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RESEARCH PAPER

Plasticizer Effect and Comparative Evaluation of Cellulose Acetate and Ethylcellulose–HPMC Combination Coatings as Semipermeable Membranes for Oral Osmotic Pumps of Naproxen Sodium

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ABSTRACT

The objective of this study was to compare the performance of cellulose acetate (CA) and ethylcellulose (EC)–HPMC combination coatings as semipermeable membranes (SPMs) for osmotic pump tablets (OPTs) of naproxen sodium (NPS) so as to deliver a constant, predetermined amount of drug in solution form over a fixed span of time, independent of external environmental conditions. Osmotic pump tablets were designed with different coating variables and optimized in terms of nature of plasticizer, membrane thickness, and orifice diameter. The effect of insertion of an inner microporous film around the NPS core to minimize deformation of the SPM due to peristaltic movement of the gut was also studied. Osmotic pump tablets composed of membranes with water-soluble plasticizer, propyleneglycol (PG), released drug mainly through diffusion, whereas those designed with CA and EC–HPMC (4:1) coats containing water-insoluble plasticizer, castor oil, released their contents by perfect zero-order kinetics over a prolonged period of time, though the average release rate that could be achieved with the EC–HPMC (4:1) membrane was only about half the rate achieved with the CA membrane for the same membrane thickness. Release rates for both the membranes decreased with increasing membrane thickness and were found to be independent of orifice diameter, agitation intensity, and pH of the dissolution medium.

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Key Words: *Oral osmotic pumps; Semipermeable membranes; Plasticizer effect; Osmotic delivery systems*

INTRODUCTION

The development of an ideal, perorally-administered drug-delivery system providing constant release of drug has been the focus of much research, mainly with the objective of providing constant drug delivery during passage through the gastrointestinal tract (GIT) irrespective of variations in pH, surface tension, and viscosity as well as motility of the GIT (1,2). Osmotically-controlled drug delivery (OCDD) is one such approach (3), and drug delivery from an appropriately designed OCDD system is not influenced by the different physiological factors within the gut lumen; the release characteristics can be predicted easily from the known properties of the drug and the dosage form (4). Cellulose acetate (CA) has been known to form semipermeable membranes (SPMs) (5,6) and is the most widely used polymer for osmotic drug delivery, although many difficulties are encountered in preparing high water-permeable membranes (7,8).

Ethylcellulose (EC) was the earliest polymer used in the development of controlled-release polymeric membranes (9), is probably the most widely used water-insoluble polymer in film coating, and also has good film-forming properties that enable tough, flexible coatings to be produced (10). However, the water-permeability of pure EC is very low, only about one-tenth of the value obtained from CA (6). This may explain the limited use of EC for osmotic pump coatings. The benefits of using water-soluble polymers such as hydroxypropyl methylcellulose (HPMC) in conjunction with EC have been well documented (11,12). Lindstedt et al. (13) have reported that cores of potassium chloride (KCl) coated with mixtures of EC and up to 24% HPMC released their content mainly through osmotic pumping. When the HPMC fraction exceeded 24%, the permeability of KCl through the films also became substantially high, but the films exhibited very low tear strength. Based on the above facts, in this study we have compared the release pattern of naproxen sodium (NPS), a potent non-steroidal anti-inflammatory drug (NSAID), from osmotic pump tablets (OPTs) coated with a mixture of EC–HPMC (4:1) with that of CA using different plasticizers.

EXPERIMENTAL

Materials

Naproxen sodium was a gift from Recon Laboratories Ltd., Bangalore, India. Cellulose acetate, 39.8% acetylation (Eastmen, New Delhi, India), ethylcellulose–HPMC (P55) (Alkem, Taloja, India), castor oil (CDH, New Delhi, India), propylene glycol (Reidal, Hapur, India), acetone, isopropyl alcohol (IPA), sodium chloride, and sodium bicarbonate (Qualigens, Mumbai, India) were used. All other chemicals were of analytical grade and used as received. Dissolution rate test apparatus (Decibel Instruments, Chandigarh, India) and an ultraviolet (UV) spectrophotometer (JASCO, Model 7800, Tokyo, Japan) were also used in the study.

