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Controlled Release Camptothecin Tablets based on Pluronic and Poly(acrylic acid) Copolymer. Effect of Fabrication Technique on Drug Stability, Tablet Structure, and Release Mode

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ABSTRACT Poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-(polyethylene oxide)-*g*-poly(acrylic acid), a graft-comb copolymer of Pluronic® 127 and poly(acrylic acid) (Pluronic-PAA), was explored as an excipient for tablet dosage form of camptothecin (CPT). The tablets were prepared by either direct compression of the drug-polymer physical blend, suspension in ethanol followed by evaporation, or compression after kneading and characterized with respect to their physical structures, drug stability, and release behavior. Porosity and water uptake rate were strongly dependent on the fabrication procedure, ranking in the order: direct compression of physical blend > compression after suspension/evaporation in ethanol > compression after kneading. Tablets prepared by compression of physical blends swelled in water with a rapid surface gel layer formation that impeded swelling and disintegration of the tablets core. These tablets were able to sustain the CPT release for a period of time longer than those observed with the tablets made by either suspension/evaporation or kneading, which disintegrated within a few minutes. Despite the tablet disintegration, the CPT release was impeded for at least 6 hr, which was attributed to the ability of the Pluronic-PAA copolymers to form micellar aggregates at the hydrated surface of the particles. Physical mixing did not alter the fraction of CPT being in the pharmaceutically active lactone form, whilst the preparation of the tablets by the other two methods caused a significant reduction in the lactone form content. Tablets prepared from the physical blends demonstrated CPT release rates increasing with the pH due to the PAA ionization leading to the increase in the rate and extent of the tablet swelling. The results obtained demonstrate the potential of the Pluronic-PAA copolymers for the oral administration of chemotherapeutic agents.

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INTRODUCTION

Oral administration of chemotherapeutic agents, the oral chemotherapy, is gaining an increasing use (DeMario & Ratain, 1998; Glaberman et al., 2005). The oral chemotherapy is patient-friendly and can provide a prolonged exposure of the cancer cells to the anticancer drugs, resulting in greater antitumor activity (Gerrits et al., 1997). This may afford lowering of the dose and, consequently, the toxicity of the treatment. Additionally, the oral chemotherapy offers an improved cost/efficiency ratio, is more flexible in dosing schedule and results in a better patient compliance and improved quality of life (DeMario & Ratain, 1998; Sparreboom et al., 2002). Some of the agents that are being used in oral treatment of cancer include tamoxifen, paclitaxel, etoposide, and camptothecin (CPT) derivatives such as irinotecan and topotecan (Glaberman et al., 2005). However, there are several limitations for the general development of efficient oral treatments, mainly low drug stability and solubility in the gastrointestinal tract, inadequate absorption, and first-pass metabolism.

Formulation of the dosage forms of the CPT and its analogues should deal with the fact that CPT can readily convert from the pharmaceutically active, closed lactone E-ring to the open, inactive carboxylate form through pH-dependent equilibrium. The lactone form of CPT is usefully cytotoxic but its solubility in water is poor. At neutral pH of the upper intestine or the human serum, the CPT lactone rapidly hydrolyses to yield the carboxylate form, which is more water-soluble but inactive against tumors and is by far more toxic (Fassberg & Stella, 1992; Mi & Burke, 1994). To overcome the aforementioned hydrolytic processes as well as the poor solubility of the CPT, development of adequate drug carriers is gaining increasing attention. The approaches include methods such as intercalation into liposomes (Burke et al., 1992; Cortesi et al., 1997), solubilization in microemulsions (Cortesi et al., 1997), entrapment in microspheres (Shenderova et al., 1999; Tong et al., 2003), formation of inclusion complexes with cyclodextrins (Kang et al., 2002), and formulation in polymeric micelles (Barreiro-Iglesias et al., 2004; Watanabe et al., 2006). We have previously shown (Barreiro-Iglesias et al., 2004) that incorporation of CPT into micelles of Pluronic-PAA copolymer, which is a conjugate between Pluronic copolymer and poly(acrylic acid), increases solubility and enhances stability of the lactone form of CPT in an aqueous buffer (pH 8). Furthermore, when compared to the unprotected CPT, the CPT hydrolysis in human serum was about 10-fold slower in the Pluronic-PAA formulations. The Pluronic-PAA conjugate combines solubilization capability of the polyether surfactants and the pH-sensitivity and bioadhesive properties of a polyelectrolyte (Bromberg et al., 1998a,b, 2001). The CPT loading occurs both via solubilization into hydrophobic PPO cores of the micelles as well as entrapment into the interfacial layers between PPO and more hydrophilic POE-PAA layers. The swelling of the micellar shell layer is pH-dependent; the shell being compact due to stabilization by hydrogen bonds at pH below the pK_a of the carboxylic groups of PAA. This makes the Pluronic-PAA copolymer useful for the development of pH-responsive drug dosage forms, such as microgel suspensions (Bromberg et al., 2003) and tablets (Barreiro-Iglesias et al., 2005).

