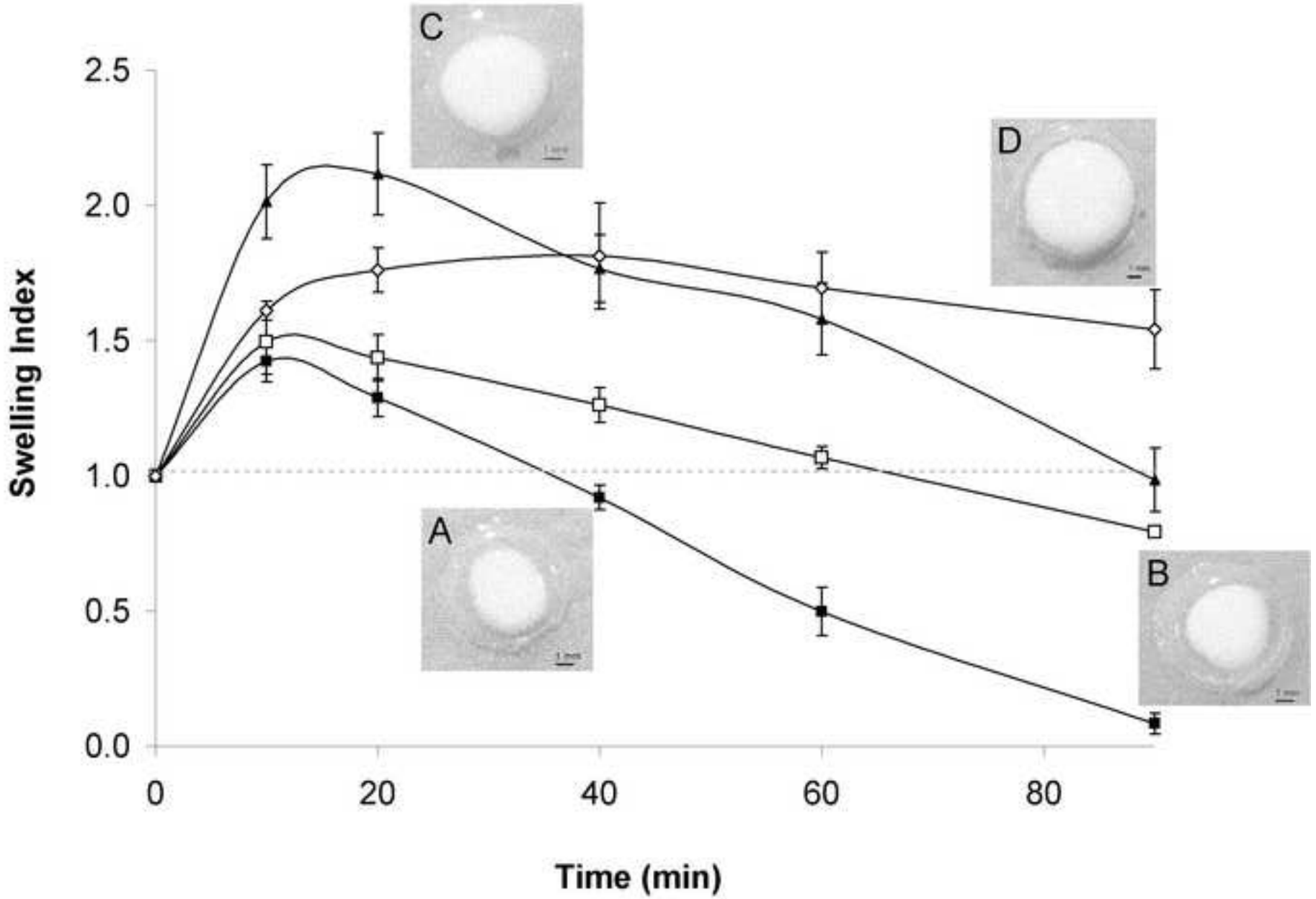
Graphical Abstract



Tablets exhibited different swelling depending on their composition. When 10% (w/w) MgCl2 was added (- - and insert B) the pattern was comparable to pure PMM (- - and insert A): tablets dissolved without swelling. Tablets containing 10 % (w/w) HPMC (- -and insert C) or both MgCl2 and HPMC (- - and insert D) formed a slight swelling layer followed by erosion.

A new mucoadhesive dosage form for the management of oral lichen planus: formulation study and clinical study

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Abstract

The work aimed to study a new mucoadhesive prolonged release tablet containing 24 μg clobetasol-17 propionate (CP) suitable for the management of oral lichen planus. Low swellable dosage forms were designed by combining a mucoadhesive polymer, i.e. poly(sodium methacrylate, methylmethacrylate), with hydroxypropylmethylcellulose and $MgCl_2$. This formulation was selected to modify the tablet erosion rate in order to obtain a release of CP over a 6 h period. A double-blind controlled study was performed using three groups of patient (n=16) which received 3 applications-a-day over 4 weeks of the developed CP tablets (group CP-T), placebo tablets (group CP-P) or commercial CP ointment for cutaneous application (123 μg/application) extemporary mixed with Orabase™ (group CP-O). At the end of the study, pain and ulceration resolved in 13/16 and 11/16 patients of group CP-T and group CP-O, respectively. In the group CP-O, a transient acute hyperaemic candidosis (n=2) and taste alteration (n=4) were also observed. No changes in clinical signs of partients in the group CP-P were evident. The application of mucoadhesive tablet containing 24 μg CP 3 times-a-day appeared to be effective, avoiding the side-effects of the generally used treatment.