Methods

Preparation of Core Tablets

Formula for core tablets (mg/tablet)	
Naproxen sodium	400
Sodium chloride	40
Sodium bicarbonate	110
Microcrystalline cellulose	80
Sodium lauryl sulfate	10
Polyvinyl pyrrolidone	50
Talc	4
Magnesium stearate	4

The above formula was used for the preparation of core tablets of all the batches of OPTs. An accurately weighed quantity of each ingredient was passed through a sieve no. 85, blended homogeneously, and granulated using a 15% w/v aqueous solution of polyvinyl pyrrolidone (PVP), dried, mixed with talc and magnesium stearate, and compressed on a single station tablet press (Manesty, Halifax, UK) equipped with 12-mm

standard deep concave punches. The compression force was adjusted to give tablets with hardness 7–8 kg/cm^2 on a Monsanto tablet hardness tester. Compressed core tablets were evaluated for appearance, weight variation, hardness, friability, and disintegration time to meet the predetermined criteria suitable for coating. The tablets were left to harden at room temperature for at least a day before being coated.

Coating of the Tablets

Coating formulation	
CA or EC–HPMC (4:1)	2% w/v
Castor oil or Propylene glycol	20% w/w of total solid polymer 10% w/w
Isopropyl alcohol	10% v/v
Acetone	q.s. to 100% v/v

The coating operation was performed on 70-g batches (100 tablets) in a conventional laboratory model stainless steel, 20-cm, pear-shaped, baffled coating pan (Scientific Instruments, New Delhi, India). Baffles, three in number, were equally spaced, 120° apart, inside the pan with a gap at the center of the pan to allow free tumbling of tablets (14). The pan speed was 20 rpm and the coating solution was manually sprayed onto the surface of the tumbling tablets with a spraygun. The inlet air temperature was 40–45°C and the manual coating procedure used was based on intermittent spraying and drying techniques (15). The coat weight and thus the thickness were controlled by the volume of coating solution consumed in the coating process. Coated tablets were weighed periodically to monitor changes in weight. After coating tablets were allowed to dry completely in a hot-air oven at 60°C and finished by standard polishing procedure. An appropriate orifice (0.3 to 1.0 mm) was drilled on one face of the tablet through the membrane by microdrill (16). Table 1 demonstrates the variables for different batches of OPTs.

Evaluation of Formulations

The designed OPTs were evaluated by visual inspection of the film for smoothness, uniformity of coating, edge coverage, and luster, and various specifications for different batches of OPTs are shown in Table 2.

Uniformity of Coating

The uniformity of coating among the tablets was estimated by determining the weight, thickness, and diameter of tablets before and after coating, using 20 individual tablets, and the corresponding average

Table 1

Membrane Characteristics of Various OPTs Designed

No.	Item	Batch of OPTs									
		A	B	C_1	C_2	C_3	C_4	E_1	E_2	E_3	E_4
1.	Coat nature[a]	MP (CA)	CM (CA)	SP (CA)	SP (CA)	SP (CA)	SP (CA)	SP (EC)	SP (EC)	SP (EC)	SP (EC)
2.	Coat weight[b] (mg) (± SD)	11.0 (0.5)	19.0 (0.5)	10.0 (0.5)	10.0 (0.4)	15.0 (0.5)	20.0 (0.5)	10.0 (0.5)	15.0 (0.5)	15.0 (0.5)	20.0 (0.5)
3.	Coat thickness[b] (μm) (± SD)	75 (6)	95 (4)	40 (4)	40 (5)	50 (4)	60 (5)	30 (5)	40 (5)	40 (5)	50 (5)
4.	Orifice diameter[b] (mm) (± SD)	1.0 (0.2)	1.0 (0.1)	1.0 (0.1)	0.3 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.3 (0.1)	1.0 (0.1)	1.0 (0.1)

[a]MP (CA): microporous cellulose acetate (CA) coat with propylene glycol (PG) plasticizer; CM (CA): composite membrane consisting of a microporous CA coating (75 μm thickness) with a PG plasticizer over the tablet followed by a semipermeable coating of CA having castor oil (CO) plasticizer; SP (CA): semipermeable CA coat with CO plasticizer; SP (EC): semipermeable EC–HPMC (4:1) coat with CO plasticizer.
[b]Mean of 20 determinations.