In the present work, we set out to evaluate several technologies of the tablet fabrication using the Pluronic (F127)-PAA copolymer as a main tablet component with the CPT as an active. The tablets were prepared using three different procedures: direct compression of physical mixtures, compression after kneading, and compression of a solid dispersion obtained by suspension/evaporation. Effects of the preparation methods on the structure of the resulting tablets (characterized by microporous structure and wettability) and on the tablet swelling pattern and CPT release rate were revealed.

MATERIALS AND METHODS

Materials

(S)-(+)-Campthotecin (95% by HPLC) was from Sigma-Aldrich (Spain). Poly(ethylene oxide)-b-poly(propylene oxide)-b-(polyethylene oxide)-g-poly(acrylic acid) copolymer (CAS #186810-81-1), in particular Pluronic F127-PAA, was synthesized by dispersion/emulsion polymerization of acrylic acid as described in detail previously (Bromberg, 1998a,b, 2001, 2002). After the synthesis, the copolymer was purified by repeated dissolution in 1 M aqueous NaOH and precipitation in 3 M HCl followed by filtering and lyophilization (7 days at −15°C and 0.009 mbar; LYPHLOCK6 freeze dry system 77530, Labconco, MS). Dried polymers were pulverized in a shear mill (IKA-Universalmühle M20,

Germany) and sieved through a 1-mm mesh. Polymer characterization was accomplished by NMR, IR, and chromatographic methods as described elsewhere (Bromberg, 1998a,b). The Pluronic:PAA weight ratio was measured to be 45:55; the mass-average molecular weight was 1.8 MDa, and the polydispersity index 1.8. The critical micellar concentration (CMC) of F127-PAA has been estimated to be 4×10^{-3} g/mL (Barreiro-Iglesias et al., 2004). The other reagents were of analytical quality.

Tablet Preparation

CPT tablets containing 4 mg of drug and 196 mg of copolymer were obtained by compression of mixtures prepared by three different procedures as follows: (i) physical blending of the Pluronic-PAA copolymer and CPT powders for 15 min at 30 rpm using a Turbula T2C mixer (WAB, Switzerland); (ii) kneading CPT and the copolymer with ethanol at solid/ethanol 1:3 w/v ratio using a mortar and pestle until a homogeneous paste resulted, which was oven-dried at 40°C for 12 hr until the ethanol was removed completely; and (iii) suspension-evaporation method consisting of preparation of a CPT/copolymer: ethanol 1:50 w:v dispersion that was stirred for two days followed by solvent removal at 40°C and pulverization of the mixture in a shear mill (IKA-Universalmühle M20, Germany) until most particles were of a size below 0.5 mm. The compression process was performed using a B-MT Bonals press (Spain) equipped with 9 mm flat punches and control instrumentation of pressure (Sensing Electronics, Spain). Piezoelectric force transducer was calibrated by Lorenz Messtechnik GmbH (Germany). Compression force was set at 10000 N in all cases. No lubricant was used. CPT tablets containing 2 mg of a drug and 198 mg of copolymer were prepared by compression of physical mixtures following the same procedure.

