Drug Delivery and Translational Research
https://doi.org/10.1007/s13346-026-02122-9

ORIGINAL ARTICLE

Solid lipid microparticles-into-film delivering clobetasol: from buccal formulation design to pilot clinical study in patients with oral lichen planus

Giulia Di Prima[1] · Maria Elena Mauceri[2] · Martina Coppini[3,4] · Cecilia La Mantia[3] · Rodolfo Mauceri[3] · Giuseppina Campisi[2,5] · Viviana De Caro[1]

Received: 10 February 2026 / Accepted: 9 April 2026

Abstract

Oral lichen planus is a chronic inflammatory disorder of the oral cavity, for which the therapeutic gold standard consists of the topical administration of corticosteroids, such as clobetasol-17-propionate (CLB). Nowadays, there are no commercially available pharmaceuticals intended for CLB delivery within the oral cavity. Then, in clinical practice, the drug is administered via magistral galenic preparations, formulated as adhesive semisolids. As they possess numerous drawbacks (e.g., limited contact time, poor patients' compliance, inaccurate dosing), the research is still focused on the development of suitable solid buccal drug delivery systems (BDDS). This work aims to: i) combine buccal film and lipid microsystem technologies, thus yielding an innovative composite BDDS and ii) preliminary assess its in vivo effectiveness. Solid Lipid Microparticles containing CLB were designed to possess a softening temperature close to body temperature, thereby facilitating the release of the drug in molecular form by fusion once applied. This lipid matrix, being tissue-affine, may also act as a penetration enhancer. Composite buccal films were then developed to facilitate microparticles administration, converting this powder into a solid mucoadhesive formulation. These Solid Lipid Microparticles-into-Film composites (SiF-composites) resulted homogeneous, highly mucoadhesive and capable of promoting CLB accumulation within the buccal mucosa. The best formulation was subjected to a pilot in vivo evaluation (5 patients per group receiving the SiF-composite or 0.05% CLB in Orafix) resulting in treatment adherence and a reduction in Thongprasom et al. scoring. The preliminary results obtained were extremely promising, thus suggest confirmation through a further larger, randomized double blind clinical trial.

Keywords Clobetasol-17-Propionate · Solid Lipid Microparticles · Buccal Film · Orafix paste · Oral Lichen Planus · Mucoadhesion

✉ Viviana De Caro
viviana.decaro@unipa.it

Giulia Di Prima
giulia.diprima@unipa.it

Maria Elena Mauceri
mariaelena.mauceri@unipa.it

Martina Coppini
martina.coppini@unipa.it

Cecilia La Mantia
cecilia.lamantia@unipa.it

Rodolfo Mauceri
rodolfo.mauceri@unipa.it

Giuseppina Campisi
giuseppina.campisi@unipa.it

[1] Department of Biological, Chemical and Pharmaceutical Sciences and Technologies (STEBICEF), University of Palermo, Via Archirafi 32, 90123 Palermo, Italy

[2] Department of Biomedicine, Neurosciences and Advanced Diagnostics (BiND) University of Palermo, Via del Vespro 129, 90127 Palermo, Italy

[3] Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.) University of Palermo, Via Liborio Giuffrè 5, 90127 Palermo, Italy

[4] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy

[5] Oral Medicine and Dentistry Unit for Medically Compromised Patients, Department of Rehabilitation, Frailty and Continuity of Care, University Hospital of Palermo, Via Liborio Giuffrè 5, 90127 Palermo, Italy

Published online: 20 April 2026

Introduction

Oral lichen planus (OLP) is a chronic, non-infectious inflammatory disease of the oral cavity. OLP affects approximately 1–2% of the adult population, with a predominance among female patients (around 65%) aged between 50 and 59 years, whereas the highest incidence among men occurs in the 40–49 age group; nonetheless, younger individuals and children may also be affected. Moreover, it is estimated that OLP occurs in 70–77% of patients with cutaneous lichen planus [1–3]. OLP appears as symmetrical and bilateral lesions, or as multiple lesions. The most commonly affected sites include the bilateral buccal mucosa, the borders and dorsum of the tongue, and the gingiva, whereas palate, lips, and floor of the mouth are less frequently involved [4]. As OLP is a chronic inflammatory disease, corticosteroids represent the gold standard therapy, although immunosuppressants, retinoids, calcineurin inhibitors, and other immunomodulatory agents may also be employed. Topical corticosteroids are widely recognized as the first-line treatment for symptomatic OLP and oral lichenoid lesions. However, the optimal formulation, concentration, and dosage regimen have not been established yet [5]. Among the most widely used high-potency topical corticosteroids clobetasol-17-propionate (CLB) stands out. It possesses potent anti-inflammatory and immunosuppressive properties and can thus rapidly reduce inflammation and relieve symptoms such as pain, erythema, and swelling of lesions. Furthermore, it suppresses abnormal immune activity, thereby reducing the immune response responsible for lesion development [6, 7]. At present, however, there are no commercially available pharmaceutical formulations specifically designed for the administration of CLB within the oral cavity. In current practice, the drug is administered through magistral (off-label) galenic preparations formulated as semisolid anhydrous adhesive oral pastes composed of pectin, sodium carboxymethylcellulose, vaseline, and polyethylene or Aerosil (e.g., Orabase or Orafix) [8]. The use of such formulations entails several drawbacks, including: i) difficult application; ii) poor solubilization of the lipophilic drug within the hydrophilic base; iii) inaccurate dosing; iv) limited contact time with the mucosa; v) need for frequent administration; vi) risk of ingestion by swallowing; vii) susceptibility to salivary wash-out; viii) unpleasant alteration of taste; ix) poor patient compliance. To overcome these limitations, current research is focused on the development of Buccal Drug Delivery Systems (BDDSs) in the form of solid, mucoadhesive preparations with defined and reproducible unit doses, suitable for easy self-administration and, consequently, patient-friendly use [9]. For instance, Cilurzo et al. developed prolonged-release mucoadhesive tablets containing 24 µg of CLB, which, when compared with a semisolid conventional formulation (CLB ointment in Orabase) containing 125 µg of CLB, demonstrated improved therapeutic efficacy and a significant reduction in the major side effects associated with drug administration [10]. In 2022, a phase 2 randomized clinical trial demonstrated that treatment with a novel mucoadhesive clobetasol patch (Rivelin®-CLO) resulted in statistically significant improvements in ulcer area, symptom severity, disease activity, pain, and quality of life compared with placebo [11]. More recently, orodispersible mucoadhesive films containing CLB and hydroxypropyl-β-cyclodextrin as a solubilizing agent have been developed and manufactured using Direct Powder Extrusion 3D printing technology, showing potential for use in the paediatric management of OLP [12]. The formulation of innovative BDDSs may address several critical factors, including: i) the limited solubility of the drug within the hydrophilic polymeric matrix; ii) the reduced drug release from the formulation; iii) the pH of the salivary microenvironment; and iv) salivation, which directly affects the contact time between the formulation and the mucosal surface [13, 14].

To exploit the advantageous characteristics of mucoadhesive buccal films (e.g., prolonged adhesion, flexibility, ease of handling, wound dressing effect) while simultaneously enhancing the solubility of CLB and its interaction with injured mucosal tissues, the aims of the present study are: i) to combine buccal film technology with lipid microsystem technology, thus yielding an innovative composite BDDS and ii) to assess its preliminary in vivo effectiveness.

Materials and methods

Materials

Clobetasol-17-propionate (CLB) and lemon essential oil (LEO) were purchased from Farmalabor. Tween 85 and Span 20 were obtained from Sigma-Aldrich (Steinheim, Germany). Cetyl decanoate (Cet.dec) was synthesized according to the patented procedure (patent no. IT201900011436, by De Caro V. and Giannola L.I.). Trans-resveratrol (RSV), 1-hexadecanol (also known as cetyl alcohol, 1-hex), Hydroxyethylcellulose (HEC) at High Viscosity—HEC-H—(EP viscosity of 8.500 cPs at 25°Cin 2% solution), or Medium Viscosity—HEC-M—(EP viscosity of 4.400 cPs at 25°C in 2% solution), Trehalose dihydrate and Kollidon 30 (polyvinylpyrrolidone K30, PVP K30) were purchased from A.C.E.F (Fiorenzuola D'Arda, PC, Italy). The isotonic solution was prepared by dissolving 9 g of NaCl in 1 L of distilled water. The 5% (w/v) isotonic trehalose solution was obtained by dissolving 9 g of NaCl and 50 g of trehalose in 1

L of distilled water. The citrate buffer pH 5.5 was prepared by dissolving 3.024 g of sodium citrate dihydrate and 0.636 g of citric acid monohydrate in 1 L of distilled water. The 3% (w/v) citrate buffer solution containing β-cyclodextrins (β-CD) was prepared by dissolving 30 g of β-CD in 1 L of citrate buffer. The artificial non-enzymatic saliva pH 6.8 was prepared by dissolving 0.126 g of NaCl, 0.937 g of KCl, 0.189 g of KSCN, 0.655 g of KH_2PO_4, 0.2 g of urea, 0.154 g of Na_2SO_4, 0.178 g of NH_4Cl, 0.130 g of $CaCl_2$, and 0.631 g of $NaHCO_3$ in 1 L of distilled water. All solvents and salts were of analytical grade and were employed without further purification processes. The semisolid reference formulation was kindly supplied by a local pharmacy and contained 0.05% of CLB in anhydrous adhesive oral paste base (Orafix™, obtained from Fagron Italia Srl, Bologna, Italy). The tissues from which the porcine buccal mucosa was obtained were kindly supplied by the Azienda Agricola Mulinello S.r.l. (Leonforte, EN, Italy).

Preparation of clobetasol-loaded Solid Lipid Microparticles (SLM-CLB)

CLB-loaded microparticles were prepared using the hot melt method, following the patented procedure and composition described in Italian Patent No. ITRM102019000011436. Accurately weighed amounts of CLB, 1-hexadecanol (1-hex), and cetyl decanoate (Cet. Dec) were placed in a 400 mL beaker and melted using a heating plate (Heidolph MR3001K Hotplate Stirrer with Heidolph EXT3001 Temperature Probe, Heidolph Instruments, Schwabach, Germany) set at 100.0 ± 0.5 °C. Once the lipid phase was completely melted, appearing as a clear solution, 15 µL of lemon essential oil (LEO) were added. To prepare the SLM-CLB, two different lipid mixtures were used (see composition in Table 1).

An appropriate amount of the hydrophilic dispersing phase (Table 2), previously brought to boiling, was added to 2 g of the molten lipid mixture. The resulting biphasic system was mixed using either a Tecnolab R50D series mechanical stirrer or an Ultraturrax homogenizer (Kinematica Polytron Model PT MR 2100), applying the stirring times and speeds reported in Table 2. Subsequently, the obtained emulsion was rapidly cooled by immersing the beaker containing the dispersion in an ice/water/NaCl bath while maintaining continuous stirring for a defined period.

The temperature reduction led to the solidification of the microparticles that were separated by flotation, collected through filtration using a pleated filter, and left to dry at room temperature for 24 h. The obtained SLM-CLB were then accurately weighed to calculate the yield % as follows:

$$Yield\ \% = \frac{Recovered\ SLM - CLB\ (g)}{Starting\ lipid\ mixture\ (g)} \times 100$$

Each formulation was prepared four times and results are expressed as the mean ($n = 4$) ± standard error (SE). All the SLM-CLB batches were stored at 4 °C until further characterization.

