative of Higuchi model or diffusion controlled release (Higuchi, 1962). However, plots of the log of the amount of drug remaining in the samples as a function of time were also linear, possibly indicative of first-order release kinetics. In order to distinguish between diffusion controlled and first-order models, the data were analyzed by the method proposed by Schwartz et al. (1968), which had been used by Burrows et al. (1994) and Geraghty et al. (1996). Fig. 5 presents the plots of release data from a sample containing 4.0% (w/w) of salicylic acid analyzed by this method. Linearity was obtained by plotting the ratio of release as a function of the reciprocal

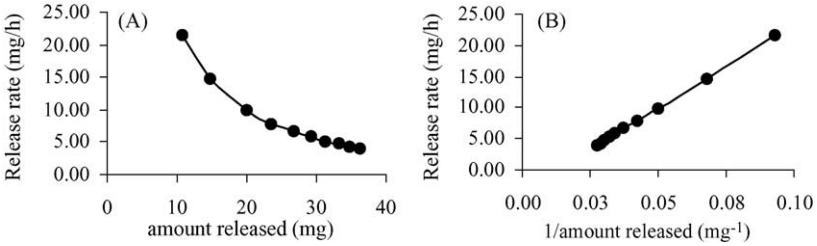

Fig. 5. Plots of the rate of salycilic acid (SA) release from a GMO/water cubic phase system containing 35% (w/w) water content and 4.0% (w/w) of salycilic acid as a function of: (A) amount of drug released and (B) 1/(amount of drug released). The rates values were obtained from the release profiles represented in Fig. 4 ($n = 3$).

Table 2
Diffusional exponents, Fickian and relaxational constants for the release of salicylic acid from GMO/water systems

Formulation	Diffusional exponent, n	Fickian kinetic constant, K_a ($h^{-0.43}$)	Relaxational kinetic constant, K_b ($h^{-0.86}$)
GMO/water systems with 35% of water			
2.0% of salicylic acid	0.41	0.27	0.008
4.0% of salicylic acid	0.42	0.27	0.006
8.0% of salicylic acid	0.41	0.29	−0.012
GMO/water systems with 20% of water			
2.0% of salicylic acid	0.42	0.23	−0.007
4.0% of salicylic acid	0.43	0.23	−0.007
8.0% of salicylic acid	0.38	0.30	−0.028

of the amount of drug released, confirming that the salicylic acid release was diffusion controlled.

In order to characterize the influence of swelling on salicylic acid release, an exponential equation (Equation (3)) proposed by Rigter and Peppas (1987) was employed. The values of n found in the present study are shown in Table 2 , with a value of 0.41 indicative of Fickian diffusion controlled release mechanism.

For a better characterization of salicylic acid release mechanism, Peppas and Sahlin (1989) model (Equation (4)) was used. Values of K_a and K_b for the salicylic acid release from GMO/water systems are also presented in Table 2, where it can be noted that K_a is greater consistently than K_b, confirming that the release followed a Fickian diffusional mechanism.

These results indicate that the presence of drug at the loadings studied had no influence on the fraction of drug released or on the release kinetics, which can be described satisfactorily by the diffusion-controlled model. It is proposed that the rate of drug release is controlled by the diffusion of molecules through the system and it decreases with time due an extended distance that the drug must diffuse through the matrix to the exterior that occurs with time, retarding its release.

4. Conclusions

GMO forms lamellar, L2, cubic and reversed hexagonal lyotropic liquid crystalline phases in the presence of water. The presence of salicylic acid at the concentrations studied did not alter the liquid crystalline structures of the GMO/water systems, whether solubilized or suspended in the system. When placed in contact with water the GMO/water systems absorbed water following second-order swelling kinetics. The drug release was independent of the initial water content, drug loading, swelling and it was demonstrated that the release mechanism was Fickian diffusion. The GMO/water cubic phase showed a very well defined drug release profile, characterized by diffusion process, which is an interesting behavior for drug administration by several routes.

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