Tensile Strength

The tensile strength of the tablets was calculated using the equation (Fell & Newton, 1968):

$$TS = \frac{2 \cdot CS}{\pi \cdot D \cdot E} \qquad (1)$$

where CS is the crushing strength; D and E denote the tablet diameter and thickness, respectively. Parameters E and CS were measured in sextuplicate using a Mitutoyo digital micrometer (Japan) and a TB 2A Erweka apparatus (Germany), respectively.

Scanning Electron Microscopy (SEM)

Surface and cross-sectional areas of the tablets were visualized using a Jeol ISM-6060 Scanning Electron Microscope. Samples were mounted on double-sided tape on aluminum stubs and sputter-coated with gold, and micrographs were taken at appropriate magnification.

Porosity

Pore size distribution of each type of tablet was evaluated, in duplicate, by mercury-intrusion porosimetry using a Micromeritics 9305 pore size apparatus (Norcross, GA) with a 4.3-mL tablet penetrometer. Working pressures were within the range 0.8–25000 psi. The apparent density of the tablets was determined in triplicate with the aid of a helium pycnometer (Quantachrome MPY-2, Syosset, NY).

Sessile Drop Testing of Tablet Surface

Liquid contact angles and drop volumes were measured at room temperature in air with a relative humidity of approximately 30% using a sessile drop method with a Kruss DSA10 mk2 drop shape analyser (Kruss Charlotte, NC). Pure water surface tension was determined from pendant drops having volumes of 5–10 μL and were found to be 73 mN/m for water, in agreement with literature values (Wu, 1982). Advancing contact angles and drop volumes were measured immediately after the drop was placed on the surface with a small syringe and needle. Average initial drop volume was 1.2 μL. The contact angle and drop volume were taken through the water phase at a 1 s interval. The drop shape analysis software reported an average value of the measured data. Contact angles were obtained on at least four separate locations of each tablet sample and on at least three independently deposited tablets for each set of tablet series. The data obtained for each tablet series were averaged.

Swelling Behavior

Tablets were immersed in water on a Petri dish and their swelling was followed under an Olympus SZ-CTV

microscope connected to a video camera (Olympus DP12, Japan).

Structural Form of CPT Inside the Tablets

The status of the active ingredient of the tablets (CPT) was determined by measuring relative content of the lactone form of CPT in the tablets using previously established chromatographic method (Warner & Burke, 1997). Triethylamine acetate buffer (pH 5.5) was prepared by dissolving triethylamine (1 v/v%) in deionized water following pH adjustment by acetic acid. The buffer was then mixed with HPLC-grade acetonitrile (aqueous/organic phases ratio 23/77 v/v) and the resulting mixture was used throughout as a mobile phase. Each tablet was placed in 2 mL of water-free dimethylsulfoxide and gently stirred overnight resulting in a fine dispersion that was then diluted 10-fold by the above-described triethylamine acetate/acetonitrile buffer. Following vortexing and a 2-hr shaking, 100 μL of the liquid was withdrawn from the dispersion via a syringe fitted with a membrane filter (pore size, 0.2 μm) and analyzed by HPLC. Waters HPLC system included two 515 Pumps, a 2487 Dual Wavelength Absorbance Detector, a 717-plus Autosampler, and a Nova-Pak C_{18} (pore, 60 Å; particle size, 4 μm; 3.9×150 mm) HPLC column. The mobile phase was passed through the column at 1 mL/min in an isocratic regime and the CPT detection was set at 365 nm. Each tablet series was measured in quadruplicate and the lactone content was compared to that in a powder form CPT sample (control) that had been kept under the same environmental conditions as the tablets, but had not undergone any processing. A separate fraction of the control CPT sample was used in all of the tablets.