1. Introduction

Oral lichen planus (OLP) is a rare chronic auto-immune muco-cutaneous inflammatory disease that may cause bilateral white striations, papules or plaques with or without erythema and ulceration involving any buccal mucosae [1, 2]. Symptoms range from none to painful oral lesions, affecting the quality of life. Current standard treatment is administered primarily, Since there is no established therapy, the current clinical treatment consists in the topical administration of high-potency topical corticosteroids, such as clobetasol propionate (CP) to control symptoms [3, 4]. Since buccal CP dosage forms are not commercially available the administration is made using semisolid preparations for skin application mixed with an adhesive paste, namely Orabase™ [5-7]. This approach presents several drawbacks, including difficulties in applying the medication at various oral sites, taste alterations, limited contact time and possible swallowing of a formulation not designed for the buccal route. Therefore, to improve the patient's compliance and reduce the risks of side effects, the development of a mucoadhesive solid dosage form could be of interest. Several mucoadhesive dosage forms, such as microparticles [8], patches [9] and tablets [10], could results suitable for the treatment of OLP. Nevertheless, considering that OLP is an orphan pathology, tablets obtained by direct compression could result advantageous because their production is easier and cheaper compared to the other two dosage forms.

The present investigation aimed to evaluate the utility of a 24 µg CP mucoadhesive tablet based upon a poly(sodium methacrylate, methylmethacrylate) (PMM), a mucoadhesive no-swellable polymer [9]. A type of hydroxymethylcellulose was selected among a series of hydrocolloids on the bases of a preliminary screening, magnesium chloride was chosen because of its ability in reducing PMM erosion rate [11]. The formulative study was focused on *in vitro* characterization of tablets in order to define which formulation fulfilled desirable clinical characteristics. The criteria of acceptance were based on mucoadhesive properties, lack of swelling and drug release over a 6-hour period.

The optimized formulation was tested in a double-blind, placebo-controlled study in individuals with OLP and compared to 125 µg CP in a conventional ointment in Orabase™.

2. Materials and methods

2.1 Formulation study

2.1.1 Materials and Tablet preparation

Clobetasol 17-propionate (CP) (SICOR, I), magnesium chloride (ACEF, I); Methocel® K4M (HPMC K4M), substitution: methoxyl = 22%, hydroxypropoxyl = 8.1%, nominal viscosity 2% in water: 4000 cP (Colorcon, I); Eudragit® S100, poly(methacrylic acid, methyl methacrylate), molar proportions of the monomer units 1:2, molecular weight ≈ 135,000 Daltons (Röhm, G); Crude (Type II) mucin from porcine stomach (Sigma Chemical Co., USA). PMM was obtained by adding 10% (w/w) NaOH aqueous solution to 15% (w/w) Eudragit® S100 aqueous suspension, untill complete salification. The aqueous solution [9] was freeze-dried (EDWARDS Modulyo, USA) and the resulting powder was milled by an Ultra Centrifugal Mill (RETSCH ZM200, G) equipped with ring sieves of 0.25 mm.

The composition of placebo and CP loaded tablets is shown in **Table 1**. Powders were mixed using a Turbula mixer (WAB Turbula, CH) for 10 min. Tablets (7 mm diameter and 80 mg weight) were prepared by direct compression using a single punch tablet press (Korsch, type EKO, G). The upper punch was set as to obtain tablets with a crushing resistance of about 7 Kp. The uniformity of CP content in mixtures and tablets was evaluated according to European Pharmacopoeia [12].

2.1.2 ATR-FTIR spectroscopy

About 15.0 mg sample was place on a ZnSe-crystal mounted in ATR cell (Perkin Elmer, USA). FTIR measurements were performed with Spectrum™ One spectrophotometer (Perkin Elmer, USA). The spectra were recorded at 2 cm^{-1} resolution and 32 scans were collected over the wavenumber region 4000 – 650 cm^{-1}. The analyses were performed on raw polymers and hydrated swelling layers. Placebo tablet

was incubated in purified water and after 20 min the hydrated layer was carefully removed from the tablet and it was directly applied on the ATR accessory of the FTIR spectrometer.

2.1.3 Swelling properties

Swelling and erosion of PMM and the relative blends were evaluated by gravity method. Tablets of 80 mg were attached by cyanoacrylate glue to a glass plate and immersed in 30 ml of deionized water under constant stirring. At predetermined time intervals, polymeric tablets were removed from the beaker, rinsed, weighed and photographed. The variation (ΔW) of tablet weight over time, namely water uptake and mass loss, was calculated according to the following equation:

$$\Delta W = (W_t - D_t) / D_t \qquad \text{eq. 1}$$

where:

- W_t = weight of wet tablets at the time t
- D_t = initial weight of dry tablets at time t.

2.1.4 Erosion rate

Placebo compacts (250 mg, 13 mm diameter, **Table 1**) were prepared using a hydraulic press (RIIC hydraulic press, UK) with a compaction force of 10 tons and a holding time of 10 min. In order to expose a single face with constant area to the medium, all surfaces except one base were coated by partial immersion in 8% w/w cellulose acetate propionate solution in dichloromethane. The erosion rate of tablets was determined quantitatively by fixing the compact eccentrically under the paddle at the distance of 1.8 cm from the rotating axis. 500 ml of deionised water at 37.0 ± 0.5 °C were used as dissolution medium and stirring speed was 100 rpm. The dissolved amounts were spectrophotometrically assayed at λ = 213 nm. Erosion rate (G) was determined from the slope, calculated by linear regression, of the curve obtained by plotting the dissolved amount of the copolymer per unit area (mg/cm^2) versus time (min).

2.1.5 In vitro mucoadhesive test

The texture analysis was performed using a software-controlled dynamometer (AG/MCL, Acquati, I) with a 5 daN force cell as previously described [9], using mucin as the adherent substrate [13-15]. Briefly, flat faced placebo and CP loaded compacts (weight: 170 mg, diameter: 11.28 mm) were obtained by applying a compression force of 10 tons for 30 s by means of a hydraulic press (Glenrothes, UK). The testing material compacts were attached to the mobile steel punch by cyanoacrylate glue. Mucin compacts (weight: 130 mg, diameter: 11.28 mm) were obtained applying a compression force of 10 tons for 60 s. The mucin compact was attached by cyanoacrylate glue to a steel plate fixed at the bottom of the tensile apparatus and hydrated with 80 µl deionized water upon 5 min to obtain a jelly surface layer. Upon making contact between the polymeric compact and the hydrated mucin, a constant force of 1.3 N was imposed for 360 s. The mucoadhesive performance was measured in terms of the force required to separate the bioadhesive compact from the mucin (maximum detachment force, MDF) upon an elongation of 10 mm at the constant rate of 0.1 mm/s. The area under the curve of the detachment force versus the elongation represents the work or energy (work of adhesion, WA) required detaching two compacts. The stainless steel punch was used as negative control and HPMC compacts as positive one. The results are expressed as mean ± standard deviation (n=4).

