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Design and Evaluation of Buccal Adhesive Hydrocortisone Acetate (HCA) Tablets

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Many studies have shown that topical buccal therapy with steroid anti-inflammatory drugs is useful in controlling ulcerative and inflammatory mucosal diseases. This local treatment is based on the concept that a high activity of steroids can be produced at the site of administration and, at the same time, the degree of systemic side effects can be minimized or avoided. In this study we developed a new formulation consisting of a mucoadhesive tablet formulation for buccal administration of hydrocortisone acetate (HCA). Three types of tablet were developed containing three mucoadhesive components: hydroxypropylmethyl cellulose (Methocel K4M), carboxyvinyl polymer (Carbopol 974P), and polycarbophyl (Noveon AA1); the first polymer is a cellulose derivative, the others are both polyacrylic acid derivatives. For each of those, three tablet batches were produced changing the quantity of the mucoadhesive component (10, 20, and 30%), resulting in 9 different formulations. The compatibility of HCA with all excipients using Differential Scanning Calorimetry (DSC) was assessed. Tablets were manufactured by wet granulation followed by compression. Technological controls on granulates (Hausner index, Carr index, granulometry and Karl-Fischer percentage humidity) and tablets (thickness, diameter, friability, hardness, uniformity of content, weigh uniformity and dissolution kinetic) were carried out. Mucoadhesion properties, ex vivo permeability through porcine buccal mucosa, in vivo behavior and compliance were evaluated.

Technological controls have demonstrated that the increase in the (percentage) of mucoadhesive causes an increase in granulometry followed by a reduction in the granulate flowability, however all the tablets have given satisfactory technological results and conformed to the 3rd Ed. European Pharmacopoeia specifications. Mucoadhesion, ex vivo permeability and in vivo behavior results notably differed among tablets, depending on the quality and quantity of the mucoadhesive component. An overall comparison of results showed the tablets containing Carbopol 20% resulted to be the best formulation among those developed.

Keywords Buccal Delivery, Buccal Mucoadhesive Tablet, Hydrocortisone Acetate, In Vitro Permeation Study

A variety of drugs have been shown to be absorbed mainly by the buccal, the sublingual or the gingival mucosa, whereas the palatal mucosa and the mucosa of the tongue were assumed to be less permeable (Chien 1983; De Vries and Junginger 1991; Harris and Robinson 1992). In fact, drug absorption via the mucosal ephitelium of the oral cavity is an established route of systemic drug delivery, which is especially useful if absorption after oral administration is incomplete or ineffective (e.g. with drugs undergoing strong first-pass effects after ingestion or which are digested on gastrointestinal transit). Previous studies showed that topical buccal therapy with steroid anti-inflammatory drugs is useful in controlling ulcerative and inflammatory mucosal diseases (Aleinikov, Jordan, and Main 1996; Carrozzo et al. 1997; Dunlap, Friesen, and Shultz 1997). This local treatment is based on the concept that a high activity of steroids can be produced at the site of administration and, at the same time, the degree of systemic side effects can be minimized (Mollmann et al. 1990) or avoided (Plemons, Rees, and Zazhariah 1990).

Several commercial products containing Hydrocortisone acetate (HCA) as a local anti-inflammatory and antiallergenic agent are available for topical use on skin. The aim of this work is to develop a mucoadhesive topical formulation for buccal administration. For buccal administration, the conventional formulation like losenges, troches, gels, oral rinses, or mouthwashes would be the simplest dosage forms for delivery of drugs through the mucosa of the oral cavity (Harris and Robinson 1992; Zegarelli 1991). However, these conventional dosage forms have two major disadvantages which consist on an initial burst of activity followed by a rapid decrease in concentration (Needleman, Lang, and Johnson 1972; Niitani et al. 1984) and in a limited permanence in situ related to the constant flow of saliva and the mobility of the involved tissues. Buccal

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mucoadhesive formulations which control the drug release are expected to overcome these problems. Bioadhesive polymers-copolymers have received considerable attention as platforms for controlled drug delivery for the following reasons: they can be localised in a specific surface which is able to absorb drugs, leading to an enhancement of the bioavailability, they prolong the residence time and ensure an optimal contact with the absorbing surface and they may have gelling properties that can be exploited to obtain a control of the drug release (Duchene and Ponchel 1989). The mechanism of bioadhesion of polymers to the mucosa is still far from completely understood and many different types of bio(muco)adhesive polymers can be used in the design of controlled drug delivery systems for the so-called alternative routes of application like the buccal mucosa route (Bettini et al. 1994; Bottemberg et al. 1989; Bouckaert et al. 1993; Park and Robinson 1987; Malataris et al. 1991). Recently, buccal mucoadhesive tablets were developed with promising results (Ceschel, Maffei, and Lombardi Borgia 2001).

In this work, we have developed an adhesive dosage form for local administration, consisting of a buccal tablet, containing HCA, using three different mucoadhesive polymers: hydroxypropylmethyl cellulose (Methocel K4M), carboxyvinyl polymer (Carbopol 974P), and polycarbophyl (Noveon AA1); the first polymer is a cellulose derivative, the others are both polyacrilic acid derivatives. The HCA content was decided to be 1 mg per tablet based to previous works with analogous steroid agents (Aleinikov, Jordan, and Main 1996; Carrozzo et al. 1997).