Release Profiles

Time-course of drug release were determined at 37°C in a Turu Grau apparatus (Spain) adapted to meet the specifications of the USP27-NF22 (2004) by a modification of method II. Tablets were held at the bottom of the vessel in a 2.8×2.8×1.1 cm rectangular basket made of 1.6 mm DIN steel mesh (Pérez-Marcos, 1991). CPT tablets with a content in drug of 4 mg were evaluated in 900 mL of deionized-distilled water (pH 5.5), at 50 rpm. CPT tablets prepared by compression of physical blends of 2 mg drug with Pluronic-PAA were evaluated in 900 mL of deionized-distilled water (pH 5.5), HCl solution (pH 3) and phosphate buffer pH 7.4 at 50 rpm. The dissolution rates of samples of 2 or 4 mg CPT powder were used as a reference. The concentration of the drug in periodically withdrawn samples was determined spectrophotometrically (HP Agilent, Germany) at 354 nm applying a validated method. To characterize the drug release profiles, the data ranged in between 10% and 70% of release were fitted to the following empirical relationship (Korsmeyer et al., 1983):

$$M_t / M_\infty = k \cdot t^n \qquad (2)$$

where M_t and M_∞ is the amount of drug released at time point t and infinite time, respectively, k is the release kinetics constant, and n is the diffusional constant.

RESULTS AND DISCUSSION

Tablets prepared by any of the applied procedures showed similar good mechanical properties, with tensile strength values of ca. 2 MPa and friability below 1%. However, the preparation process strongly influenced the tablets' internal structure, surface wetting ability, and drug release characteristics.

Typical SEM photographs of the cross-sectional area of each type of tablets under study are presented in Fig. 1. Physical blending resulted in larger particles with rough surface and larger voids than in tablets prepared by kneading and suspension/evaporation methods. The latter methods resulted in a tighter particle fusion and smoother surfaces of the voids. Porosimetry results confirmed these observations. Fig. 2 shows cumulative pore size distribution in the tablets fabricated by all three methods. Pores with diameters above 7 μ were predominant in all of the tablets. The percentage of the pore volume corresponding to the pores above this size is summarized in Table 1. A population of smaller pores around 0.01 micron can also be seen in Fig. 2, but these pores should play a minor role in the water penetration and the rate of tablet swelling. The Hg porosimetry results clearly indicated that, although the pore size distributions were similar for all tablets, the total porosity ranked in the order: *Physical mixture* > *Suspension-evaporation* > *Kneading*. The porosity

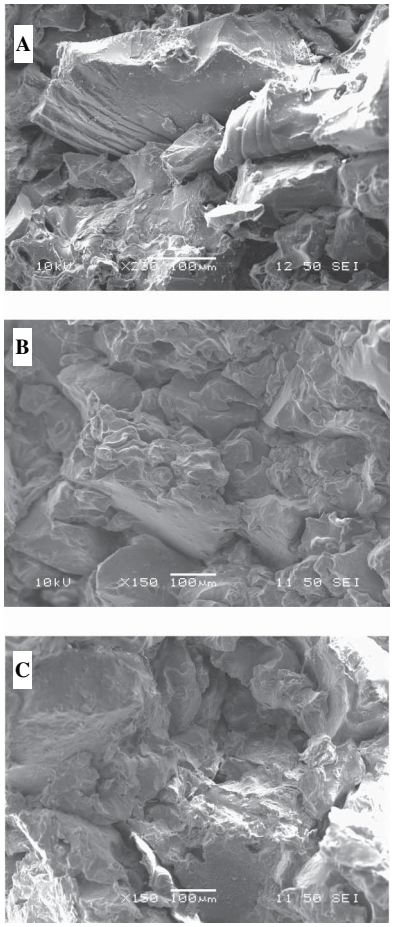

FIGURE 1 **SEM Micrographs of Cross-sections of Tablets made by (A) Physical Blending, (B) Kneading, and (C) Suspension/Evaporation Methods, Respectively.**

