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Mucoadhesive Bilayered Tablets for Buccal Sustained Release of Flurbiprofen

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ABSTRACT

The aim of this work was the design of sustained-release mucoadhesive bilayered tablets, using mixtures of mucoadhesive polymers and an inorganic matrix (hydrotalcite), for the topical administration of flurbiprofen in the oral cavity. The first layer, responsible for the tablet retention on the mucosa, was prepared by compression of a cellulose derivative and polyacrylic derivative blend. The second layer, responsible for buccal drug delivery, was obtained by compression of a mixture of the same (first layer) mucoadhesive polymers and hydrotalcite containing flurbiprofen. Nonmedicated tablets were evaluated in terms of swelling, mucosal adhesion, and organoleptic characteristics; in vitro and in vivo release studies of flurbiprofen-loaded tablets were performed as well.

The best results were obtained from the tablets containing 20 mg of flurbiprofen, which allowed a good anti-inflammatory sustained release in the buccal cavity for 12 hours, ensuring efficacious salivary concentrations, and led to no irritation. This mucoadhesive formulation offers many advantages over buccal lozenges because it allows for reduction in daily administrations and daily drug dosage and is suitable for the treatment of irritation, pain, and discomfort associated with gingivitis, sore throats, laryngopharyngitis, cold, and periodontal surgery. Moreover, it adheres well to the gum and is simple to apply, which means that patient compliance is improved.

KEYWORDS: Bilayer tablets, mucoadhesion, polyacrylic acid derivatives, cellulose derivatives, hydrotalcite, flurbiprofen, buccal delivery.

INTRODUCTION

Inflammatory processes cause most oral cavity diseases. This problem is managed with the topical administration of the nonsteroidal anti-inflammatory drug 2-(2-fluoro-4-biphenylyl) propionic acid, flurbiprofen (FLUR). This drug is widely employed because of its successful use in the treatment of oral ulcers and aphthous stomatitis,[1] postsurgical dental pain,[1-3] gingivitis,[4] laryngopharyngitis, and sore throat[5,6]; moreover, it reduces bone resorption in periodontal disease.[7]

Traditionally, anti-inflammatory and analgesic topical therapy in the oral cavity is restricted to very limited formulations such as mouthwash, sprays, gels, or lozenges, which cannot be used successfully since they do not adhere well, are washed away by saliva, and hence are quickly removed. In recent years, the development of bioadhesive buccal delivery systems has been the subject of intensive research in order to increase the retention of drug in the oral cavity.[8] Mucoadhesive tablets, immobilized drug delivery systems, can consist of monolithic, partially coated, or multilayered matrices.[8] In the case of bilayered tablets, drug release can be rendered almost unidirectional; if the drug can be incorporated in the upper nonadhesive layer, its delivery occurs into the whole oral cavity.

The aim of this study was the preparation of bilayered buccal adhesive tablets to obtain buccal sustained release of FLUR. New mucoadhesive tablets, using different mixtures of cellulose derivatives (hydroxyethylcellulose [HEC], hydroxypropyl methylcellulose [HPMC] K15M), polyacrylic derivatives (Carbomer 940, Carbopol 971), and an inorganic matrix, namely hydrotalcite (HTlc), have been developed. The first layer, responsible for the tablet retention on the mucosa, was obtained by compression of cellulose derivative and polyacrylic derivative (1:1) blend. The second layer, responsible for buccal drug delivery, was obtained by compression of a mixture of the same (first layer) mucoadhesive polymers and HTlc containing FLUR (Figure 1).

HTlc is an inorganic and biocompatible anionic layered solid[9] able to intercalate anti-inflammatory drugs and modify their release.[10] Layered magnesium aluminum HTlc in the chloride form (HTlc-Cl),[10] employed as a controlled-release matrix, had the formula $[Mg_{0.63}Al_{0.397}(OH)_2]Cl_{0.397} \cdot 0.66\ H_2O$ and was used as a host. The intercalation compound (HTlc-FLUR) was prepared by $Cl^-/FLUR^-$ anionic exchange, as previously described,[10] and the drug loading was 49.3% wt/wt (1000 mg of HTlc-FLUR contains 493 mg of anti-inflammatory drug). The present study involved the following steps:

