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Research Article

Pluronic and Tetronic Copolymers with Polyglycolyzed Oils as Self-Emulsifying Drug Delivery Systems

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Abstract. The potential of poly(ethylene oxide)-poly(propylene oxide) block copolymers Pluronic® F127 (PF127) and Tetronic® 304 (T304), 904 (T904) and 1307 (T1307) as components of solid self-(micro) emulsifying dosage forms, S(M)EDDS, was evaluated. The dependence of the self-associative properties of Tetronics on pH explained the low ability of the micelles to solubilize griseofulvin at acid pH (sevenfold increase) compared to at alkaline pH (12-fold). Blends of polyglycolyzed glycerides (Labrasol, Labrafac CC, and Labrafil M 1944CS) with each copolymer at two different weight ratios (80:20 and 60:40) were prepared, diluted in water, and characterized in terms of globule size, appearance and griseofulvin solubility. The blends with Labrasol led to microemulsions that are able to increase drug solubility up to 30-fold. SMEDD hard gelatine capsules filled with griseofulvin and Labrasol or Labrasol/copolymer 80:20 showed a remarkable increase in drug solubility and dissolution rate, particularly when T904, T1307 or PF127 was present in the blend. This effect was more remarkable when the volume of the dissolution medium was 200 ml (compared to 900 ml), which can be related to a higher stability of the microemulsion when there is a greater concentration of the copolymer and glyceride in the medium.

KEY WORDS: hydrophobic drugs; poloxamer; poloxamine; polymeric micelles; SMEDDS.

INTRODUCTION

Over the last few years the development of solid self-(micro)emulsifying delivery systems, S(M)EDDS, for poorly-soluble drugs, based on mixtures of surfactants and oils, has been receiving an increasing attention (1–3). Polyoxyethylene sorbitan fatty acid esters (Tween®) or polyglycolyzed glycerides (e.g. Labrasol®) surfactants and modified or hydrolyzed vegetable oils have been shown to be particularly adequate for preparing S(M)EDDS (2,4). Under the temperature and waving conditions of the gastrointestinal tract, SMEDDS can give rise *in situ* to microemulsions with enhanced drug solubility and improved oral absorption (1,5). SMEDDS for oral delivery can be formulated as, among others, soft and hard gelatin capsules (6–8), tablets (9) and pellets (10–12). However, the list of oil/surfactant combinations that provide SMEDDS is still short and important attempts to widen the range of components suitable for this application are happening. Particularly, the use of conventional surfactants at relatively high concentrations is not exempt of adverse reactions and, thus, to find safe alternatives with enough emulsifying capacity is of great practical relevance (2).

Self-assembling amphiphilic copolymers with the ability to form nanoscopic core-shell micelles in aqueous medium have a recognized interest as drug solubilizers and stabilizers in liquid and semisolid drug dosage forms (13–17). Poloxamer (Pluronic®) and poloxamine (Tetronic®) block copolymers, constituted by poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO), easily spread in water and are commercially available in a wide range of HLB values (18,19). Differently from linear Pluronics, the X-shaped Tetronics, are formed by four PPO-PEO chains bonded to an ethylene diamine central group, which provides pH-responsive micellization properties (20,21). Despite the utility of Pluronics and Tetronics as stabilizers of oily phases (22–24), Pluronics and Tetronics have received minimal (25) or no attention as S(M) EDDS components.

The aim of this work was to explore the possibilities of using Pluronic® F127 (PF127) and Tetronic® 304 (T304), 904 (T904) and 1307 (T1307) as components of S(M)EDDS that also comprise glyceride derivatives. In this way, the evaluation of the effect of the copolymer architecture when the molecular weight and HLB are similar (T1307 and PF127), and of the effect of HLB and molecular weight when the architecture is the same (T304, T904 and T1307) becomes possible. Since the knowledge about Tetronic micellization is still limited (19,20,26,27), this was the issue to be tackled in first place. Secondly, the ability of the copolymers to solubilize griseofulvin [a Class II drug of the BCS (28)] in aqueous media covering a wide range of pH values was evaluated. Afterwards, aqueous dispersions of several mix-

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tures of each copolymer with Labrasol®, Labrafac® and Labrafil® were prepared and characterized regarding the size of the droplets and griseofulvin solubilization ability. Hard gelatin capsules were filled with the most efficient glyceride: copolymer mixtures and the ability of the formulations to promote griseofulvin dissolution was evaluated.

MATERIALS AND METHODS

Materials

Tetronic® 304 [$(OE_3OP_4)_2NCH_2CH_2N(OP_4OE_3)_2$], Tetronic® 904 [$(OE_{15}OP_{17})_2NCH_2CH_2N(OP_{17}OE_{15})_2$] and Tetronic® 1307 [$(OE_{72}OP_{23})_2NCH_2CH_2N(OP_{23}OE_{72})_2$] were from BASF, Germany; Pluronic® F127 [$P(EO_{99})$–$P(PO_{69})$–$P(EO_{99})$] and griseofulvin were from Sigma-Aldrich Chemie, Germany. Labrafil® M 1944 CS (mixture of oleic acid 62.65%, linoleic acid 26.7%, palmitic acid 4.74%, and mono- and di-fatty acid esters of PEG-6), Labrasol® [saturated polyglycolysed (PEG-8) caprylic/capric glycerides] and Labrafac® CC (caprylic acid 54.4%, capric acid 44.8%) were from Gattefossé España S.A. Purified water (resistivity> 18.2 MOhm·cm; MilliQ®, Millipore Spain) was obtained by reverse osmosis. All other reagents were of analytical grade.