The study consisted in varying the type and the ratio of the mucoadhesive component in order to investigate the influence of these parameters on the technological and biopharmaceutical behavior of the tablet. The compatibility between the drug and the different excipients (using differential scanning calorimetry) (Boscolo et al. 1989) and the technological characteristics of the granulate (Hausner 1969) and of the tablets were determined. Moreover studies for the evaluation of the bioadhesive force (Peppas 1984; Smart 1991), the release of the drug from the dosage form and the diffusion of the drug through a porcine buccal mucosa were carried out. The compliance of the tablet was also determined by an in vivo test in 10 healthy volunteers.

MATERIAL METHODS

Materials

Hydrocortisone acetate was supplied by Steroid (Cologno Monzese, Italy), carboxyvyinl-polymer (Carbopol 974P) and polycarbophil (Noveon AA1) were supplied by BF Goodrich Chemical Italia S.r.l. (Milan, Italy), hydroxypropylmetylcellulose (Methocel K4) by Eingenmann and Veronelli S.p.A, lactose 200 mesh and magnesium stearate by G. Faravelli (Milan, Italy), microcrystalline cellulose (Avicel PH102) by Prodotti Gianni (Milan, Italy), Talc by Tradeco (Milan, Italy), and PVP PK30 by C.F.M (Milan, Italy). All the materials were used as received.

Study of Compatibility: Differential Scanning Calorimetry (DSC) Studies

DSC was used as a screening technique for assessing the compatibility of HCA with all the excipients. The sample was analysed in a range of between 140° and 230°C, chosen on the basis of the melting point of HCA in USP (223°C). A scan rate of 10.0°C/min was used. Samples of the excipients were analysed in a range of temperatures going from 50°C to 230°C at scan rate of 10.0°C/min.

Manufacturing of Mucoadhesive Tablets

Mucoadhesive tablets were developed for buccal administration: to reach a good adhesion with the buccal mucosa, tablets with a small diameter (6 mm) and thickness (between 1.87 and 1.98 mm) and a flat surface were developed. Each tablet contained 1 mg of hydrocortisone acetate; tablet compositions in percentage are given in Table 1. Three types of tablets were developed using three different mucoadhesive components. For each of them, three batches were produced changing the quantity of the mucoadhesive component, 10, 20, and 30%, resulting in 9 different formulations.

Lactose, microcrystalline cellulose and HCA were carefully mixed with mortar and pestle. The mixture was sifted through a 1 mm sieve and then wet granulated with a 9% povidone ethanol solution. The granulate was dried at 60°C for 3 hours and subsequently sifted through a 0.850 mm sieve and mixed with a mucoadhesive polymer and others additives. The addition of the mucoadhesive component was carried out after the granulation because in a preliminary phase of the study a decrease of adhesive properties of the mucoadhesive component was observed after granulation (data not shown). The granulate was

TABLE 1
Composition of the tablets

%	Formulation with 10% of mucoadhesive polymer	Formulation with 20% of mucoadhesive polymer	Formulation with 30% of mucoadhesive polymer
Hydrocortisone acetate	1.66	1.66	1.66
Microcrystalline cellulose	42.17	37.17	32.17
Lactose 200 mesh	42.17	37.17	32.17
Mucoadhesive*	10	20	30
PVP PK30	3	3	3
Magnesium stearate	0.5	0.5	0.5
Talc	0.5	0.5	0.5

* = Carboxyvinyl polymer (Carbopol 974P) or Polycarbophyl (Noveon AA1) or Hydroxypropylmethyl cellulose (Methocel K4M).

then compressed on a Ronchi compressing machine equipped with a 6.0 mm flat circle shaped punch.

Technological Controls

Technological controls were carried out both for the granules and for the tablets. For the granules apparent density, Hausner index, Carr index, granulometry and Karl-Fischer percentage humidity were determined (Hausner 1969). The tablets were tested for thickness, diameter, friability, hardness, and, according to the European Pharmacopoeia 3 Ed., for uniformity of content, uniformity of weight and dissolution rate.

Dissolution Tests

The dissolution test for each tablet was conducted following USP 23/NF 19, modifying the dissolution medium with a solution of water: ethanol (6:4) because of the low solubility of the HCA in physiological buffer; samples were withdrawn at intervals of 15, 30, 60, 120, 240, 360, 480 min, filtered and essayed for HCA by high performance liquid chromatography (HPLC) technique. The tablet was designed in order to absorb water and swell, changing into a gelling mass that would release a high percentage of the drug before disintegration occurred. Therefore we can consider the drug release from the tablet as release from a swelling matrix rather than a release from a disintegrating matrix. The release kinetics of each tablet can be assessed by inserting the experimental data in the semi-empirical equation described by Ritger and Peppas (1987):

$$\frac{M_t}{M_\infty} = Kt^n$$

where M_t/M_∞ is the fractional amount of the drug at the time t, K is a kinetic constant of the system indicative rate of the release and the n is the release exponent, indicative of the mechanism of release.

