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COMMUNICATION

Hydrogels Formed by Cross-Linked Polyvinylalcohol as Colon-Specific Drug Delivery Systems

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ABSTRACT

Polyvinylalcohol (PVA) of different molecular weights was cross-linked with succinyl, adipoyl, or sebacoyl chloride to obtain hydrogel-forming polymers and to determine their suitability as colon-specific drug delivery systems. Diclofenac sodium, propranolol hydrochloride, and vitamin B6 hydrochloride were used as hydrophilic model drugs with colon-specific release that should yield high concentrations in the large intestine, minimizing release in the upper part of the gastrointestinal tract. Spray-dried mixtures of the drugs and the polymer (at a 1 : 2 w/w ratio) were prepared, and the release of the drugs from the mixtures was evaluated in vitro at pH 2.0, 5.5, and 7.4. The results indicated the ability of the cross-linked polymers to slow the release of the drugs analyzed with respect to the pure drug dissolution at each pH. The lengthening of the cross-linker acyl chain was noted to decrease drug release further.

Key Words: *Colon-specific release; Cross-linked polyvinylalcohol; Hydrogels; Hydrophilic drugs; Spray-dried mixtures*

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INTRODUCTION

It is well known that the selective delivery of drugs to the colon is of interest for peptides and low molecular weight drugs for the treatment of colon diseases. The colon-specific delivery of drugs is mainly based on pH-sensitive polymers (1–6), matrices and prodrugs that undergo enzymatic degradation by colonic bacteria (7–12), and time-dependent delivery systems based on the relatively constant intestinal transit time (13,14). This work investigated the possibility of using polyvinylalcohol (PVA) cross-linked with succinyl (PVA-SU), adipoyl (PVA-AD), and sebacoyl (PVA-SE) chlorides (Fig. 1) as colon-specific release systems containing hydrophilic drugs. This was based on the possibility of obtaining drug-polymer interactions in solution, delaying the release beyond the gastrointestinal transit time. Polyvinylalcohol was selected because it is a biocompatible polymer and harmless to the human body (15), and the presence of the oxydryl groups allows cross-linkage by bifunctional cross-linking agents. We prepared spray-dried mixtures of the cross-linked polymers and the drugs and evaluated their main physicochemical characteristics in relation to their functional properties.

EXPERIMENTAL

Materials

Polyvinylalcohol (molecular weights [MW] of 10,000, 15,000, 49,000, 100,000); succinyl, adipoyl, sebacoyl chlorides; diclofenac sodium; propranolol hydrochloride; and vitamin B6 hydrochloride were from Fluka, and all the solvents employed were from Carlo Erba (Milan, Italy).

Preparation of the Cross-Linked Polyvinylalcohols

The cross-linked polyvinylalcohols (Fig. 1) were prepared by dissolving the polymer (1.23 g, 25 mmol of monomer) in 20 ml of anhydrous *N*-methylpyrrolidone at 50°C and subsequently adding the cross-linkers succinyl, adipolyl, or sebacoyl chlorides in amounts corresponding to 1 : 10, 1 : 50, 1 : 100 moles cross-linker per moles monomer. Stirring was carried out at room temperature for 24 h. Thin-layer chromatography (TLC) indicated maximum conversion (stationary phase silica gel, mobile phase *N*-methylpyrrolidone : diethylether 9 : 1 v/v).

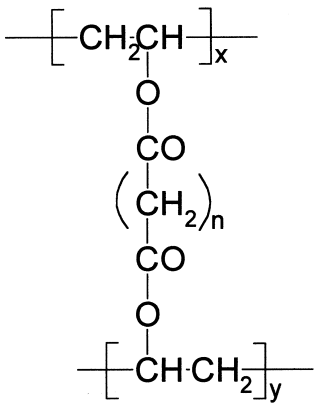

Figure 1. Structure of PVA with cross-linkers of succinyl (SU) ($n=2$), adipoyl (AD) ($n=4$), and sebacoyl (SE) ($n=8$).

The solution obtained was supplemented with diethyl ether to induce precipitation of the substituted polymer. The product was subsequently dissolved in water and dialyzed against water for 24 h using a cellulose membrane (MW co 10,000). The dialyzed solution was finally spray-dried to obtain the solid polymer.