Table 1 Weight percentage composition of the lipid mixtures used to prepare the SLM-CLB

	CLB (%)	1-hex (%)	Cet.Dec (%)	LEO (µL)
Mix A	1.5	78.5	20.0	15.0
Mix B	1.5	68.5	30.0	15.0

Table 2 Operative parameters for the preparation of the SLM-CLB

Formula code	H_2O (mL)	Tween 85 (g)	Span 20 (g)	Agitation speed (rpm)	Hot agitation time (min)	Cold agitation time (min)
SLM-CLB-A1	75	/	/	800	1	14
SLM-CLB-B1	75	/	/	800	1	14
SLM-CLB-B2	75	/	/	1000	1	14
SLM-CLB-B3	100	/	/	1000	1	14
SLM-CLB-B4	75	0.050	/	1000	1	14
SLM-CLB-B5	100	0.013	/	1000	1	14
SLM-CLB-B6	100	/	0.228	1000	1	14
SLM-CLB-B7	100	/	0.057	1000	1	14
SLM-CLB-B8	100	/	0.114	1000	1	14
SLM-CLB-B9	100/NaCl	/	/	1000	1	14
SLM-CLB-B10	100	/	/	11.000 (ultraturrax)	1	14
SLM-CLB-B11	100	/	/	1500	5	10

Evaluation of the SLM-CLB melting temperature range

The softening temperature and melting point of the SLM-CLB were determined by placing small amounts of each sample inside glass capillaries and using a Stuart SMP30 melting point apparatus. The analyses were performed in duplicate for each batch of microspheres, starting at a temperature of 27 °C and setting a heating rate of 2 °C/min. The results are reported as the mean ($n = 8$) ± SE.

Thermogravimetric analysis (TGA) coupled with differential thermal analysis (DTA)

TGA/DTA was performed using a Netzsch Jupiter F1 STA 449 instrument (NETZSCH B.V. & Co. Holding KG, Selb, Germany) over a temperature range of 20–1000 °C, at a heating rate of 10 °C min^{-1}, and under a dynamic atmosphere consisting of nitrogen and air, each supplied at a flow rate of 20 mL min^{-1}. The samples analyzed were CLB, 1-hexadecanol, cetyl decanoate, and SLM-CLB-B11.

DL% and LE% determination

To evaluate the actual encapsulation of CLB into the obtained microparticles, quantitative analyses were performed using a Shimadzu UV–Vis spectrophotometer, model Pharma Spec 1601 (Kyoto, Japan). A calibration curve was preliminarily constructed by analyzing seven CLB standard methanolic solutions (concentration range: 0.020–0.002 mg/mL) and recording the absorbance value at $\lambda_{MAX} = 239$ nm. The obtained calibration equation was as follows: Abs = 37.711 [mg/mL] + 0.0033 (R = 0.9999). The analytical method was proven to be robust and reproducible. Intraday and interday variations were lower than sensitivity. Then, 5 mg of SLM-CLB were accurately weighed (METTLER AE 240 analytical balance), placed in a 5 mL volumetric flask, and dissolved in methanol. The resulting clear solutions were analyzed by UV–Vis spectrophotometry and the results obtained were processed to calculate the Drug Loading % (DL%) and Loading Efficacy % (LE%) using the following equations:

$$DL\% = \frac{CLB_{in}\ (mg)}{SLM - CLB\ (mg)} \times 100$$

$$LE\% = \frac{DL_{experimental}}{DL_{theoretical}} \times 100$$

Each analysis was performed in triplicate for each batch, and results are reported as mean ($n = 12$) ± SE. Moreover, as the presence of lipids should potentially interfere with CLB quantification, blank microparticles were prepared according to the lipid composition of the CLB-loaded ones and subjected to UV–Vis measurement as previously described. No interferences were reported.

Quantification of LEO into the SLM-CLB-B11

Since the main component of LEO is (+)-limonene, the amount of LEO into the SLM-CLB-B11 was monitored by HPLC–DAD analysis in term of limonene peak using an Agilent 1260 Infinity system equipped with a G1311B quaternary pump, coupled with a 1260 Infinity II Diode Array detector, and an integrated G7129C automatic sampler (20 µL injection) with a column thermostat oven, along with automated integration software (OpenLAB CDS ChemStation Workstation, Stockholm, Sweden). Chromatographic separation was achieved using a reverse-phase Ace® Excel Super C18 column (125 × 4.60 mm; 100 Å; 5 µm) column and analyzing the resulting chromatograms registered at 210 nm (DAD range; 190–640 nm). As mobile phase a mixture consisting of a 0.1% (v/v) TFA solution in HPLC-grade water (solvent A) and acetonitrile (solvent B) was used in gradient elution. To quantify the LEO content in SLM-CLB the following calibration curve was constructed analyzing five LEO standard solutions in methanol having concentration range 0.0250–0.0005 µL/mL at $\lambda = 210$ nm. The limonene retention time was 23.8 min. Under these conditions the linear equation was: Area = 14,977.22 [µL/mL] – 0.39 (R = 0.999). Subsequently, 5 mg samples of SLM-CLB-B11 were dissolved in methanol and brought to volume in a 10 mL volumetric flask, filtered, and injected. Analyses were performed in duplicate for each batch, and the results are reported as the mean ($n = 8$) ± SE.

Dimensional distribution assessment

The sieving method was employed for the particle size analysis and dimensional distribution study of the SLM-CLB. Each batch of microparticles was accurately weighed and placed on the first of a series of 5 standard stainless-steel sieves (Endecotts LTD, England) with mesh sizes of 425, 300, 180, 106 and 90 µm. The sieves were arranged on a vibratory sieve shaker (Endecotts, Octagon 200) and subjected to mechanical agitation for 15 min. The fractions retained on each sieve were then collected and weighed to determine the percentage of each particle size class. Results are reported as mean ($n = 4$) ± SE.

Morphological analysis of SLM-CLB by optical microscopy

The morphological analysis of SLM-CLB was performed using a optical microscope Microstar 110 (Reichert, Inc., Depew, NY, USA) to evaluate the geometric characteristics

of the SLM-CLB microparticles. Images were acquired with an external camera at magnifications of 10× and 4×.

Evaluation of bulk and tapped volume and density of SLM-CLB

The bulk and tapped volumes of the SLM-CLB were determined according to European Pharmacopoeia 11th Edition (Ph. Eur.) by pouring an accurately weighed amount of microparticles into a graduated cylinder. The bulk volume (V_{Bulk}) was immediately recorded. Subsequently, the cylinder was subjected to a series of taps (10, 500, and 1250 taps) to facilitate the packing of the powder and reduce the interparticle voids. After the tapping process, the tapped volume (V_{Tapped}) was measured. The analyses were performed in triplicate using a mixture of the prepared batch corresponding to the same composition, and the results are expressed as the mean ($n=3$) ± SE. Based on the obtained data, the bulk density (ρ_{Bulk}) and tapped density (ρ_{Tapped}) were mathematically calculated by relating the mass of the microspheres to their respective volumes. Results are expressed as mean ($n=3$) ± SE.

Theoretical flow properties studies: determination of the compressibility index and Hausner ratio

The obtained bulk and tapped volumes/densities were used to calculate the Hausner ratio and the Compressibility index according to the following equations reported in Ph. Eur.:

$$Hausner\ ratio = \frac{V_{Bulk}}{V_{Tapped}} = \frac{\rho_{Tapped}}{\rho_{Bulk}}$$

$$Compressibility\ index\ \% = \frac{(V_{Bulk} - V_{Tapped})}{V_{Bulk}} \times 100 = \frac{(\rho_{Tapped} - \rho_{Bulk})}{\rho_{Tapped}} \times 100$$

Results are expressed as mean ($n=3$) ± SE.

Experimental flow properties studies: determination of the drained angle of repose

The flowability angle of repose was evaluated according to the Ph. Eur. guidelines. The test was conducted using a stainless-steel instrument (Copley Scientific Flowability Tester Model BEP2) consisting of a funnel with an adjustable orifice diameter, positioned above a Petri dish with a diameter of 55 mm. 8 g of SLM-CLB were poured into the funnel and allowed to flow freely until the entire surface of the Petri dish was covered, forming a cone. The height of the cone was measured using a dedicated device (Mitutoyo Absolute Digimatic Height Gauge). The powder's angle of repose (Φ) was then calculated as follows:

$$\Phi = arctg\left(\frac{h}{r}\right)$$

where h is the cone height and r is the radius of the Petri dish. For the evaluation of the angle of repose of the SLM-CLB an orifice with a 15 mm diameter was used. The experiment was repeated six times, and results are expressed as the mean ($n=6$) ± SE.

Preparation of the SLM-into-Film composite (SiF-composite)

An accurately weighed amount of distilled water (96.06 g) was heated (60.0 ± 0.5 °C) and then trehalose (0.53 g), PVP K30 (0.53 g), and HEC (2.85 g) were added in the reported order, ensuring that each component was fully solubilized or homogeneously dispersed before adding the next one. The resulting dispersion was maintained under magnetic stirring for two hours at 60.0 ± 0.5 °C. Finally, the gel was subjected to ultrasonic treatment for 2 h, until it appeared homogeneous, compact, and transparent. The obtained gel was then kept at 4 °C overnight. Two different gels were prepared using either HEC-M or HEC-H and indicated as Gel_M and Gel_H respectively. Afterwards, accurately weighed amounts of each gel were gently mixed with the SLM-CLB and 4.9 g of the resulting homogeneous suspensions were poured into silicone molds (area: 20.25 cm^2) and left to dry in an oven at 30 °C and 60% of humidity for 48 h. The obtained SiF-composites (wet and dry composition in Table 3) were equilibrated at room temperature for 2 h, weighted and then sealed in polyethylene pouches and stored at 4 °C. Each composite was prepared 5 times and results (in terms of dry weight) are reported as mean ($n=5$) ± SE.

Table 3 Wet and dry composition of the prepared SiF-composites

Formula Code	Gel			SLM-CLB
		Wet	Dry	Wet&Dry
SiF_M-composite	Gel_M	4.58 g	Trehalose – 24 mg PVP K30–24 mg HEC-M – 131 mg	320 mg
SiF_H-composite	Gel_H	4.58 g	Trehalose – 24 mg PVP K30–24 mg HEC-H – 131 mg	320 mg

Folding endurance evaluation

The SiF-composites were repeatedly folded at the same point until they broke or up to a maximum of 300 times (end point). The number of folds tolerated by each composite was recorded as the folding endurance value [15].

SiF-composites uniformity: weight, thickness and CLB content evaluations

Weight uniformity was assessed by cutting 3 discs having area equal to 0.52 cm^2 from each SiF-composite and accurately weighing them with an analytical balance (METTLER AE 240). The results are reported as mean $(n = 15) \pm$ SE.

The thickness was measured at five different points (in the center and at the four corners of each composite) using a DIN 863 digital micrometer (measurement range: 0–25 mm; sensitivity: 0.001 mm; Vogel, Germany GmbH & Co. KG). The results are reported as mean $(n = 25) \pm$ SE.

Finally, the previously obtained discs were soaked in 10 mL of methanol and subjected to ultrasonic bath treatment for 20 min. The resulting clear solutions were then subjected to UV–Vis analyses as previously described. Results are reported as the mean $(n = 15) \pm$ SE.

Swelling/disintegration assay

The swelling/disintegration capacity of the SiF-composites in physiological fluids was evaluated by monitoring their weight and through visual assessment. Discs having surface area of 0.38 cm^2 were accurately weighed (W_0), placed on a watch glass, moistened with 100 µL of artificial salivary fluid pH 6.8, and incubated for predefined time intervals. At each time point, the disc was blotted with filter paper to remove any excess fluid and weighed (W_t) to calculate the Swelling Index as follows:

$$Swelling\ Index\ =\ \frac{W_t - W_0}{W_0}$$

The assay was conducted in triplicate, and results are reported as mean $(n = 3) \pm$ SE [16]. Furthermore, to visualize the morphological changes of the SiF-composite over time, discs having area of 0.38 cm^2 were placed on a microscope slide, under which a sheet of graph paper was positioned. The discs were moistened with 100 µL of artificial salivary fluid pH 6.8 and observed for 1 h. During the experiment, photographs were taken using a camera to assess both the planar two-dimensional and the frontal two-dimensional planes. The diameter and the thickness of the discs were measured at predefined time intervals. The experiment was repeated in triplicate and results are reported as mean $(n = 3) \pm$ SE.

