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Research paper

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

Francesco Cilurzo [a], Chiara G.M. Gennari [a], Francesca Selmin [a], Joel B. Epstein [b], Giovanni M. Gaeta [c], Giuseppe Colella [d], Paola Minghetti [a,*]

[a] Department of Pharmaceutical Science "Pietro Pratesi", Università degli Studi di Milano, Italy
[b] Department of Oral Medicine and Diagnostic Sciences, University of Illinois, Chicago, United States
[c] Department of Odontostomatology, University of Cagliari, Italy
[d] Department of Head and Neck Pathology, II University of Naples, Italy

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ABSTRACT

The work aimed at studying 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 ($n = 16$) who received three 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 patients 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 autoimmune mucocutaneous 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 at evaluating the utility of a 24 μg CP mucoadhesive tablet based upon a poly(sodium methacrylate, methylmethacrylate) (PMM), a mucoadhesive non-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-h 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™.

* Corresponding author. Address: Department of Pharmaceutical Sciences "Pietro Pratesi", via G. Colombo, 71, 20133 Milan, Italy. Tel.: +39 0 2 50324639; fax: +39 0 2 50324657.
E-mail address: paola.minghetti@unimi.it (P. Minghetti).

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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® K4 M (HPMC K4 M), 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, until 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 placed 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:

$$\Delta W = (W_t - D_t)/D_t \quad (1)$$

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. As dissolution medium, 500 ml of deionised water at 37.0 ± 0.5 °C were used 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 by 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).

Table 1
Composition of placebo (series P), CP-loaded tablets (series F) and technological characterization.

Form.	Composition (%, w/w)				CP content (µg)	G_{100}[a] (mg min/cm^2)	MDF[b] (N)	WA[c] (mJ)	IVRT[d] (min)
	CP	PMM	HPMC	$MgCl_2$					
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	–

[a] G100: erosion rate.
[b] MDF: maximum detachment force.
[c] WA: work of adhesion.
[d] IVRT: in vivo residence time.