Methods

Copolymer Dispersions

Potentiometric Titration of Tetronic. Titration of poloxamine copolymers was performed using a pH-meter Crison, model GLP22 (Barcelona, Spain), equipped with a sensor for viscous medium (Ag/AgCl). Hydrochloric acid (0.01 M, 25 ml) was added to 0.01 M Tetronic solutions (25 ml), which were then titrated with 0.01 M sodium hydroxide. The concentrations of the monoprotonated and the diprotonated forms were estimated from the expressions of the dissociation constants K_{a1} and K_{a2} as follows (20):

$$[TH^+] = \frac{[T][H^+]}{K_{a2}} \quad (1)$$

and

$$[TH_2^{2+}] = \frac{[T][H^+]^2}{K_{a2}K_{a1}} \quad (2)$$

The concentration of un-ionized poloxamine molecules is given by:

$$[T] = \frac{[T_{total}]}{1 + ([H^+]/K_{a2}) + \left([H^+]^2 \Big/ K_{a2}K_{a1}\right)} \left(\frac{V_{initial}}{V_{initial} + V_{base}}\right) \quad (3)$$

where $V_{initial}$ is given by the volume of poloxamine solution and of HCl solution, and V_{base} is the volume of NaOH solution added.

Surface Tension Measurements. Adequate amounts of each copolymer were added to water up to a final concentration of 10^{-2} M and magnetic stirring was applied until complete dissolution. Sets of diluted solutions (10^{-2} to 10^{-7} M) were prepared and left to rest for at least 24 h. Then, the surface tension was measured, in triplicate at 25 °C, using the platinum ring method (Lauda tensiometer/densimeter TD1, Germany).

Dynamic Light Scattering (DLS). The DLS measurements were performed using an ALV-5000F optical system equipped with a CW diode-pump Nd:YAG solid-state laser (400 mW) operated at 532 nm (Coherent Inc., Santa Clara CA, USA). The intensity scale was calibrated against scattering from toluene. Ten percent copolymer solutions were filtered (Millipore® 0.45 μm, Ireland) into the quartz cell (previously washed with condensing acetone vapor) and maintained at 20 °C. The diffusion coefficient was deduced from the standard second-order cumulant analysis of the autocorrelation functions measured at 90° angle. The experiments were

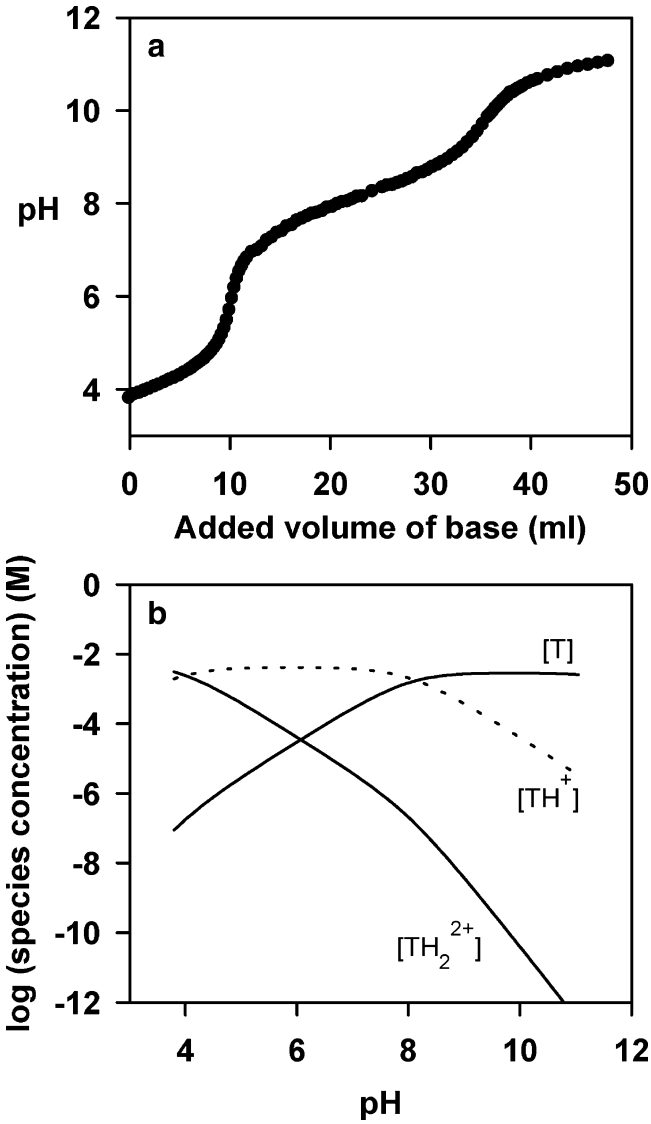

Fig. 1. Potentiometric titration curve obtained for T304 (**a**) and dependence of the concentrations of the non-protonated and protonated forms of T304 as a function of pH (**b**)

Table I. Structural Properties, CMC, and Parameters Used to Characterize the Ability of the Copolymers to Solubilize Griseofulvin

Copolymer	Molecular Weight	HLB[a]	pK_{a1}, pK_{a2}	CMC (mM)	χ	*P* Value	ΔG_s^0 (kJ/mol)
T304	1,650	12–18	4.30; 8.14	5.0	0.012	11.75	−13.26
T904	6,700	12–18	4.03; 7.81	0.3	0.050	3.90	−16.65
T1307	18,000	> 24	4.62; 7.80	0.1	0.045	3.67	−16.40
PF127	12,600	22	–	0.1	0.024	1.16	−14.85

[a] Data taken from the supplier data sheets (35)

carried out in triplicate and the apparent hydrodynamic radius ($r_{h,app}$) of the micelles was calculated from the apparent diffusion coefficients.