The degree of cross-linkage of the polymer was determined by elemental analysis performed using a Perkin Elmer model 240B elemental analyzer. Infrared spectra were taken with a Hitachi 275-50 infrared spectrophotometer.

Preparation of the Drug-Polymer Spray-Dried Mixtures

Drug and polymer solid mixtures in a 1 : 2 w/w ratio were solubilized in water at a concentration of 6 mg/ml. The solutions were spray-dried, and a fine, spherically shaped, homogeneously dispersed powder was obtained; the particle diameters ranged from 2 to 10 μm.

DLS Measurements of the Polymer Size in Aqueous Solution

The size of PVA and cross-linked PVA in the aqueous buffers was measured to evaluate the gelling properties of the cross-linked polymers. The measurements were carried out by an instrument equipped with a 50-mW He–Ne laser (532 nm) and thermoregulated at 37°C (90 Plus Particle Sizer Analyzer, Brookhaven, NY). The solutions of the

polymers were prepared at 0.7 mg/ml because at lower concentrations the decreased mean count rate hindered the measurements and at higher concentrations multiple light scattering appeared. The solutions of the polymers were filtrated by a 0.22-μm filter (Millex-HV, Millipore) before measurement.

Measurements were carried out by fixing the scattering angle at 90°. Results were the combination of three 5-minute runs for a total correlation function (ACF) accumulation time of 15 min. The diffusion coefficient was evaluated from the time autocorrelation function $g^2(\tau)$ using the forced single-exponential fit (Eq. 1):

$$g^2\tau = Ae^{-2\Gamma\tau} + B \tag{1}$$

$$\Gamma = D\boldsymbol{q}^2 \tag{2}$$

$$\boldsymbol{q} = \left(\frac{4\pi n}{\lambda_o}\right)\sin\frac{\theta}{2} \tag{3}$$

where τ is the delay time, both A and B are constants, D is the translational diffusion coefficient, $\boldsymbol{q}$ is the scattering vector, n is the refractive index of pure solvent, λ_0 is the wavelength of incident light in vacuo, and θ is the scattering angle. The hydrodynamic radius R_H was calculated using the Einstein-Stokes equation:

$$R_H = \frac{k_B T}{6\pi\eta D_0} \tag{4}$$

where k_B, T, and η are the Boltzmann constant, the absolute temperature, and the solvent viscosity, respectively.

Partition Coefficient of the Drugs Between the Polymer and the Aqueous Solution

The partition coefficient at 37°C of the drugs between the cross-linked polymer solubilized in the aqueous buffer and the aqueous phase was evaluated by determination, after 24 h, of the free drug in the solutions containing the drug and the polymer. The solutions were obtained by dissolving the polymer (20 mg) in 10 ml of the aqueous buffer and adding the drugs at concentrations compatible with their solubilities: diclofenac sodium at 1 mg/ml in pH 7.4, 0.1 mg/ml in pH 5.5, and 0.03 mg/ml in pH 2.0; propranolol hydrochloride and vitamin B6 hydrochloride at 1 mg/ml in each pH analyzed. The free drug was spectrophotometrically determined in the aqueous phase obtained by ultrafiltration (10,000 MW cutoff; ultrafilter device Lida) of the solutions containing the drug and the polymer.

In Vitro Release Studies

The spray-dried mixtures (30 mg) or the pure drug (10 mg) were placed in a donor cell containing 3 ml of aqueous buffer (pH 2.0, 5.5, 7.4) separated by a dialysis membrane (MW cutoff 10,000) from a receiving compartment containing 10 ml of the same aqueous buffer used in the donor cell, which was replaced after time intervals suitable to guarantee sink conditions throughout the runs. The system was thermostated at 37°C. The drug was spectrophotometrically analyzed in the receiving phase over time. The cross-linked polymers treated in the same way as the coprecipitates were used as blanks.