Mucoadhesion studies

Ex vivo qualitative evaluation of SiF-composites mucoadhesiveness

To perform the ex vivo qualitative mucoadhesion assays, tissue specimens were collected from the vestibular area of the retromolar trigone immediately after the sacrifice of domestic 12-month-old pigs. These samples were kept into refrigerated containers to allow transport to the laboratory within 2 h. Here, the tissues were washed with isotonic solution, and the excess of connective and adipose tissues was carefully removed. Afterwards, samples were treated for 1 h with an isotonic solution containing trehalose 5% (w/v) as cryoprotectant [17] and subsequently stored at −80 °C until subsequent utilization. The frozen tissues were used up to a maximum of 6 months following freezing. For the mucoadhesion tests, tissue samples were thawed and conditioned in artificial saliva (pH 6.8) at 37.0 ± 0.5 °C for 10 min. The tissues were then placed on a Petri dish, and a SiF-composite sample (2 × 1 cm) was positioned on the surface of the buccal mucosa. A 20 g weight was then applied for 10 s to simulate the adhesion due to buccal application and then the tissue samples were inverted to induce patch detachment under gravitational force. Furthermore, the tissue was subjected to multiple movements aimed at mimicking the normal oral cavity motions in order to evaluate the flexibility of the SiF-composites after tissue adhesion. The experiment was repeated in triplicate for each composite and photographs and video were acquired.

Ex vivo quantitative evaluation of SiF-composites mucoadhesiveness

To perform the ex vivo quantitative mucoadhesion assay, the previously mentioned porcine tissue samples were subjected to thermal shock to separate the mucosal epithelium from the adipose and submucosal connective tissue. To achieve this, the samples were immersed for 1 min in a preheated isotonic solution (60.0 ± 0.5 °C), and the mucosa was manually separated from the underlying tissue using tweezers [18, 19] and used for testing up to 24 h after treatment. The mucoadhesive properties of the SiF-composites were evaluated using a Texture Analyzer TX-700 (Lamy Rheology, Champagne au Mont d'Or, France) equipped with a 10 N load cell (resolution 0.001 N) and a cylindrical polymethylmethacrylate (PMMA) probe (Model TX-BLMPG; Diameter: 12.7 mm; Height: 30 mm; Contact area: 1.26 cm^2). The previously isolated porcine buccal mucosa was fixed onto a custom-made

PMMA support and maintained in a moist state using artificial salivary fluid pH 6.8. Simultaneously, disks of area 1.26 cm^2 were obtained from the SiF-composite and affixed to the lower surface of the probe using double-sided adhesive tape. The mucoadhesion test was carried out as follows: i) in the resting position, the mucosa and the formulation were placed 9.4 cm apart, with the probe bearing the formulation exerting no force on the mucosa; ii) the experiment commenced as the probe descended and touched the mucosa, promoting firm contact between the mucosa and the formulation (probe descent speed: 0.2 mm/s; compression distance: 1 mm); iii) a constant force was applied for increasing time intervals (contact position: 1 mm; contact time: 10, 20, 30 or 45 s); iv) the probe was then withdrawn to the resting position (withdrawal speed: 0.1 mm/s), and the force required to detach the formulation from the mucosal surface was recorded (detection threshold: 0.04 N). The data were obtained as force (N) versus time (sec) or distance (mm) curves. Adhesion force values (corresponding to the "minimum force" given by the instrument) were normalized to the surface area of the formulation, and the Detachment Force was calculated using the following formula:

$$Detachment\ Force\left(\frac{N}{m^2}\right) = \frac{Force\ of\ adhesion\ (N)}{Formulation\ area\ (m^2)}$$

Moreover, to quantify mucoadhesion also the hysteresis area of the force-distance curves was calculated. Each experiment was repeated 6 times for each initial contact time and results are reported as mean ($n = 6$) ± SE.

Ex vivo permeation/penetration assays

Preliminary in vitro solubility test

CLB solubility was tested in citrate buffer pH 5.5 and citrate buffer pH 5.5 containing β-CD 3% (w/v). An excess of CLB was added to 2.5 mL of each tested media until the presence of a substantial precipitate was observed. The obtained suspensions were kept under constant stirring at 25.0 ± 0.5 °C (Heidolph MR3001K Hotplate Stirrer with Heidolph EXT3001 Temperature Probe, Heidolph Instruments, Schwabach, Germany) for 120 min. Suspensions were then centrifuged for 15 min at 12,500 rpm (microcentrifuge mySPIN™ 12 Mini Centrifuge, Thermo Fisher Scientific) and the supernatant was successively withdrawn, filtrated through a 0.22 µm PTFE filter (Millipore, Burlington, KS, USA), diluted with methanol and subjected to UV–Vis measurement as previously described, using the appropriate blank and calibration curve. Each experiment was repeated in triplicate and results are reported in terms of mean concentration (mg/mL) ± SE.

Ex vivo permeation

The porcine mucosal epithelium obtained by the aforementioned thermal shock treatment was washed and conditioned in an isotonic solution before each experiment and stored in a refrigerator overnight. Then, it was equilibrated to room temperature and repeatedly washed with an isotonic solution to remove any residual biological material that could interfere with subsequent UV–Vis analyses. Afterwards, appropriate mucosal sections were cut and placed between the two compartments of a vertical Franz diffusion cell (Permeagear, unjacketed, flat flange joint, 9 mm orifice diameter, 15 mL acceptor volume, SES GmbH-Analysesysteme, Bechenheim, Germany). The assembly of the Franz cells involved an initial conditioning period of the acceptor compartment filled with the acceptor medium (citrate buffer pH 5.5 containing β-CD 3% w/v) at 37.0 ± 0.5 °C. Subsequently, the mucosa and the donor compartment were positioned. Once the cell was assembled, it was further conditioned for approximately 15 min at 37.0 ± 0.5 °C. Finally, the citrate buffer pH 5.5 previously inserted into the donor compartment was removed and promptly replaced with a SiF_H-composite disc having area of 0.52 cm^2 or 200 mg of 0.05% CLB in Orafix paste both soaked with 200 L of citrate buffer pH 5.5. The system was maintained at 37.0 ± 0.5 °C and up to a maximum of 1 h. At predetermined time intervals, 0.4 mL aliquots were withdrawn from the acceptor fluid and immediately replaced with the same volume of fresh acceptor fluid to allow the maintenance of the sink conditions. The collected samples were subjected to UV–Vis analyses for CLB quantification. Each experiment was conducted six times, and the results are reported as mean ($n = 6$) ± SE.

Evaluation of the amount of CLB accumulated into the buccal tissue

At the end of each permeation experiment the Franz cell was disassembled, and the buccal mucosa was recovered, washed and subjected by extraction by being placed into 2 mL of methanol heated up to 60.0 ± 0.5 °C for 2 min. The extraction procedure was repeated twice. The collected liquors were combined in a 5 mL volumetric flask and brought to volume with methanol. The amount of CLB extracted was then determined by HPLC–DAD using the same method described for LEO quantification. Preliminarily, the calibration curve of CLB was constructed by analyzing seven methanolic standard solutions over the concentration range 0.000515–0.103000 mg/mL at λ = 238 nm. CLB retention time was 18.3 min. Under these conditions the linear equation was: Area = 34,780.59 [mg/mL] (R = 0.999). Each

experiment was repeated six times and results are reported as mean ($n = 6$) ± SE.

Chemical stability study of CLB into the SiF_H-composite overtime

SiF_H-composite discs with an area of 0.38 cm^2 were packaged in polyethylene bags and stored under refrigerated conditions (4 °C) to ensure microparticles physical stability, given their softening temperature of approximately 30 °C. At predetermined time points (2, 4, 7, 11 and 16 weeks), the CLB content was assessed by HPLC–DAD analysis, as previously described, following complete solubilization of the disc in 10 mL of methanol. Results are expressed as percentage change in CLB content in relation to the initial content at time zero. Each experiment was repeated in duplicate on three independent batch and reported as mean ($n = 6$) ± SE.

In vivo pilot study

A pilot evaluation was conducted following approval by the Ethics Committee of University of Palermo (protocol n. 22/2024, ClinicalTrials.gov ID NCT07100613). The study complied with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants prior to enrolment. Patients with a clinical suspicion of OLP were recruited from the Unit of Dentistry for Medically Fragile Patients, Department of Rehabilitation, Fragility, and Continuity of Care, University Hospital "Paolo Giaccone," Palermo, Italy. All patients underwent a punch biopsy under local anesthesia. Histopathological examination was subsequently performed at the Department of Pathology of the same institution to confirm the diagnosis.

Inclusion criteria comprised adults (> 18 years) with no prior diagnosis or treatment for OLP and with clinical and histopathological features consistent with the 2020 World Health Organization (WHO) criteria.

Exclusion criteria included any previous topical or systemic corticosteroid therapy for any condition; the presence of oral lichenoid lesions as defined by the 2020 WHO criteria; pregnancy or breastfeeding; and hematologic or immunodeficiency disorders.

Before treatment initiation, all participants underwent a comprehensive oral examination, and any potential sources of local trauma, such as incongruous prosthetic components or sharp dental cusps, were identified and corrected.

Study design and interventions

This pilot exploratory study was aimed at generating preliminary clinical evidence on the potential efficacy of the reported innovative drug delivery system based on Solid Lipid Microparticles-into-Film for the treatment of OLP. In this context, the study also sought to explore its therapeutic performance in comparison with a conventional treatment, namely 0.05% clobetasol formulated in a mucoadhesive vehicle (Orafix), in order to provide initial insights that may support the design of future, larger controlled studies [20]. Ten patients with histologically confirmed diagnosis of OLP were enrolled and assigned consecutively and unselectively, non-randomly, to one of two study groups. Participants (nr. 5) in the test group applied the 2 × 1 cm SiF_H-composite once daily for the first 15 days, followed by the administration of a 1 × 1 cm SiF_H-composite (corresponding to a 50% dose reduction) for the subsequent 15 days. Participants (nr. 5) in the control group applied conventional treatment with 0.05% CLB in a mucoadhesive vehicle (Orafix) three times daily for the first 15 days and twice daily for the remaining 15 days. All participants were instructed to refrain from eating or drinking for at least one hour after each application to ensure optimal mucosal drug absorption. Demographic and clinical data, including age, sex, medical history, medication use, and smoking habits, were recorded in individual medical charts. Each patient underwent photographic documentation, and lesion sites, clinical appearance, and associated symptoms were recorded systematically. Only descriptive statistical analysis was performed. Lesion severity was evaluated at baseline and at follow-up visits using the Thongprasom et al. scoring [21, 22]:

- Score 0: indicates no lesion, with the mucosa appearing normal;
- Score 1: refers to mild white striae only, without atrophy or erosion;
- Score 2: describes the presence of white striae with an atrophic area of less than 1 cm^2;
- Score 3: indicates white striae with an atrophic area greater than or equal to 1 cm^2;
- Score 4: represents white striae with an erosive area of 1 cm^2 or less;
- Score 5: is used for white striae with an erosive area greater than or equal to 1 cm^2.

Data analysis

The in vitro and ex vivo data are expressed as mean ± standard error (SE). All differences were statistically evaluated with Student's t-test or the one-way analysis of variance (ANOVA or F-test) with the minimum levels of significance with $p < 0.05$.

Results and discussion

SLM-CLB optimization

The buccal administration of lipophilic active molecules such as CLB can be extremely challenging since the oral environment is mainly hydrophilic. It is well known that drug-mucosa interactions, as well as drug accumulation within the mucosa, are only possible if the drug is dispersed in its molecular form. As a result, Solid Lipid Microparticles (SLMs) can represent an innovative solution. They can also act as penetration enhancers if appropriately designed in terms of quali-quantitative lipid compositions to be compatible with the drug and capable of softening or melting once at the body temperature thus releasing the loaded active while also promoting its contact with the natural lipids of the mucosae [23, 24]. In this work 1-hexadecanol (1-hex) and cetyl decanoate (Cet.Dec) were chosen due to their biocompatibility, non-toxicity, safety and biodegradability. Additionally, lemon essential oil (LEO) was chosen due to its high D-limonene content (60.0–70.0%) as limonene can enhances CLB accumulation into the buccal mucosa. Here the "hot melt" technique was used to encapsulate 1.5% (w/w) of CLB into the SLMs. This method was chosen due to its high process reproducibility, rapid execution, and operational simplicity. Additionally, it is considered a green method since it does not require the use of organic solvents, which could otherwise lead to the presence of toxic residues in the final product. As reported in the "Materials and methods" section, several attempts were made to obtain the final optimized formulation by varying: i) the lipid mixture composition; ii) the type of hydrophilic phase (e.g., water or solution, presence and quantity of surfactants, electrolytes, viscosity modifiers, etc.); iii) the ratio between lipophilic and hydrophilic phases; iv) the stirring speed of the biphasic dispersion; v) the agitation time, both during the heating and cooling stages. To determine the optimal parameters, all the obtained SLM-CLB batches were immediately evaluated in terms of softening/melting temperature range/point as well as in terms of particle size, particle size distribution and particle shape. Table 4 reports the softening temperature range and each other observations regarding the obtained SLM-CLB formulations. As a result, the lipid mixture A, determined a softening point higher than the desired range for oral cavity administration. The successful lipid mixture B was then prepared by increasing the amount of Cet.Dec, which is the low meltable lipid component of the whole mixture.