Oscillatory Rheometry. The influence of temperature on the storage or elastic (G') and the loss or viscous (G'') moduli of 10% copolymer solutions was recorded in triplicate at 1 rad/s from 20 °C to 60 °C, with a heating rate of 1.5 °C/min, in a Rheolyst AR-1000N rheometer (TA Instruments, UK) equipped with an AR2500 data analyzer, a Peltier plate and a cone geometry (6 cm diameter, 2.1°). An adequate solvent trap was used to prevent evaporation.

Copolymer/Glyceride Systems

Preparation. Glyceride/copolymer 60:40 and 80:20 *w/w* systems were prepared adding 6 g of glyceride and 4 g copolymer to 30.0 ml water, or 8 g of glyceride and 2 g copolymer to 15.0 ml water. Heating (60 °C) and magnetic stirring was applied to enable the complete dispersion of the components. Then, water was added to obtain dispersions with copolymer concentrations of 0.1, 0.5, 1, and 5 mM.

Size of the Droplets. The resultant systems were visually inspected and the size of the drops of internal phase was evaluated using an optical microscope Nikon Optiphot-pol (Japan) connected to an Olympus (Japan) video-camera with a magnification of ×40.

Griseofulvin Solubility Studies. Griseofulvin solubility was evaluated in the copolymer aqueous solutions, in the pure glycerides, and in the aqueous dispersions of glyceride/copolymer mixtures. Four milliliters of each medium were poured in glass ampoules containing 40 mg of griseofulvin. The ampoules were flame-sealed and then tumbled in a water bath for 7 days at 25 °C. The experiments were performed in duplicate. Samples were filtered (0.45 μm cellulose acetate membrane, Albet, Barcelona, Spain) and the concentration of griseofulvin dissolved was quantified at 294 nm (Agilent 8453, Böblingen, Germany), against a blank of copolymer solution of the corresponding concentration, using a calibration curve obtained with griseofulvin solutions in ethanol/water 50:50. The ability of the copolymers to solubilize griseofulvin was evaluated using three descriptors (29):

(a) the molar solubilization capacity, χ, i..e. the number of moles of drug that can be solubilized by one mol of micellar surfactant:

$$\chi = \frac{S_{tot} - S_w}{C_{copol} - CMC} \quad (4)$$

In this equation S_{tot} is the total drug solubility, S_w is the water drug solubility and C_{surf} is the molar concentration of surfactant in solution. Since above CMC the copolymer unimers concentration remains constant and equals to CMC, the surfactant concentration in the micellar form can be estimated as $C_{copol}-CMC$;

(b) the micelle-water partition coefficient, *P*, which is the ratio of drug concentration in the micelle to the drug

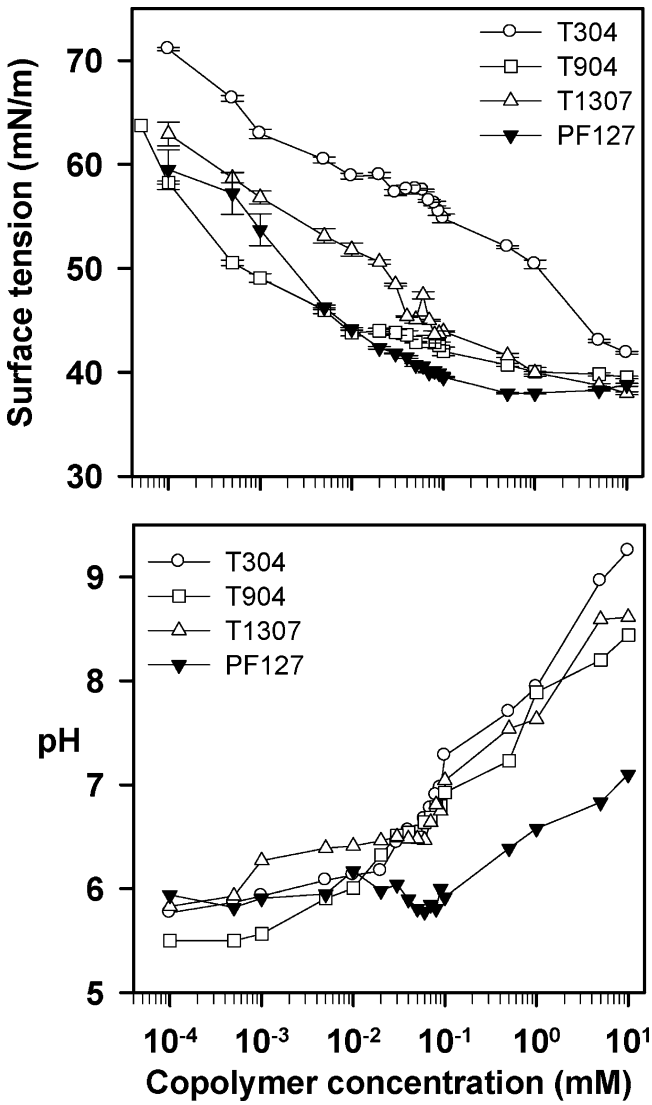

Fig. 2. Dependence of the surface tension and of the pH on the copolymers concentration in water at 25 °C

concentration in water for a particular copolymer concentration:

