Formulation and *in Vitro–in Vivo* Evaluation of Buccoadhesive Morphine Sulfate Tablets

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Buccoadhesive controlled-release systems for the delivery of morphine sulfate were prepared by compression of hydroxypropyl methylcellulose (HPMC) with carbomer (CP), which served as the bioactive adhesive compound. The release behavior of systems containing 30 mg of morphine sulfate and various amounts of the two polymers was found to be non-Fickian. The adhesion force was significantly affected by the mixing ratio of HPMC and CP in the tablet, and the weakest adhesion force was observed at a ratio of 1:1 (HPMC:CP). Interpolymer complex formation was confirmed between HPMC and CP in acidic medium by turbidity, viscosity, and FT-IR measurements. The amount absorbed (percentage of the drug loaded) of the controlled-release buccoadhesive tablets in six healthy volunteers and was 30 ± 5%.

KEY WORDS: morphine; buccoadhesion; compressed tablet; interpolymer complex; buccal absorption.

INTRODUCTION

Morphine sulfate is an effective analgesic when administered by the parenteral or oral route (1). However, the amount of morphine reaching the systemic circulation after oral administration is reduced by first-pass metabolism in the gut wall and liver (2). In addition, the absorption of orally administered morphine requires a functional gastrointestinal tract. This limits the use of oral morphine after operation. Both these problems may be overcome by the administration of morphine via the buccal route.

Bioadhesive polymers such as sodium carboxymethylcellulose; Carbopol 934, and hydroxypropylcellulose or hydroxypropyl methylcellulose (HPMC) are suitable for use in buccoadhesive preparations because, when hydrated with water, they can adhere to the oral mucosa and withstand salivation, tongue movements, and swallowing for a significant period of time. Oral mucosal dosage forms have been investigated for the systemic administration of insulin (3), nifedipine (4), codeine phosphate (5), cetylpridinium chloride (6), and morphine (7–9). In these systems, Nagai and co-workers used mixtures of hydroxypropylcellulose and Carbopol 934 as the adhesive base.

HPMC and carbomer (CP) have been used as principal excipients to achieve adhesion to the oral mucous membrane and to control the drug release from the tablet. One objective of the present study was to elucidate factors affecting the bioadhesion property of compressed tablets consisting of HPMC and CP. In this connection, the interpolymer complex formation between HPMC and CP seems to be particularly noteworthy. The existence of the interaction was confirmed by turbidity, viscosity, and Fourier-transform infrared spectroscopy (FT-IR) measurements. The other objective was to examine the bioadhesion and *in vitro* release characteristics of morphine sulfate from different buccoadhesive matrix tablets in order to assess the suitability of such formulations. In addition, the absorption of morphine for the selected formulation by *in vivo* experiments was evaluated.

MATERIALS AND METHODS

Materials

Morphine sulfate, $5H_2O$ (TMO, Alkasan, Turkey), HPMC (Methocel K100M, Colorcon, England), carbomer (Carbopol 910, B. F. Goodrich, Belgium), magnesium stearate (E. Merck, Germany), and polymethylmethacrylate (Eudragit RSPM, Röhm Pharma, Germany) were used.

Turbidity Measurement

HPMC solution (2.5 mL, 0–0.02%) was mixed with CP solution (2.5 mL, 0–0.02%) at 37°C for 1 hr to prepare the sample solution. Buffer solutions (pH 3.0, 4.5, and 6.0) were used to dissolve samples. The total polymer concentration was fixed at 0.02% in all samples. The turbidity of each sample solution was determined at 600 nm, where there was no absorption due to the polymers in solution, using a UV-160A Shimadzu spectrophotometer.

Viscosity Measurement

HPMC solution (10 mL, 0–1%) mixed with CP solution (10 mL, 0–1%) was incubated at 37°C for 7 days. Total polymer concentration was fixed by dilution with buffer solution at 0.5% in all samples. After centrifugation for 20 min at 15,000 rpm in a Sorvall Superspeed Centrifuge SS-3, the viscosity of the dispersion-free supernatant solution was determined at 37°C by the use of an Ubbelohde viscometer (Schott-Gen Mainz, K:0.004765). Buffer solution, pH 3, was used to prepare the sample solution.