RESULTS AND DISCUSSION

Characterization of the Substituted Polymers

The infrared spectra (KBr) of the cross-linked PVA showed the absorption band of the ester carbonyl at 1730 cm^{-1} resulting from the linkage of PVA with the cross-linker. Elemental analysis revealed cross-linking degrees corresponding to the cross-linker : monomer ratio used in the preparative solution only at the lower cross-linking : monomer ratio (1 : 100) and the lower PVA molecular weight (10,000), while at the higher ratios and PVA molecular weights, the cross-linking degree strongly decreased with respect to the cross-linker : monomer ratio used in the preparative solution, indicating an incomplete reaction of the cross-linker with the monomers. Thus, only the 1 : 100, 10,000 MW cross-linked PVA was selected for the present study.

DLS Studies on the Polymers in Aqueous Solution

Table 1 reports the hydrodynamic diameters of PVA and cross-linked PVA solubilized at 37°C in the different buffers; it shows that the PVA was always smaller than the cross-linked PVA, suggesting the ability of the cross-linked polymers to swell in an aqueous environment, forming nanogelled structures. The nanogels decreased in size from PVA-SU to PVA-AD and PVA-SE, indicating that the lengthening of the acyl chain of the cross-linker decreases the hydrophilicity of the cross-linked

structure. The pH of the aqueous buffer did not significantly influence the hydration ability of the cross-linked polymers.

Partition Coefficient Studies

The partition coefficient of the drugs between the polymer and the aqueous phase increased by lengthening the acyl chain of the cross-linking agent because the decrease in hydrophilicity of the cross-linked polymer favored its interaction with the drugs. The drug-polymer interaction was also favored by a decrease in hydrophilicity of the drug, as evidenced by the higher partition coefficient of diclofenac sodium with respect to propanolol hydrochloride and vitamin B6 hydrochloride (Table 2). The decrease in pH strongly increased the partition coefficient of diclofenac sodium, according to its conversion to the hydrophobic acid, and did not significantly influence the partition coefficient of propranolol hydrochloride and vitamin B6 hydrochloride, according to their high solubility in both protonated and deprotonated forms.

Table 1

Mean Diameter (nm) ± DS at 37°C of the Cross-Linked Polyvinyl Alcohol (PVA) in Aqueous Buffers at 0.7 mg/ml[a]

	Mean Diameter at Buffer pH		
Polymer Type	2.0	5.5	7.4
PVA	64.1 ± 0.2	66.0 ± 0.2	65.4 ± 0.2
PVA-SU	95.4 ± 0.4	86.7 ± 0.5	90.8 ± 0.9
PVA-AD	85.2 ± 0.6	77.1 ± 0.7	83.2 ± 0.6
PVA-SE	84.7 ± 0.5	84.3 ± 0.3	80.3 ± 0.8

Level of significance $p \leq .01$.
AD, adipoyl; SE, sebacoyl; SU, succinyl.
[a]Each value represents the mean of experiments.

Release Behavior

Free drug availability, expressed as fractional release over time (Figs. 2–4) or fractional amount released after 4 h (Table 3), was lower from the spray-dried mixtures than from the pure drugs at each pH analyzed. This may be attributed to the establishment of interactions between the drug and the gelled polymer in solution, which decreases the free drug concentration in the releasing aqueous phase. The enhancement of these interactions, expressed by the enhanced partition coefficient (Table 2), was expected to decrease the free drug availability further. Indeed, the reduction in the free drug availability from the polymer with respect to the pure drug was more evident for diclofenac sodium than propranolol hydrochloride and vitamin B6 hydrochloride due to the higher partition coefficient of diclofenac sodium, and for each drug analyzed, the free drug availability decreased from

Table 2

Partition Coefficients ± DS of Diclofenac Sodium, Propranolol Hydrochloride, and Vitamin B_6 Hydrochloride Between the Cross-Linked Polyvinylalcohol (PVA) and the Aqueous Buffers at 37°C[a]