Table 2

Specifications for Different Batches of OPTs Designed [Mean (SD) (n = 20)]

No.	Specification	Batch of OPTs							
		A	B	[a]C_1, C_2	C_3	C_4	E_1	[a]E_2, E_3	E_4
1.	OPT weight (g)	0.7289 (0.0185)	0.7281 (0.0210)	0.6805 (0.0213)	0.6950 (0.0217)	0.7015 (0.0218)	0.6936 (0.0181)	0.6986 (0.0087)	0.7036 (0.0180)
2.	Thickness (mm)	5.6106 (0.1043)	5.5883 (0.1263)	5.1433 (0.1883)	0.51438 (0.1786)	0.5134 (0.1687)	4.7081 (0.1019)	4.7021 (0.1016)	4.7120 (0.1029)
3.	Diameter (mm)	12.7321 (0.0143)	12.7231 (0.0134)	12.7567 (0.0433)	12.7469 (0.0438)	12.7467 (0.0429)	12.8316 (0.0168)	12.8211 (0.0179)	12.8319 (0.0185)
4.	Drug content (%)	98.28 (1.82)	97.64 (1.74)	90.30 (4.27)	95.28 (1.26)	94.25 (1.38)	93.28 (1.21)	88.27 (4.29)	94.82 (1.62)
5.	Surface area[b] (cm^2)	3.8501	3.8503	3.8285	3.8286	3.8278	3.6834	3.6634	3.6747
6.	Volume[b] (cm^3)	0.5493	0.5496	0.5214	0.5218	0.5209	0.4674	0.4661	0.4668

[a]Formulation variable is orifice diameter only.
[b]Calculated from geometry of the tablet.

values (*m*), standard deviations (SD), and coefficients of variation (CV) were calculated.

Coat Weight and Thickness

The coat weight and thickness were determined ($n = 20$) from depleted devices after careful washing and drying of the film (17) using a standard analytical balance and screw gauge, respectively, and their corresponding CVs were calculated.

Orifice Diameter

The average orifice diameter of the OPTs was determined microscopically ($n = 20$) using a precalibrated ocular micrometer (17).

Drug Content

The NPS content of OPTs was determined from the mixed powder sample of 20 tablets in each batch, after dissolving in distilled water and analyzing spectrophotometrically at 317 nm.

In Vitro Release

In vitro release kinetics of NPS from various OPTs were investigated using the standard USP dissolution apparatus II at 50 rpm. One tablet was placed in 900 mL of distilled water equilibrated to 37±0.1°C. Then 5-mL samples were withdrawn, from the point halfway between the surface of the dissolution medium and the top of the paddle, with pipettes connected to a polyethylene tube covered with cotton wool, at different time intervals, replacing with an equal volume of prewarmed (37±0.1°C) fresh dissolution medium, and analyzed spectrophotometrically at 317 nm after suitable dilution. Each study was done in triplicate and the mean values are reported.

Drug Release as a Function of Agitation Intensity

To study the effect of agitation intensity, drug release studies were performed at a relatively high (100 rpm) and low (50 rpm) agitation intensity and at static conditions using the USP dissolution apparatus in distilled water, similarly as described above. Under static conditions, samples at different times were taken after uniform mixing of the medium to preclude any possible sampling error.

Effect of pH of the Dissolution Medium on Release Rate

Release rates of NPS from OPTs in phosphate buffer of pH 7.4 and in distilled water were compared using USP dissolution apparatus at 50 rpm, similarly as described above.

RESULTS AND DISCUSSION

In the present study, using pharmacokinetic parameters of NPS (18), the amount of active material required in the OPT, the required zero-order delivery rate, and the dosage interval were estimated to be 400 mg, 32.76 mg/hr, and 12 hr, respectively. The OPTs were fabricated with different membrane coating variables, and optimized in terms of nature of plasticizer, membrane thickness, and orifice diameter.