Preparation of the Interpolymer Complex

HPMC solution at pH 3 (20 mL, 0–0.1%) was mixed with CP solution at pH 3 (20 mL, 0–0.1%). The sample solution was then incubated at 37°C for 10 days. The total polymer concentration was fixed by dilution with buffer solution, pH 3, at 0.05% in all samples. After the removal of water in the sample solution by the use of a lyophilizator (Virtis, Model Freeze Mobile 6), the interpolymer complex

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formed that remained was dried in a vacuum for 3 days at room temperature.

IR Absorption Spectroscopy

FT-IR spectroscopy of HPMC CP interpolymer complexes used a Nicolet 520 FT-IR spectrometer

Preparation of Buccoadhesive Tablets

The formulas used for direct compression are shown in Table I. HPMC, CP, and morphine sulfate were mixed and compressed with 1% magnesium stearate incorporated as a lubricant prior to compression. Tablets were compressed on a single-punch tablet machine (Korsch EK/0), using a flat nonbeveled punch of 12-mm diameter. In addition to these samples, drug-free tablets were prepared without lubricant.

Bioadhesion Experiments

For this purpose, the tensile experiment reported in the literature (10) was adapted using the Instron (Model 4301, Instron Ltd., UK) apparatus. Cyanoacrylate adhesive was used to fix the tablet and the bovine sublingual mucosa to the upper and lower metallic supports, respectively.

Bovine tongue along with tissue was collected immediately after sacrificing the animal and frozen at −20°C until use. Just before use, it was thawed to 4°C in normal saline solution, and ~2-mm-thick mucosa was cut carefully and placed on the lower support of the Instron apparatus. During the experiment, 20 μL of distilled water was placed on the tablet surface and the two surfaces (tablet and mucus) were brought in contact with a force of 0.5 *N* and kept in this condition for 10 min. Then the tensile experiment was performed at a constant extension rate of 5 mm/min.

In Vitro Release of Morphine Sulfate from Tablets

The manufactured tablets were tested for dissolution in 500 mL of McIlvaine buffer (pH 6.6) using the USP XXII Apparatus II, Prolabo (Paris) dissolution tester, at 50 rpm and 37 ± 0.2°C. Each tablet was inserted in a metal die having a central hole 12 mm in diameter which was sealed at the lower end with paraffin wax so that the drug could be released only from the upper face of the device. Samples were collected at appropriate time intervals, filtered, and assayed for morphine sulfate using a UV-160A Shimadzu spectrophotometer.

Table I. Formulation of Buccoadhesive Morphine Sulfate Tablets Studied

Formulation	CP (mg)	HPMC (mg)	Morphine sulfate (mg)	Magnesium stearate (mg)
MS-0-K	210	—	30	2.4
MS-10-K	189	21	30	2.4
MS-20-K	168	42	30	2.4
MS-30-K	147	63	30	2.4
MS-40-K	126	84	30	2.4
MS-50-K	105	105	30	2.4
MS-60-K	84	126	30	2.4
MS-70-K	63	147	30	2.4
MS-80-K	42	168	30	2.4
MS-90-K	21	189	30	2.4
MS-100-K	—	210	30	2.4

In Vivo Studies

After explanation of the experimental protocol, six healthy volunteers, five females and one male, agreed to participate in the study. The age of the subjects ranged between 21 and 42 years (29 ± 8 years) and their weights were between 52 and 72 kg (59 ± 7 kg). The subjects were clinically examined and found to have no hepatic, renal, or cardiovascular disease or history of alcohol or drug abuse, or to be receiving treatment with any other medication. The study was approved by the Hacettepe University Ethics Committee and written informed consent was obtained from each patient. Present State Examination Tests (PSET) of the volunteers were conducted by a physician before admission to the study. The subjects remained under his supervision during the study. The same PSET was applied to volunteers after completing *in vivo* experiments.

Initially the tablets were coated manually on all sides except one with the water-impermeable polymer Eudragit RSPM. The coating solution used was prepared as follows: 12.5% dry Eudragit RSPM was dissolved in a mixture of 60% (w/w) isopropyl alcohol and 40% (w/w) acetone. The coating was dried at room temperature. When the permeability of the drug from the coating was tested, it was found to be impermeable. These coated tablets were then placed in the buccal sulcus, below or above the canine tooth of each of six volunteers for 1, 2, 3, 4, 5, 6, 7, and 8 hr.

Fresh tablets were applied at each time point. The site of application was monitored for signs of local irritation. A minimum period of 24 hr was allowed between replicate applications to the same subject.