- preparation of nonmedicated tablets
- in vitro characterization and ex vivo and in vivo studies

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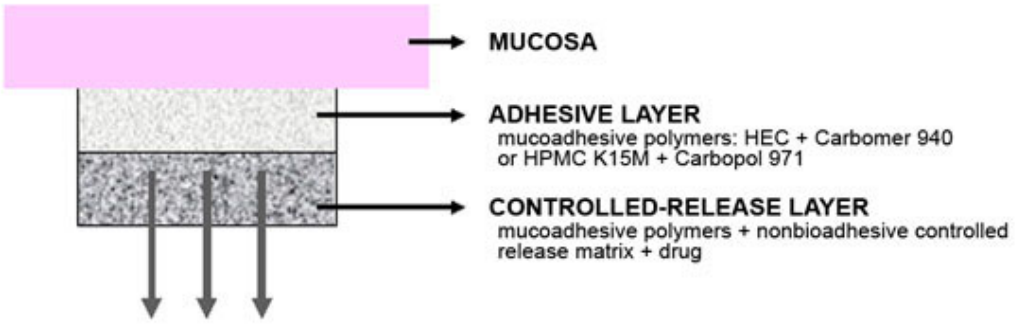

Figure 1. Schematic explanation of the structure of mucoadhesive bilayered devices. HEC indicates hydroxyethylcellulose; HPMC, hydroxypropyl methylcellulose.

- choice of mucoadhesive tablets showing the best performances
- preparation of medicated tablets with FLUR
- evaluation of in vitro drug release
- evaluation of in vivo drug release, in comparison to traditional lozenges[5,6]

Materials and Methods

Materials

HEC (Natrosol-250HHX) was obtained from Aqualon (Hercules Incorporated, Bologna, Italy). HPMC (Methocel K15M) was supplied by Colorcon (Dartford, UK). Carbopol 971 was obtained from Noveon (Milano, Italy). Carbomer 940 was purchased from Galeno (Firenze, Italy). FLUR was obtained from Angelini (Ancona, Italy). HTlc-Cl and HTlc-FLUR were prepared in our laboratories.[10] Pig buccal mucosa was furnished by the Veterinary Service of USL N.1 Città di Castello (Perugia, Italy). Benactiv (Boots Co PLC, Nottingham, UK) traditional lozenges to be dissolved in the buccal cavity were purchased at a retail pharmacy. Methyl blue was purchased from Carlo Erba (Milano, Italy). All other materials were of reagent grade.

Nonmedicated Tablet Preparation

Blends were prepared by triturating with a pestle and a mortar, and bilayer tablets were prepared in 2 stages using a 13-mm-diameter die on an infrared hydraulic press (Perkin-Elmer, Cambridge, UK) with a compression force of $5{\cdot}10^3$ kg for a total time of 30 seconds. Initially, 100 mg of the first-layer mucoadhesive polymer blend was compressed for 1 or 5 seconds (first tableting time) (Table 1) to obtain the mucoadhesive layer (dye methyl blue was added to mark the nonmedicated layer). Following first compression, the punch was lifted, 100 mg of the second-layer blend (Table 1) was added, and a second compression ($5{\cdot}10^3$ kg) was performed for 29 or 25 seconds (second tableting time) to obtain the bilayered tablet. The tablet thickness was measured (in triplicate) by a micrometer (Borletti, Cremona, Italy).

Swelling Studies

The swelling properties and the erosion characteristics of tablets were evaluated by determination of the percentage of hydration and matrix erosion or dissolution (DS). The percent values were calculated according to the following equations:

$$\%\ \text{of Hydration} = \frac{(W2 - W1)}{W2} * 100 \qquad (1)$$

$$DS = \frac{W1 - W3}{W1} * 100 \qquad (2)$$

Each tablet was weighed (W1) and immersed in a simulated salivary fluid[11] at pH 6.75 for predetermined times (0.5, 1, 2, 4, 8, and 24 hours). After immersion, excess surface water was removed from the tablets using filter paper and weighed (W2). The swollen tablets were dried at 60°C for 24 hours in an oven and kept in a desiccator for 48 hours prior to reweighing (W3).[12,13] This experiment was performed in triplicate.