To obtain the optimal particle size range for a stable and free-flowing powder (20–300 µm), key process parameters were systematically varied to evaluate their impact on the final product properties.

Overall, the results indicated that increasing the volume of the dispersing phase effectively reduced droplet aggregation, thereby yielding smaller particle sizes. The incorporation of surfactants or electrolytes did not consistently facilitate SLM-CLB formation and, in several cases, resulted in a pronounced increase in the softening temperature range. The use of an Ultraturrax homogenizer was proved as unsuitable, as the high shear forces induced particle fragmentation rather than stable droplet formation. In contrast, fine-tuning the aqueous phase volume together with the agitation time during both heating and cooling stages optimized emulsion stability and lipid microdroplets solidification behavior. Consequently, these conditions yielded the most favorable

Table 4 Screening results for all the prepared SLM-CLB formulations, presenting the softening temperature range (°C, mean ± SE; $n = 8$) and other general observations

Formula code	Softening temperature range (°C)	Observations
SLM-CLB-A1	40.00 ± 0.01	Softening temperature range too high
SLM-CLB-B1	35.28 ± 0.43	> 20% of SLM-CLB larger than 425 µm
SLM-CLB-B2	35.50 ± 2.00	> 10% of SLM-CLB larger than 425 µm
SLM-CLB-B3	38.00 ± 0.01	> 10% of SLM-CLB larger than 425 µm
SLM-CLB-B4	/	Opalescent filtered waters, sample not considered
SLM-CLB-B5	/	Opalescent filtered waters, sample not considered
SLM-CLB-B6	41.83 ± 0.33	Softening temperature range too high
SLM-CLB-B7	40.69 ± 0.22	Softening temperature range too high
SLM-CLB-B8	39.83 ± 1.33	Softening temperature range too high
SLM-CLB-B9	39.00 ± 0.01	Softening temperature range too high
SLM-CLB-B10	38.20 ± 1.02	Non-spherical SLM-CLB; they appeared crushed by the ultraturrax use
SLM-CLB-B11	34.46 ± 0.26	Best sample. Desired softening temperature range and < 5% of SLM-CLB larger than 425 µm

results, and the complete characterization of the optimized SLM-CLB-B11 formulation was presented herein.

SLM-CLB-B11 characterization

A high yield was obtained (101.24 ± 0.23%), demonstrating both the efficiency of the preparation technique and the effectiveness of the flotation-filtration process employed for SLM-CLB recovery. As previously discussed, the analyses of the softening/melting temperature range/point highlighted the initial softening of the microparticles at 34.46 ± 0.26 °C, identified by the appearance of "droplets" along the walls of the capillary, and the complete melting at 48.65 ± 0.22 °C. The design of such thermosensitive microparticles was crucial to ensure their softening upon close contact with the lesioned tissue once exposed to the physiological temperature of the oral cavity. Following softening and partial melting, the system, being composed of biocompatible lipids with affinity for oromucosal physiological lipids, might promote their interpenetration, thereby facilitating the partitioning of CLB in its molecular form and enhancing its accumulation at the site of action. A more comprehensive characterization of the thermal behavior of the microparticles was carried out by means of TGA/DTA analysis, comparing the thermal behavior of the drug, the individual lipid components (1-hexadecanol and cetyl decanoate), and the SLM-CLB. The TGA curves (Fig. 1, panel A) revealed that pure CLB undergoes a multi-step degradation process over a broad temperature range (approximately 200–700 °C), whereas the lipid excipients showed a single and sharp mass loss between ≈ 250 and 380 °C. The SLM-CLB displayed a degradation profile closely resembling that of the lipids, with no distinct degradation step attributable to CLB, suggesting that the drug is homogeneously dispersed within the lipid matrix rather than present as a separate crystalline phase. The DTA curves (Fig. 1, panel B) further support these findings. Pure CLB exhibited multiple endothermic and exothermic events, consistent with its complex degradation pathway, while lipid components showed well-defined thermal events at lower temperatures, including sharp endothermic peaks associated with melting transitions (≈ 30–50 °C). SLM-CLB showed a broader and less defined melting peak around 50 °C, in agreement with softening/melting temperature observed, indicating the formation of a disordered amorphous system in which the characteristic melting peak of pure CLB is no longer detectable. Overall, the TGA/DTA analysis confirmed the successful incorporation of CLB into the lipid matrix, with evidence of homogeneous dispersion, reduced crystallinity, and good physicochemical compatibility among the components.

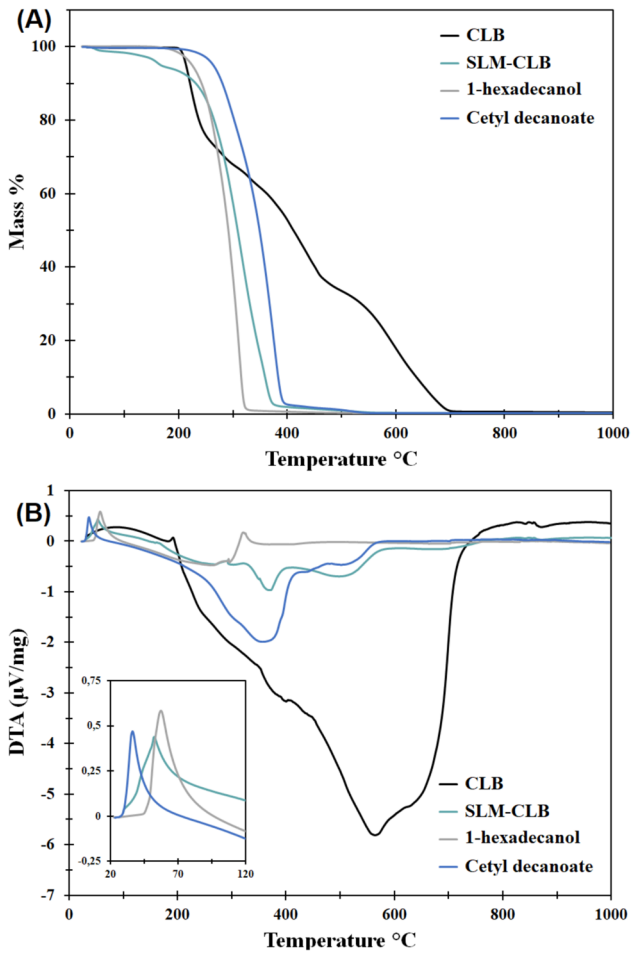

Fig. 1 (**A**) TGA curves and (**B**) DTA curves for CLB (black), SLM-CLB (green), 1-hexadecanol (grey) and cetyl decanoate (blue)

Once the feasibility of the formulation's application within the oral cavity was confirmed, the SLM-CLB were subjected to quantitative CLB analysis by UV–Vis spectrophotometry to determine the actual drug content and the efficiency of preparation process. Drug loading (DL%) and loading efficiency (LE%) were determined using both indirect and direct analytical approaches. The indirect method involved quantifying the residual CLB concentration in the filtration waters and calculating the entrapped amount by difference, whereas the direct method consisted of solubilizing accurately weighed aliquots of microparticles to determine the drug content. Both methods provided consistent results, confirming a DL% of 1.38 ± 0.01% and a LE% of 92.00 ± 0.01%. The minimal drug loss observed was attributed to partial solubilization of CLB in the aqueous phase, likely enhanced by the surfactant activity of 1-hexadecanol. Nevertheless, these results were considered satisfactory, as the LE% exceeded 90%. Moreover, the effective incorporation of LEO into the obtained SLMs was carefully assessed. Limonene, the main component of lemon essential oil, is a volatile monoterpene with high vapor pressure, responsible for its characteristic citrus aroma. Consequently, some loss could occur during the hot-melt preparation process

(≈100 °C). However, HPLC–DAD analysis allowed the determination of a loading efficiency (LE%) of 85 ± 1% of LEO in the SLM-CLB formulation, demonstrating that, despite the high temperature applied during the encapsulation process, LEO was effectively retained within the microparticles. This result was further supported by the strong odor released when the SLMs were crushed between the fingers.

Based on these findings, the obtained SLM-CLB-B11 powder can be considered as a good candidate for the subsequent development of microcomposite patches and, therefore, was further evaluated in terms of its individual and bulk properties, as these characteristics can influence the powder flowability and handling, the drug release and bioavailability.

The individual properties of SLM-CLB-B11 powder were determined in terms of size, size distribution and shape of particles. Particle size analyses were carried out through sieving, a simple, rapid, and effective technique both for assessing percentage-based size distribution and separate particles fractions, while optical microscopy was chosen for the morphological evaluation. The percentage particle size distribution was displayed in Fig. 2.

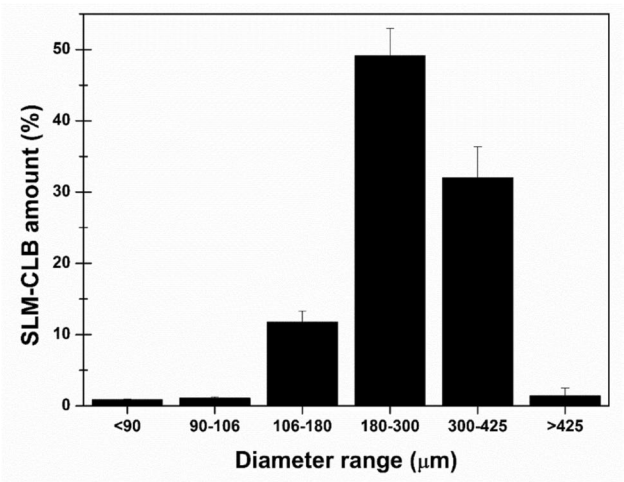

Fig. 2 Percentage particle size distribution of SLM-CLB-B11 powder. Means ± SE ($n = 4$)

As observable, the 99.88% of SLM-CLB-B11 displayed a mean diameter between 425 μm and 106 μm. Notably, very large (> 425 μm) and very small (< 106 μm) particles were scarcely represented. Nevertheless, for the further use of SLM-CLB-B11 the largest fraction (> 425 μm) was always discarded. Moreover, the optical microscopy images (Fig. 3) highlighted the spherical and regular SLM-CLB-B11 shape, which is maintained in any dimensional distribution class.