It was confirmed by a preliminary experiment that the order and position of application were of no significance. The percentage (%) of morphine sulfate absorbed was calculated from the amount remaining in the dosage form after removing it completely from the site of application. The amount of drug remaining in buccoadhesive tablets after each application was determined by grinding in a mortar and pestle. The drug was extracted into water using ultrasonication for 3 hr at 37°C and determined with a UV spectrophotometer.

Statistical Analysis

Comparisons of bioadhesion force for buccoadhesive tablets of different polymer mixing ratios were performed by two-way ANOVA. Significant differences identified at the 5% level were further defined by calculation of the 95% confidence interval of the difference between the two means by use of the pooled estimate of variance.

RESULTS AND DISCUSSION

Conformation of Interpolymer Complex Formation

Figure 1 shows the turbidity as a function of the weight ratio of HPMC-CP in media of various pH values. Maximum

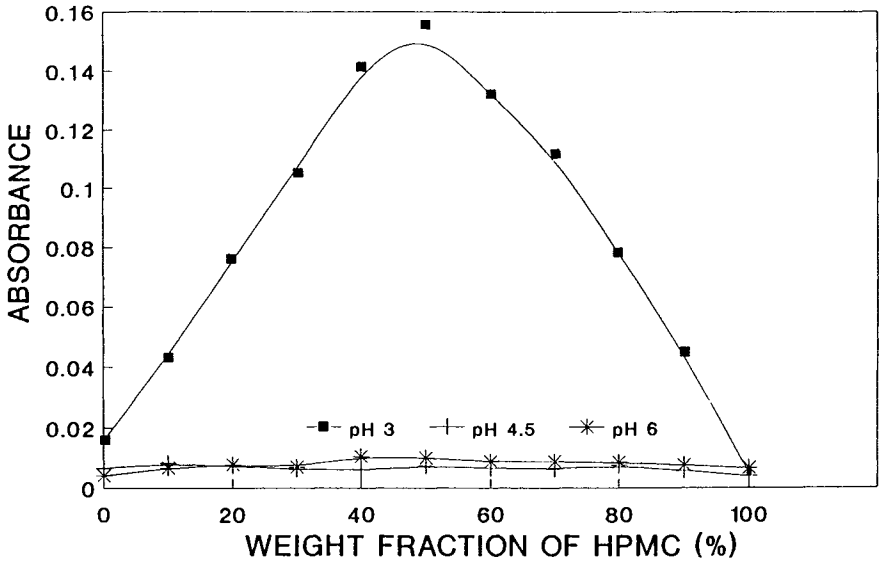

Fig. 1. Turbidity of the HPMC/CP system as a function of polymer mixing ratio in media of various pH values at 37°C (total polymer concentration, 0.02%).

turbidity was observed at a weight ratio of 1:1 in the acidic medium (pH 3.0). This result suggested that the interpolymer complex of HPMC/CP could be formed in the acidic medium at a weight ratio of 1:1. No interpolymer complex formation was observed in the higher pH region (pH 4.5 and 6.0), since the pK_a value of acrylic acid, the main monomer of CP, was reported to be 4.25 at 25°C (11). The dissociation of carboxyl groups of CP might be important for the balance of complexation and decomlexation. The viscosity of the supernatant of the HPMC/CP mixture solution as a function of the weight ratio of HPMC and CP in the acidic medium (pH 3.0) is shown in Fig. 2. When the weight fraction of HPMC in samples was 20 to 50%, the viscosity of the supernatant in the HPMC/CP solution was similar to that in the medium. In the case of HPMC alone or CP, the viscosity of these solutions increased continuously with increases in polymer concentration. Therefore, the decrease in viscosity observed in the HPMC/CP mixture system showed that the interpolymer complex was formed in the acidic medium and was removed by centrifugation.

FT-IR spectra of KBr disks of the samples are given in Fig. 3. The carboxyl groups of CP gave a broad band at about 1713 cm^{-1}, corresponding to the C=0 stretching vibration. HPMC had no absorption in this range. In addition to the shift in frequency of the stretching vibration of the carbonyl group in CP from 1713 to 1700 cm^{-1} upon the addition of HPMC, splitting of this absorption peak was also observed, with the formation of a shoulder at 1670 cm^{-1} (Fig. 3). This splitting became more pronounced as the HPMC content of the complex was increased.