$$P = \frac{S_{tot} - S_w}{S_w} \quad (5)$$

(c) the standard free energy of solubilization that was estimated from the molar micelle–water partition coefficient, P_M (i.e. P for $C_{copolymer}$=1 M), as follows:

$$\Delta G_s^0 = -RT \ln \frac{\chi(1 - CMC)}{S_w} \quad (6)$$

SMEDDS Capsules

Griseofulvin (1.5 g) was dispersed in Labrasol or Labrasol:copolymer 80:20 mixtures (13.5 g) at 60 °C under stirring, and then 1 ml was injected (needle of 0.8 mm inner diameter) into the body of colorless hard capsules (number 00, Guinama, Valencia, Spain). The amount of griseofulvin in each capsule was 100 mg. Drug release rate was evaluated using a USP 24 type II (Turu Grau, Barcelona, Spain) apparatus at 75 rpm and 37 °C, in 900 ml of pH 7.4 phosphate buffer. At given time intervals, samples (5 ml) were taken and the withdrawn volume replaced by the same volume of fresh dissolution medium. The samples were filtered and, when needed, diluted using ethanol/water 50:50 solution. The concentration of the drug was determined spectrophotometrically (Agilent 8453, Böblingen, Germany) at 294 nm. Additional experiments were carried out in 200 ml of HCl 0.1 M, water or pH 7.4 phosphate buffer in a thermostated beaker (37 °C) under mild stirring (magnetic bar).

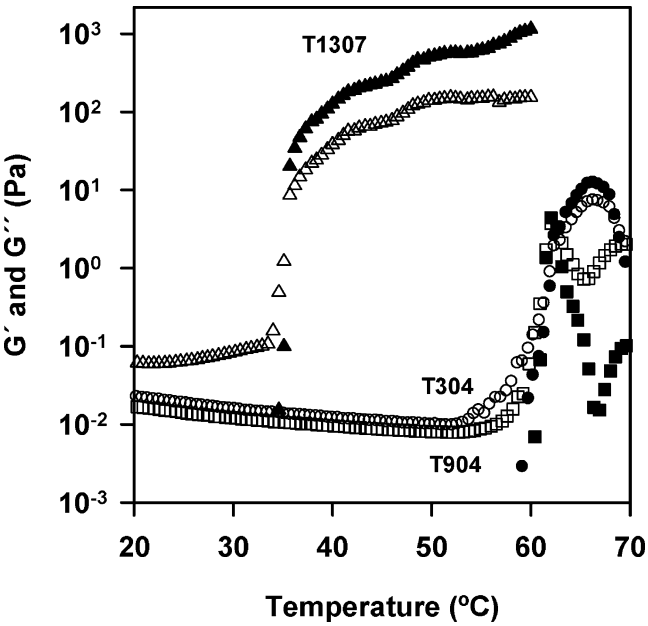

Fig. 3. Effect of temperature on the storage (G', *solid symbols*) and loss (G'', *open symbols*) moduli of 10% Tetronic solutions. Legend as in Fig. 2

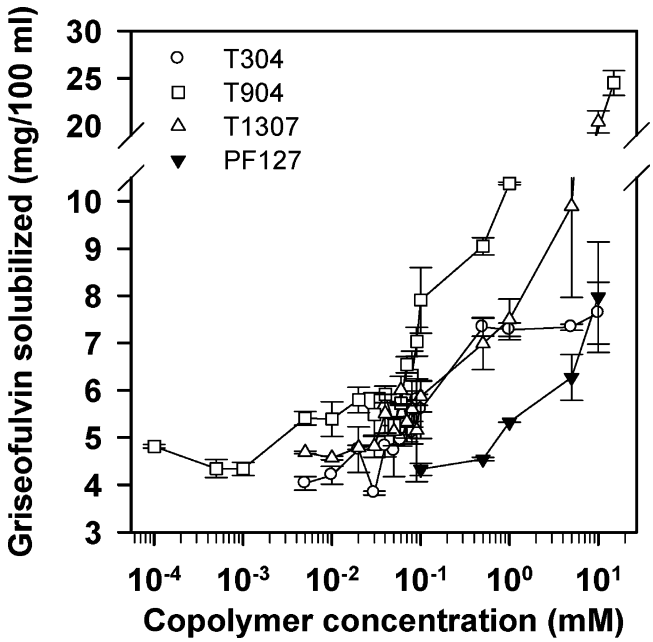

Fig. 4. Griseofulvin solubility in aqueous solutions of the copolymers evaluated

RESULTS AND DISCUSSION

Copolymer Dispersions

The deprotonation–micellization of T904 has been previously found to become more difficult as the pH decreases, shifting the CMC to greater values (21). Proton dissociation of the central ethylene diamine group of Tetronics is a previous condition for micellization; the balance