Ex Vivo Mucoadhesion Time

The ex vivo mucoadhesion time studies were performed (in triplicate) after application of tablets on freshly cut porcine buccal mucosa.[14] The porcine buccal tissues were fixed on the internal side of the beaker with cyanoacrylate glue. A side of each tablet was wetted with 50 μL of simulated salivary fluid and was attached to the porcine buccal tissue by applying a light force with a fingertip for 20 seconds. The beaker was filled with 800 mL of simulated salivary fluid and kept at 37°C; after 2 minutes a stirring rate of 150 rpm was applied to simulate the buccal cavity. Tablet behavior

Table 1. Composition and Characteristics of Tablets Without Drug*

	Composition															
	First Layer (mg)				Second Layer (mg)					Tableting Time (s)		Thickness mm (±0.01) ± confidence (n = 3; α = 0.05)	Ex Vivo Muco-adhesive Time (h)	In Vivo Muco-Adhesive Time (h)	Ex Vivo Mucoadhesive force ± conf. (n = 3; α = 0.05)
N	HEC	Carbomer 940	HPMC K15M	Carbopol 971	HEC	Carbomer 940	HPMC K15M	Carbopol 971	HTlc-Cl	First Time	Second Time				
1	50	50	—	—	25	25	—	—	50	5	25	1.07 ± 0.02	20	13	0.85 ± 0.02
2	50	50	—	—	25	25	—	—	50	1	29	1.09 ± 0.01	30	13	1.50 ± 0.16
3	—	—	50	50	—	—	25	25	50	5	25	1.07 ± 0.01	29	14	1.25 ± 0.16
4	—	—	50	50	—	—	25	25	50	1	29	1.09 ± 0.02	30	14	1.58 ± 0.13

*HEC indicates hydroxyethylcellulose; HPMC, hydroxypropyl methylcellulose; HTlc, hydrotalcite.

and mucoadhesive time (Table 1) were monitored until complete detachment or DS occurred.

In Vivo Mucoadhesive Performance of Tablets Without Drug

In vivo studies were performed (in triplicate) by applying tablets on 5 healthy volunteer gums to assess the residence time, the organoleptic characteristics, the fragment loss, the salivary level variation, and the possible production of irritation or pain. Each tablet was attached to the gum by applying a light force with a fingertip for 20 seconds. Tablet behavior and mucoadhesion time (Table 1) were monitored.

Ex Vivo Mucoadhesion Force

The ex vivo adhesion strength was assessed by a dynamometer[15] (Lehrmittelbau, Bonn, Germany) using the above-mentioned porcine mucosa. For mucoadhesive measurements, tablets were attached on a support, connected to the dynamometer, using cyanoacrylate glue. A piece of porcine buccal mucosa was glued onto a support and kept in a vessel placed in a thermostatic bath at 37°C (±0.1). The free side of the tablet was wetted with 50 μL of simulated salivary fluid and attached to porcine buccal tissues by applying a light force with a fingertip for 20 seconds. The vessel was filled with simulated salivary fluid and kept at 37°C. The measurements started after 2 minutes. The maximum adhesive forces were the average of 3 measurements (n = 3), and the confidence interval was determined at a 0.05 significance level (Table 1).

Drug-Loaded Tablet Preparation

Two series of drug-loaded tablets containing different anti-inflammatory doses were prepared as above-described. Series a (1a, 2a, 3a, 4a) contained 10 mg of FLUR (corresponding to 20.28 mg of HTlc-FLUR), and series b (1b, 2b, 3b, 4b) contained 20 mg of FLUR (corresponding to 40.56 mg of HTlc-FLUR); the second-layer weight (100 mg) was obtained by adding HTlc-Cl (Table 2).