		Partition Coefficient at Buffer pH		
Polymer Type	Drug	2.0	5.5	7.4
PVA-SU	Diclofenac sodium	2909.5 ± 12.2	871.6 ± 13.1	104.0 ± 5.3
	Propranolol hydrochloride	33.3 ± 1.4	33.4 ± 1.3	36.3 ± 1.7
	Vitamin B_6 hydrochloride	16.6 ± 0.7	16.9 ± 0.3	34.0 ± 1.2
PVA-AD	Diclofenac sodium	2990.1 ± 13.3	912.5 ± 15.6	152.9 ± 8.2
	Propranolol hydrochloride	33.9 ± 0.9	33.8 ± 1.3	37.9 ± 1.3
	Vitamin B_6 hydrochloride	19.1 ± 1.9	19.2 ± 1.9	34.7 ± 1.2
PVA-SE	Diclofenac sodium	3082.2 ± 14.1	1161.3 ± 16.5	193.5 ± 9.0
	Propranolol hydrochloride	34.2 ± 1.4	34.7 ± 1.5	39.0 ± 1.5
	Vitamin B_6 hydrochloride	21.3 ± 2.2	26.1 ± 1.0	34.9 ± 1.6

Level of significance $P \leq .05$.
AD, adipoyl; SE, sebacoyl; SU, succinyl.
[a]Each value represents the mean of 3 experiments.

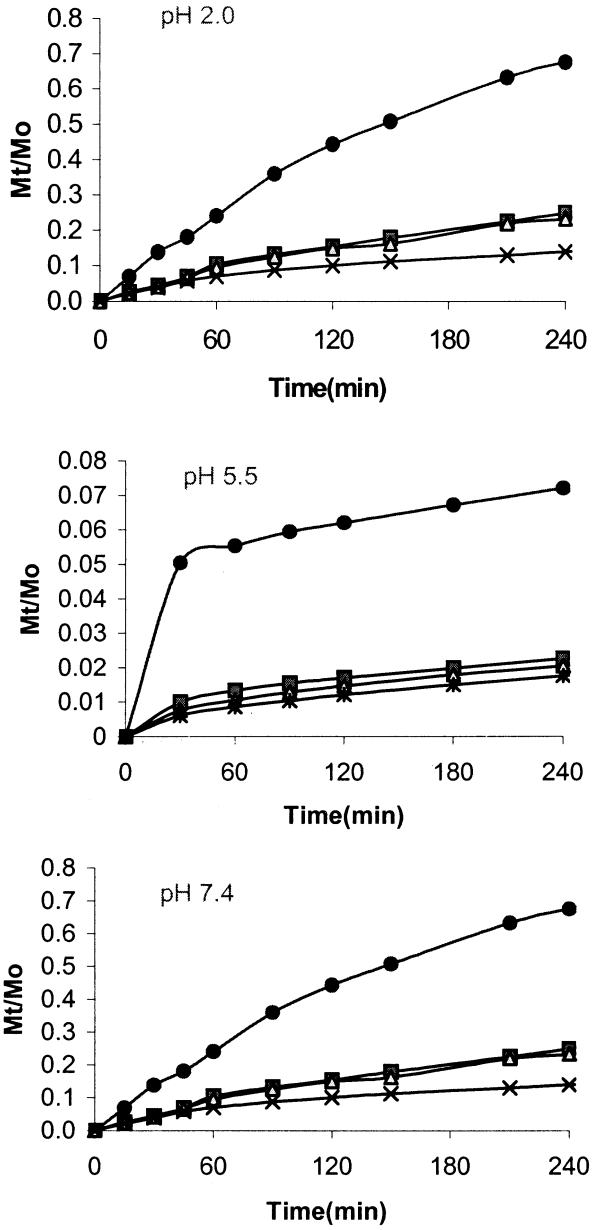

Figure 2. Release of diclofenac sodium at pH 2.0 to 7.4 from ■, PVA-SU/diclofenac sodium (2 : 1 w/w) spray-dried mixture; ▲, PVA-AD/diclofenac sodium (2 : 1 w/w) spray-dried mixture; * PVA-SE/diclofenac sodium (2 : 1 w/w) spray-dried mixture; and ● dissolution of spray-dried diclofenac sodium at pH 2.0 to 7.4.