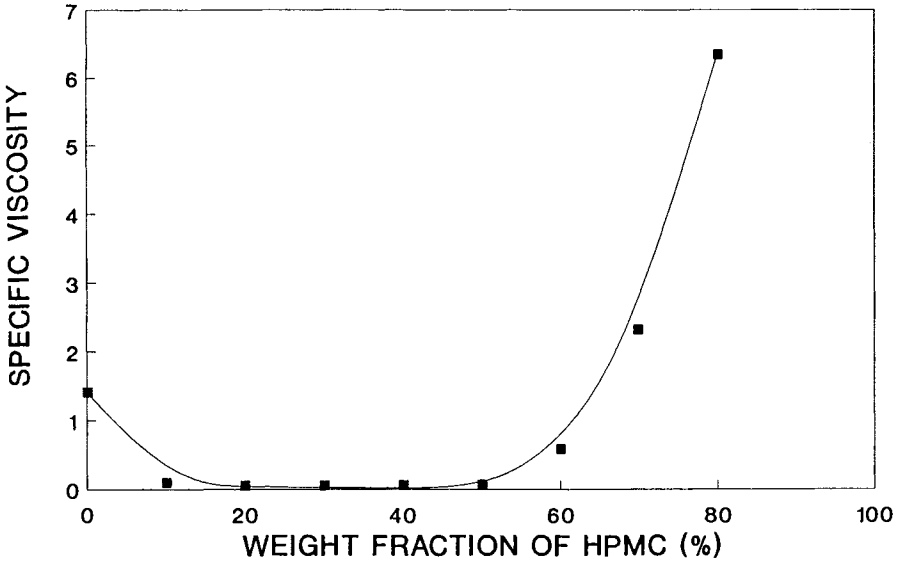

Fig. 2. Viscosity of supernatant solution in the HPMC/CP systems as a function of polymer mixing ratio at pH 3 and 37°C (total polymer concentration, 0.5%).

Qualitative analysis of the FT-IR spectra was made by taking the ratio of band intensities at ~1700 cm^{-1}, corresponding to the C=0 stretching frequency of uncomplexed carbonyl, and ~1670 cm^{-1}, the stretching frequency of the same group in the complex. The results indicated that the intensity ratio did not change significantly up to 30% HPMC, decreased significantly at higher HPMC concentrations, and reached a constant value above 50% HPMC. It is concluded that complex formation in the HPMC/CP system was achieved between 40 and 80% HPMC and that this complex involved hydrogen bond formation between the OH groups of HPMC and the carboxyl group in CP.