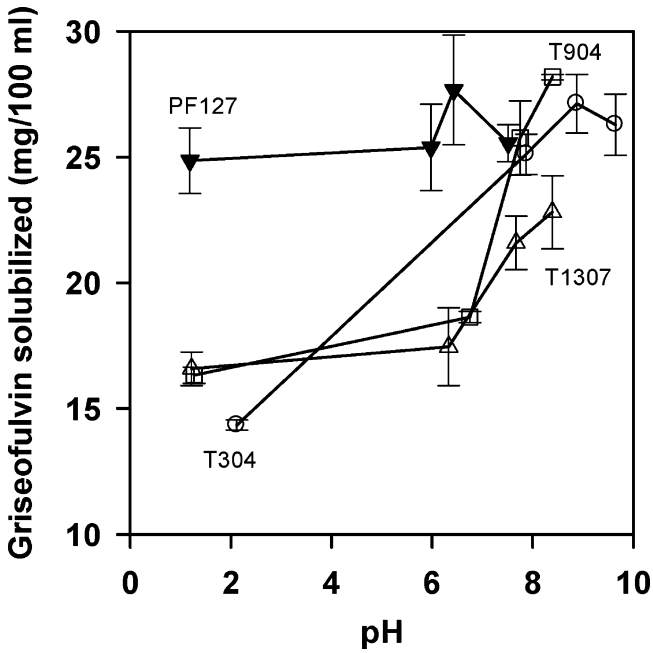

Fig. 5. Griseofulvin solubility in 10% *w/w* copolymer solutions prepared in media of different pH. The copolymer concentrations were 60.6 mM T304, 14.9 mM T904, 5.55 mM T1307, and 0.80 mM PF127. The solubility of griseofulvin was pH-independent (3 mg/100 ml). Legend as in Fig. 2

between the free energy of micellization and the free energy of protonization determining the possibility of micelle formation at pH below pK_a (20). Therefore, the pK_a of T304, T904, and T1307 should be known to be able to understand the self-aggregation and the surface-active properties of the copolymers. The titration profiles showed two inflection points that correspond to dissociation of the each proton of the ethylene diamine group (Fig. 1a). The pK_a values were similar for the three varieties (Table I) and close to the pK_a values previously reported for T701 and T803 (20). At 25 °C, the diprotonated form predominates at pH values below 4 and even up to pH 5.8 the concentration of the diprotonated form is greater than the concentration of the non-protonated form. The mono-protonated form holds the majority in the pH range between pK_{a1} and pK_{a2} (Fig. 1b).

The dependence of the surface tension on the copolymer concentration is shown in Fig. 2. The critical micellar concentration (CMC) of PF127 was 0.1 mM, which is in agreement with the values previously reported for this copolymer (13). The profiles of the Tetronics did not show a clear plateau and the CMC was estimated as the concentration at which a decrease in the slope occurred (Table I). T304 showed the lowest surface activity and the greatest CMC. Since hydrophobic interactions among PO groups are mainly responsible for the self-association in water, the differences in CMC may be explained by differences in the structure of the copolymers (Table I). T304 contains four chains of three EO groups and four PO groups each. T1037 and PF127 have a much greater content in EO and PO groups than T304. T904 occupies an intermediate place. In the case of Pluronics, the greater the content in PO groups, the lower the CMC was. Conversely, an increase in the lengths of the EO blocks elevates the probability of contacts of the PO units with the EO units within the core of the micelles, which decreases the hydrophobicity of the core and results in destabilization of the micelle (13). A similar trend is observed for Tetronics. The pH of the copolymer solutions increased as the concentration in Tetronic rises, which is related to the weak base behavior of the central diamine group (Fig. 2).

DLS analysis of 10% copolymer solutions showed unimodal distributions with a mean hydrodynamic radius of 10 nm for PF127, 4 nm for T904 and T1307, and 0.9 nm for T304. The results confirm that T304 has the weakest self-associative capability owing to the shortest hydrophobic blocks.

At room temperature, all the copolymer solutions at 10% showed a mainly viscous behavior with negligible storage moduli (G' below 10^{-5} Pa). An abrupt rise of G' occurred when the samples were heated; the gel temperature being 35.7 °C for T1307 and 62.4 °C for T304 and T904 (Fig. 3). In general, PPO-PEO block copolymers become less hydrophilic as the temperature rises owing to the progressive dehydration of the blocks. This promotes the formation of more micelles and, eventually, the packing into body centered cubic phase gels (26). The highest values of both moduli occur at the temperature at which the volume fraction of micelles is maximum. At greater temperatures, the dehydration of PPO chains, and even of PEO blocks, causes the polymer to phase separate, and G′ and G″ values to decrease. The differences in the gel temperature among the Tetronic varieties may be again explained by the longer of PPO and PEO segments of T1307 (Table I). Compared to T304 and T904, T1307 has a greater ability to bind water to its structure because T1307 has sufficient EO groups per block for adopting an helicoidal conformation in which interfacial (freezing bound) water may exist (27). Interfacial water is easily lost during the heating process. Additionally, the hydrophobic association requires a minimum number of PO units per block. For a given content in EO groups, the longer the PO block of Pluronics, the lower the gel temperature (30). The preceding reasons explain the low gel temperature of T1307 compared to T904 and T304.

Table II. Griseofulvin Solubility (mg/100 ml) in Clear Aqueous Dispersions of Glyceride/Copolymer Blends