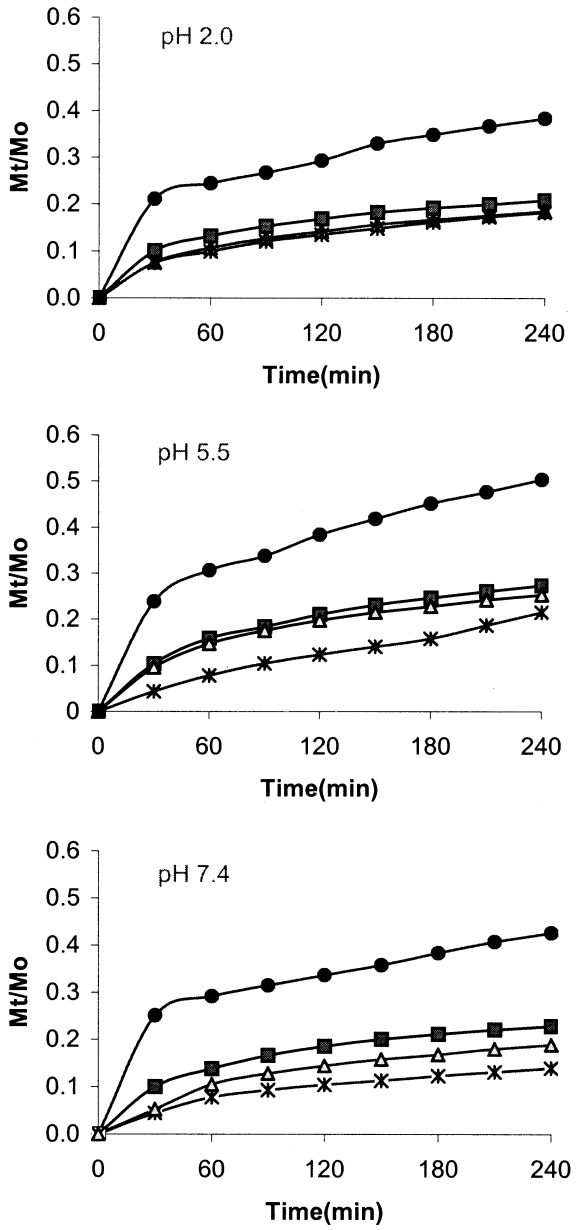

Figure 3. Release of propranolol hydrochloride at pH 2.0 to 7.4 from ■, PVA-SU/propranolol hydrochloride (2 : 1 w/w) spray-dried mixture; ▲, PVA-AD/propranolol hydrochloride (2 : 1 w/w) spray-dried mixture; * PVA-SE/propranolol hydrochloride (2 : 1 w/w) spray-dried mixture; and ●, dissolution of propranolol hydrochloride at pH 2.0 to 7.4.

PVA-SU to PVA-AD to PVA-SE according to the increase in the partition coefficient.

As regards the suitability of these polymers as colon-specific drug delivery systems, Table 3 shows that the maximum fractional amount released after the mean residence time in the stomach (pH about 2.0 and mean residence time about 4 h) and the small intestine (pH ranging from 5.5 to about 7.4,