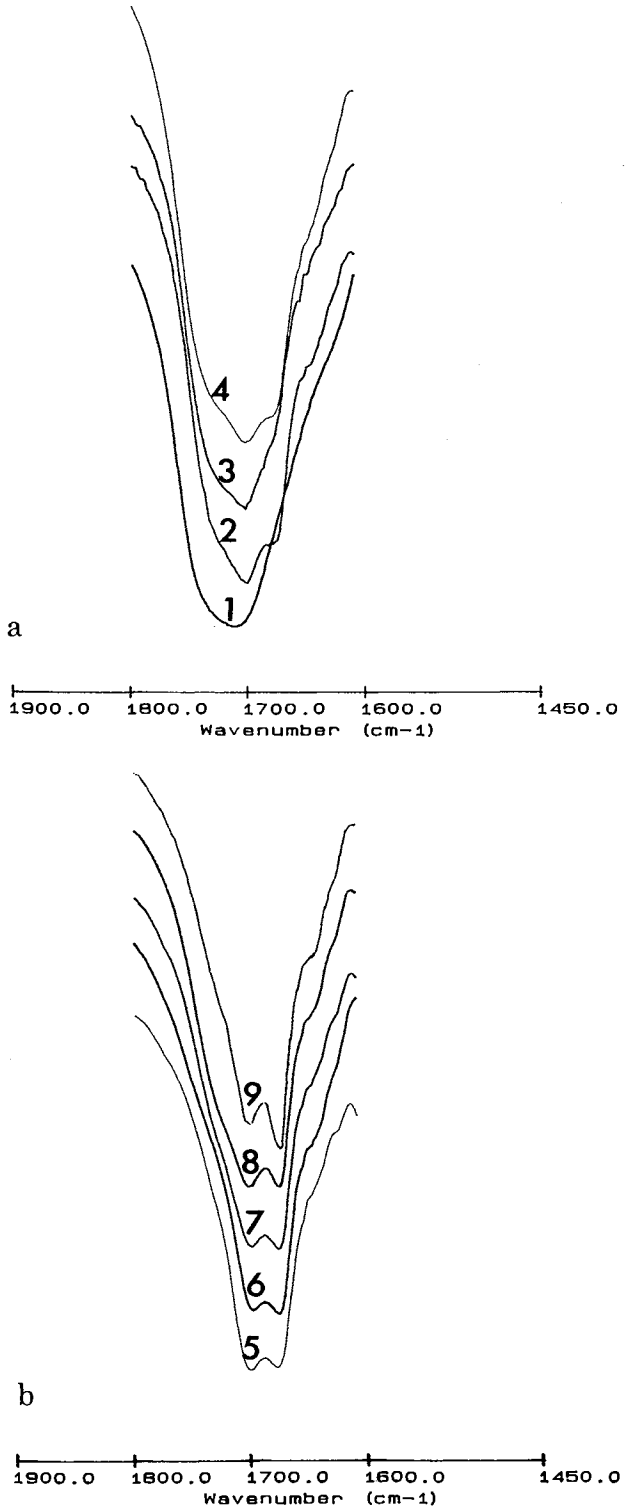

Fig. 3. FT-IR spectra of HPMC/CP complexes. HPMC-CP ratio: (a) 1, CP alone; 2, 1:9; 3, 2:8; 4, 3:7; and (b) 5, 4:6; 6, 5:5; 7, 6:4; 8, 8:2; 9, 9:1.

Bioadhesion Properties of HPMC/CP Tablets

Table II shows the adhesion force of HPMC/CP tablets to the bovine sublingual mucus at various mixing ratios of HPMC/CP. The results of this study clearly demonstrate that the adhesion force observed at a mixing ratio of 1:1 (HPMC:CP) was less than in tablets of other mixing ratios. Table II also shows that the interpolymer complex formation between HPMC and CP inhibited the adhesion force of the tablet, as observed in bovine sublingual mucus.

It is clear that very thin and strong gel layer formation at the boundary might be necessary for adhesion. In this connection, the interpolymer complex formed in the gel layer acts as an inhibitor of the adhesion due to its hydrophobicity. Ponchel *et al.* (10) investigated the effect of the Carbopol 934 percentage in the polymer mixture on the bioadhesive properties of controlled-release systems. They concluded that due to the strong penetrating characteristics of the un-cross-linked polyacrylic acid (PAA) chains in the bovine mucus, excessive amounts of PAA were not necessary to achieve the maximum bioadhesive strength and that only about 30–40 wt% PAA was sufficient. The results of our bioadhesive analysis with the morphine sulfate-containing tablets indicate that the presence of drug had a great effect on the bioadhesive strength formed.

According to ANOVA results, there was a significant difference between the mean adhesion force values of the drug-free and the drug-containing systems ($P < 0.05$); the decrease of 30–45% in the force of adhesion due to the presence of the drug-containing systems is shown in Table II. But the influence of HPMC percentage, between 30 and 80%, was not significant among drug-containing systems ($P > 0.05$).

However, the use of different percentages of HPMC appeared to affect the bioadhesion force on the drug-free systems. No significant differences were observed among replicate measurements ($P > 0.05$). The results were in agreement with several reports given in the literature (5,10).

In Vitro Release Studies

To calculate the release rate constant of morphine sulfate, the percentage release (M_t/M_∞)-versus-time profile was evaluated by the goodness-of-fit method. For all formulations, a zero-order equation showed a significantly better fit than first-order, Higuchi's square-root, and cube-root equations, as determined by F test (Table III). The details of the use of this statistical technique are given by Bamba *et al.* (12) and Çiftçi *et al.* (13). In general, as the CP content increased, there was an increase in the amount of drug released. This phenomenon was explained by the swelling behavior of the HPMC/CP systems. These systems were swellable in water and a minimum time of 1–2 hr was needed for their complete swelling. Therefore, during this early portion of the release

Table II. Bioadhesion Force for Buccoadhesive Tablets in Contact with Bovine Sublingual Mucus (n = 8)

% HPMC	Mean ± SD	
	Without drug	With drug
0	12.4 ± 3.7	10.9 ± 2.1
10	14.7 ± 2.9	8.5 ± 1.3
20	13.0 ± 1.7	7.1 ± 0.9
30	10.5 ± 1.3	6.8 ± 1.0
40	9.5 ± 0.6	6.5 ± 1.6
50	8.7 ± 0.7	6.2 ± 0.4
60	12.4 ± 1.9	6.8 ± 1.2
70	10.1 ± 1.2	6.9 ± 0.8
80	9.6 ± 1.2	6.5 ± 1.1

kinetics the behavior was similar for all systems. Thus, the higher release rates for the tablets with a high CP content were an indication of the higher and faster swelling of CP, which would lead to higher drug diffusion coefficients.