2.1.6 Drug content assay

The tablets were crushed in a mortar and the powder was suspended in 20 ml mobile phase (AcCN/H_2O, 50/50 v/v). The CP content was determined by the following HPLC method using HP1100 Chemstation (Hewlett Packard, USA). *Chromatographic conditions.* Analytical column: Waters Spherisorb ODS2 (4.6 x 150mm, 3µm); mobile phase: AcCN/H_2O (50/50 v/v); flow rate: 1.0 ml/min; wavelength set: 240 nm; injection volume: 20 µl. The drug concentrations were determined from standard curves in the range of 0.05-5 µg/ml.

2.1.7 In vitro drug release

Dissolution test was carried out in closed vials and stirred in a shaker incubator (50 strokes/min) at 37±0.5 °C. The tablets were glued to the bottom of 5 ml vials containing 4 ml dissolution medium (deionized water). At each time point, the medium was completely withdrawn for analysis, diluted with 1 ml acetonitrile and the amount of CP released was tested by HPLC (section 2.1.6). The withdrawn water was replaced with equal volumes of fresh medium.

2.1. 8 In vivo mucoadhesion study

The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and followed the ICH-GCP guidelines of 17/01/1997, and was in compliance with local regulatory requirements. All subjects were completely informed concerning the pertinent details and the purpose of the study. A written consent form was completed by each subject prior to dispensing test materials. The study was conducted on 6 healthy human volunteers (aged 25-28 years) using 25 mg placebo tablets attached to upper buccal sulcus, in the canine fossa. Volunteers were allowed to drink during the study, while solid food and smoking were prohibited. Volunteers were asked to record the time of insertion and time at end of adhesion (permanence time), and any mucosal irritation or discomfort in mouth.

2.1. 9 Statistical analyses

Tests for significant differences between means were performed by Student t-test or one-way ANOVA by using the software SPSS 11 (Spss Inc., USA). Differences were considered significant at the $p<0.05$ level.

2.2 Double-blind controlled clinical trial

2.2.1 Subject.

One investigator recruited subjects and evaluated the outcomes of therapy.

Inclusion criteria

The diagnosis of OLP was made following the clinical and histological criteria defined by the World Health Organization (WHO) [16]. . Patients were observed in the Department of Oral Medicine of the Università degli Studi di Napoli Federico II for a minimum of three months before the beginning of the trial and presented clinical signs of OLP [17-18]. The diagnosis determined by clinical observance was confirmed by reviewing pre-treatment biopsies samples taken within a week before the beginning of the trial as reported in section 2.2.3. A score system for signs of OLP was assigned on the basis of increasing severity and symptoms (**Table 2**). HCV + patients also were enrolled.

*Exclusion criteria***.**

Patients who showed severely impaired renal or hepatic function, and women of childbearing age were excluded. Patients with a history of glaucoma were excluded.

Based on these criteria, 48 Caucasian patients were enrolled in the study (26 women and 22 men, aged 32-72 years, median 51.5 years).Each enrolled patient signed informed consent, and the procedures of this study were in accordance with the ethical standards on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Following informed consent the inclusion and exclusion criteria were confirmed.

2.2.2 Randomizing protocol and study design

The patients were assigned to 3 groups consisting of 16 subjects by the investigators.

Treatment assignment was blind to the clinical investigator. Before randomization, a letter was assigned to a prearranged therapeutic protocol. This sequence of numbers was known only to another investigator who provided the study medications for each group.

Patient of each group received the developed CP tablets (group CP-T), the corresponding placebo tablet (group CP-P) or CP semisolid preparation (123 μg/application) (group CP-O). CP tablets and placebo tablets were dispensed in identical white containers marked A and B. The CP semisolid preparation was prepared by using a commercial CP ointment for cutaneous application (Clobesol®, Shering Plough) extemporary mixed with Orabase™.

Patients of each group received the products to apply three times a day over a 4 week period.

Patients were instructed in how to place tablets in the canine fossa. Subjects of group CP-O were informed how to prepare and apply the ointment in Orabase™. Patients were asked to record the length of the adhesion time of the tablet and potential side-effects. Subjects and the clinical investigator did not know the therapy to which they were assigned.

At weekly visits during the four-week trial, the clinical investigator recorded the symptoms in a four-point descriptive-qualitative scale as follows: 0 = no evidence of disease; 1 = mild involvement; 2 = moderate involvement; 3 = severe involvement. All patients were monitored for adverse events and were evaluated for clinical signs and symptoms of candidiasis (white adherent patches, erythema and oral burning), the presence of moon face, hirsutism, fluid retention, and weight increase. Patients were tested for blood glucose levels and blood pressure. Patients were also interviewed to assess mood changes, gastrointestinal disorders, easy bruising and taste loss.

2.2.3.Biopsy collection

Biopsies (8 mm diameter tissue samples) were taken from all subjects within one week of the clinical trial, and two weeks following completion of treatment from the same region. All specimens were fixed in formalin 10% PBS buffer, embedded in paraffin and processed for haematoxylin-eosin staining. At time 0 and after the therapy, 5 ml blood samples were collected by venipuncture, in oxalated vacutainers and centrifuged for cortisol levels.