Values for n and K for each system were obtained by plotting the logarithm of the fractional release against the logarithm of time, considering data between the first withdrawal at 5 minutes and the one corresponding to the release of the 60% of the dose (Ritger and Peppas 1987). The slope of the line is n while log K is the intercept. The values of n and K were calculated by regression analysis and the statistical parameter R^2 was established to evaluate the fitting of the semi-empirical equation to the kinetics of release.

Mucoadhesive Measurements

The mucoadhesive measurements were performed with glass plates according to Gurny's method using a Instron tester (Peppas 1984; Smart 1991). The bioadhesive strength was estimated in terms of maximum adhesion force and work of adhesion shear required to separate the tablets from the glass plates.

In Vitro Permeation Study

All the in vitro permeation studies were carried out in Franz's diffusion cells with 9 mm diameter and 0,64 cm^2 diffusion area. The receptor compartment had a volume of 4.8 ml and was filled with a solution of water:ethanol 6:4 (v/v) maintained at 37°C by means of thermostated water circulating in a jacket surrounding the cells. The solution in the receptor compartment was continuously stirred at 600 rpm using a Teflon coated magnetic stirrer. Drug permeation tests of HCA from tablets and from a suspension of HCA in purified water, used as a reference to ensure the maximum thermodynamic activity, were carried out. The tested tablets were placed on the membrane in the donor compartment and a 0.3 ml of buffered solution was also placed into the compartment. A porcine oral mucosa was used as membrane between the donor and receptor compartment of the cells. The porcine oral mucosa is largely used for ex-vivo experiments because the permeability of this mucosa is very similar to human mucosa (Bronaugh and Maibach 1991; Shah et al. 1991). Samples from the donor receptor (2 ml) were withdrawn at intervals of 1, 2, 4, 8, 12, 24 hr, filtered and essayed for HCA by an HPLC technique. The solution in the receptor compartment was restored after each withdrawal with an equal volume of fresh solution.

A test on the reference suspension was carried out by placing 2 ml of the suspension in the donor compartment. The suspension was obtained adding an excess of drug in purified water at room temperature; the system was heated up to 50°C in order to dissolve the drug and then equilibrated at 37°C ± 0.5°C for 24 hr. For the determination of the HCA solubility, 3 aliquots of the HCA suspension were filtered through Millipore filters (W-13-2, Tosoh Company), diluted with mobile phase and analysed by HPLC.

Permeation through the membrane can be considered as a passive diffusion process and can be described by Fick's law equation:

$$J_s = \frac{dQ_r}{Adt}$$

where J_s is the steady-state buccal mucosa flux in $\mu g/cm^2$ per h, dQ_r is the change in quantity of material passing through the membrane into the receptor compartment expressed in μg, A is the active diffusion area in cm^2, and dt is the change in time in hours. The steady state flux of HCA through the porcine buccal mucosa was calculated from the slope of the linear portion of the cumulative amount permeated through the membrane per unit area versus time plot. For the HCA suspension the permeability coefficient was calculated using the equation:

$$K_p = \frac{J_s}{C_d}$$

where K_p is the permeability coefficient, J_s is the flux calculated at the steady-time and C_d is the donor concentration (Zhang and Robinson 1996).

Tissue Preparation

Porcine buccal mucosa with some underlying connective tissue was surgically removed from the oral cavity of a freshly killed male pig obtained, on each study day, from a local slaughterhouse (CLAI Imola, Bologna). The buccal mucosa was placed in ice-cold phosphate buffer, 0.15 M. The connective tissue of the mucosa was carefully removed using fine-point forceps and surgical scissors. The cleaned mucosa was then placed in ice-cold buffer solution, 1/15 M, until it was mounted in the diffusion cells. The thickness of the porcine buccal mucosa was measured by means of an electronic callipers, and was 1.0 mm $\pm$ 0.1 thick (Ceschel et al. 2000).

Analysis

The determination of the (amount) of HCA diffused through porcine buccal mucosa was carried out by HPLC (Model 600E, Water) equipped with a variable-wavelength UV detector (model 848, Water) and an integrator (Power Mate 2, NEC; software Maxima 825). A μBondapack C18 Lichrosorb (300 $\times$ 3.9 mm, 5 μm, Merck) column was used. Elution was carried out at room temperature with a mobile phase consisting of acetonitrile (45%), methanol (10%) and 1% phosphoric acid solution (45%); the injecting volume was 20 μl. The flow rate was 1.0 ml/min and the detection was at 238 nm. Under these conditions the retention time of HCA was 10 min.

In Vivo Test

After a preliminary study, an in vivo double-blind test was used to allow a quantification of the time needed to obtain adhesion and time of disgregation or detachment of the tablet.

The in vivo test was conducted on 10 healthy volunteers who had given informed consent for the experiment. In order to test all tablets, each volunteer received daily one different tablet, for 9 days. The volunteers were instructed to finish breakfast no later than 9.00 a.m. Thirty minutes later, the mucoadhesive tablet was administered. During the experiments the volunteers were allowed to drink water ad libitum from 60 min after administration of the tablet. The tablet was placed on the attached gingiva, in the region of the right upper canine and fixed with a slight manual pressure for 10 seconds. Next the tablet was moistened with the tongue to prevent sticking to the lip and to check the adhesion to the gingiva. If adhesion did not occur the procedure was repeated with the same tablet for a second and eventually a third time. The time needed to obtain adhesion was recorded. If a tablet did not adhere within the 3rd attempt, it was classified as "unacceptable" and the in vivo test was considered concluded.