Bulk properties refer to the characteristics of the entire powder mass rather than those of the individual microspheres. Since bulk properties influence wettability, packing behavior, and interparticle interactions, they play a key role in the dispersion of powders within semisolid systems. In particular, cohesive powders with low bulk density tend to trap air and exhibit poor wettability, which can promote agglomeration [25]. Accordingly, bulk volume, bulk density, and flowability were evaluated. Bulk density (ρ_B), is defined as the ratio between the mass of the SLM-CLB and their bulk volume (V_{Bulk}). The analyses, conducted according to the European Pharmacopoeia 11th Edition (Ph. Eur.) revealed a bulk density of 0.46 ± 0.01 g/mL, whereas the tapped density (ρ_{Tapped}), calculated based on the volume after tapping (V_{Tapped}), was 0.53 ± 0.02 g/mL. Again, according to the Ph. Eur., predictive and indirect assessment of powder flowability can be achieved via determination of the Hausner ratio and Compressibility index. Table 1S (see Supplementary Materials) presents the correlation between Compressibility index, Hausner ratio, and predicted powder flow characteristics. For the SLM-CLB-B11, the Hausner ratio was 1.15 ± 0.03 and the Compressibility index was 13.10 ± 2.06%, indicative of a powder with good flowability. To confirm this statement, the flowability of the microparticles was also directly evaluated by measuring the angle of repose (θ); i.e., the angle between the base and height of the powder cone formed when a known amount of SLM-CLB falls from a funnel set at a certain height above a round surface of known diameter. Specifically, θ resulted of 28.14 ± 0.30° supporting the predictions derived from the

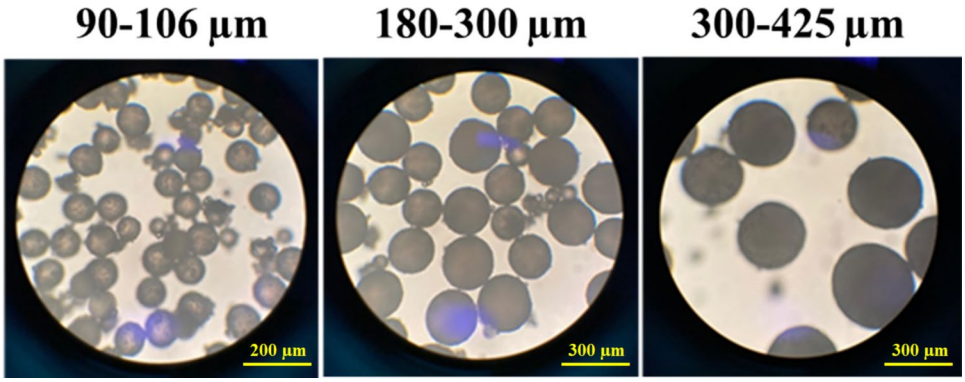

Fig. 3 Morphological analysis of SLM-CLB-B11 performed using a Microstar 110 optical microscope. Images of the various dimensional classes of SLM-CLB-B11 were manually acquired using an external camera

calculated Hausner ratio and Compressibility index. Therefore, SLM-CLB-B11 demonstrates excellent flowability and homogeneity, confirming its suitability as a well-defined pharmaceutical intermediate for the development of buccal patches intended for the treatment of OLP. Indeed, the direct application of the proposed microspheres onto the buccal mucosa could be technically challenging and imprecise, potentially compromising both patient compliance and therapeutic efficacy [23]. Furthermore, owing to their lipidic nature, these microparticles may exhibit limited mucoadhesion, which could result in accidental swallowing or removal from the application site due to salivary flow. Therefore, based on these observations, the SLM-CLB powder exhibits properties favorable for subsequent handling and processing.

SiF-composites development and characterization

A novel mucoadhesive buccal delivery system capable of promoting CLB accumulation at the site of diseased mucosa while simultaneously protecting the lesion through a wound-dressing effect would offer significant advantages for OLP treatment. Such a system could overcome the limitations of current extemporaneous preparations (e.g., 0.05% CLB in Orabase or Orafix) and address the absence of a commercially available product. The rational design of an innovative film-based delivery system could enable high local CLB concentrations and prolonged residence at the lesion site, thereby reducing dosing frequency and enhancing patient compliance.

The aim of this work was to develop a composite system consisting of a dry-state hydrophilic polymeric matrix in which microspheres are embedded (SLM-into-Film composite, or SiF composite). The resulting SiF-composite system was designed to be thin, flexible, homogeneous, mucoadhesive, and easy to apply directly to the lesion site. To prepare the composite film, a gel (hydrophilic base) was formulated, into which appropriate amounts of microspheres were subsequently added. The selected gel components were: i) trehalose, as plasticizer and capable of imparting a pleasant taste to the formulation; ii) PVP 30 K, as a mucoadhesive polymer; iii) Hydroxyethylcellulose (HEC), as main matrixing as well as mucoadhesive polymer. Both medium (Gel_M to prepare SiF_M-composite) and high (Gel_H to prepare SiF_H-composite) viscosity HEC were evaluated to achieve the best SiF-composite formulation. The aforementioned components were mixed in suitable proportions to produce a compact, clear, and viscous gel capable of entrapping the microspheres within its mesh, preventing sedimentation or migration during subsequent drying steps aimed at obtaining the final composites. The ratio between hydrophilic gel and SLM-CLB-B11 was selected in order to both obtain a thin final formulation and achieve a CLB dose of 0.2 mg/cm^2, useful for further clinical studies. The SiF-composites were prepared using the "solvent casting" method, a green approach which involves pouring the microsphere + gel suspension into a mold of 20.25 cm^2 area and drying it in an oven at 30.0 ± 0.5 °C, 60% of humidity for 48 h. Higher temperatures led to the melting of the microspheres, while longer exposure times resulted in stiffer patches. Following obtainment, the patches were left exposed to ambient air to allow them to reach equilibrium with environmental conditions. The SiF-composites were then characterized to assess their potential as innovative buccal delivery systems. A critical requirement for formulations intended for buccal application is deformability, assessed in terms of folding endurance. Both composites exhibited excellent folding endurance, remaining intact after 300 folds, indicating a high degree of flexibility. This represents a major advantage, enabling good adaptability to the application site and ensuring patient comfort during normal activities such as speaking or swallowing. A video displaying the notable flexibility of the formulations is reported as Supplementary Material (V1). Then, to validate the preparation method, the SiF-composites were characterized in terms of weight, thickness, and content uniformity. The results are shown in Table 5.

The data obtained revealed uniformity in both weight and thickness across all composites. SiF-composite uniformity was assessed by taking multiple measurements at different areas of the film or by analyzing disks obtained from the same film. As the standard errors were minimal, both SiF-composites could be considered homogeneous. Notably, they exhibited a very thin profile, making them suitable for buccal administration.

A relevant assessed parameter was the swelling index of the formulations, together with their disintegration time upon exposure to hydrophilic media such as salivary fluid. The swelling behavior of the buccal formulations reflects their ability to absorb water from the oral environment,

Table 5 SiF-composites characterization: weight of the entire patch ($n = 5$); uniformity of the SiF-composites in terms of weight ($n = 15$), thickness ($n = 25$) and CLB content ($n = 15$) of patch portions (0.52 cm^2 disk). Means ± SE

		SiF_M-composite	SiF_H-composite
Weight of the composite (mg)		485.22 ± 5.38	489.67 ± 3.33
Weight of composite 0.52 cm^2 disk (mg)		9.73 ± 0.54	10.32 ± 0.24
Thickness (mm)		0.37 ± 0.03	0.50 ± 0.01
CLB content	mg/cm^2	0.19 ± 0.01	0.20 ± 0.01
	DL% (w/w)	0.95 ± 0.03	1.06 ± 0.01

leading to expansion and an increase in dimension/weight. This phenomenon affects mucoadhesion, SLM-CLB release, and patient compliance. Indeed, excessive swelling can cause the formulation to become bulky and uncomfortable, despite being initially thin and suitable for buccal application. Swelling was monitored in terms of weight increase (swelling index) as well as thickness and diameter variation of SiF-composite disks at various time points for up to one hour. As observable in Fig. 1S (see Supplementary Materials) the use of HEC-M led to a complete composite dissolution between 15 and 20 min. Afterwards, the SLM-CLB migration throughout the medium is observed. Conversely, by employing HEC-H (Fig. 2S, see Supplementary Materials), the resulting composite swelled within the first few minutes and completely dissolved after around 45 min. No microsphere migration was observed. In both cases the thickness increase was not significant. From a quantitative standpoint, the swelling index was monitored by measuring the weight increase of the formulation due to water absorption, while variations in thickness and diameter were also recorded. As shown in Fig. 4, the SiF_M-composite swelled almost immediately upon contact with artificial saliva. No statistically significant differences were observed among the swelling indexes calculated at different time points for the same formulation. Similarly, an increase in diameter was measured, although it remained nearly constant overtime. In contrast, SiF_H-composite exhibited slower swelling, reaching a maximum after 15 min, followed by a decreasing trend. This behavior could be attributable to the dissolution of some components together with a continuous increase in diameter due to a higher water absorption capacity. It was also observed that the high-viscosity HEC-based formulation reached a maximum swelling index of approximately 9, compared with ≈ 5 observed for the medium-viscosity HEC-based formulation. It should also be noted that the dimensional increase was limited to the diameter, with no impact on the thickness of the composites. Consequently, despite the substantial swelling observed in both formulations, they were not expected to cause notable discomfort to the patient.

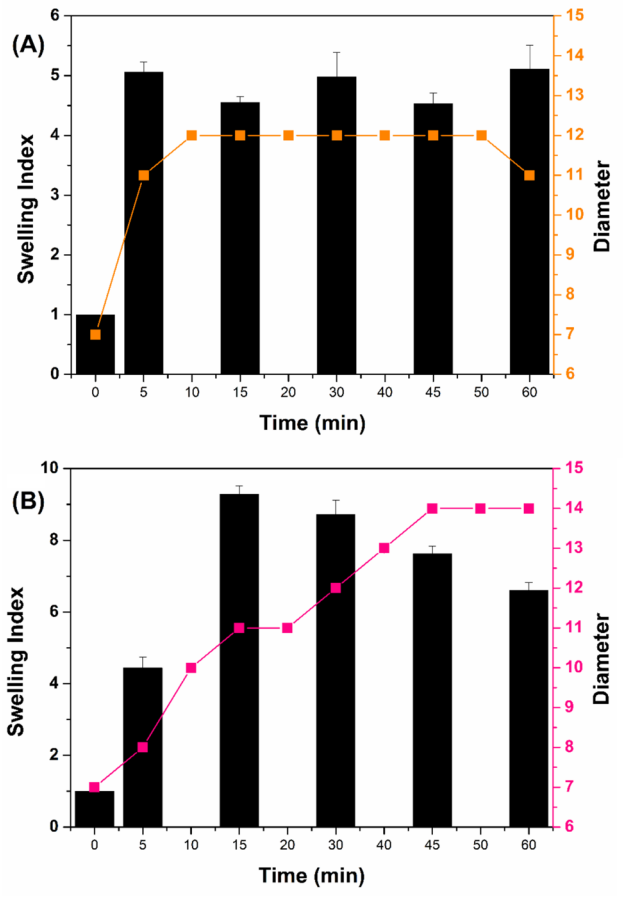

Fig. 4 Quantitative results of the swelling/disintegration assay, showing swelling index (bars) and diameter (squares) measurements for the SiF_M-composite (**A**) and the SiF_H-composite (**B**)

Overall, as SiF_M-composite dissolves faster than the SiF_H-composite, it should not represent the best choice for the purpose of the study, since it could not remain on the lesion long enough to provide a sustained and beneficial wound dressing effect or prolonged therapeutic coverage to reduce dosing frequency. Consequently, only the SiF_H-composite was selected for further evaluations.

Ex vivo evaluations

Mucoadhesiveness

As previously noted, mucoadhesion represents a critical property for an effective buccal delivery system. A mucoadhesive formulation adheres firmly to the mucosal surface, ensuring intimate and prolonged contact between the microspheres, and consequently the drug, and the target tissue. This adhesion minimizes unintentional swallowing of the formulation and enhances patient compliance, thereby improving the overall therapeutic efficacy of the treatment. To qualitatively assess the mucoadhesive behavior of the proposed formulations, 2 × 1 cm strips were applied to pretreated porcine buccal tissue previously moistened with artificial saliva maintained at body temperature. As shown in Fig. 3S (see Supplementary Materials), the formulations exhibited complete adhesion to the mucosal surface. Even when subjected to mechanical stress such as turning, bending, or folding, the SiF_H-composites remained firmly attached. Moreover, the formulations demonstrated the ability to conform to the dynamic movements of the tissue, in agreement with the folding endurance results (Fig. 4S, see Supplementary Materials). No significant qualitative differences were observed between the two formulations. The quantitative assessment of mucoadhesiveness was carried

out using a Texture Analyser, which recorded force–time (N/s) and force–distance (N/mm) profiles during detachment tests. These measurements enabled the determination of the adhesion force, subsequently normalized to the contact area between the mucosa and the formulation, thereby allowing the calculation of the detachment force. Moreover, since mucoadhesion is a multiphasic phenomenon, it is essential to evaluate the formulation's mucoadhesive performance as a function of the initial contact time with the mucosa, a critical parameter influencing the formation and stabilization of interfacial bonds Accordingly, the detachment force was measured at varying initial contact times, ranging from 10 to 60 s prior to traction (Fig. 5). Furthermore, to obtain results that more closely reflect in vivo conditions, given that ex vivo tissues lack their native mucus layer, the same experiments were also conducted in the presence of mucins, which were reintroduced by moistening the tissue surface with a mucin-containing dispersion [26–29].