In Vitro Release Study

A Farmacopea Ufficiale XI Ed (F.U.XI) standard basket apparatus, properly modified,[16] was used to evaluate drug release. A side of the tablet was wetted with 50 μL of simulated salivary fluid and attached to the bottom flat end of the stirring rod instead of the basket fixture. After 2 minutes, the vessel was filled with simulated salivary fluid at 37°C and stirred at 100 rpm. Four-milliliter samples were collected at predetermined time intervals and replaced with an equal volume of simulated salivary fluid. The FLUR

Table 2. Drug-Loaded Tablet Composition

	Composition											
	First Layer (mg)				Second Layer (mg)						Tableting Time(s)	
N	HEC	Carbomer 940	HPMC K15M	Carbopol 971	HEC	Carbomer 940	HPMC K15M	Carbopol 971	HTlc-FLUR	HTlc-Cl	First Time	Second Time
1a	50	50	—	—	25	25	—	—	20.28	29.79	5	25
1b	50	50	—	—	25	25	—	—	40.56	9.44	5	25
2a	50	50	—	—	25	25	—	—	20.28	29.72	1	29
2b	50	50	—	—	25	25	—	—	40.56	9.44	1	29
3a	—	—	50	50	—	—	25	25	20.28	29.79	5	25
3b	—	—	50	50	—	—	25	25	40.56	9.44	5	25
4a	—	—	50	50	—	—	25	25	20.28	29.79	1	29
4b	—	—	50	50	—	—	25	25	40.56	9.44	1	29

*HEC indicates hydroxyethylcellulose; HPMC, hydroxypropyl methylcellulose; HTlc, hydrotalcite; FLUR, flurbiprofen.

concentration in each sample was determined by UV spectrophotometry at λ_{max} = 247.2 nm with a spectrophotometer (Jasco Ltd V-520, Great Dunmow, Essex, UK) and reported as an average of 3 determinations. Drug release profiles were compared with those from FLUR 8.75 mg lozenges (Benactiv). The latter were performed through an unmodified basket apparatus (F.U.XI).

In Vivo Release Study

In vivo release studies were performed by applying tablets, after approval from the Ethics Committee of the Aziende Sanitarie dell'Umbria, to 5 healthy volunteers' gums upon the volunteers' written consent. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (regional) and with the Helsinki Declaration promulgated in 1964. Volunteers were instructed to press the tablet against their gums for 20 seconds without moistening it before application. Volunteers did not consume water or food during the half-hour before the study. The fast was strictly observed throughout the experiment. Drinking was allowed ad libitum 30 minutes after administration of the tablet, but no drinking was allowed 10 minutes before the collection of salivary samples.[17] Care was taken to ensure that the tongue did not contact the tablet during the 10 minutes before sampling, to avoid abnormally high drug levels.[18] Residence tablet time, possible irritation, loss of fragments, bad taste, and dry mouth or excessive salivation were evaluated.

Samples of saliva were collected prior to the application of tablets and at predetermined times. One milliliter of each sample was diluted to 10 mL with simulated salivary fluid and filtered through a Millipore cellulose acetate membrane filter (Billerica, MA) (0.45 μm). The FLUR concentration in each sample was determined by means of UV spectrophotometry at λ_{max} = 247.2 nm according to a previously determined calibration curve (y = 19362x + 0.0703, r = 0.9995) and using saliva (filtered and diluted 1:10 with simulated salivary fluid) as a blank. Salivary drug levels were compared with those obtained from Benactiv. In this case, lozenges were simply dissolved in the buccal cavity and not pressed against the gum.

Results and Discussion

Swelling-Hydration and DS Studies

Generally, all tablets hydrated very quickly, reaching 70% to 80% hydration after 2 hours and 87% to 92% after 12 hours. This means that the presence of an inorganic matrix (HTlc) does not hinder water sorption and does not interfere with formulation swelling. Tablet 1 hydration was very rapid and complete (67.45% after 30 minutes, 86.50% after 4 hours, 92% after 12 hours), while tablets 2 to 4 hydrated more slowly and reached hydration percent values <90% after 12 hours.

During mucoadhesive formulation development, tablet hydration capacity is very important to be considered because the water penetration is responsible for drug release. However, since swelling and gel formation can make tablets erodible, it is very important to know if and when the formulation loses its integrity. For this reason DS was investigated by comparing the initial and final tablet weight after immersion in water. The negative DS values after 2 hours confirmed the good hydration of all tablets and, according to previous observations, tablet 1 showed greater negative DS data. Only tablet 4 showed positive DS values between 8 and 12 hours (32.44% after 12 hours) because of the erosion effect.