After the adhesion had occurred, the volunteers were asked to check the tablet for detachment or disgregation time every 15 minutes. A time of detachment was defined when the tablet or a part of it corresponding at least at about 2/3 of the original mass, partially or completely gelled, becomes detached from or slides off the gingiva. On the other hand it was defined as a disintegregation time when the tablet gels and progressively wastes away, leaving at the application site, a mass corresponding at about 1/3 of the original mass. Finally, the volunteers were asked to record their remarks regarding their experience with the tablet concerning irritancy, taste, drymouth, salivation, and heaviness.

RESULTS AND DISCUSSION

DSC Analysis

The DSC of HCA showed a single sharp endothermic peak at its melting point of 223.6°C. In all curves of the mixed system (data not shown), the peak due to the HCA was identifiable and it showed a negligible shifting of the peak, meaning that there is no interaction between the HCA and the excipients.

Technological Controls

Results of technological controls on granulates are shown in Table 2. The flowability of the granulates was quite good according to the Carr Index and Hausner Ratio. Moreover results showed that the granulate behavior is affected by both the type and the ratio of the mucoadhesive component. The increase in the mucoadhesive percentage causes an increase in granulometry followed by a reduction in the granulate flowability and in the apparent density. The granules containing Methocel K4M showed remarkable differences when compared to the granulates containing Carbopol 974P and Noveon AA1 (which are very similar). It confirms the fact that the polymers are member of two different classes, cellulose derivatives and polyacrylic acid derivatives respectively. Karl-Fischer percentage humidity results were found to be satisfactory for all formulations.

TABLE 2
Technological controls carried out on granules

	Carbopol			Noveon			Methocel		
	10%	20%	30%	10%	20%	30%	10%	20%	30%
Apparent density (g/ml)	0.476	0.459	0.413	0.481	0.453	0.418	0.451	0.422	0.395
Hausner ratio	1.123	1.233	1.288	1.232	1.253	1.294	1.268	1.289	1.318
Carr index (%)	18	19	22	18	20	22	21	22	25
Granulometry (mm)	78	117	164	82	122	162	95	138	138
Karl-Fischer humidity (%)	0.98	0.95	0.95	0.95	1.02	0.98	1.03	0.96	0.95

TABLE 3
Technological controls carried out in the tablets

	Carbopol			Noveon			Methocel		
	10%	20%	30%	10%	20%	30%	10%	20%	30%
Thickness (mm)	1,98	1,91	1,87	1,95	1,94	1,88	1,87	1,84	1,93
Diameter (mm)	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25	0,25
Weight (mg)	59,6	59,3	59,8	61,2	62,3	61,4	61,3	61,2	61,2
Hardness (Kg)	5,6	6,1	6,6	5,7	5,6	6,0	5,5	6,5	5,7
Friability in %	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Content in HCA (mg)	1,059	0,985	0,989	1,016	0,949	1,054	1,048	1,040	1,018
Ds	0,032	0,030	0,030	0,030	0,028	0,032	0,031	0,031	0,031

Technological controls carried out on the tablets, shown in Table 3, gave satisfactory hardness and friability results; the final content of HCA was essentially the same in all the different tablets, being 1 mg ± 0.1. Results were compliant with the specifications of the European Pharmacopoeia 3° Ed.

Mucoadhesive Measurements

The results of the mucoadhesion tests are given in Table 4. The results showed a linear dependence of the mucoadhesive capacity versus the polymer percentage shown both by the adhesion force and by the work of shear. On the basis of the mucoadhesion characteristics observed it is possible to classify the three polymers, in accordance with Longer and Robinson (1989): Carbopol 974P > Methocel K4M > Noveon AA1.