3. Results and discussion

3.1 Formulation study

3.1.1 Placebo tablets

Upon contact with water, Tablets P1 made of the pure PMM rapidly hydrated and a slight increase in their size was observed within 10 min. Then, PMM started to erode with concomitant weight loss and the tablet

completely dissolved in about 90 min. Tablets P2 containing 10% w/w $MgCl_2$ did not swell significantly and a decrease with time in tablet weight loss was measured. The addition of HPMC (Tablet P3) caused a significant increase in tablet weight and diameter which increased from 7 mm to 10.5 mm; afterwards, the tablet weight loss was similar to the formulation containing $MgCl_2$ (**Fig. 1**). When the mixture of HPMC and $MgCl_2$ was added to PMM (Tablet P4), the increase in tablet dimension due to hydration was closer to that of the pure PMM and its weight remained almost constant over 90 minutes. Moreover, the determination of the tablet erosion rate (G) evidenced that this formulation was the most effective in reducing the PMM dissolution (**Table 1**).

In order to explain the differences observed in the tablet behaviour upon hydration, ATR-FTIR spectroscopy measurements were performed. After hydration of tablets, a band at 1645 cm^{-1} assigned to the symmetric stretch of the water molecules was clearly detectable in all the formulations. ATR-FTIR spectra of Tablet P1 made of the pure PMM (**Fig. 2**) showed the characteristic band of the C=O stretching vibration of the esteric group at about 1712 cm^{-1} and two bands at 1548 cm^{-1} and 1347 cm^{-1} corresponding to the anti-symmetrical $\nu a(COO^-)$ and symmetrical $\nu s(COO^-)$ vibration of the $-COO^-$ structure, respectively [19]. Moreover, the bands at 1249, 1197 and 1163 cm^{-1} arise mainly from stretching modes of the ester group [20].

The spectrum of hydrated HPMC showed two main bands at about 3370 cm^{-1} and 1640 cm^{-1} which were attributed to water (**Fig. 2**) and a broad band between 1200 and 900 cm^{-1} corresponding to C-O and CH_x [21]. The latter peaks were not detected in Tablets P3 and P4 as they were masked behind the bands of PMM. Furthermore, in the case of Tablet P3 no shifts of the PMM bands were recorded (**Fig. 2**) suggesting the absence of interactions between the two materials.

The spectra of the hydrated tablets containing $MgCl_2$ were mainly characterized by changes in the bands of PMM ester groups. As already described, in the hydrated Tablets P2 the metal ion strongly interacted with the C=O and COO^- moieties of PMM [19] which led to a change in the charge distribution on the C-O esteric vibration. Indeed, the bands attributed to the stretching vibrations of C-O-C moiety of the esteric group shifted towards higher wavenumbers (**Fig. 2**). When both $MgCl_2$ and HPMC were present (Tablet

P4), changes involved ν(C-C-O) that significantly shifted towards higher wavenumbers (from 1249 to 1260 cm^{-1}). This data suggested that Mg^{2+} in the hydrated tablet caused a different distribution of the charge on the esteric group of PMM forming hydrogen bonds with HPMC. Such hypothesis was supported by the shift of ν(C-O-C) band towards lower wavenumbers with respect to those registered in the gel layer of Tablet P2. The interactions among PMM, Mg^{2+} and HPMC can reduce the ability of water to hydrate Tablet P4 causing a marked reduction of the tablet erosion rate and swelling.

The mucoadhesive properties of the formulations are shown in **Table 1**. As already described, the presence of the $MgCl_2$ (Tablet P2 and P3) caused a statistically significant decrease of the MDF of PMM ($p<0.04$) due to physical cross-linking of the copolymer. The formation of cross-links between the polymer chains did not allow them the freedom of movement and flexibility required for the penetration into the mucus gel network. Moreover, diffusion of water into the polymer network occurs at a lower rate resulting in decreased swelling of the polymer and a decreased rate of interpenetration between PMM and mucin. However, MDF and WA values were statistically higher than those registered with the negative control (MDF: 2.81±0.20 N; WA: 0.65±0.01 mJ).

Comment [FS1]: P?

Information reported by volunteers of the panel test confirmed the in vitro data. The residence time was longest for tablets containing HPMC and $MgCl_2$ (**Table 1**) and the volunteers described discomfort due to increased swelling only tablets made of both PMM and HPMC (Tablets P3). In all cases no mucosal irritation was reported.

3.1.2 Drug loaded tablets

As expected, the presence of CP in the polymer blends did not further modify both the tablet erosion rate and the in vitro mucoadhesive properties and texture profiles. The results showed that only for the Tablet F4, MDF and WA were significantly lower than those of the corresponding placebo blends ($p<0.05$). The non-interference of CP on mucoadhesive properties and erosion rate can be justified considering that the drug content was less than 0.025% and the drug, being a crystalline solid, does not modify the structure of

the polymeric network. Indeed, the wavenumber and geometry of the main bands of the spectra recorded on the dry and hydrated CP loaded tablets overlapped with the corresponding spectra of placebo tablets (data not shown).

The in vitro release of CP from the tablet made of pure PMM (Tablet F1) was complete in 90 min (**Fig. 3**) as predicted by the erosion rate of the polymer (**Table 1**). The addition of 10% w/w $MgCl_2$ (Tablet F2) caused a decrease in drug release due to the cross-linking in polymer chains in presence of Mg^{2+}. A similar release profile was evident when 10% w/w HPMC was added (tablet F3). As expected by the characterization of the placebo tablets, only the combination of 10% w/w $MgCl_2$ and 10% w/w HPMC in formulation F4 resulted effective in prolonging CP release over a six hours period (**Fig. 3**). Possible explanation of the results could be the cross-linking of PMM chains in presence of magnesium ions, that might lower the mobility of water molecules entrapped into polymer network. In this case the drug release was delayed from Tablet F4 because of the formation of a highly viscous gel barrier of the entrapped HPMC that was effective in maintaining tablet cohesiveness.

Since Tablet F4 could effectively control CP release over a 4-h period and the corresponding placebo tablets (Tablet P4) had an in vivo residence time of about 6 h, this formulation was selected for the clinical study.