Mucoadhesive Studies

Ex Vivo Mucoadhesive Behavior

Empty bilayered tablets were attached to porcine buccal tissue and monitored until their detachment or complete erosion occurred. All tablets attached very well to mucosa, and

in particular tablets 2 and 4 adhered immediately, showing more conformability and adaptability to tissue than 1 and 3. This difference could be due to the minor tableting time applied to the first layer (1s vs 5s) (Table 1), which causes less layer rigidity and permits easier link formation between mucoadhesive polymers and mucus chains.

During the experiment, all tablets showed remarkable swelling, but the gel formation was different; tablets 1 and 2, according to hydration percentage, hydrated very quickly and underwent considerable swelling after 15 minutes. The salivary fluid penetrated easily through the compact formed gel, and it was possible to note after 5 hours (tablet 1) and 3 hours (tablet 2) a remarkable reduction of the white central core.

Tablets 3 and 4 hydrated and swelled more slowly. The gel layer formation was diminished, and the tablet central core remained present until 20 hours (tablet 3) and 25 hours (tablet 4). Moreover, the formed gel was rather rigid and not compact and gave rise to fragment loss, according to DS data.

The dissimilar gel consistencies and behaviors could be explained on the basis of the different cellulose derivative used: the HEC hydrophilic properties permitted a compact and stable gel formation, while HPMC was responsible for the slower swelling and the insoluble gel obtained gave rise to fragment loss from tablets.

All tablets showed high mucoadhesion times (Table 1), with the exception of tablet 1, which had the lowest residence time (20 hours).

These results are very interesting because they confirm the tablets' capacity for hydration, swelling, and good mucoadhesion in the presence of HTlc, an inorganic material that is insoluble in water and was expected to lead to rigid tablets that could not be hydrated.

Moreover, from tablet behavior monitoring it was possible to hypothesize that tablets 1 and 2 are more suitable than tablets 3 and 4 for preparing mucoadhesive devices for buccal drug release.

In Vivo Mucoadhesive Studies

All tablets adhered immediately to the gum and showed residence times above 12 hours (Table 1). No tablets caused a bad taste, irritation, or pain.

Tablet 1 (Figure 2) adhered completely to the gum immediately (a); 1 hour after application (b), it was possible to note hydration and swelling. The first layer of the system proved to be well attached and perfectly adherent to the gum, while the second layer showed gel formation at the surface and increased border erosion (c). From 5 hours to 10 hours, a progressive tablet core decrease (second layer) and the appearance of the first layer dark colored (methyl blue) were observed (d). The swelling and erosion processes of the second layer were completed at 12 hours (data not shown).

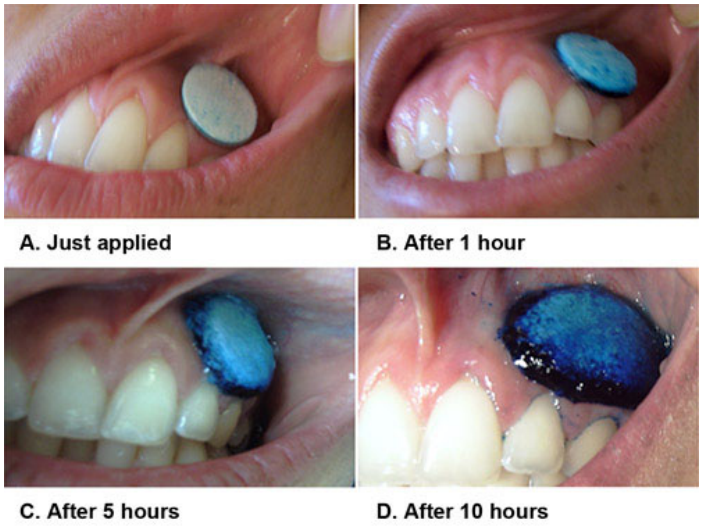

Figure 2. In vivo mucoadhesion behavior of tablet 1 when just applied and after 1, 5, and 10 hours.