Copolymer	Labrasol/Copolymer		Labrafil/Copolymer		Labrafac/Copolymer	
T304	80:20 *w/w*	60:40*w/w*	80:20*w/w*	60:40*w/w*	80:20*w/w*	60:40*w/w*
0.1 mM	19.58 (0.01)	4.40 (0.87)	2.67 (0.01)	22.26 (0.57)	5.31 (0.28)	6.54 (0.05)
0.5 mM	T	19.46 (0.81)	T	T	10.32 (0.06)	10.21 (0.13)
1 mM	T	19.89 (2.55)	T	T	12.21 (0.75)	21.56 (3.34)
5 mM	T	T	T	T	T	T
T904						
0.1 mM	3.25 (0.12)	3.35 (0.29)	3.14 (0.02)	4.69 (0.25)	7.37 (0.01)	26.44 (1.03)
0.5 mM	5.46 (0.07)	2.67 (0.02)	T	T	13.13 (0.18)	54.75 (6.72)
1 mM	14.25 (0.65)	9.07 (0.70)	T	T	T	T
5 mM	65.60 (5.36)	29.48 (1.24)	PS	PS	PS	PS
T1307						
0.1 mM	T	T	PS	T	T	T
0.5 mM	27.95 (0.49)	36.31 (0.05)	PS	PS	PS	PS
1 mM	34.13 (3.90)	17.55 (2.26)	PS	PS	PS	PS
5 mM	19.18 (3.26)	9.05 (0.20)	W	W	PS	PS
PF127						
0.1 mM	13.71 (0.35)	8.17 (0.03)	T	T	T	T
0.5 mM	24.15 (0.14)	7.97 (0.01)	T	T	T	T
1 mM	13.37 (0.60)	12.61 (0.01)	T	T	T	T
5 mM	T	62.42 (0.71)	T	T	T	PS

Copolymer concentration is indicated in the first column. Mean values and, between brackets, standard deviations
T Turbid, *W* white, *PS* phase separation

Solubilization of Griseofulvin in Copolymer Solutions

Griseofulvin is a representative Class II drug. Griseofulvin absorption from the gastrointestinal tract is variable and incomplete mainly because of the difficulty of achieving in vivo solubility enough to dissolve the commonly used doses (100–250 mg). The pH-independent solubility of griseofulvin makes the evaluation of the incidence of pH on the performance of the formulation as solubilizing system feasible. The solubility of griseofulvin significantly increased in copolymer solutions of concentration above CMC (Fig. 4). Compared to PF127, Tetronics showed an even greater solubilization capability between 0.1 and 10 mM, particularly in the case of T904. The molar solubilization capacity, χ, and the micelle–water partition coefficient, *P*, calculated for a 5 mM copolymer concentration (except for T304 which was 60.6 mM being well above CMC), and the standard free energy of solubilization, ΔG_s^0 , are shown in Table I. The values of this last parameter indicate that the process of incorporation of the drug to the micelles was, in all cases, spontaneous, and that T904 and T1307 have an even greater solubilization capacity of griseofulvin than PF127. To solubilize one mol of griseofulvin, 41 mol of T304, 20.8 mol of T904, 20.4 mol of T1307, or 50 mol of PF127 are required. The ratios obtained are similar or even better than the ratios previously found for other surfactants such as cholate (321 mol), deoxicholate (394 mol), sodium dodecylsulfate (16.7 mol), cetyl trimethyl ammonium bromide (18.2 mol), Tween 80 (62.5 mol), or Cremophor EL (39.2 mol) (31,32). The drug/copolymer molar ratios together with the relatively low CMC of T904, T1307 and PF127 suggest that the evaluated copolymers could act as efficient solubilizer agents, able to form micellar systems resistant to the dilution when entering into contact with biological fluids.

Figure 5 shows the effect of the pH on the solubility of griseofulvin in 10% copolymer solutions. As expected, no influence of pH was observed for PF127 systems since PF127 concentration is well above CMC and the slight effect of salts on the self-aggregation becomes negligible. By contrast, the solubilization performance of Tetronic-based systems was clearly lower at acidic pH than at neutral-alkaline pH. Protonization of the central diamine group makes micellization more difficult and, consequently, there are less micelles available for hosting the drug.