Dissolution Test

In Figures 1, 2, and 3 the percentage of drug released from tablets containing the different mucoadhesive polymers at the different concentrations is represented. In Table 5 the values of n, K and R^2 for these release rates are represented. The R^2 values showed that the semi-empirical equation described by Ritger and Peppas (1987) is able to fit the release from tablets containing Carbopol and Noveon ($0.9926 < R^2 < 0.9798$) but not the release from tablets containing Methocel ($0.9073 < R^2 < 0.9108$), then n and K values have not significance in this case. The plots showed that tablets containing Methocel K4M have an initial burst with a release, on average, of 50% in the 1st hour followed by a rapid decrease. The acrylic polymers, Carbopol 947P and Noveon AA1 showed a better modulation capacity, with a release on average, of 26 and 16% respectively at the 1st hour. This aspect is shown by the comparison between tablets containing the three mucoadhesive polymers, at 10% of concentration, in Figure 4. Methocel did not allow a significant controlled release; the shape of the release suggested that it was determined by a rapid disgregation of the tablet. Tablets containing Carbopol and Noveon showed a controlled release, characterised by an exponent n that changed according to the type of mucoadhesive polymer. For tablets containing Carbopol, n was between 0.745 and 1.196 and for Noveon between 0.5961 and 0.6752. A n value of 0.5 indicates a Fickian process that describes release of a drug from a matrix governed by diffusion; on the other hand, a n value of 1 indicates linear kinetics that describes release governed by dissolution. Our results suggested that the release of HCA from tablets is determined both by diffusion and dissolution. First, as a simple matrix, tablets wet and swell releasing the drug by diffusion, then a disintegregation process allows an increase of the release kinetics, dependent on dissolution. The K values decreased following the increase in the mucoadhesive amount in all tablets, showing that the percentage of mucoadhesive polymer had an appreciable influence on the released drug amount. Finally, considering the drug release characteristics, tablets containing Carbopol were found to be the better formulations because they showed linear kinetics and they allowed drug release between 77.7 and 94.2% at 8 hr followed by Noveon formulations which showed a lower drug release (between 46.3 and 69.4% at 8 h). Tablets containing Methocel did not show a good release profile because they released an major portion of drug within the first hour.

TABLE 4
Force of detachment of the different tablets

	Carbopol			Noveon			Methocel		
	110%	120%	130%	10%	20%	30%	10%	20%	30%
Adhesion force (mN)	18,35	22,08	27,31	11,56	16,81	21,27	16,52	20,86	26,34
Ds	1,285	1,546	1,912	0,809	1,177	1,489	1,156	1,460	1,844
Work of shear (mJ)	1,29	2,98	5,75	0,83	3,83	6,08	1,03	1,99	4,42
Ds	0,103	0,236	0,460	0,066	0,306	0,436	0,082	0,159	0,354

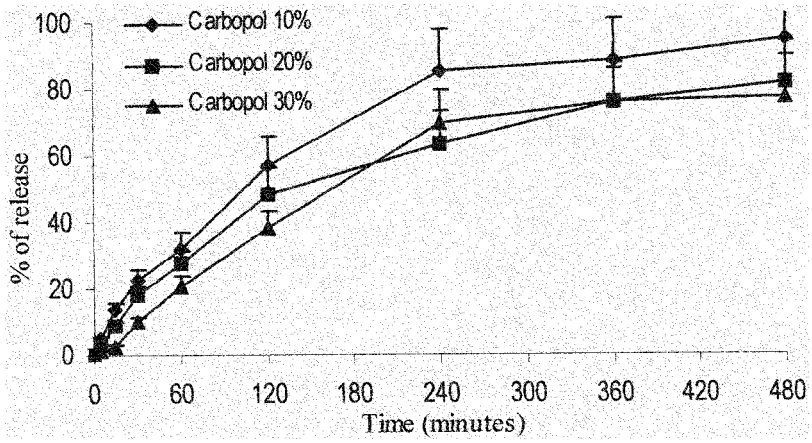

FIG. 1. Percentage release of the tablets containing Carbopol 974P at different concentrations.

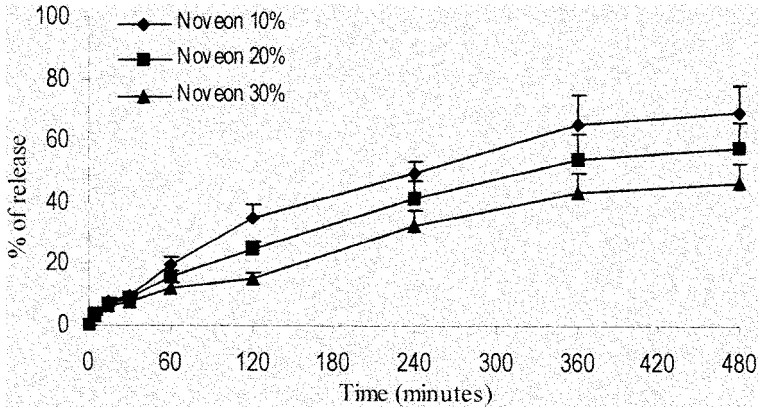

FIG. 2. Percentage release of the tablets containing Noveon AA1 at different concentrations.

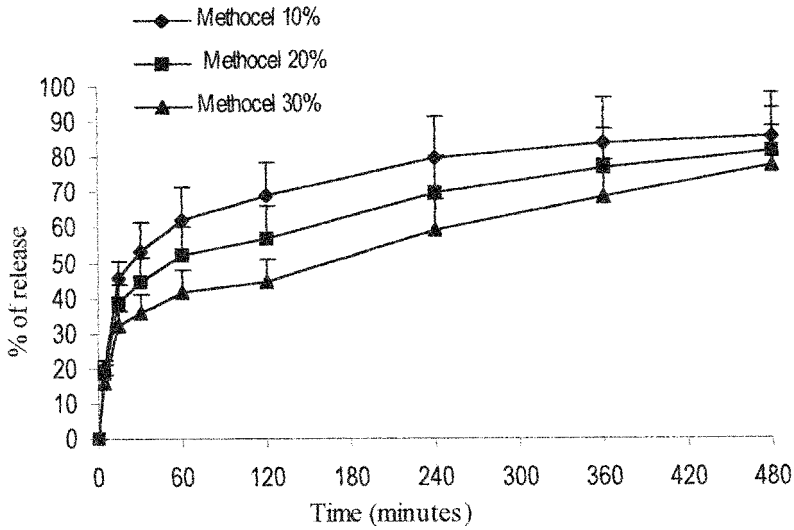

FIG. 3. Percentage release of the tablets containing Methocel K4M at different concentrations.