3.2 Clinical trial of OLP

The patients enrolled in the groups CP-T and CP-P reported the excellent adhesion of the CP tablets in the buccal cavity with residence time averaging 4–6 h. The mucoadhesive tablets did not cause irritation or pain and the subjects reported the tablet tasted neutral or slightly salty.

Data on the pre- and post-treatment evolution of OLP are displayed in **Table 3** and **Table 4**. No patient dropouts occurred in the study. The histological findings showed a reduction of hyperkeratosis and acanthosis of the epithelium at the end of the treatment and a decrease of the band-like inflammatory

infiltrate in the samples from the groups CP-T and group CP-O, and no changes were seen in the placebo group (group CP-P).

Blood cortisol levels, normally ranging from 5 to 25 µg/dl in the morning, were not statistically different among the three groups pre- (group CP-T: 6.8 µg/dl to 23.5 µg/dl; group CP-P: 4.5 µg/dl to 21.3 µg/dl; group CP-O: 8.1 µg/dl to 25 µg/dl) and post-treatment (group CP-T: 5.5 µg/dl to 19.5 µg/dl; group CP-P: 5.9 µg/dl to 22.4 µg/dl; group CP-O: 5.1 µg/dl to 23 µg/dl), indicating limited systemic absorption of CP.

No adverse effects related to the treatment were recorded, except for 2 episodes of transient acute erythematous candidosis during the last treatment week for two patients in group CP-O who were treated with with nystatin at the end of the trial. Taste loss was reported for 4 patients of the group CP-O. In the individuals of group CP-P, there was an increase in symptoms, as reported in **Table 4**.

To assess the utility topical therapy of OLP, 16 patients with different clinical types of OLP (severe reticular, atrophic and erosive) were treated by applying mucoadhesive tablets containing a low dose of CP (24 µg/tablet) three times a day.

At the end of the treatment period, oral pain and ulceration had resolved (complete response) in 13/16 patients in group CP-T (**Fig. 4**) and 11/16 in the group CP-O with remission of atrophy and erosion and reticular lesions (score 0). There was no change in the group CP-P subjects (placebo tablets). 2/16 patients of the group CP-T and 3/16 of group CP-O showed score 1 for signs and symptoms and 1/16 of the group CP-T and 2/16 of the group CP-O reported score 2 for signs and 1 for symptoms.

The results of this study showed that the use of low concentration CP in mucoadhesive tablets offers an efficacious treatment of different clinical types of OLP.

Previous studies of topical steroid for management of oral mucosal disease have assessed drug delivery in non-sustained release forms. Lo Muzio et al. treated oral aphthous lesions and lichen planus by applying CP with a bioadhesive system with improvement in oral lesions [5]. Lozada-Nur et al. used CP mixed in an adhesive paste to treat patients with severe erosive disease of the oral mucosa, reporting a complete response in 62.5% of patients and an excellent response in 29.7%; they described the treatment as efficacious and safe [4]. Silverman et al. used 0.025% fluocinolone in Orabase™ paste to treat patients

with erosive OLP. They concluded that the treatment was of some benefit to 61.9% (96/155) of the patients in their series, even though only 14.1% (22/155) of the patients were symptom-free [2]. Gonzalez-Moles et al. have recently shown excellent outcomes in the treatment of severe erosive gingival lesions by topical application of CP in custom trays with 100% of success attributed to the improved delivery to all lesions through the use of the tray, the higher concentration used (0.05% vs. 0.025%), and the duration of contact between the drug and the lesion [22]. Nevertheless in this study a control group was not enrolled and 100,000 IU/cc of nystatin in paste was also administered because of the large surface area in contact with the drug, the high concentration of CP used and the occlusive nature of the tray method.

Because OLP is chronic condition, treating the symptoms is extremely important in addressing quality-of-life. This study aimed to increase the contact time to about 5 hours to allow a decrease in steroid concentration in order to reduce potential side-effects (i.e. candida infection) and improve the patients' compliance. The mucoadhesive tablet did not cause side effects, cortisol levels in plasma were not altered, no findings of Candida infection was seen during the treatment and the administration of an anti-mycotic agent was not required. Moreover, there were no increases in blood pressure or episodes of hyperglycaemia among patients with a history of diabetes or controlled hypertension.

In conclusion, HPMC and $MgCl_2$ are effective in controlling PMM hydration/erosion and, consequently, drug release without significantly modifying mucoadhesion. Moreover, the lack of mucosal irritation and adverse effects confirmed the suitability of this combination to prepare mucoadhesive tablets. The application of 24 µg CP tablet may be an efficacious and safe treatment of OLP then semisolid preparation. This preliminary study suggests that this vehicle may have utility in the delivery of anti-inflammatory medications and other agents for treatment of oral conditions.

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Figure captions:

Fig. 1 – The swelling properties of the four tablet formulations over time. The mixture exhibited a different performance upon hydration depending on the tablet composition. When 10% (w/w) $MgCl_2$ was added (-□- and insert B) the pattern was comparable to that of pure PMM (-■- and insert A): the tablets dissolved without swelling. Tablets containing 10 % (w/w) HPMC (-▲-and insert C) or both $MgCl_2$ and HPMC (-◇- and insert D) formed a slight swelling layer within the first 10 min followed by erosion.

Fig. 2 – ATR-FTIR spectra of hydrated placebo formulations.

Fig. 3 – Release (%) of CP from the buccoadhesive tablets made of the pure PMM (-■-), or mixing 10% w/w $MgCl_2$ (-□-), or 10% w/w HPMC (-▲-) or a mixture thereof (-◇-).

Fig. 4 - Reticular-erosive lichen planus before (a) and after (b) treatment with low concentration of CP in mucoadhesive tablets.

Table 1.

Composition of placebo (series P), CP loaded tablets (series F) and technological characterization.