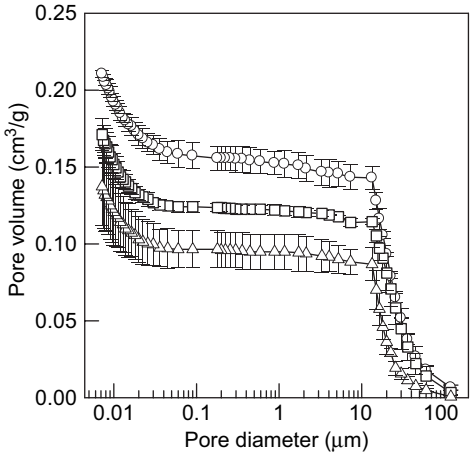

FIGURE 2 **Cumulative Pore Volume Distribution for the Tablets Prepared by Physical Blending (Circles), Suspension/ Evaporation (Squares) and Kneading (Triangles).**

values above a 10% indicates that most pores can be interconnected and form a percolating network inside the tablets structure (Holman, 1991; van Veen, 2005).

TABLE 1 **Physical Characteristics of the Tablets Prepared via the Fabrication Techniques Under Study**

Property	Physical blend	Suspension/ evaporation	Kneading
Apparent density (g/cm^3)	1.29 (0.01)	1.31 (0.01)	1.30 (0.01)
Total porosity (%)	21.1 (0.0)	18.1 (0.1)	14.3 (3.0)
Percentage of porosity due to pores > 7 μm	68 (3)	67 (3)	65 (6)

Water uptake is commonly determined by hydration studies that involve immersion of the matrix into an aqueous medium. Fig. 3 shows the aspects of the tablets at 30 min after the swelling commencement. Tablets prepared with the physical mixture swelled to

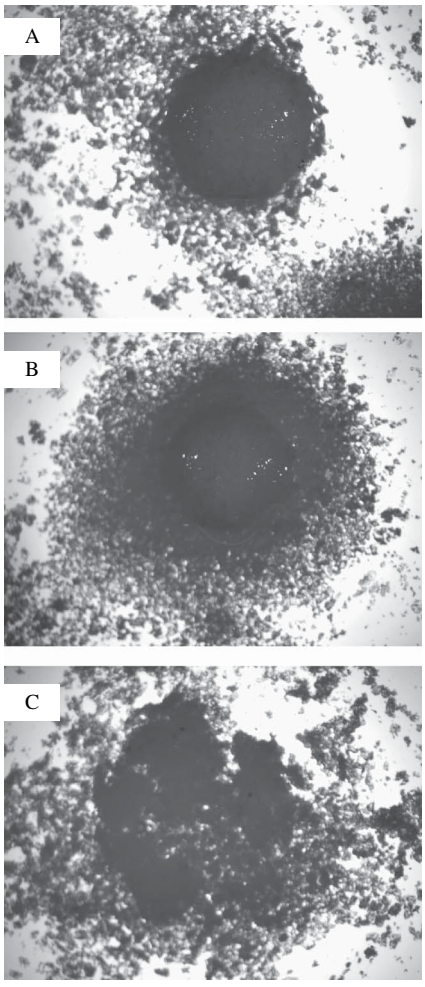

FIGURE 3 **Pictures of Tablets After 30 min of Being Immersed in Water: (A) Physical Mixture; (B) Suspension-Evaporation; (C) Kneading.**

a low extent in the first minutes and then the swelling decelerated and the shapes of the tablets were maintained for another 40 min. Tablets prepared using the suspension/evaporation procedure disintegrated within 25 min, without swelling. Finally, tablets prepared by kneading showed an intense swelling that caused the breakage and disintegration of the tablets within 30 min. The tablet swelling and disintegration leading to irregularly shaped pieces upon tablet immersion in water precluded us from the quantification of the capacity of the matrix to incorporate water.