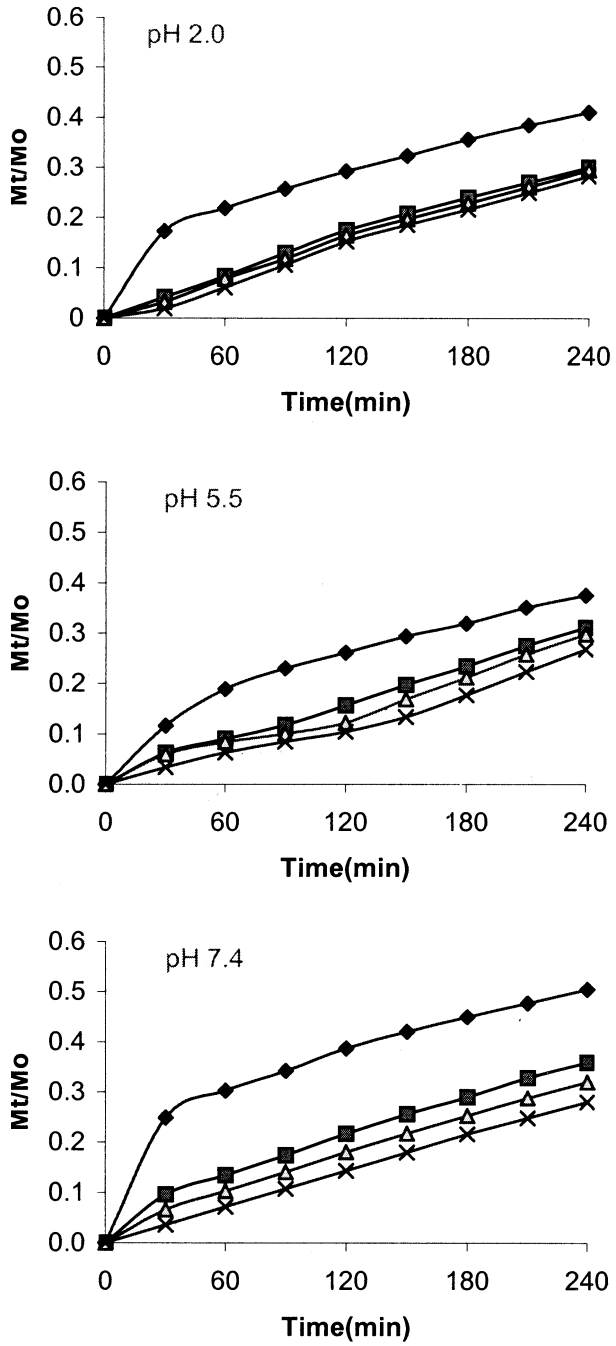

Figure 4. Release of vitamin B_6 hydrochloride at pH 2.0 to 7.4 from ■, PVA-SU/vitamin B_6 hydrochloride (2 : 1 w/w) spray-dried mixture; ▲, PVA-AD/vitamin B_6 hydrochloride (2 : 1 w/w) spray-dried mixture; * PVA-SE/vitamin B_6 hydrochloride (2 : 1 w/w) spray-dried mixture; and ●, dissolution of vitamin B_6 hydrochloride at pH 2.0 to 7.4.

mean residence time 8 h) (16) were 0.27 ($0.0023 + 0.0226 + 0.2490 = 0.2739$) for diclofenac sodium, 0.71 ($0.2084 + 0.2732 + 0.2283 = 0.7099$) for propranolol hydrochloride, and 0.97 ($0.2997 + 0.3110 + 0.3591 = 0.9698$) for vitamin B6 hydrochloride, indicating that a significant delay in release after gastrointestinal transit may only be obtained in the presence of diclofenac sodium, the drug that most strongly interacted with the polymers analyzed. Moreover, a minimum of 0.7249 and a maximum of 0.9287 fractional amounts of diclofenac sodium were released in 30 h at pH 7.4, indicating that most of the release took place after gastrointestinal transit in time periods compatible with the residence time in the large intestine (6–72 h) (16).

The kinetic analysis of release, conducted according to the general equation $Mt/Mo = kt^n$ (17), revealed different kinetic behaviors in the presence of the different drugs. In the presence of diclofenac sodium, the release kinetics ranged from Fickian to anomalous (n values increasing from a minimum of 0.40 to a maximum of 0.78; Table 3) with increasing pH and decreasing length of the cross-linking agent (i.e., decreasing the drug-polymer partition coefficient). This indicates that the decrease in drug-polymer affinity increases the drug diffusibility through the gel shifts the release from diffusion controlled to dissolution controlled. Thus, in the presence of pH values favorable to drug release, an almost constant release rate may be obtained. In the presence of propranolol hydrochloride and vitamin B6, the n values ranged from 0.60 to 0.66 and from 0.75 to 1.06, respectively, indicating release kinetics that were anomalous and approaching zero order. No significant differences were observed among the different polymers and the different pH. This behavior may be attributed to the weak drug-polymer affinity favoring drug diffusibility in the gelled polymer and strongly shifting the release toward a dissolution-controlled mechanism.