Form.	Composition (%, w/w)				CP content	G_{100} *	MDF§	WA#	IVRT†
	CP	PMM	HPMC	$MgCl_2$	(µg)	(mg*min/cm^2)	(N)	(mJ)	(min)
P1	-	100	-	-	-	4.820±0.211	5.56±0.62	2.58±0.23	257±58
P2	-	90	-	10	-	3.551±0.226	4.41±0.77	2.08±1.17	281±74
P3	-	90	10	-	-	3.107±0.214	4.42±1.63	2.28±0.75	288±86
P4	-	80	10	10	-	1.579±0.196	3.25±0.11	1.26±0.10	330±34
F1	0.03	100	-	-	23±1	4.970±0.159	5.63±1.37	3.39±1.18	-
F2	0.03	90	-	10	25±0	3.423±0.201	4.22±0.31	1.56±0.09	-
F3	0.03	90	10	-	24±1	3.307±0.192	4.51±1.00	2.75±1.14	-
F4	0.03	80	10	10	24±0	1.502±0.183	3.81±0.42	2.39±0.16	-

* G100: erosion rate; § MDF: maximum detachment force; # WA: work of adhesion; † IVRT: in vivo residence time.

Table 2.
Signs and symptomatic scoring systems

Sign	Symptom	score
-	asymptomatic patients	0
Reticular	patients with mild symptoms that did not affect quality of life	1
Atrophic	moderate symptoms that were bothersome to the patients and needed medical attention	2
erosive	severe symptoms that significantly interfered with patients' quality of life	3*

* in the case of patients with intraoral manifestations of more than one type of OLP, the highest score was recorded.

Table 3.
Classification of OLP in patients enrolled in each group (22 men, 26 woman, average age 51.5).

OLP type	Group CP-T		Group CP-P		Group CP-O	
	start	**end**	**start**	**end**	**start**	**end**
Reticular	5	0	6	3	4	0
Atrophic	3	1	3	3	2	1
Erosive	4	0	5	5	5	2
Mixed	4	2	2	2	5	2
No signs	0	13	0	3	0	11
Total	**16**	**16**	**16**	**16**	**16**	**16**

Table 4.
Score for symptoms at the beginning and the end of the study.

Symptom (score)	**Group CP-T**		**Group CP-P**		**Group CP-O**	
	start	**end**	**start**	**end**	**start**	**end**
absence of symptoms (0)	2	13	3	3	4	11
mild symptoms (1)	5	2	8	7	6	3
moderate symptoms (2)	6	1	4	4	5	2
severe symptoms (3)	3	0	1	2	1	0
Total	**16**	**16**	**16**	**16**	**16**	**16**

Figure 1

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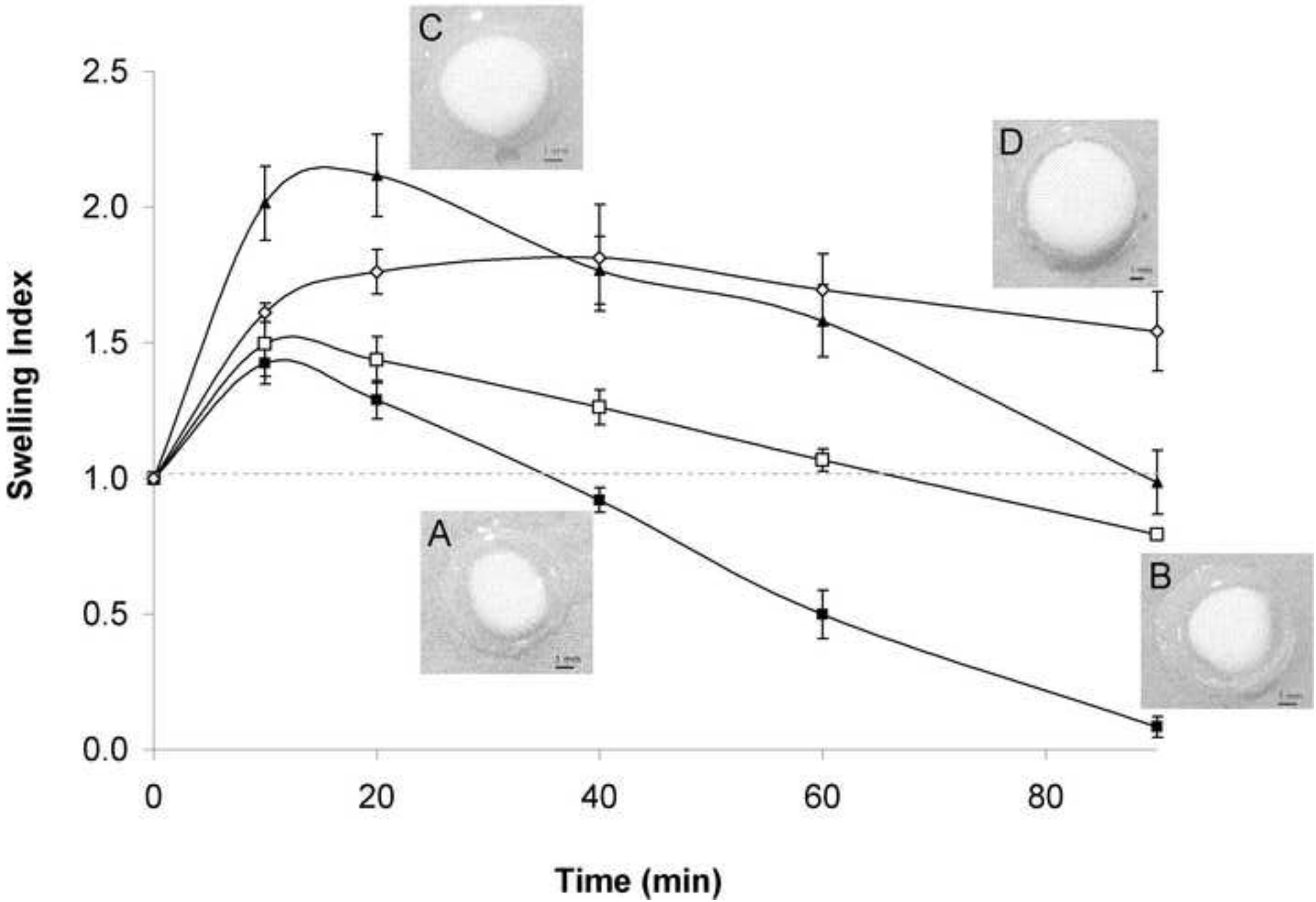