A 2% polymer solution was used in the coating formulation in order to minimize tablet-to-tablet variations in coating thickness. The variation will be smaller if there are a larger number of coatings. In other words, the uniform application of a given amount of polymer is best accomplished with a larger number of coatings using a more dilute solution than with a smaller number of coatings using a more concentrated solution (19). A plasticizer was included in the coating formulation in order to improve the stability of the film by increasing the flexibility of the membrane. The inclusion of a suitable plasticizer in polymeric films has been studied (20,21). By lowering the glass transition temperature of the polymer (22), the plasticizer serves to alter physical properties such as flexibility, hardness, tensile strength, and elasticity.

Uniformity of Coating

The uniformity of coating among the tablets was demonstrated through a comparison of CVs, calculated as $(SD/m) \times 100$, before and after coating (14). A relatively consistent CV (Table 3) in terms of both total tablet measurements and actual coating measurements indicates a uniform coating distribution among the tablets within and between batches.

Kinetics of Drug Release

In vitro release profiles of NPS from OPTs designed with different membranes are shown in Fig. 1. To explain the kinetics of drug release more clearly, release data were fitted to the modified Korsmeyer equation $Q(t) = Kt^n$, where $Q(t)$ is the fraction of drug released after time t, k is a constant, and n is the time exponent that characterizes the drug transport mechanism (23). When the logarithm of the cumulative percentage released (CPR) is plotted against the logarithm of the time in minutes, the slope of the graph will give the value of the time

Table 3

Demonstration of Uniformity of Coating

No.	Item		Batch of OPTs							
			A	B	C_1, C_2	C_3	C_4	E_1	E_2, E_3	E_4
1.	Coefficient of weight variation	Before coating	3.0504	2.9518	3.7997	3.1256	3.1664	2.3189	2.4225	2.4534
		After coating	2.5333	2.8842	3.1256	3.1664	2.6333	2.4225	2.4534	2.4268
2.	Coefficient of thickness variation	Before coating	2.4656	2.4230	4.4265	3.1819	2.9757	0.7918	0.6617	0.8124
		After coating	1.8589	2.2601	3.1819	2.9757	2.1994	0.6617	0.8124	0.7286
3.	Coefficient of diameter variation	Before coating	0.1278	0.1271	0.3825	0.3394	0.2534	0.2521	0.1528	0.1396
		After coating	0.1124	0.1053	0.3394	0.2534	0.1288	0.1528	0.1396	0.1397
4.	Coefficient of coat weight variation		4.5453	2.6247	4.9464	3.3321	2.4864	4.9864	3.3312	2.4648
5.	Coefficient of coat thickness variation		7.8746	4.2054	9.9785	8.0123	8.3246	10.0683	8.4632	7.8795

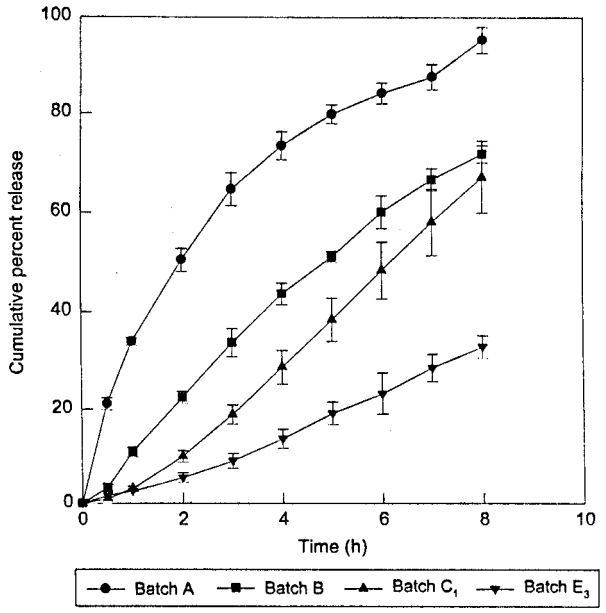

Figure 1. Release profiles of NPS from OPTs coated with different membranes in distilled water. Bars represent SD ($n = 3$).

exponent n. Calculated values of n, along with other release characteristics such as lag time, average release rate, and CPR at 8 hr, for various batches of OPTs, are listed in Table 4 for comparison.