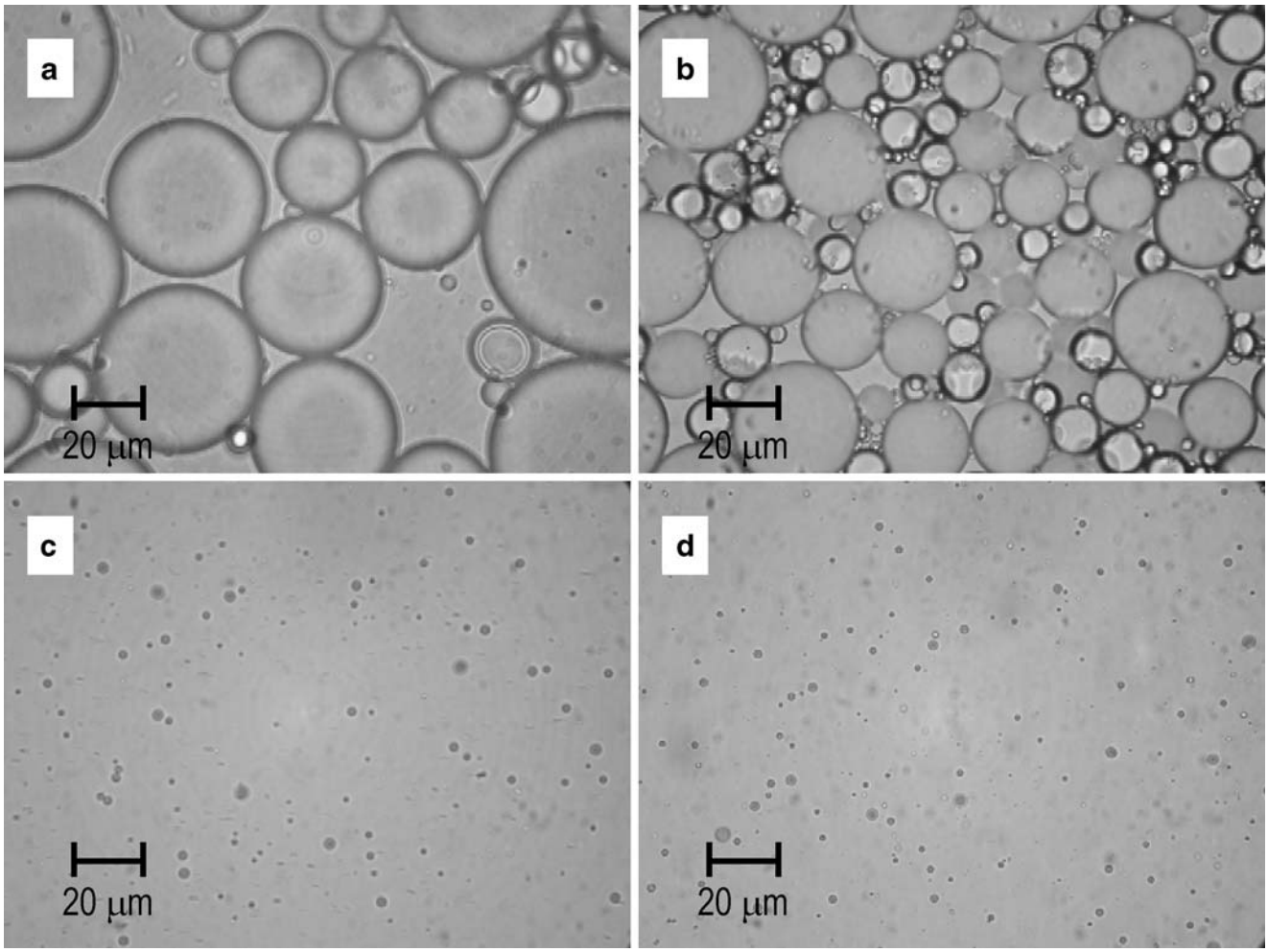

Fig. 6. Optical microscope view (×40) of **a** Labrafac/PF127 (1 mM) 80:20, **b** Labrafac/T1307 (0.5 mM) 80:20, **c** Labrasol:T1307 (1 mM) 60:40, **d** Labrasol:T904 (0.5 mM) 80:20 aqueous dispersions

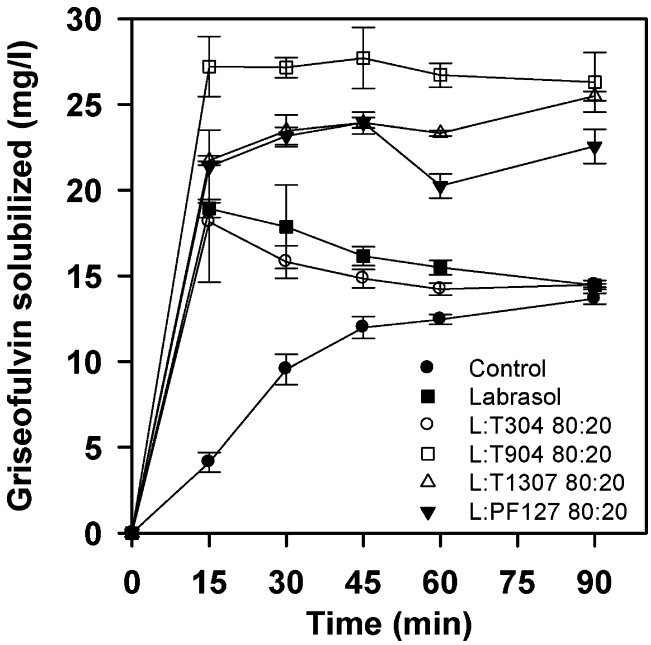

Fig. 7. Griseofulvin release rate in pH 7.4 phosphate buffer (900 ml) from capsules prepared with 100 mg drug and 900 mg excipient (i.e. Labrasol alone or mixed with T304, T904, T1307 or PF127 at a 80:20 weight ratio)

Glyceride/Copolymer Systems

Once the solubilization ability of the copolymers solutions was established, the next step was to evaluate the miscibility with various polyglycolyzed glycerides of different HLB which can act as oily phases or as co-surfactants in microemulsions formulations (33,34). The copolymers and the polyglycolized oils may form together colloidal structures like microemulsions particularly with glycerides of low HLB, such as Labrafil M 1944 CS (HLB 4) or Labrafac CC (HLB 1), or even mixed micelles with Labrasol (HLB 14). Before preparing the dispersions with both components, the solubility of griseofulvin in the pure glycerides (without adding water) was evaluated. Griseofulvin solubility ranged as follows: 248.6 (39.1) mg/100 ml of Labrasol, 85.2 (6.7) mg/100 ml of Labrafil, and 57.0 (5.2) mg/100 ml of Labrafac. Although the solubility was not directly tested in the pure copolymers due to the solid/paste consistency of most Tetronics and Pluronics, the results obtained with the copolymer solutions and the pure glycerides indicate that as a whole the solubility is largely promoted in media with components of intermediate HLB (12–18).

Glyceride/copolymer 80:20 or 60:40 *w*/*w* mixtures were dispersed in a volume of water adequate to achieve a copolymer concentration ranging between 0.1 and 5 mM (i.e. around or above CMC). The appearance of the systems is reported in Table II. T304 and T904 led to the most homogeneous systems with any glyceride. By contrast, T1307 and PF127, both of much higher HLB (22–24) were only miscible with Labrasol, which is the most hydrophilic glyceride evaluated. The systems that evidenced phase separation, or were off-white or turbid contained droplets of much greater size (20–60 μm) than the clear-translucent systems (<1 μm; Fig. 6). Griseofulvin solubility could only be evaluated in the few mixtures that really provide microemulsions (Table II). In some glyceride/copolymer aqueous dispersions the solubility of griseofulvin was markedly greater than in the copolymer alone solution, although in no case was the solubility observed in the pure glyceride attained.