In our previous work (14), it was demonstrated that under acidic conditions up to pH 4, swelling of the CP increased slightly. Swelling was greatly increased between pH 4 and pH 5 and continued to increase at pH 6 and 7, whereas it was reduced at more alkaline pH levels. CP with a pK_a of ~4.75 will be almost fully ionized at pH 6.6. Since HPMC is a nonionic polymer, pH has no effect on the swelling behavior of HPMC. Therefore the swelling rate of HPMC is less than that of CP.

When 90, 80, and 70% CP was incorporated into the formulation, the amount of morphine sulfate released decreased from 34.4 ± 3.2 to 29.6 ± 1.6 and 24 ± 1.6% respectively (Table III). Release phenomena of morphine sulfate from the tablets containing 50% CP were investigated considering the effect of interpolymer complex formation. We showed that the complex formation between HPMC and CP was observed only in the acid medium, and not in the media of pH ≥4.5. Although the interpolymer complex could be formed in the tablet owing to the acidity of CP independent of the pH value of the dissolution medium in the initial dissolution stage, the acidity in the tablet is expected to decrease with the penetration of the dissolution medium. This may cause decomplexation between HPMC and CP in the tablet. Consequently, the fastest dissolution rate of morphine sulfate was observed for the buccoadhesive tablets containing 50% CP, among the formulations tested in this study.

Table III. Release Rate Contants (hr^{-1}) of Buccoadhesive Morphine Sulfate Tablets (n = 6)

Formulation	Release rate constant (hr^{-1}), mean ± SD (CV)	Intercept (mg)
MS-10-K	4.3 ± 0.4 (9.3%)	−1.1
MS-20-K	3.7 ± 0.2 (5.4%)	−3.2
MS-30-K	3.0 ± 0.2 (6.6%)	2.4
MS-40-K	3.1 ± 0.3 (9.6%)	0.4
MS-50-K	5.2 ± 0.2 (3.8%)	−1.3
MS-60-K	4.5 ± 0.5 (11.1%)	1.7
MS-70-K	3.2 ± 0.1 (3.1%)	2.9
MS-80-K	3.3 ± 0.2 (6.0%)	2.3

Table IV. Kinetic Constants (k), Release Exponents (n), and Determination Coefficients (r^2) Following Linear Regression of Dissolution Data of Buccoadhesive Morphine Sulfate Tablets (n = 6)

Formulation	n (mean ± SD)	k	r^2
MS-10-K	1.00 ± 0.09	3.98	0.984
MS-20-K	1.00 ± 0.06	3.66	0.993
MS-30-K	0.74 ± 0.05	5.38	0.997
MS-40-K	0.95 ± 0.08	3.50	0.983
MS-50-K	0.95 ± 0.04	5.09	0.981
MS-60-K	0.92 ± 0.10	5.69	0.975
MS-70-K	0.73 ± 0.03	5.99	0.997
MS-80-K	0.86 ± 0.04	4.90	0.994

To investigate the mechanism of release, the following semiempirical equation was used (15):

$$M_t/M_\infty = kt^n$$

where M_t/M_∞ is the fraction of drug released up to time t, n is a diffusional exponent, k is the apparent release rate, and M_∞ is the amount of drug incorporated in the tablet, i.e., 30 mg. In all cases, n was close to 1, indicating that the release of morphine sulfate from the tablet consisting of a mixture of CP and HPMC could be regarded as following an apparent zero-order mechanism (Table IV).

In the case of an insoluble and nonswellable polymer matrix, drug release has generally been expressed by a Fickian diffusion mechanism, that is, the time dependence of the square root of time (n = 0.5). Therefore, the non-Fickian release behavior obtained here may suggest that the release of morphine sulfate was controlled by a combination of diffusion of morphine sulfate from the matrix and the three-dimensional network structure which was produced by the complex formation following water penetration into the tablet. Similar phenomena have been reported in the release behavior of metranidazole from tablets consisting of Methocel K4M and Carbopol 934 (10) by Takayama *et al.* (16). They concluded that this system behaves as a swellable system and that its release behavior is controlled by diffusion and chain relaxation.