In contrast to the predominantly zero-order release profile of batch C_1, the release profile of batch A, coated with CA with propylene glycol (PG) plasticizer, was almost diffusion-controlled, as inferred from the shape of the curve as well as from the value of the time exponent n (0.5410), which was attributed to the formation of spongelike microporous membrane in aqueous environment, as the water-soluble PG leached out, allowing free diffusion of drug molecules. For the same reason no significant lag period was observed in this batch. On the other hand, batch C_1, whose membrane was composed of CA with water-insoluble plasticizer, castor oil, released drug only through an orifice, with a short initial lag period (1.01 hr) followed by an almost perfect zero-order release pattern until 8 hr. Thus drug release through a porous film is by diffusion, leading to a non-linear release profile, whereas drug release through the orifice in OPT is by convection (24), resulting in a linear profile.

The OPTs designed with EC–HPMC (4:1) coating, with castor oil plasticizer (batch E_3), were also able to deliver the NPS at a constant rate, over a prolonged period. But the rate that could be achieved with this membrane was only about half the rate achieved with CA for the same membrane thickness (batch C_1).

The OPTs of batch B, in which a microporous membrane was inserted below the SPM of CA to help minimize deformation of the SPM due to peristaltic movement of the gut (25), also released their content by almost zero-order kinetics ($n = 1.072$), and no significant lag time was observed. This lack of lag period may be because of the underlying

Table 4

Comparison of Release Characteristics and the Time Exponent n of OPTs with Different Coats

Batch No.	Average ($n = 3$) Lag Time (hr)	Average ($n = 3$) Release Rate (mg/hr)	Variance Estimate[a] S^2	Mean CPR[b] ± SD at 8 hr (%)	Time Exponent n	Coefficient of Determination r^2
A	Zero	37.79	84.5879	95.11 ± 2.74	0.5410	0.9948
B	Zero	33.15	10.5274	72.02 ± 1.65	1.0723	0.9878
C_1	1.01	36.64	0.0903	67.37 ± 7.23	0.9887	0.9995
E_3	0.97	15.04	0.2599	32.98 ± 2.30	0.9443	0.9929

[a]The variance, as computed here, is an estimate of the error in line fitting due to the fact that a straight line might not be an accurate representation of the data,where:

$$S^2 = \frac{\{\Sigma[Y - (a + bx)]^2\}}{N - 2}$$

A high value of variance estimate denotes considerable deviation of the release profile from linearity.
[b]CPR = cumulative percentage release.

microporous membrane and a relatively thin semi-permeable membrane covering it.

Effect of Membrane Thickness

To study the effect of the membrane thickness on the kinetics of drug release, OPTs were designed with different membrane thicknesses using both CA and EC–HPMC (4:1) combination coatings and their release profiles, in distilled water, are shown in Fig. 2. It was observed that the release rate decreased with increasing membrane thickness, which can be explained by an osmotic pressure-driven release mechanism according to the following equation (26):