SMEDD Capsules

To gain an insight into the repercussions of the observed increases in drug solubility on the dissolution rate from a solid dosage form, capsules were prepared containing 100 mg of drug and 900 mg of Labrasol alone or mixed with each copolymer at a 80:20 weight ratio. All mixtures had a viscosity low enough to make the filling of the capsules through the needle of a syringe possible after mixing with the drug and heating at 60 °C. Two different types of dissolution experiments were carried out: (1) the classical test using the type II USP apparatus with 900 ml of buffer phosphate; and (2) a dissolution experiment using 200 ml medium to mimic the solvent volume (a glass of water) that is used in the BCS to estimate if a given amount of drug would have solubility problems when orally administered (28). In the case of the S(M)EDDS, the volume of the medium would be particularly relevant since self-aggregation and formation/stability of microemulsions are greatly conditioned by the volume of the external phase. Although this aspect has not received any adequate attention in previous papers, a better performance of S(M)EDDS when the volume of water is relatively low (as observed in Table II) may be expected.

Figure 7 shows griseofulvin release profiles in 900 ml medium. The presence of glyceride/copolymer 80:20 clearly promotes both dissolution rate and total solubility, despite the

Table III. Griseofulvin Dissolved (mg/l) from Capsules Immersed in 200 ml of Medium (Controls with Griseofulvin Alone Gave 20±0.5 mg/l)

	HCl 0.1 M		Water		pH 7.4 Phosphate Buffer	
Excipient	15 min	45 min	15 min	45 min	15 min	45 min
Labrasol	27.3	20.8	38.2	33.4	22.8	20.1
Labrasol/T304, 80:20	35.9	19.8	53.0	55.6	22.7	18.0
Labrasol/T904, 80:20	43.5	18.5	85.1	79.1	40.4	34.1
Labrasol/T1307, 80:20	77.8	26.3	69.1	77.3	58.2	40.3
Labrasol/PF127, 80:20	77.0	76.9	56.2	69.6	70.2	61.6

Deviations below 5%

copolymer concentration (0.016 mM PF127, 0.121 mM T304, 0.030 mM T904, and 0.011 mM T1307) being well below CMC, even when the content of the capsule is totally dispersed in the release medium. The most efficient system was the mixture containing T904. Capsules prepared with T1307 or PF127 had a slightly slower release rate which could be related to the gelation process of the copolymer/glyceride mixture when enters into contact with the medium at 37 °C. The other glyceride/copolymer capsules showed the maximum amount dissolved between 15–30 min, and then a more or less marked decrease in dissolved griseofulvin was observed. This phenomenon can be explained as follows: once the content of the capsule is wetted, a relatively high local concentration in glyceride and copolymer promotes self-association and formation of a microemulsion; then a micro-enviroment propitious for dissolving griseofulvin is created. As the system progressively dilutes in the bulk of the dissolution medium, some colloidal structures would disintegrate, releasing griseofulvin to water and causing a partial precipitation of the drug initially dissolved. The more stable the colloidal nanostructure (systems containing T904, T1307 or PF127), the less the precipitation.

Table III summarizes the results of the dissolution experiments carried out in 200 ml medium. In general, greater drug solubility values are attained using this volume than 900 ml, which indicates that the volume of the medium is a critical variable when evaluating the performance of S(M) EDDS. The general criteria applied to drug dissolution from solid dosage forms, exclusively based on drug solubility (searching for sink conditions), should be revised when evaluating a S(M)EDDS.

A clear effect of both pH and time was also observed. The lower the pH was, the lower the solubilization capability of Tetronic-containing capsules and the greater the instability of the colloidal system. Samples were taken at 15 min after beginning the experiment and observed under light microscope. In the case of capsules containing T304 and T904 (with low molecular weight and short PPO blocks) no colloidal structures could be observed in HCl 0.1 M, which explains that the drug solubility was similar to the value obtained without excipients. By contrast, in water or in pH 7.4 buffer the enhancement in solubility promoted by the glyceride/copolymer mixtures became evident. This effect was more remarkable in water since the Tetronics can provide a relatively more alkaline microenvironment than the buffer (as shown in Fig. 2), reducing the protonization of the central diamine group and enhancing the stability of the colloidal system. Observation of the release medium under optical microscope evidenced the formation of droplets of similar size to the droplets pictured in Fig. 6c,d. The pH-sensitiveness of the self-associative properties of Tetronics may be an advantage for some drugs that are unstable at acidic pH or that may cause untoward reactions if a fast dissolution in the stomach occurs.

CONCLUSIONS

Tetronic micellar systems are more, or at least equally, efficient to dissolve griseofulvin in water or alkaline medium than the micelles of Pluronic F127 or several other conventional surfactants. If adequate proportions and dilutions are used, T304, T904, T1307 and PF127 mixed with polyglycolyzed glycerides form clear or translucent colloidal systems in aqueous medium. SMEDDS capsules containing blends of Tetronic or Pluronic with Labrasol notably enhance griseofulvin solubility and dissolution rate, particularly when the volume of medium is equivalent to a glass of water, which should be taken with a solid oral dosage form. The results obtained also highlight the relevance of the pH of the medium on the performance of Tetronic-based SMEDDS.

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