Ex Vivo Mucoadhesive Force

All tablets showed good mucoadhesive forces ranging from 0.85 to 1.58 N (Table 1). It is possible to note that, for tablets with the same polymer composition, the mucoadhesion force was higher when the first-layer tableting time was lower (2 > 1 and 4 > 3). The minor tableting time (1 second vs 5 seconds), permitting a faster polymer chain relaxation, creates the possibility of forming a hydrogen bond (first) with water and (then) with mucus chains. Tablet 1 shows the lowest mucoadhesive force: in this case HEC's hydrophilic properties could have promoted the linking with water.

The same test was performed on drug-loaded tablets, and no relevant differences were observed between drug-loaded and blank tablets (data not shown).

In Vitro Release Studies

After these studies, drug-loaded tablets were prepared according to what is reported in Materials and Methods. FLUR loading was 10 mg for tablets 1a, 2a, 3a, and 4a and 20 mg for tablets 1b, 2b, 3b, and 4b (Table 2). All tablets were submitted to in vitro release studies in sink conditions and monitored for 24 hours (Figure 3). Data are reported for only the period from 1 hour to 12 hours since no variations occurred between 12 and 24 hours.

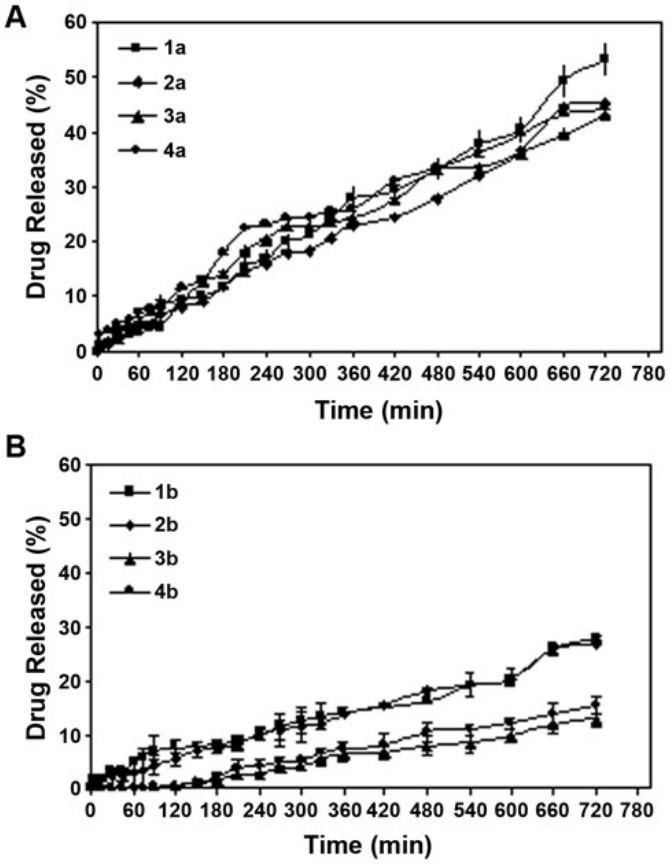

Figure 3. In vitro release profiles (n = 3, $\alpha = 0.05$) of mucoadhesive tablets containing 10 mg (A) and 20 mg (B) of flurbiprofen.

Tablets 1a to 4a (Figure 3A) showed slow and gradual drug release throughout the experimental time without reaching 100% of total anti-inflammatory content. The greatest amount of drug was released by tablet 1a (53.26%), followed by 2a (45.13%), 4a (44.21%), and finally 3a (43.03%).

Tablets 1b to 4b's release, reported in Figure 3B, was gradual, and the percentages were lower than for 1a to 4a. Tablet 1b had the largest drug release (27.81%), followed by 2b (26.83%), 4b (15.40%), and 3b (13.01%). The 8.75 mg FLUR lozenges (Benactiv) were enclosed in vitro drug release studies: the FLUR release was complete after 10 minutes (data not reported).