As shown in Fig. 5, the detachment force reached a plateau at contact times ≥ 20 s in absence of mucins, whereas it continued to increase with longer initial contact times, reaching a plateau at an initial contact time of 45 s in presence of mucins. These results suggested that the kinetic of film-tissue interaction differ from those of the film–tissue–mucin interaction. Furthermore, consistent with the established role of mucins in mucoadhesion, soaking the specimens with a mucin-containing dispersion resulted in a marked 3- to eight-fold increase in detachment force. It should be noted that, due to the variety of experimental protocols available in the literature to assess mucoadhesion, no universally accepted detachment force values exist to define when a formulation can be considered mucoadhesive [30]. However, indicative ranges can be extrapolated as detachment forces between 200 and 1000 N/m^2 are generally associated with moderate mucoadhesion [15], whereas values exceeding 1000 N/m^2 indicate strong mucoadhesion [31, 32]. In the present study, considering an initial contact time of 20 s, the detachment force significantly exceeded the 1000 N/m^2 threshold both in absence and presence of mucins. These results suggest that a patient would only need to apply brief, continuous pressure to the formulation to achieve strong adhesion of the SiF_H-composite to the diseased tissue, minimizing both discomfort and pain during application.

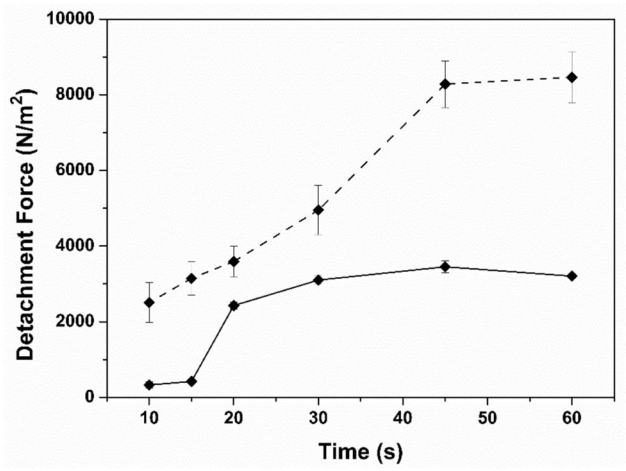

Fig. 5 Ex vivo quantitative mucoadhesion test. Detachment force (N/m^2) plotted as a function of contact time for the SiF_H-composite, in the absence (solid line) and presence (dash line) of mucins

Another key parameter to be considered is the work of adhesion, which is the hysteresis area of the force–distance curves. The existence of such hysteresis area is indicative of the interaction between two viscoelastic materials e.g., the ex vivo buccal mucosa and the hydrophilic base of the SiF_H composite. Indeed, the adhesion-detachment curves are not superimposed if an irreversible dissipation of energy occurs during the cycle. For the SiF_H composite, the presence of a hysteresis area was consistently observed, as it did not behave as a purely elastic solid for several reasons, including surface chemical heterogeneity (polymeric gel composed of multiple hydrophilic materials embedding lipid microparticles), deformability, surface roughness (due to the presence of microparticles), and swelling capacity [33]. The relationship between work of adhesion and contact time or detachment force was reported in Fig. 6.

As observable, for the series of experiments conducted in the absence of mucin (solid symbols, solid line), the hysteresis area progressively increases with both contact time and the corresponding detachment force. In accordance with the correlation identified between contact time and detachment force, this trend suggested that the duration of contact influenced the formation and stabilization of film–tissue interactions, promoting the establishment of mucoadhesive bonds whose disruption during detachment resulted in irreversible energy dissipation. Conversely, when the tissue is wetted with a mucin-containing dispersion (open symbols, dash line), a nearly constant hysteresis area was observed at shorter contact times (being higher than that measured in the absence of mucin) followed by a marked increase at longer contact times. This indicates that the presence of mucin initially enhanced the capacity to establish mucoadhesive interactions (in line with the higher detachment force values), the rupture of which gave rise to greater energy dissipation. In both experimental sets, it was also evident that the hysteresis area continued to increase even when the detachment force remains constant, suggesting enhanced viscoelastic deformation of the SiF_H composite as a function of time [34, 35].

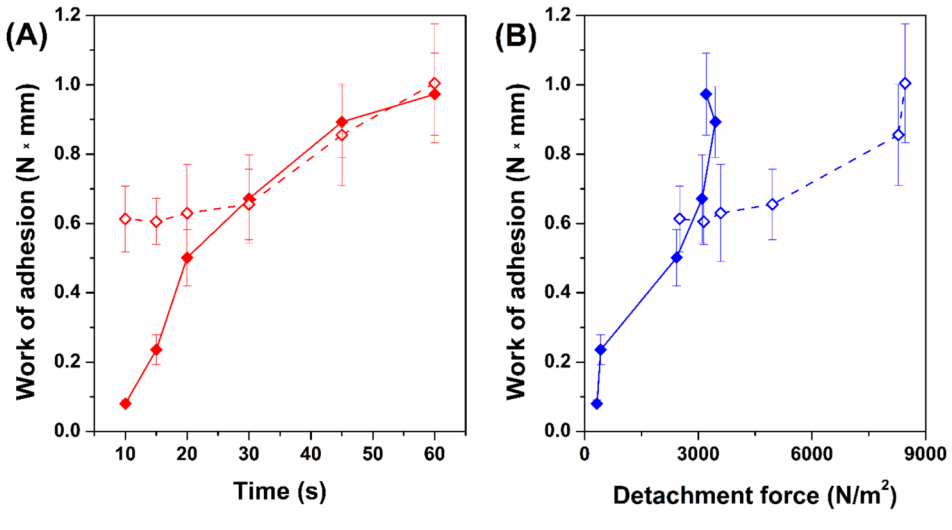

Fig. 6 Work of adhesion (N • mm) versus (**A**) time (s) or (**B**) detachment force (N/m^2) for the SiF_H-composite, in the absence (solid line) and presence (dash line) of mucins

Comparison of SiF_H-composite and 0.05% CLB in Orafix for promoting CLB accumulation into ex vivo buccal mucosa

Finally, the ex vivo permeation/penetration studies were conducted to assess the ability of CLB to penetrate and/or permeate through the buccal mucosa. These studies were performed using vertical Franz diffusion cells, which allow simulation of in vivo conditions, and porcine buccal mucosa, chosen for its morphological and structural similarity to human tissue, including a comparable bilayer phospholipid architecture and distribution [18]. The ex vivo studies were performed to compare the behavior of the innovative SiF_H-composite formulation to that of a semisolid adhesive oral paste (Orafix) containing 0.05% CLB. To avoid misleading results both the innovative and the conventional extemporaneous formulations were tested introducing into the donor chamber a dose of each formulation corresponding to the same total amount of CLB. The duration of the experiments was set up for a maximum of 1 h, according to the swelling studies which highlighted that the SiF_H-composite fully dissolved after approximately 45 min. Moreover, although the donor and acceptor media would normally be designed to simulate saliva and plasma, respectively, a buffer at pH 5.5 was selected for both compartments, as has been reported that CLB exhibits greater stability in acidic conditions [36]. Furthermore, β-CD were added into the acceptor fluid as solubilizing agents for CLB to ensure the maintenance of sink conditions during the experiment. Although PubChem reports a CLB solubility of approximately 2 µg/mL, the solubility test performed in citrate buffer at pH 5.5 did not allow the quantification of CLB by UV–Vis analysis. In contrast, the solubility of CLB in the presence of 3% w/w β-CD was found to be 0.120 ± 0.001 mg/mL, which is consistent with maintaining sink conditions throughout the experiment, given that the total amount of drug loaded into the donor compartment was 0.104 mg.

It was observed that after 1 h of application, CLB was not able to permeate through the buccal mucosa and reach the receptor compartment. These findings were entirely satisfactory, as the intended purpose of formulations is to deliver a localized topical therapy. Systemic absorption would merely result in drug loss and potential systemic side effects. The topical and localized effect is instead closely linked to the

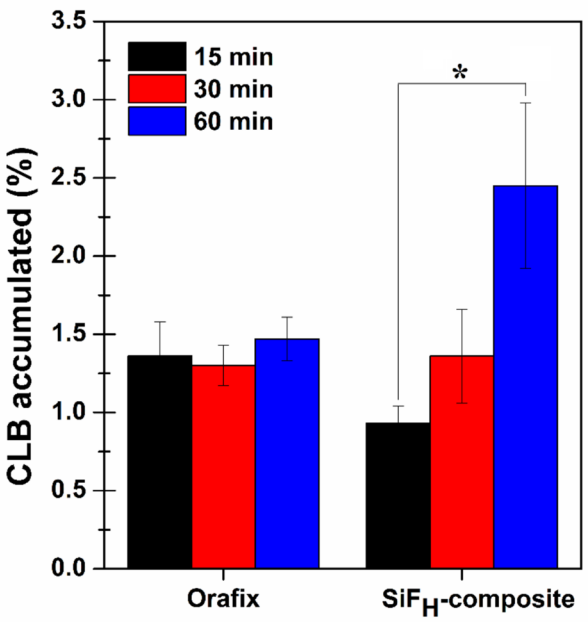

Fig. 7 Percentage of CLB entrapped in the buccal mucosa after 15, 30 or 60 min following administration of the conventional extemporaneous formulation (0.05% CLB in Orafix) versus the SiF_H-composite (*: $p < 0.05$)

ability of the drug to be delivered into, and accumulate within the mucosal tissue affected by the lesion. Consequently, the amount of CLB entrapped within the porcine membrane was assessed as a function of time.

Figure 7 reports the percentage of CLB retained within the mucosa (relative to the total amount of CLB contained in the formulation aliquot loaded into the donor chamber) at the end of the permeation experiments stopped at different time points. The longest time point was selected according to the swelling and dissolution test results previously discussed. As observable, the two formulations exhibit markedly different behaviors. The application of the conventional paste resulted in the immediate accumulation of a certain amount of CLB within the mucosa; however, this value did not increase substantially with longer contact times. In contrast, administration of the SiF_H-composite produced a time-dependent increase in drug accumulation within the tissue. It is worth noting that, after 15 min, the results appeared more favorable for the Orafix paste, whereas after 30 min the SiF_H-composite displayed a behavior comparable to that of the conventional semisolid. Finally, after 1 h, the SiF_H-composite proved to be significantly more effective in promoting CLB retention within the tissue. This time-dependent behavior is clearly associated with the swelling dynamics of the formulation: initially, the composite appeared less effective simply because it requires time to absorb water, swell, and release the microspheres from the polymeric network. Once this process occurs, intimate contact between the drug and the target tissue is progressively enhanced. In addition, this phenomenon may itself be considered a reliable indicator of the formulation's ability to release the drug at the target site, as the proposed complex release mechanism of CLB from SiF_H-composite is not readily captured by conventional in vitro release methods. The enhancement of CLB retention into the tissue could be attributable to the combined action of the microparticles, as a built-in penetration enhancer strategy, coupled with the presence of limonene, the main constituent of LEO. Furthermore, at the end of each ex vivo permeation experiment, upon disassembly of the Franz cells, the composite disks were found to have swollen to cover the entire available mucosal surface, establishing firm interaction and remaining strongly adhered throughout the study, in full agreement with the previously reported characterization results.

Long-term chemical stability of CLB into the SiF_H-composite

Considering the low softening and melting temperatures of the microparticles, 4 °C were selected as standardized and reproducible storage temperature conditions. Indeed, at higher ambient temperatures, which may occur during certain periods of the year, the SLM-CLB would soften, leading to alterations in the physical integrity of the SiF_H-composite.