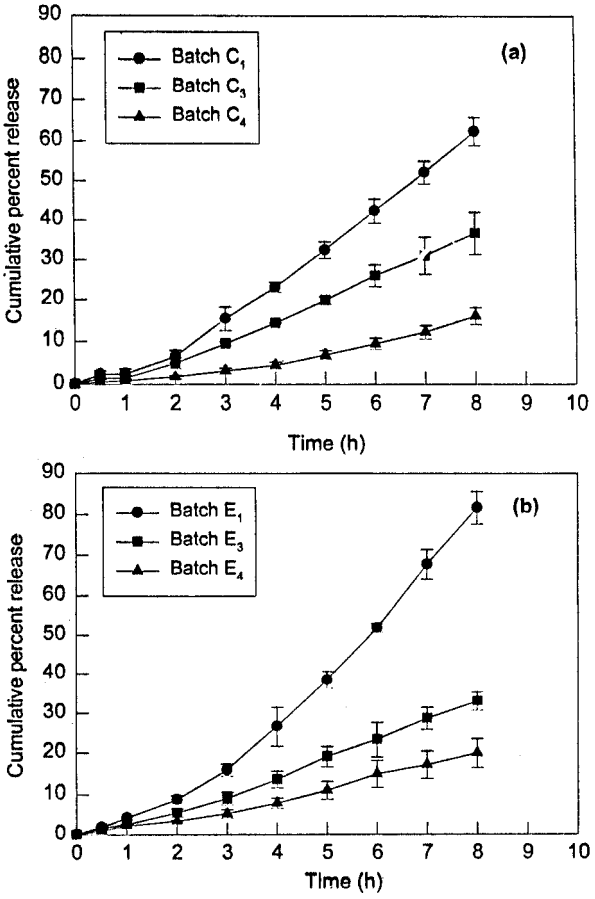

Figure 2. Effect of membrane thickness on release profiles of NPS from OPTs coated with (a) CA and (b) EC–HPMC (4:1) combination in distilled water. Bars represent SD ($n = 3$).

$$dm/dt = (AS/h)L_p\sigma\Delta\pi \quad (1)$$

where dm/dt is the zero-order release rate of the drug, A is the surface area of the film-coated membrane, h is the membrane thickness, $\Delta\pi$ is the osmotic pressure difference across the membrane at saturation, S is the solubility, L_p is the hydraulic permeability of the membrane, and σ is the reflection coefficient having the value of 'one' for an ideal SPM like CA and 'zero' for a non-selective membrane.

The weight of the membrane (W) was shown to be related to the membrane thickness as follows (26):

$$W = \rho_m Ah \quad (2)$$

where ρ_m is the membrane density. Consequently, the release rate can be expressed as a function of the membrane weight (W) by substituting Eq. (2) into Eq. (1):

$$dm/dt = (A^2S/W)\rho_m L_p\sigma\Delta\pi \quad (3)$$

From Eq. (3) it is inferred that the release rate is inversely related to the weight of the membrane. Figure 3 is a plot of the release rate, calculated from the zero-order release portions of the release profiles, vs. the inverse of the membrane weight. The relationship, for both membranes, was linear ($r^2 > 0.99$) by regression following Eq. (3).

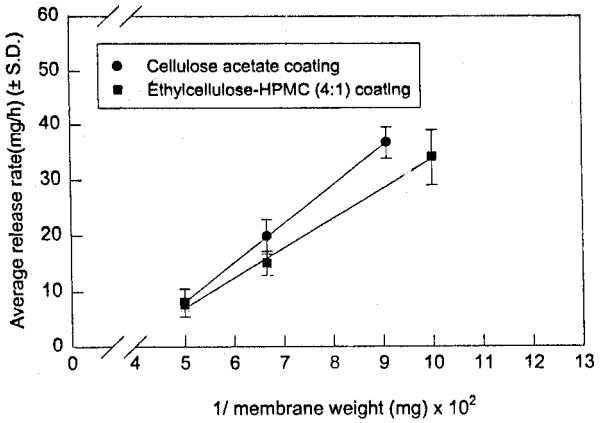

Figure 3. Relation between average release rate and weight of the membrane coating.

Optimum/Operational Orifice Size

The size of the orifice should be sufficiently large to prevent the hydrostatic pressure developed inside the device from rupturing the membrane, and at the same time it should not be so large that it allows free diffusion of solute leading to loss of control over the release rate. To determine the optimal diameter of the delivery orifice in the membranes, apertures were made in the range of 0.3 to 1.0 mm. Release rate profiles of NPS from these systems, in distilled water, are compared in Fig. 4. It was found that the size of the delivery orifice at a wide range of 0.3 to 1.0 mm does not affect significantly ($P > .01$) the rate or the extent of release of NPS from the OPTs. Therefore the orifice size, in this range, has successfully prevented the membrane from rupturing by effectively relieving hydrostatic and osmotic pressures developed inside the system and at the same time is able to deliver the drug at a reasonably constant rate over a sufficiently long period of time, indicating that the range studied was well within the optimum orifice range as described by Theeuwes (5) and Ramadan and Tawashi (27).