In Vivo Release Studies

Taking into account hydration, mucoadhesion, and in vitro release, we chose only tablets 1a and 1b for the in vivo drug release studies (Figure 4). To evaluate whether these tablets produce suitable anti-inflammatory efficacious doses, Benactiv lozenges were included in the study and compared with 1a and 1b. Benactiv lozenges dissolved very quickly (5-10 minutes), and FLUR lasted in saliva for 3 hours (8 lozenges/day was assumed to be a therapeutic dose, as indicated in the Benactiv package leaflet), giving rise to a concentration range, for the observed period, of 8.79 to 138.34 μg/mL.

Mucoadhesive tablet 1a (10 mg) released FLUR throughout the period (12 hours), but the salivary concentrations were rather low. Only between the third and the seventh hour did the drug reach efficacious levels (>8.79 μg/mL). This means that 10 mg is not suitable for a 12-hour sustained-release formulation. Tablet 1b (20 mg) produced higher salivary drug concentration values (efficacious if compared with Benactiv) throughout the 12-hour period. This means

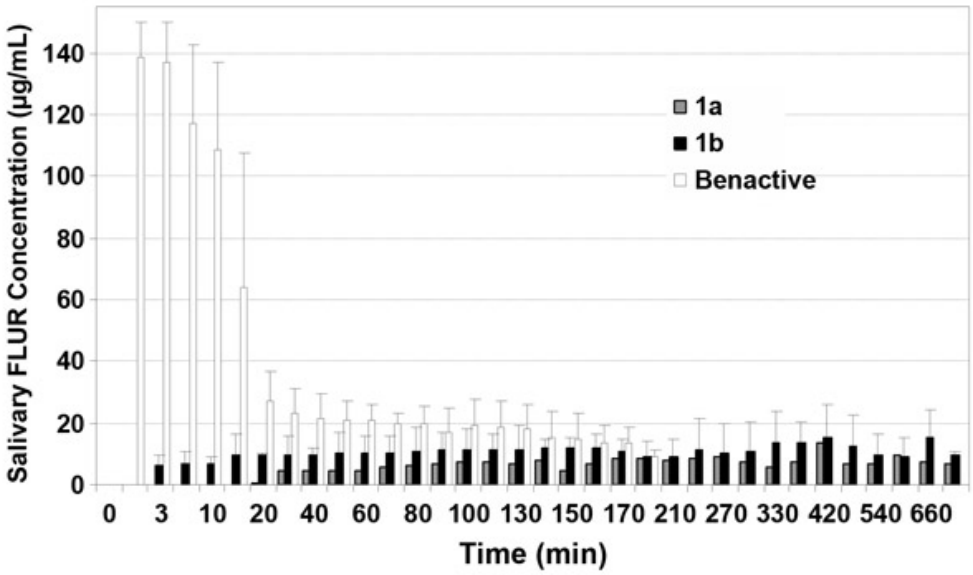

Figure 4. FLUR salivary concentration with mucoadhesive tablets 1a and 1b and Benactiv lozenges (n = 5, $\alpha = 0.05$). FLUR indicates flurbiprofen.

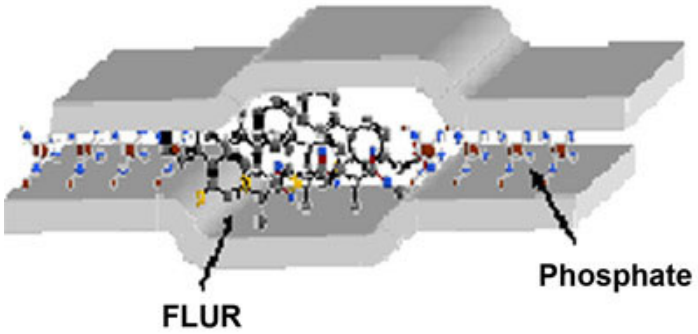

Figure 5. Grafting reaction. FLUR indicates flurbiprofen.

that a 20-mg FLUR-loaded tablet was the best for producing a buccal anti-inflammatory effect for 12 hours.

In Vitro–In Vivo Correlation

Tablet 1b's in vitro and in vivo drug release profiles were not well correlated; in fact, the in vitro maximum release resulted in a figure of only 27.81% after 12 hours, while in the buccal cavity the FLUR had a good release and a consistent efficacious dose was maintained for 12 hours. This can be explained as follows:

1. The in vitro conditions do not reproduce the physiological buccal condition.
2. The drug release mechanisms in vitro and in vivo are not the same.