Dynamic contact angle measurement of small sessile water drops on the tablet surface may be a more appropriate method than measurements of the tablet mass or volume, as the small drop size ensures the absence of drop deformation due to gravity, hence giving accurate contact angle values by axisymmetric drop shape analysis technique (Chan et al., 2006). Fig. 4 shows the drop volumes for single water droplets absorbing into the surfaces of the three tablet series under study. In each case the drops spread to a radius where the wetting line pinned in less than 100 ms, yielding contact angles between 79° and 106°. The high initial contact angles are indicative of the rather significant hydrophobicity of the surface, which however, rapidly decreased with the commencement of the wetting process. The absorption proceeded with the drop volume decreasing rapidly through the droplet imbibitions by the tablet pores. The predominance of the vertical imbibitions that occur via the water penetration through the pores in the overall water absorption process is evident from the linear dependence of the drop volume on $t^{0.5}$ (see inset in Fig. 4), predicted by the Lucas-Washburn theory of penetration into capillaries (Marmur, 2003). The rate scale of imbibition for the tablet series is in the order *Physical mixture* > *Suspension-evaporation* > *Kneading*, which corresponds to the tablet series with higher total porosity and porosity due to the pores exceeding 7 μm (see Table 1). This observation further confirms the effect of the methods of the tablet fabrication and resulting porosity on the tablet performance in water absorption. The kinetics of water absorption, in turn, is of paramount importance for the tablet performance in oral drug administration (Juang & Storey, 2003; Huang & Schwartz, 1995; Majid Khan & Zhu, 1999; Varma et al., 2005).

CPT release profiles in water are shown in Fig. 5. Tablets prepared with the physical mixture showed the slowest release pattern. These tablets, despite of having a greater total porosity, require more time to complete the disintegration than the ones obtained by kneading and suspension-evaporation (compare with Fig. 3). The release patterns may be explained as being the result of two concomitant effects: (i) rapid formation of a stiff gel layer in the surface of the most porous tablets (as described above), which controls the release of the drug and obstructs deeper layers of the tablet from swelling/dissolution. The formed gel consists of closely packed swollen particles additionally stabilized

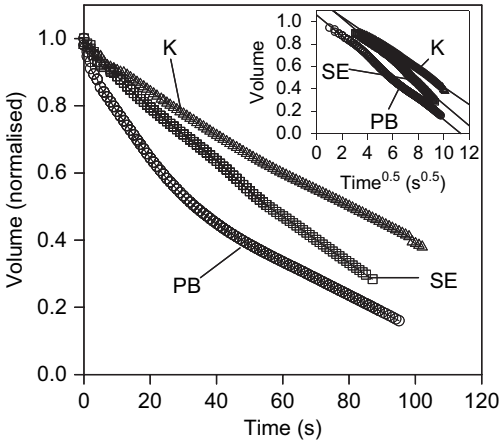

FIGURE 4 **Variation of Normalized Volume as a Function of Time for Water Droplets on the Tablet Series Made by Physical Blending (Circles, PB), Suspension/Evaporation (Squares, SE) and Kneading (Triangles, K). Inset Shows Volume *vs* Time$^{0.5}$ Plots With Linear Fits After 2–5 s of the Beginning of the Imbibition. For All Fits, $R^2 > 0.98$.**

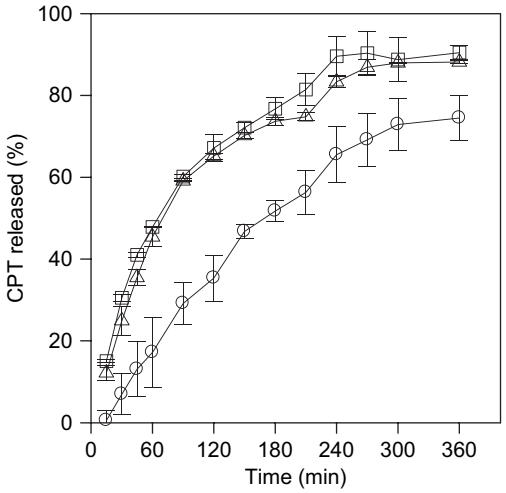

FIGURE 5 **Cumulative Release of Camptothecin in Water (pH 5.5) From Tablets Containing 4 mg of Drug and 196 mg of Pluronic-PAA, and Prepared by Physical Blending (Circles), Suspension/Evaporation (Squares) and Kneading (Triangles).**