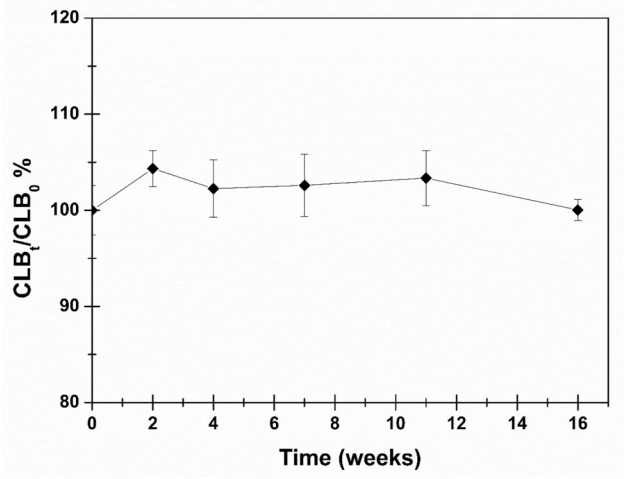

Fig. 8 Percentage CLB amount into the SiF_H-composite referred to the starting amount of CLB as a function of storage time up to 16 weeks

Since no visual alterations of the formulation have been observed over time at present, the chemical stability of CLB over time was assessed by HPLC–DAD analyses. Results are reported in Fig. 8 and highlight the stability of CLB over the time period investigated.

In vivo preliminary data

During the pilot study period, ten patients were enrolled, completed the protocol and were available for the analysis. They were mostly females (70%), with a mean age 61.3 ± 12.4 years.

All the enrolled patients presented OLP lesion on buccal mucosa; in the Test Group 1 patients were also affected by desquamative gingivitis. While in the control group, 2 patients showed lesion also on the tongue, 1 patient showed desquamative gingivitis and 1 patient exhibited OLP also on the edentulous ridge.

Tables 6 and 7 summarize patients' characteristics and Thongprasom et al. scores (TS).

To establish the dosing regimen for both the control and test groups, the primary challenge was determining dose equivalence of CLB administered via the conventional semisolid formulation versus the innovative solid SiF_H-composite. The main issue relies on the poor dosing accuracy of semisolid formulations, the amount applied may vary considerably between individuals and according to lesion extent. To approximate a realistic use scenario, a quantity of formulation deemed reasonably sufficient for application to an oromucosal lesion was manually withdrawn. This procedure was repeated multiple times by different operators, and the collected aliquots were weighed, yielding an average mass of approximately 300 mg. At

this point, a standardized dosing regimen was established for the conventional semisolid formulation, consisting of three applications per day for the first 15 days and two applications per day for the subsequent 15 days. Consequently, it was calculated that, for the first 15 days of therapy, this corresponds to a total daily dose of 900 mg of formulation, equivalent to 0.45 mg of CLB; for the subsequent 15 days, the daily dose amounts to 600 mg of formulation, containing 0.3 mg of CLB. Based on these considerations, the study design involved applying a 2×1 cm

Table 6 Characteristics and Tongprasom et al. score of the Test Group

Nr	Gender	Age	Systemic Disease/Other Manifestation of Lichen	Smoking Habits	Lesion Location	TS_{T0}	TS_{T1} (15 Days)	TS_{T2} (30 Days)
1	F	42	None	NO	Buccal mucosa	2	1	1
2	F	69	Hypertension	EX	Buccal mucosa, desquamative gingivitis	4	3	1
3	F	81	Hypertension, diabetes	NO	Buccal mucosa	4	3	1
4	F	58	Depression, hypothyroidism	YES	Buccal mucosa	4	2	2
5	M	55	None	YES	Buccal mucosa	4	3	1

Table 7 Characteristics and Tongprasom et al. score of the Control Group

Nr	Gender	Age	Systemic Disease/Other Manifestation of Lichen	Smoking Habits	Lesion Location	TS_{T0}	TS_{T1} (15 Days)	TS_{T2} (30 Days)
1	F	67	Hypertension, diabetes, hypercholesterolemia, depression	NO	Buccal mucosa, desquamative gingivitis	4	2	2
2	M	48	Hypertension	EX	Buccal mucosa tongue	4	2	2
3	F	72	Hypertension, diabetes, irritable bowel syndrome, cutaneous lichen planus	YES	Buccal mucosa, edentulous ridge	2	2	1
4	F	51	Heart disease	NO	Buccal mucosa, tongue	2	2	1
5	M	70	Hypertension	EX	Buccal mucosa	2	2	1

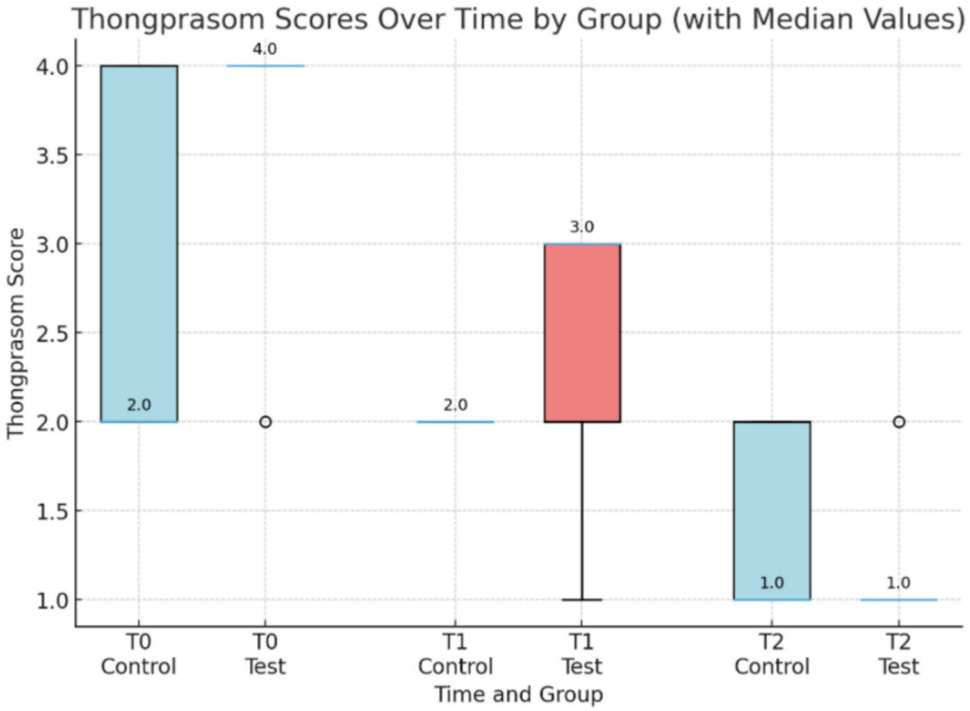

Fig. 9 Thongprason et al. scores (TS) over time by group

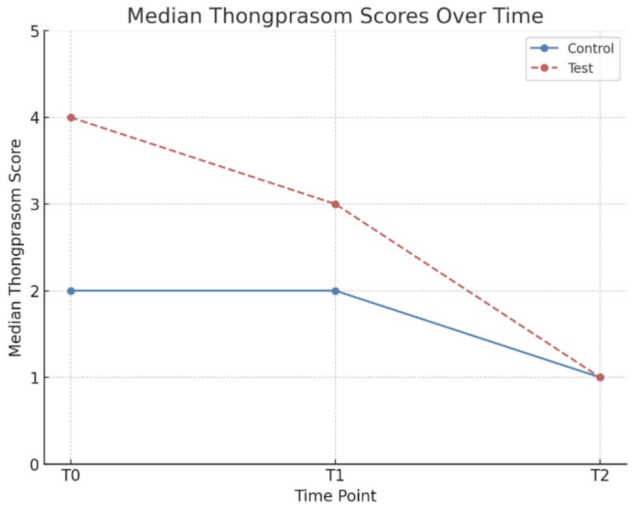

Fig. 10 Median Thongprason et al. scores (TS) over time by group

SiF_H-composite once daily, corresponding to a standardized dose of 0.4 mg of CLB during the first 15 days of treatment, followed by the administration a 1 × 1 cm film containing 0.2 mg of CLB for the subsequent 15 days, comparable to the theoretical CLB dose delivered by the semisolid formulation. It is relevant to emphasize that a primary advantage of the SiF_H-composite is the precise and simple standardization of the administered dose.

Analysis of TS (Figs. 9 and 10) revealed a progressive reduction in lesion severity in both groups over time. At baseline (T0), both groups exhibited TS ranging from 2 to 4, indicating a comparable range of disease severity. However, TS had a median value of 2 for Control Group and 4 for the Test Group, suggesting greater initial severity in the latter. After 15 days (T1), lesion severity decreased in both groups, with median scores of 2 (all the patients reported a TS of 2) in the Control Group, and 3 (Q1 = 2; Q3 = 3) in the Test Group. At 30 days (T2), a further improvement was observed in both groups. Both groups reported the same median, Q1, and Q3 values (all equal to 1). The interquartile range also narrowed at T2.

Overall, both groups were found to register clinically remarkable improvement over time, with the Test Group showing a slightly better reduction in TS, indicating good and potentially greater homogeneity in treatment response across both groups. No adverse effects were reported, and treatment adherence was satisfactory throughout the study period. However, given the limited sample size of the present pilot study, these preliminary in vivo findings warrant confirmation through larger, randomized double blind clinical trials.

Limitations of the pilot clinical study

The present study possesses some limitations that should be acknowledged. First, the small sample size ($n = 10$) limited the statistical power of the analysis and precludes robust statistical comparisons. For this reason, the results were primarily reported using descriptive statistics and should be interpreted as preliminary and hypothesis-generating.

Second, the study was not randomized or blinded. While this design reflects the exploratory nature of this pilot investigation, the absence of randomization and blinding may influence the interpretation of the clinical outcomes. However, it is important to emphasize that, as we made the ethical decision not to administer a placebo to patients with painful ulcerative lesions, the proposed study could not be conducted in a blinded manner. Indeed, the study was designed to evaluate the efficacy of an innovative formulation versus a conventional one, which differ markedly in their physical form, being solid and semisolid formulations, respectively, thus precluding the possibility of blinding.

Moreover, the difficulty in determining dose equivalence of CLB administered in the control group versus the test group should not be underestimated. The main issue lies in the poor dosing accuracy of semisolid formulations, as each subject may apply variable amounts of the preparation necessitating finger-mediated application.

Finally, the residence time of the patch in vivo was not systematically assessed. Preliminary preclinical observations using empty patches in healthy volunteers suggested a residence time ranging from approximately 20 min to about 1 h; however, in the clinical study, all patients were instructed to apply the device before going to sleep, which prevented a reliable estimation of the actual residence time. Moreover, no objective method for measuring device retention was included in the study design.

Overall, the findings should therefore be interpreted with caution, and further studies with larger cohorts will be useful to confirm the reported encouraging preliminary observations.

Conclusions

The proposed work is clearly aligned with the current interests of the scientific community and introduces several innovations compared to the recent state of the art. While early alternatives to semisolid formulations for OLP treatment were primarily represented by tablets [10], more recently researchers increased the focus on buccal films due to their superior performance in enhancing patient compliance and treatment adherence [11]. As highlighted in recent studies, the main challenge associated with the formulation of CLB-loaded buccal films lies in the poor

aqueous solubility of the drug, as only molecularly dispersed actives are readily available for retention within the mucosal tissues, where they can exert their therapeutic effect. The work by Racaniello et. in 2023 addressed this limitation through the use of hydroxypropyl-β-cyclodextrins [12]. Conversely, the technological innovation presented herein is particularly significant, as it successfully combines the need to enhance CLB solubilization with a more targeted oromucosal delivery strategy. This was achieved through an innovative approach based on lipid microparticles, specifically engineered to exhibit thermosensitive behavior, thereby serving not only as carriers for molecularly dispersed CLB but also as built-in penetration enhancers. Furthermore, the integration of this technology with buccal film formulations enables easy dose tailoring via film cutting, offering a promising platform for the development of a personalized therapeutic approach. Finally, it is worth emphasizing that the entire formulation strategy is consistent with the ever-growing principles of green chemistry, as both the production of the SLM-CLB and the final SiF_H-composite are entirely organic solvents-free.