The low release percentage in vitro could be ascribed to the phosphate ions, whose presence is higher in simulated salivary fluid than in saliva. At pH 6.75 the H_3PO_4 generates anions $HPO_4^{=}$ and $H_2PO_4^{-}$, able to intercalate between the HTlc lamellar structure. In particular, the acidic ion $H_2PO_4^{-}$ is more suitable for reacting with the hydroxyls of the layer, producing thus a layered Al hydroxyphosphate; this is known as a grafting reaction.[19] In this strongly bound form, phosphates are not exchangeable and can obstruct the drug release of entrapped FLUR ions from the internal matrix layer (Figure 5).

The in vitro FLUR release mechanism depended both on the gel-forming rate on the tablet surface and on simulated salivary fluid anion action on the inorganic matrix (anion exchange). Moreover, during the in vivo study, tablet erosion (Figure 2) contributed to FLUR release.

In Vitro Release Kinetics

Tablet 1b's in vitro release profile was fitted to the Ritger and Peppas[20] kinetic mathematical model, applied to swelling matrices, and the Bhaskar et al[21] model, for exchange-ionic resins, to investigate the kind of mechanism responsible for FLUR release (Table 3). According to the correlation obtained for the Ritger and Peppas model, the FLUR release from the swellable tablet system was mainly driven by anomalous transport (not Fickian). In fact, the *r* value was seen to increase as the release exponent n increased, and the highest value ($r = 0.9882$) was achieved for $n = 1$. This behavior was correlated with the peculiar process involved in the release of drugs from swellable matrices, for which the chain unfolding and stretching deeply affect the drug diffusion rate. In particular, in this case, an additional lag time can be ascribed to the need for $FLUR^{-}$ displacement from the HTlc matrix prior to drug diffusion. In this regard, the fitting to the Bhaskar model ($r = 0.9685$) showed a lower correlation with respect to the zero-order kinetics; this is likely due to the higher rate of the ion exchange process compared with diffusion. In addition, the anomalous non-Fickian transport recorded can be correlated to tablet erosion, which contributes to FLUR release from the swellable system. This is more evident if one considers the much greater extent of FLUR release observed in vivo, where erosion appeared to be one of the main mechanisms responsible for drug diffusion. On the other hand, in vitro the observed

Table 3. Interpretation of Diffusional Release Mechanism From In Vitro Drug Release Data From Tablet 1b

Release Exponent (n)	Drug Transport Mechanism	Rate (dM_t/dt) as Function of Time	Equation	Correlation Coefficient (*r*)
	$\frac{M_t}{M_\infty} = Kt^n$ **swellable systems**			
0.5	Fickian diffusion	$t^{-0.5}$	y = 0.0097x – 0.0302	0.9658
0.6	Anomalous (non-Fickian transport)	t^{n-1}	y = 0.0048x – 0.0130	0.9747
0.7	Anomalous (non-Fickian transport)	t^{n-1}	y = 0.0024x – 0.0002	0.9810
0.8	Anomalous (non-Fickian transport)	t^{n-1}	y = 0.0012x – 0.0098	0.9850
0.9	Anomalous (non-Fickian transport)	t^{n-1}	y = 0.0006x – 0.0178	0.9874
1	Case II transport	Zero-order release	y = 0.0003x – 0.0244	0.9882
	$\ln\frac{M_t}{M_\infty} = 1.59\left(\frac{6}{d_p}\right)^{1.3} D^{0.65}t^{0.65}$ **resins**			
0.65	Exchange ionic	$t^{0.65}$	y = 0.0017x + 0.0063	0.9685

release was much lower as a consequence of less pronounced erosion of the device.

CONCLUSION

Tablet 1b, loaded with 20 mg FLUR, showed the best results, allowing good anti-inflammatory sustained release in the buccal cavity for 12 hours and permitting thus a reduction in daily administration (2 tablets vs 8 of Benactiv) and daily drug dosage (40 mg vs 70 mg).

The proposed device represents a remarkable dosage reduction (40 mg vs 300 mg) if compared with oral therapy (Froben 100 mg, 3 tablets/day).

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