Figure 2

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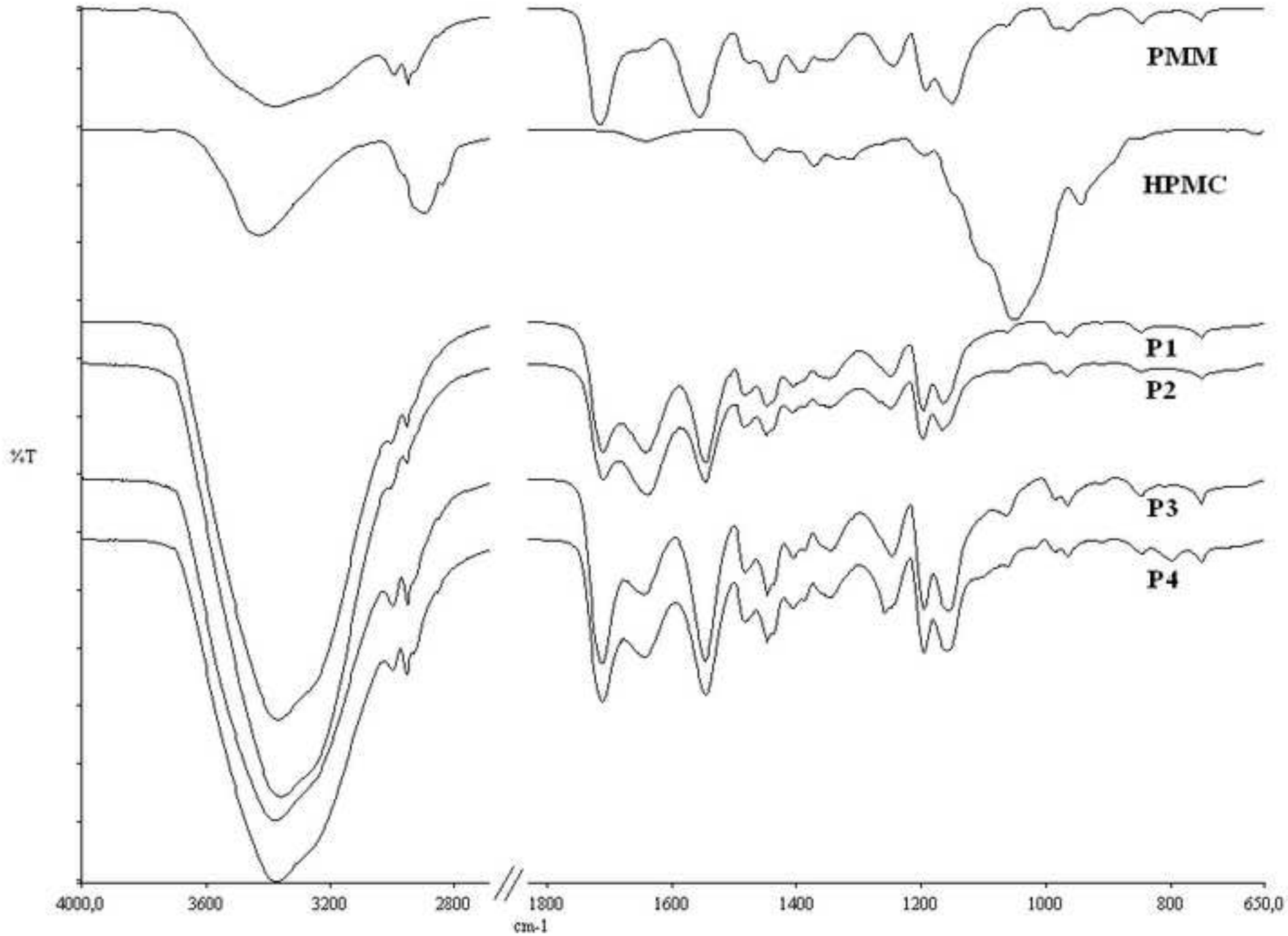