Effect of Agitation Intensity

In vitro release rate profiles of the drug from OPTs coated with different membranes, under static and stirred (50 and 100 rpm) conditions in distilled

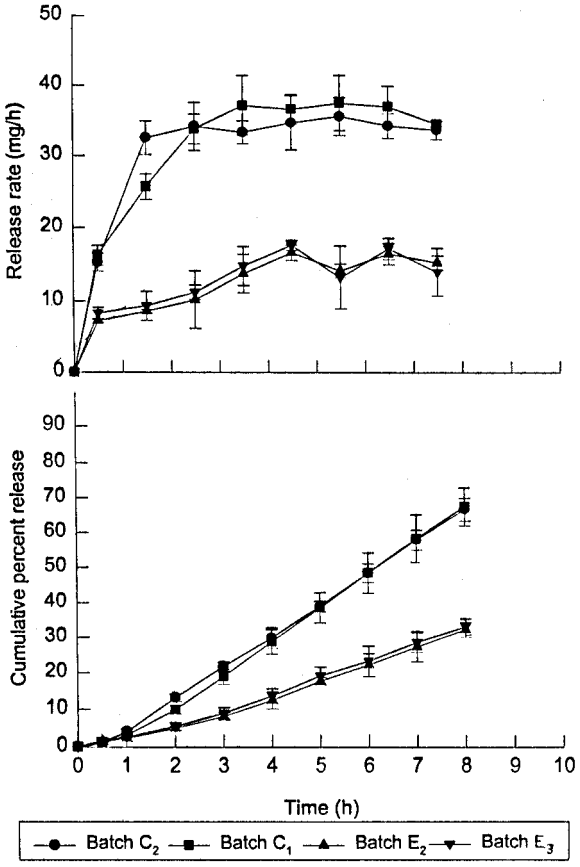

Figure 4. Effect of orifice diameter on release rate profiles of NPS from OPTs coated with CA (batch C_1 and C_2) and EC–HPMC (4:1) (batch E_2 and E_3) in distilled water. Bars represent SD ($n = 3$).

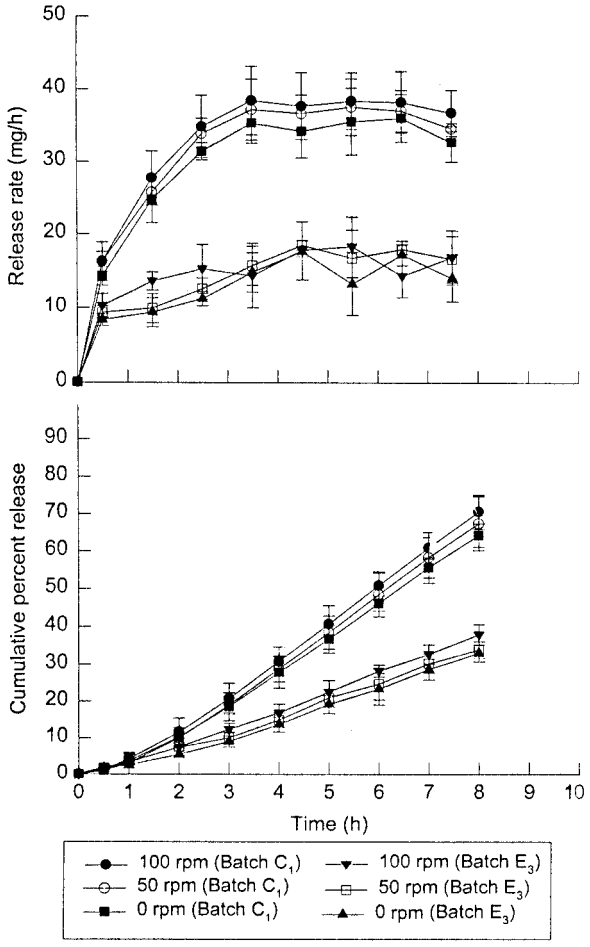

Figure 5. Effect of agitation intensity on release rate profiles of NPS from OPTs coated with CA (batch C_1) and EC–HPMC (4:1) (batch E_3) in distilled water. Bars represent SD ($n = 3$).