TABLE 5
n and K values of the different tablets

	Carbopol			Noveon			Methocel		
	10%	20%	30%	10%	20%	30%	10%	20%	30%
K (cm $*$ h^{-1})	0,0164	0,008	0,0014	0,0122	0,0117	0,0112	0,4539	0,3339	0,3004
n	0,745	0,87	1,196	0,6752	0,6394	0,5961	0,4539	0,3339	0,3004
R^2	0,9905	0,9926	0,9852	0,9798	0,9937	0,9812	0,9073	0,8885	0,9108

Permeation Tests

The permeation profile of the HCA suspension in water is shown in Figure 5, while Figures 6, 7, and 8 show permeation profiles of tablets.

The solubility of HCA in water at 37°C was found to be 10.0 μg/ml with a standard deviation of 0.23 μg/ml. The fluxes in these profiles are reported in Table 6 that also shows the Kp for the HCA suspension in water. The permeation parameters are calculated the linear portion of the permeation profile.

Permeation tests from the HCA suspension showed a Kp value of 8.72×10^{-2} corresponding to a flux of 0.872 μg/h $*$ cm^2. Tablet permeation profiles are lower than those obtained from the suspension (tablet fluxes as a whole fell under 0.0773 and 0.2991 μg/h $*$ cm^2). It can be explained when considering that HCA present in tablets must be dissolved and released before permeation occurs: these steps limit the amount of drug in solution and its permeation.

From the comparison of profiles of the different tablets we observed that changing the mucoadhesive component, permeability behavior was not statistically different ($P > 0.1$). The higher fluxes shown by Methocel can be explained by its rapid disgregation. On the other hand, in all tablets, the cumulative amount of permeated HCA increased in respect to the concentration of the mucoadhesive polymer, probably because an increase in the mucoadhesive component allowed a closer contact between the tablet and the mucosa.

In Vivo Test

The mucoadhesive tablet formulation was well accepted by volunteers and no irritation was recorded during the period of study. Tablets were reported to be adequately comfortable, none of the volunteers reported dry mouth or intense salivation. No side effects, like taste alteration or heaviness, were reported. Results concerning the time needed to obtain tablet adhesion are shown in Table 7, while results concerning tablet detachment or disgregation are shown in Table 8.

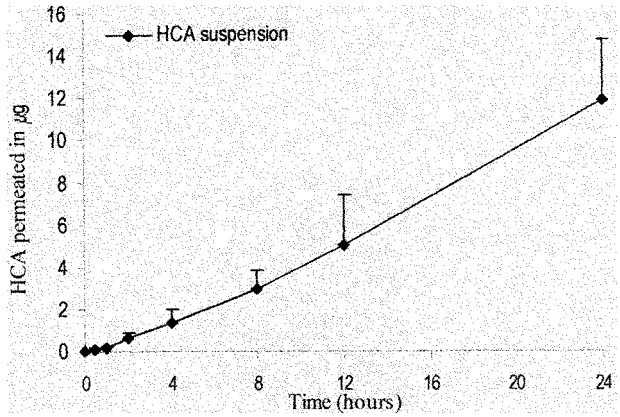

FIG. 5. Cumulative amount of permeated HCA from a saturated solution in purified water.

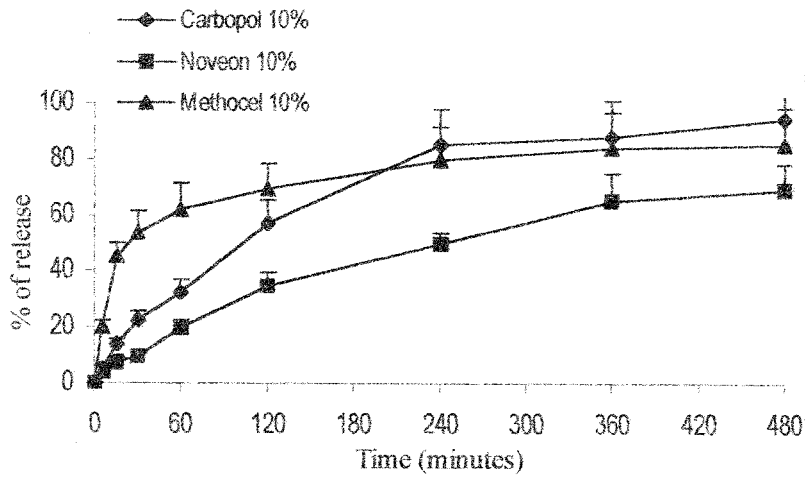

FIG. 4. Comparison between the percentage release of tablets containing the three mucoadhesive polymers at the 10%.