by micellar aggregates of the poly(propylene oxide) segments of Pluronic, which delay drug release from the matrices.; (ii) possible changes in the drug structure that can occur during the processing with the polymer, before and/or during compression. The first effect has been reported for a variety of formulations in which the surface layer swelling formed a plug-like structure that prevented further swelling of the tablet core and lead to a slower drug release (Varma et al., 2005).

Fitting the experimental data in Fig. 5 to Eq. (2) yielded the values of n exponents (Table 2). The values of the constant n reflect on the prevalence of the Fickian diffusion or polymer relaxation/swelling effects, depending on the fabrication procedure. In the case of tablets made by direct compression of the physical blends, the observed $n \approx 0.5$ for a cylindrical tablet shape indicates prevalence of the Fickian diffusion through the swollen layers on the tablet surface. Conversely, the n values of ca. 0.7 obtained for tablets prepared using the other two procedures suggest an anomalous (non-Fickian) transport, which can be related to the contribution of the tablet disintegration/erosion to the release process. These results strongly corroborate the observation of the relative tablet erosion rate (Fig. 4). We should note that the self-assembly of the Pluronic-PAA macromolecules into micelles when their concentration exceeds that of the critical micellization concentration (CMC) could affect the drug release profile, since at the initial stages of the tablet swelling/dissolution the polymer concentration in the swelling and erosion fronts is above CMC. The drug entrapment into the micellar aggregates, themselves fixed in the erosion front, may further slower the overall release rate.

Taking into account the greater promise of sustained release from the tablets prepared by direct compression of the physical blends, further experiments were performed using these tablets to evaluate effects of pH on the release rate, in the pH ranges of the gastrointestinal tract. Release profiles plotted in Fig. 6 and n values collected in Table 3 clearly show that the release rate increased as the pH of the medium rose, and the Fickian diffusion was more prevalent at neutral pH. These findings can be explained by the increase in the rate of the tablet swelling with pH, due to the increased ionization of the carboxyl groups in the Pluronic-PAA copolymers. The dissociation of the carboxyl groups in the gel leads to the availability of protons. The electroneutrality of the hydrogel is maintained by cations such as Na^+ entering the gel along with the OH^- ions. The increased ion concentrations within the gel give rise to an osmotic pressure that causes the gel to swell. The higher the initial difference in the concentration of the base between the solutions inside and outside the gel at higher pH values, the higher is the osmotic pressure and thus the faster are the kinetics of the gel swelling. At acidic pH, the hydrogen bond formation among the PAA chains and the polyether blocks of Pluronic is promoted (Bromberg, 1998c,d; Bromberg & Temchenko, 1999). Thus, once the matrix tablet enters into contact with the pH 3 medium, the swelling is low, the tablet has no tendency to disintegrate and the drug can be efficiently retained in the matrix. In contrast, at pH above $pK_a \approx 5$ (Bromberg et al., 2003), the ionization of the carboxylic

TABLE 2 **Release Parameters Obtained by Fitting Eq. 2 to the Release Profiles Shown in Fig. 5**

Tablets	k (%·min^{-n})	n	R^2
Physical blend	5.57	0.50	0.994
Suspension/evaporation	2.93	0.66	0.962
Kneading	2.09	0.72	0.969