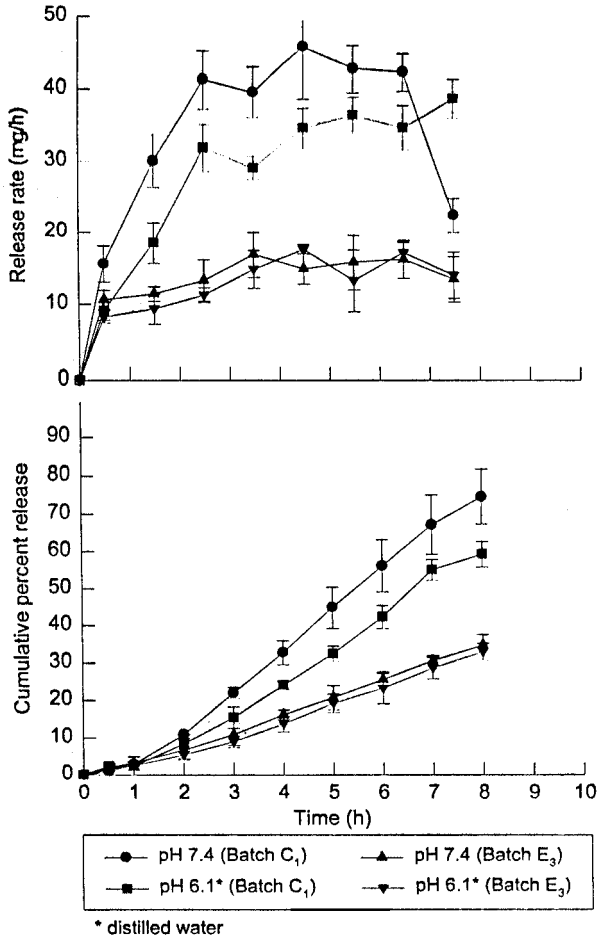

Figure 6. Effect of pH of the dissolution medium on release rate profiles of NPS from OPTs coated with CA (batch C_1) and EC–HPMC (4:1) (batch E_3). Bars represent SD ($n = 3$).

water, as shown in Fig. 5, indicated no significant ($P > .01$) difference in the rate or extent of drug release.

Effect of pH of the Dissolution Medium

To verify that the drug delivery profile from OPTs is independent of environmental pH, in vitro tests were also conducted in phosphate buffer of pH 7.4, in addition to those in distilled water. This is an important performance test because, if the SPM is truly selective, ions should not be able to diffuse into the osmotic pump and affect the release profiles. The release profiles of batches C_1 and E_3 in different dissolution media are compared in Fig. 6. The average release rates in different media were tested for a statistically significant difference using a two-tailed Student's *t*-test and the results indicated no significant ($P > .05$) difference.

An important consideration for the in vivo use of this delivery system is the mechanical stability and resistance of the film coating to rupture during passage through the gastrointestinal tract. None of the tablets ruptured during the dissolution studies, as observed visually, and as indicated by the absence of a burst in drug release. Empty polymeric shells retained their original shape and floated on the dissolution medium after completion of drug release. Although coatings did not rupture when deformed by hand, they were flexible and fluid was pumped out from the empty shells under hand pressure.

Release rates independent of the hydrodynamic conditions and the pH of the environment, and inversely proportional to the membrane thickness according to Eq. (3), suggest that both the membrane coatings, CA and EC–HPMC (4:1) combination, with castor oil plasticizer, behaved like true SPMs permitting only water molecules to pass through, thereby pumping their contents mainly through an osmotically-driven release mechanism. This semipermeable nature of the membrane is believed to involve the passage of solvent through the membrane by a diffusion process or by dissolving the material of the membrane in which the solute is insoluble (28). In other cases, the membrane may also act as a sieve, having a pore size sufficiently large to allow the passage of solvent but not of solute molecules. The kinetics of drug release remain linear as long as the transport mechanism is unidirectional (29).

CONCLUSION

In summary, OPTs fabricated with both CA and EC–HPMC (4:1) coatings, with castor oil plasticizer, released their contents at almost a constant rate, independent of environmental conditions, over a prolonged period of time. However, the release rate that could be achieved with the EC–HPMC (4:1) membrane was only about half the rate achieved with the CA membrane for the same membrane thickness.

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