From a clinical point-of-view, the proposed SiF_H-composite demonstrated clear superiority over the galenic semisolid formulation for several reasons: (i) it provides precise and reproducible drug dosing, which is not achievable with a semisolid preparation; (ii) the release of CLB, and consequently its absorption, does not depend on the semisolid vehicle selected each time by the physician or pharmacist; (iii) as a solid dosage form, it can be applied easily and consistently by the patient; (iv) therapy can be tailored, thereby modulating both the drug dose and the area of lesion coverage, an advantage that also facilitates dose tapering during the healing process.

However, these in vitro, ex vivo, and preliminary in vivo findings warrant confirmation through larger, randomized double blind clinical trials, which are already ongoing.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13346-026-02122-9.

Acknowledgements The authors thank Azienda Agricola Mulinello S.r.l. (EN) Sicilia, for supplying mucosal tissues from pigs and the veterinary Carmelo Giadone for their collection.

Author contributions Conceptualization and Supervision: Giuseppina Campisi, Viviana De Caro; Investigation and data curation: Giulia Di Prima, Maria Elena Mauceri, Martina Coppini; Formal analysis: Giulia Di Prima, Maria Elena Mauceri, Martina Coppini, Cecilia La Mantia; Funding acquisition, project administration and resources: Giuseppina Campisi, Viviana De Caro; Methodology: Giulia Di Prima, Maria Elena Mauceri, Cecilia La Mantia, Rodolfo Mauceri; Software and visualization: Giulia Di Prima, Maria Elena Mauceri; Validation: Rodolfo Mauceri; Writing – original draft: Giulia Di Prima, Maria Elena Mauceri, Cecilia La Mantia; Writing – review and editing: Rodolfo Mauceri, Giuseppina Campisi, Viviana De Caro.

Funding Open access funding provided by Università degli Studi di Palermo within the CRUI-CARE Agreement. This work was funded by Ministero dell'Università e della Ricerca and European Union—Next Generation EU, cod. PNRR M4.C2.1.1—2022CLLMCP_002 and funded by Ministero della Salute Project GENESIS- ATI, cod. T3-AN-11.

Data availability All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Competing interests The authors declare no competing interests.

References

1. Scully C, Carrozzo M. Oral mucosal disease: lichen planus. Br J Oral Maxillofac Surg. 2008;46:15–21. https://doi.org/10.1016/j.bjoms.2007.07.199.
2. Buchanan GA, Hayton AG, MacGregor J. Comment on urban et al. "Assessment of human health risks posed by consumption of fish from the Lower Passaic River (LPR), New Jersey" (2009, 10.1016/j.scitotenv.2009.03.004). Sci Total Environ. 2010;408:2002–3. https://doi.org/10.1016/j.scitotenv.2010.01.045.
3. Parashar P. Oral lichen planus. Otolaryngol Clin North Am. 2011;44:89–107. https://doi.org/10.1016/j.otc.2010.09.004.
4. Carrozzo M, Porter S, Mercadante V, Fedele S. Oral lichen planus: a disease or a spectrum of tissue reactions? Types, causes, diagnostic algorhythms, prognosis, management strategies. Periodontol 2000. 2019;80:105–25. https://doi.org/10.1111/PRD.12260.
5. Chan ES, Thornhill M, Zakrzewska JJ. Interventions for treating oral lichen planus. Cochrane Database Syst Rev. 2000. https://doi.org/10.1002/14651858.CD001168.
6. Mortazavi H, Amid R, Moscowchi A, Yousefi-Koma AA, Yousefi-Koma H. Differential diagnosis and treatment protocols for desquamative gingivitis: a systematic review. Dent Med Probl. 2024;61:747–58. https://doi.org/10.17219/DMP/156167.
7. Zheng T, Liu CY, Wang YT, Zhou R, Wu D, Tan J, et al. Efficacy and safety of topical clobetasol propionate in comparison with alternative treatments in oral lichen planus: an updated systematic review and meta-analysis. Front Med. 2024. https://doi.org/10.3389/FMED.2024.1391754.
8. Schroeder FMM, Pedraça ES, Palma VM, Carrard VC, Martins MAT, Maito FLDM, et al. Topical tacrolimus orabase versus topical clobetasol propionate orabase in the treatment of symptomatic oral lichen planus: a pilot randomized study. Clin Oral Investig. 2024. https://doi.org/10.1007/S00784-024-05943-5.
9. Mauceri ME, Coppini M, De Caro V, Di Prima G, Mauceri R, Panzarella V, et al. Mucoadhesive drug delivery systems for oral

chronic inflammatory mucosal diseases. The future is already present. A systematic review. Oral Dis. 2025. https://doi.org/10.1111/ODI.70042.
10. Cilurzo F, Gennari CGM, Selmin F, Epstein JB, Gaeta GM, Colella G, et al. A new mucoadhesive dosage form for the management of oral lichen planus: formulation study and clinical study. Eur J Pharm Biopharm. 2010;76:437–42. https://doi.org/10.1016/j.ejpb.2010.07.014.
11. Brennan MT, Madsen LS, Saunders DP, Napenas JJ, McCreary C, Ni Riordain R, et al. Efficacy and safety of a novel mucoadhesive clobetasol patch for treatment of erosive oral lichen planus: a phase 2 randomized clinical trial. J Oral Pathol Med. 2022;51:86–97. https://doi.org/10.1111/JOP.13270.
12. Racaniello GF, Pistone M, Meazzini C, Lopedota A, Arduino I, Rizzi R, et al. 3D printed mucoadhesive orodispersible films manufactured by direct powder extrusion for personalized clobetasol propionate based paediatric therapies. Int J Pharm. 2023. https://doi.org/10.1016/j.ijpharm.2023.123214.
13. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery–a promising option for orally less efficient drugs. J Control Release. 2006;114:15–40. https://doi.org/10.1016/j.jconrel.2006.04.012.
14. He S, Mu H. Microenvironmental pH modification in buccal/sublingual dosage forms for systemic drug delivery. Pharmaceutics. 2023. https://doi.org/10.3390/PHARMACEUTICS15020637.
15. De Caro V, Angellotti G, D'Agostino F, Di Prima G. Buccal thin films as potent permeation enhancers for cytisine transbuccal delivery. Membranes (Basel). 2022. https://doi.org/10.3390/MEMBRANES12111169.
16. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian J Pharm Sci. 2008;70:43. https://doi.org/10.4103/0250-474X.40330.
17. Marxen E, Axelsen MC, Pedersen AML, Jacobsen J. Effect of cryoprotectants for maintaining drug permeability barriers in porcine buccal mucosa. Int J Pharm. 2016;511:599–605. https://doi.org/10.1016/j.ijpharm.2016.07.014.
18. Del Consuelo ID, Pizzolato GP, Falson F, Guy RH, Jacques Y. Evaluation of pig esophageal mucosa as a permeability barrier model for buccal tissue. J Pharm Sci. 2005;94:2777–88. https://doi.org/10.1002/JPS.20409.
19. De Caro V, Giandalia G, Siragusa MG, Sutera FM, Giannola LI. New prospective in treatment of Parkinson's disease: studies on permeation of ropinirole through buccal mucosa. Int J Pharm. 2012;429:78–83. https://doi.org/10.1016/j.ijpharm.2012.03.022.
20. Teresi JA, Yu X, Stewart AL, Hays RD. Guidelines for designing and evaluating feasibility pilot studies. Med Care. 2022;60:95–103. https://doi.org/10.1097/MLR.0000000000001664.
21. Thongprasom K, Luangjarmekorn L, Sererat T, Taweesap W. Relative efficacy of fluocinolone acetonide compared with triamcinolone acetonide in treatment of oral lichen planus. J Oral Pathol Med. 1992;21:456–8. https://doi.org/10.1111/J.1600-0714.1992.TB00974.X.
22. Unnikrishnan SP, Rampersaud E, Mcgee A, Cruickshank ME, Abu-Eid R, Hijazi K. Disease severity scoring systems in mucosal lichen planus: a systematic review. Oral Dis. 2023;29:3136–51. https://doi.org/10.1111/ODI.14447.
23. Campisi G, Giandalia G, De Caro V, Di Liberto C, Aricò P, Giannola LI. A new delivery system of clobetasol-17-propionate (lipid-loaded microspheres 0.025%) compared with a conventional formulation (lipophilic ointment in a hydrophilic phase 0.025%) in topical treatment of atrophic/erosive oral lichen planus. A phase IV, ran…. Br J Dermatol. 2004;150:984–90. https://doi.org/10.1111/J.1365-2133.2004.05943.X.
24. De Caro V, Giannola LI, Di Prima G. Solid and semisolid innovative formulations containing miconazole-loaded solid lipid microparticles to promote drug entrapment into the buccal mucosa. Pharmaceutics. 2021. https://doi.org/10.3390/PHARMACEUTICS13091361.
25. Brubaker J, Moghtadernejad S. A comprehensive review of the rheological properties of powders in pharmaceuticals. Powders. 2024;3(2):233–54. https://doi.org/10.3390/powders3020015.
26. Subramanian P, Subramanian P. Mucoadhesive delivery system: a smart way to improve bioavailability of nutraceuticals. Foods. 2021;10:10. https://doi.org/10.3390/FOODS10061362.
27. Pestana AM, Calixto GMF, Bezerra AAC, de Morais Ribeiro LN, da Costa AC, Moraes ÂM, et al. Analysis of key factors for evaluating mucosal adhesion using swine buccal tissue. J Pharm Sci. 2024;113:2413–9. https://doi.org/10.1016/j.xphs.2024.04.018.
28. Meng-Lund E, Marxen E, Pedersen AML, Müllertz A, Hyrup B, Holm R, et al. Ex vivo correlation of the permeability of metoprolol across human and porcine buccal mucosa. J Pharm Sci. 2014;103:2053–61. https://doi.org/10.1002/JPS.24010.
29. Alopaeus JF, Hellfritzsch M, Gutowski T, Scherließ R, Almeida A, Sarmento B, et al. Mucoadhesive buccal films based on a graft co-polymer – a mucin-retentive hydrogel scaffold. Eur J Pharm Sci. 2020;142:105142. https://doi.org/10.1016/J.EJPS.2019.105142.
30. Müller L, Rosenbaum C, Krause J, Weitschies W. Characterization of an in vitro/ex vivo mucoadhesiveness measurement method of PVA films. Polymers. 2022. https://doi.org/10.3390/POLYM14235146.
31. De Caro V, Murgia D, Seidita F, Bologna E, Alotta G, Zingales M, et al. Enhanced in situ availability of *Aphanizomenon flos-aquae* constituents entrapped in buccal films for the treatment of oxidative stress-related oral diseases: biomechanical characterization and in vitro/ex vivo evaluation. Pharmaceutics. 2019;11:35. https://doi.org/10.3390/pharmaceutics11010035.
32. Di Prima G, Conigliaro A, De Caro V. Mucoadhesive polymeric films to enhance barbaloin penetration into buccal mucosa: a novel approach to chemoprevention. AAPS PharmSciTech. 2019. https://doi.org/10.1208/s12249-018-1202-1.
33. Popov VL. Adhesion hysteresis due to chemical heterogeneity. Springer Tracts Mech Eng 2021;473–483. https://doi.org/10.1007/978-3-030-60124-9_20/FIGURES/6
34. Jones DS, Laverty TP, Morris C, Andrews GP. Statistical modelling of the rheological and mucoadhesive properties of aqueous poly(methylvinylether-co-maleic acid) networks: redefining biomedical applications and the relationship between viscoelasticity and mucoadhesion. Colloids Surf B Biointerfaces. 2016;144:125–34. https://doi.org/10.1016/j.colsurfb.2016.03.008.
35. Raos G, Zappone B. Polymer adhesion: seeking new solutions for an old problem#. Macromolecules. 2021;54:10617–44. https://doi.org/10.1021/ACS.MACROMOL.1C01182.
36. Chen LM, Wang B, Zhou YF, Wu MH. Chemical stability of the aqueous clobetasol propionate solution. J China Pharm Univ. 2006;37:226–9.