CONCLUSIONS

Polyvinylalcohol cross-linked with succinyl, adipoyl, or sebacoyl chloride provided nanogelled structures in an aqueous environment able to interact with hydrophilic drugs such as diclofenac sodium, propranolol hydrochloride, and vitamin B6 hydrochloride. The drug-polymer interactions increased with decreasing drug hydrophilicity. The

Table 3

Fractional Drug Amount Released After 4 h ($Mt/Mo_4 \pm DS$) and After 30 h ($Mt/Mo_{30} \pm DS$) from the Different Spray-Dried Mixtures and Fractional Amount Dissolved from the Pure Drug at the Various pH—Diffusional Exponent Values ($n \pm DS$) Obtained from the Different Systems[a]

Polymer Type	Buffer pH	(Mt/Mo_4)	(Mt/Mo_{30})	n
Diclofenac sodium				
PVA-SU	2.0	0.0023 ± 0.0001		0.49 ± 0.05
	5.5	0.0226 ± 0.0005		0.60 ± 0.01
	7.4	0.2490 ± 0.0393	0.9287 ± 0.0077	0.78 ± 0.10
PVA-AD	2.0	0.0021 ± 0.0001		0.46 ± 0.11
	5.5	0.0204 ± 0.0030		0.58 ± 0.03
	7.4	0.2332 ± 0.0215	0.8104 ± 0.0081	0.65 ± 0.04
PVA-SE	2.0	0.0012 ± 0.0005		0.40 ± 0.03
	5.5	0.0176 ± 0.0007		0.52 ± 0.05
	7.4	0.1390 ± 0.0112	0.7249 ± 0.0043	0.63 ± 0.04
Pure drug	2.0	0.0209 ± 0.0002		
	5.5	0.0721 ± 0.0007		
	7.4	0.6752 ± 0.0034	1.0000 ± 0.0000	
Propranolol hydrochloride				
PVA-SU	2.0	0.2084 ± 0.0210		0.65 ± 0.02
	5.5	0.2732 ± 0.0395		0.65 ± 0.03
	7.4	0.2283 ± 0.0254	0.7112 ± 0.0049	0.60 ± 0.03
PVA-AD	2.0	0.1853 ± 0.0174		0.63 ± 0.03
	5.5	0.2529 ± 0.0297		0.66 ± 0.04
	7.4	0.1893 ± 0.0175	0.5899 ± 0.0032	0.60 ± 0.05
PVA-SE	2.0	0.1823 ± 0.0154		0.65 ± 0.04
	5.5	0.2150 ± 0.0292		0.63 ± 0.06
	7.4	0.1393 ± 0.0125	0.5623 ± 0.0042	0.62 ± 0.04
Pure drug	2.0	0.3837 ± 0.0025		
	5.5	0.5033 ± 0.0091		
	7.4	0.4259 ± 0.0085	0.7774 ± 0.0055	
Vitamin B_6 hydrochloride				
PVA-SU	2.0	0.2997 ± 0.0187		0.95 ± 0.04
	5.5	0.3110 ± 0.0274		0.80 ± 0.06
	7.4	0.3591 ± 0.0285	0.8176 ± 0.0083	0.75 ± 0.05
PVA-AD	2.0	0.2952 ± 0.0181		0.90 ± 0.05
	5.5	0.2975 ± 0.0252		0.79 ± 0.06
	7.4	0.3197 ± 0.0299	0.8101 ± 0.0079	0.77 ± 0.05
PVA-SE	2.0	0.2830 ± 0.0397		1.06 ± 0.06
	5.5	0.2679 ± 0.0421		0.97 ± 0.06
	7.4	0.2803 ± 0.0301	0.8076 ± 0.0075	0.99 ± 0.06
Pure drug	2.0	0.4101 ± 0.0081		
	5.5	0.3748 ± 0.0031		
	7.4	0.5045 ± 0.0099	0.8326 ± 0.0089	

Level of significance $P \leq .01$.
AD, adipoyl; SE, sebacoyl; SU, succinyl.
[a]Each value represents the mean of experiments.

drug-polymer systems characterized by the strongest interactions, such as those obtained in the presence of diclofenac sodium, may delay drug release for periods compatible with gastrointestinal transit, thus appearing good candidates for colon-specific release. The drug-polymer systems characterized by the weaker interactions, such as those obtained in the presence of propranolol hydrochloride and vitamin B6 hydrochloride, provided high release rates unsuitable for colon-specific release, but had release kinetics approaching zero order, making them good candidates for the control of hydrophilic drug release after oral administration.

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