TABLE 6
Flux and Kp values of HCA from tablets and from the suspension in purified water

	Carbopol			Noveon			Methocel			HCA suspension in purified water
	10%	20%	30%	10%	20%	30%	110%	120%	130%	
J (mg $*$ h^{-1})	0.0773	0.131	0.238	0.220	0.156	0.236	0.177	0.183	0.299	0.872
ds	0,0169	0,0169	0,0195	0,0167	0,0217	0,0210	0,0151	0,0135	0,0256	0,225
Kp (mg $*$ cm^{-2} $*$ h^{-1})	–	–	–	–	–	–	–	–	–	8.72×10^{-2}
ds	–	–	–	–	–	–	–	–	–	2.26×10^{-2}

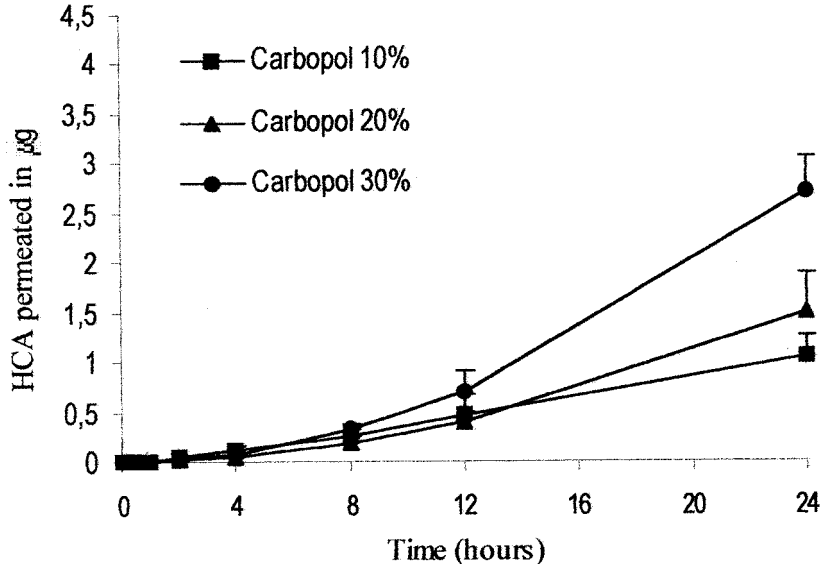

FIG. 6. Cumulative amount of permeated HCA from the tablets containing Carbopol 974P vs. time.

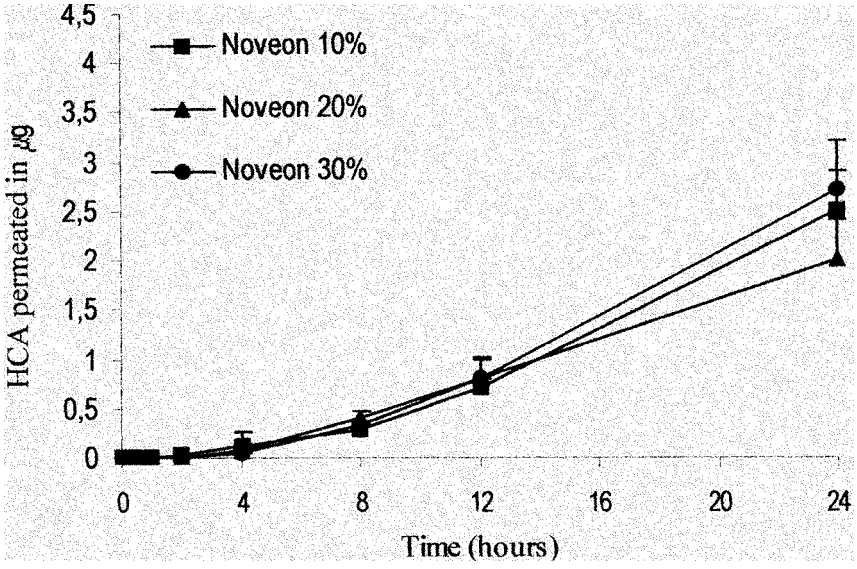

FIG. 7. Cumulative amount of permeated HCA from the tablets containing Noveon AA1 vs. time.

TABLE 7
Results of the in vivo test concerning the time needed to obtain adhesion. Each square contains the number of volunteers that needed the same time to obtain adhesion

Time needed to obtain adhesion (sec)	Carbopol			Noveon			Methocel		
	10%	20%	30%	10%	20%	30%	10%	20%	30%
10 (1st attempt)	2	9	5	0	1	5	0	3	4
20 (2nd attempt)	4	1	1	0	2	1	2	3	5
30 (3rd attempt)	4	0	4	6	5	4	2	4	1
>30 unacceptable	0	0	0	4	2	0	6	0	0

TABLE 8
Results of the in vivo test on the tablet detachment or disgregation time. Each square contains the number of volunteers and the average time, expressed in hours and minutes, in whom the detachment or the disgregation occurred