Figure 3

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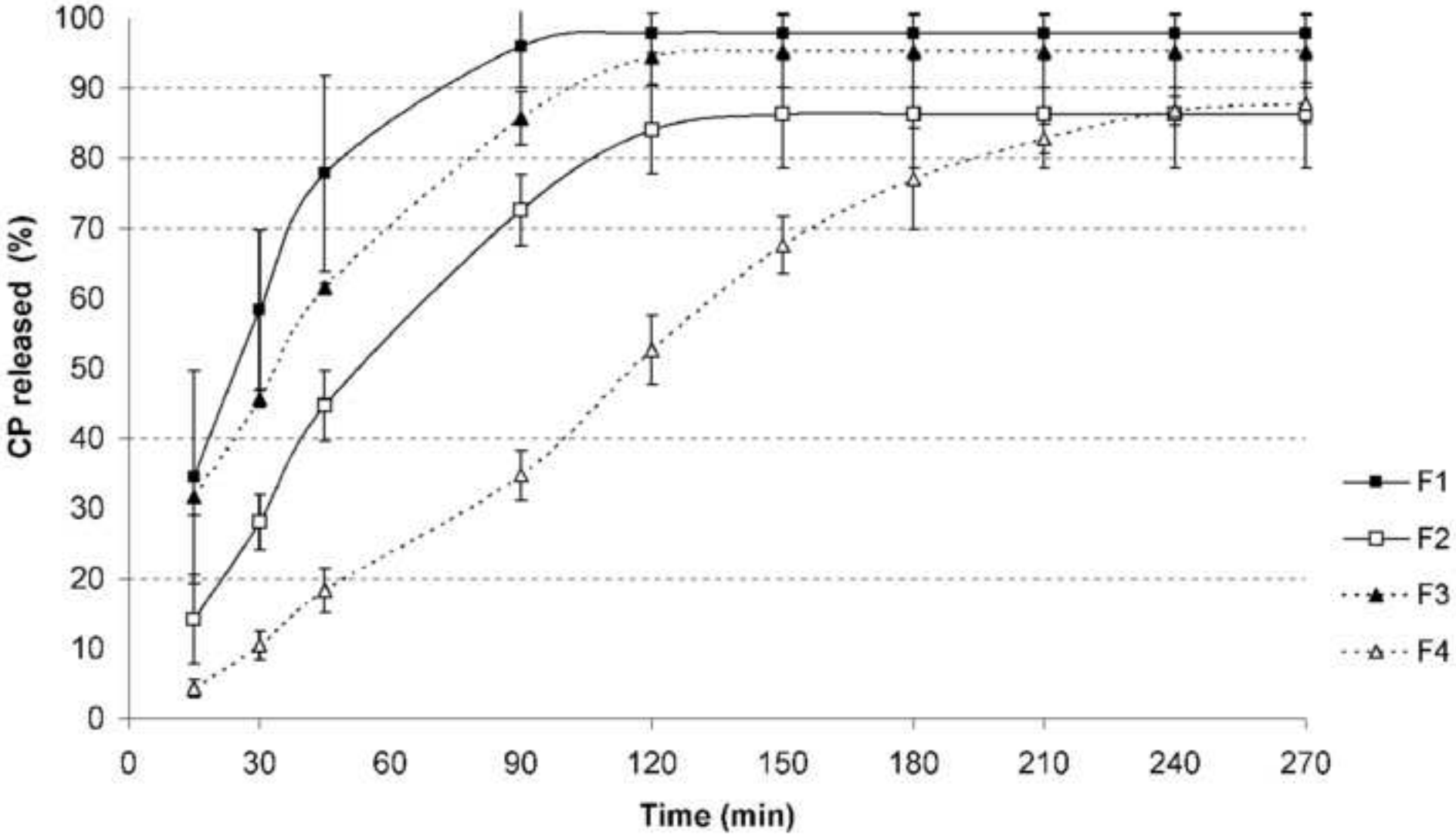

Figure 4b

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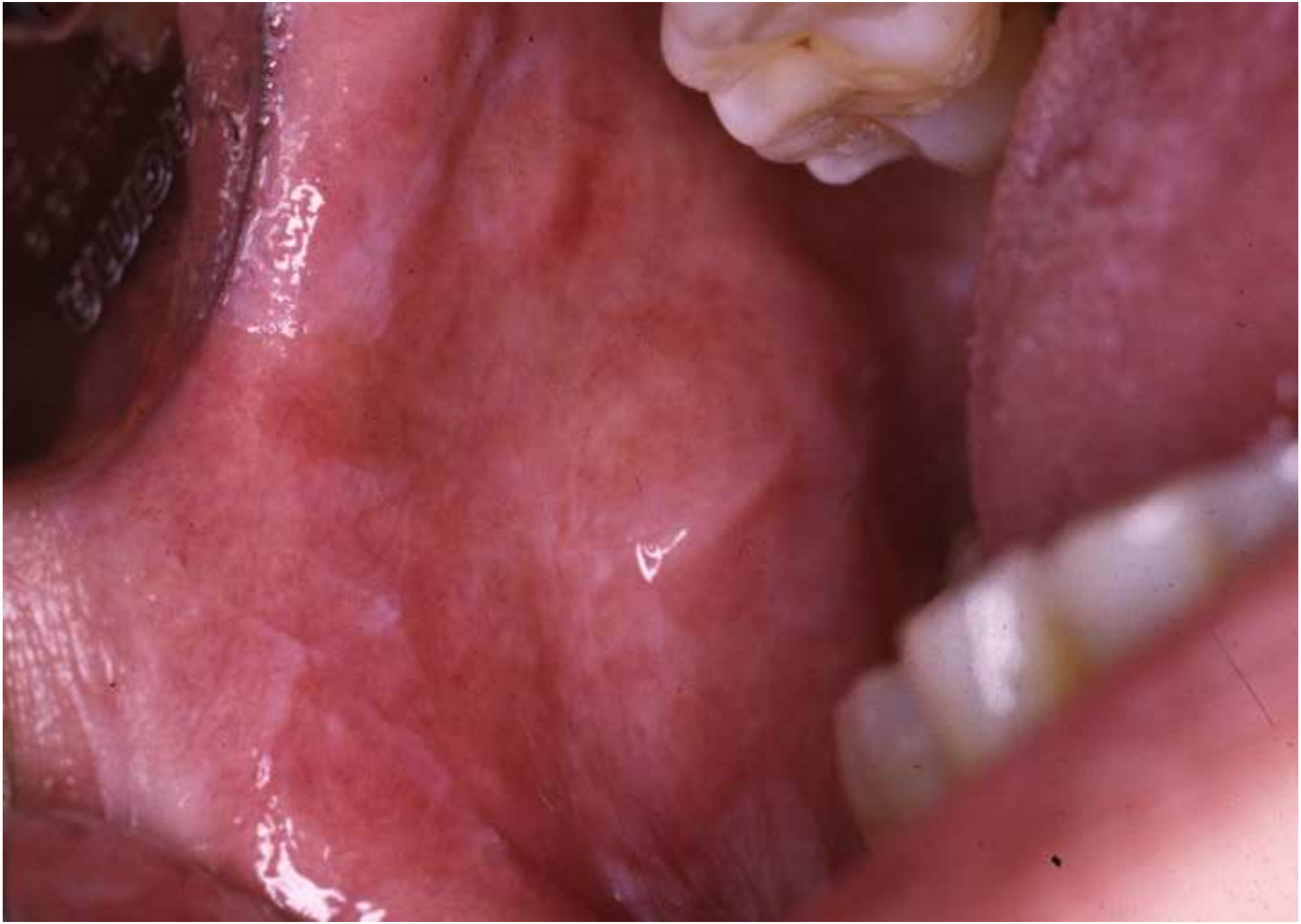

Figure 4a

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