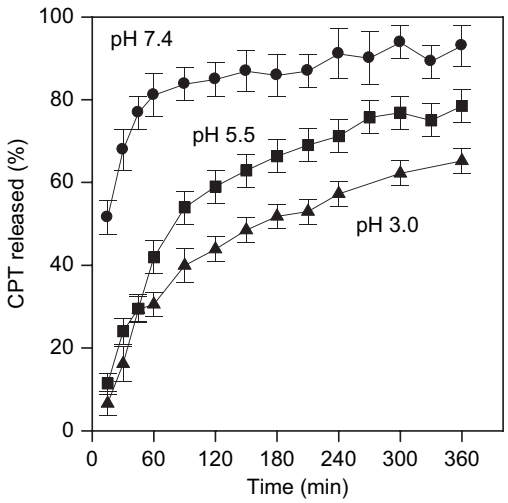

FIGURE 6 **Effect of pH on Cumulative Camptothecin Release From Tablets Made by Physical Blending.**

TABLE 3 **Release parameters obtained by fitting Eq. 2 to the release profiles shown in Fig. 6**

pH	k (%·min^{-n})	n	R^2
3.0	3.85	0.50	0.954
5.5	5.01	0.50	0.955
7.4	21.3	0.33	0.984

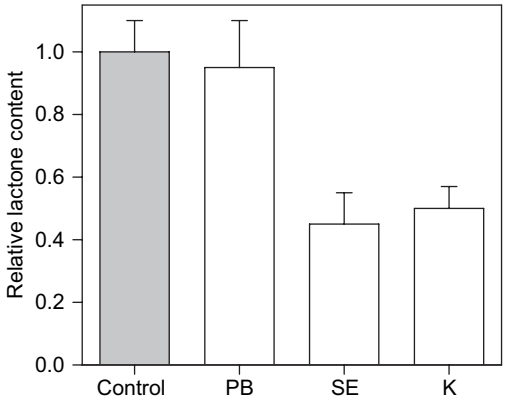

FIGURE 7 **Lactone Content in Tablets Fabricated by Various Procedures (Physical Blending PB, Suspension/Evaporation SE, and Kneading K) Relative to the CPT Control.**

groups lead to the mutual repulsion of the polymer chains, which swelled and eroded rapidly, resulting in the increase of the drug release rate. The analysis of drug profiles using Eq. (2) confirms the Fickian diffusion as the main mechanism of drug release in acid pH medium. In pH 7.4 buffer, the low values of the n exponent can come from a combined release mechanism consisting in the diffusion partially through the swollen matrix and partially through water-filled pores (Peppas, 1985). This last component is especially relevant owing to the fast swelling of the matrix when the copolymer is ionized.

Changes in the status of the active during tableting can be important in the case of CPT owing to the tendency of the lactone ring to open and become the carboxylate form, altering its stability and physical-chemical properties, especially the solubility. This aspect was studied by quantifying the proportion of CPT in lactone form present in the tablets using a previously established chromatographic method. Fig. 7 shows the relative lactone form fraction in the tablets compared to that in the CPT powder used to prepare them. Physical mixing did not alter the relative lactone content, while in the tablets made by the other two methods the lactone fraction was significantly reduced compared to the control. This increase in the carboxylate form may promote, to some extent, the dissolution rate of the drug inside the tablet and, as a consequence, its release.

CONCLUSION

Pluronic F127-PAA copolymer has been found to be a suitable excipient for preparing CPT tablets intended for oral chemotherapy. The polymer enabled a pH-dependent drug release and prevented the drug conversion from its lactone to carboxylic form, particularly when the tablets were obtained by direct compression of the physical blends of the CPT and copolymer. Very low release rates at pH below pKa of the carboxylic groups of the polymeric excipient and a more rapid release at neutral pH support a notion of a site-specific drug release in the lower gastrointestinal tract. Compared to the tablets obtained by kneading or suspension/evaporation that rapidly disintegrated in water, the tablets resulting from compressed physical blends demonstrated formation of a robust Pluronic-PAA gel layer surrounding the tablet core that was capable of slowing the drug release down. The CPT release from the tablets prepared by direct compression of physical blends was dominated by Fickian diffusion of the drug, while the tablets obtained by suspension/evaporation or kneading exhibited the release dominated by the tablet erosion.

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