	Carbopol			Noveon			Methocel		
	10%	20%	30%	10%	20%	30%	10%	20%	30%
Disgregation	0	10 (2 h 37′ $ds = 41'$)	10 (3 h 16′ $ds = 37'$)	0	5 (2 h 48′ $ds = 0.44$)	10 (3 h 15′ $ds = 26'$)	0	5 (2 h 25′ $ds = 1$ h 12′)	6 (2 h 3′ $ds = 27'$)
Detachment	10 (1 h 24′ $ds = 37'$)	0	0	6 (0 h 55′ $ds = 36'$)	3 (0 h 40′ $ds = 17'$)	0	4 (0 h 25′ $ds = 13'$)	5 (0 h 50′ $ds = 30'$)	4 (0 h 45′ $ds = 25'$)

As expected, the time to obtain adhesion decreased when the mucoadhesive concentration was increased. All tablets containing Carbopol were acceptable while 6 tablets at 10% Methocel, 4 tablets at 10% Noveon, and 2 tablets 20% Noveon were found to be unacceptable.

Tablets containing Carbopol were found to require less time to adhere when compared to the other tablets. Moreover it was found that Carbopol at 20% concentration had a behavior that was better than the tablet containing Carbopol at 30% concentration. To investigate this point volunteers were asked to describe

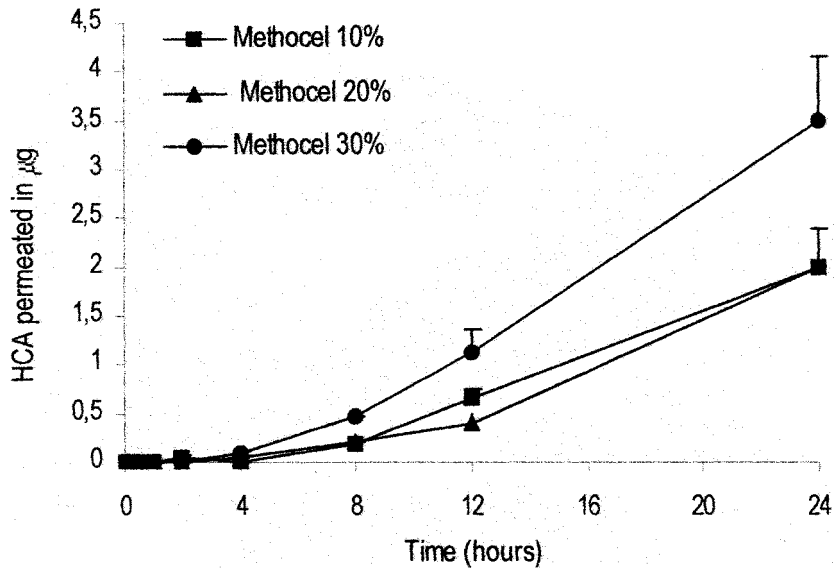

FIG. 8. Cumulative amount of permeated HCA from the tablets containing Methocel K4M vs. time.

their experiences with tablets at 30%. It was found that the tablets quickly adhered to the gengiva, and also to the buccal mucosa and attaching the tablet in the gengiva required more than one attempt. This behavior was observed only for tablets containing Carbopol at 30% concentration.

Concerning the in situ behavior of tablets during the test, it was found that a concentration more than 10% is needed to avoid tablet detachment and that the disgregation time increased with an increase of the mucoadhesive concentration according with the in vitro adhesion results. Tablets containing Carbopol at 20 and 30% and Noveon at 30% disintegrated in all volunteers, while 5 tablets containing Noveon 20% and respectively 5 and 6 tablets containing Methocel 20 and 30% detached before the disintegration occurred and were considered unacceptable. Tablets containing Carbopol at 30% and Noveon at 30% showed the best disgregation times (about 3 h 15′) followed by tablets containing Carbopol at the 20% (about 2 h 37′). Although tablets containing Carbopol and Noveon at 30% showed the best disintegregation time, considering also the adhesion aspect the tablet that gave the best performance was that containing Carbopol 20%.

CONCLUSION

All granulates and tablets satisfied the industrial requirements and the European Pharmacopoeia specifications. DSC studies showed that there is no interaction between the HCA and the excipients.

The HCA release kinetics showed that tablets containing Carbopol were the best formulations because they showed a prolonged drug release with linear kinetics, followed by Noveon formulations which showed a lower drug release. Tablets containing Methocel did not show a good release profile because they released significant portion of drug within the first hour, thus they did not allow a prolonged drug release.

Permeability tests showed that all tablets showed a satisfactory drug permeability flux, compared with the flux from a saturated solution in water. The permeability behavior was not statistically different ($P > 0.1$) on changing the mucoadhesive component.

The in vivo test revealed adequate tablet comfort: no irritation, no dry mouth, no intense salivation, or no side effects were recorded. Tablets that showed satisfactory release kinetics were finally rejected when adhesion problems or detachment phenomenon were checked in the in vivo test. The tablet that gave best performance in in vivo tests was the formulation containing Carbopol at the 20% which was rapidly adhered to the mucosa. They remained the application site for the longest time, with the exception of tablet containing Carbopol at the 30% that unfortunately did not show a good adhesion aspect.

In conclusion, the developed mucoadhesive tablet for buccal administration containing Carbopol at 20% of concentration, has a potential clinical usefulness for the treatment of ulcerative and inflammatory oral diseases.

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