The buccoadhesive morphine sulfate tablets containing 20% HPMC showed suitable release kinetics ($n \cong 1$) and adhesive properties to the buccal mucous membrane. In addition, this selected percentage of HPMC/CP was free of complexation between two polymers. Therefore, both polymers could act independently, and the *in vivo* experiments were carried out with this formula.

In Vivo Studies

The percentages of morphine sulfate absorbed are presented in Table V. An average of 30 ± 5% of the drug loaded was absorbed in 8 hr. These results are based on residual assay determination and may be overestimates of the amount absorbed across the mucosa. Also, none of the subjects in the study complained of a bitter taste, suggesting that morphine sulfate does not dissolve in saliva. Thus, the transfer of morphine into the systemic circulation occurred only

Table V. *In Vivo* Evaluation of Morphine Sulfate Buccoadhesive Tablets

Subject	% of drug absorbed							
	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr
BT	14.4	17.0	17.8	22.1	23.0	24.7	26.4	28.1
ÇT	3.3	5.0	8.5	9.3	17.8	20.4	30.7	31.5
KÇ	2.5	8.5	14.4	17.0	19.3	20.4	20.4	22.1
MY	3.3	4.2	11.8	17.0	21.3	24.7	26.4	29.8
ŞA	13.6	14.4	16.1	22.9	24.7	28.1	29.8	34.9
YÇ	3.3	11.8	13.6	23.0	26.5	29.0	30.7	34.9
Mean ± SD	6.7 ± 5.6	10.1 ± 5.1	13.7 ± 3.3	18.5 ± 5.3	22.1 ± 3.3	24.5 ± 3.6	27.4 ± 3.9	30.2 ± 4.8

from the buccal sulcus. The objective of avoiding first-pass metabolism therefore was probably achieved.

A fresh dry, tablet placed in the buccal sulcus is associated with a variable period of instability in location until it becomes sufficiently dampened to stick firmly to the mucosa. The surface area of contact between tablet and mucosa at this stage is dependent upon the topography of the mucosal surface immediately adjacent to the tablet. For these reasons, morphine absorption showed great intersubject variation (Table V).

This sort of variation might also occur within an individual on different occasions. Hoskin *et al.* (17) estimated that the absolute bioavailability of morphine was 23% for an oral solution and 18% for a buccal tablet over 12 hr. Since information about the formulation and *in vitro* evaluation of buccal morphine sulfate tablets was not available in their report, it was not possible to discuss and compare our results.

A quantitative relationship was obtained between the percentage morphine sulfate absorbed and its *in vitro* release for morphine sulfate buccoadhesive tablets (MS-20-K). The *in vitro–in vivo* correlation equation ($y = 0.92x + 4.01$; $r = 0.987$) was constructed by taking corresponding amounts (percentage) for *in vivo* and *in vitro* release at the same 1-hr interval up to 8 hr. There was a high *in vitro–in vivo* correlation, with a determination coefficient of 0.987 for the buccoadhesive morphine sulfate tablets. The linear relationship between the mean *in vitro* release pattern of the buccoadhesive formulations and that *in vivo* indicates that the rate of drug release was almost constant. The 1:1 *in vitro–in vivo* correlation suggests that drug release from the tablet is the rate-limiting step of the process provided that the entire amount of drug released from the tablet is topically absorbed in the tissue.

In conclusion, a new buccoadhesive system for the release of morphine sulfate was developed using HPMC and CP in various amounts. The release rate of morphine sulfate from HPMC/CP tablets was greatly affected by changes in the polymer mixing ratio, suggesting a possible interaction between HPMC and CP in the tablet following water penetration into the tablet. The results obtained here, non-Fickian release behavior, suggest that the release of morphine sulfate is controlled by a combination of diffusion of morphine sulfate in the matrix and swelling of the matrix followed by water penetration into the tablet. This new system showed significant bioadhesive characteristics in contact with bovine sublingual mucus, as a function of CP content and interpolymer complex formation. This buccoadhesive therapeutic system may be useful for buccal administration of morphine sulfate.

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