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Exploring new buccal films based on hydroxyethyl cellulose and Linecaps® combination for the pediatric delivery of hydrophobic molecules

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ABSTRACT

Polysaccharides and starch derivatives can play a role in the development of buccal films and patches. Buccal films are a valid approach to the transmucosal administration of drugs. These drug-delivery systems are adaptable to the mucosal surface, while being particularly suitable for the pediatric population. This study explores the combination of polysaccharide-based films for the buccal administration of the poorly soluble drug, ibuprofen. The films were obtained *via* the freeze-thaw technique using an innovative combination of two film-forming polymers of natural origin, *i.e.* hydroxyethylcellulose and a pea starch derivate (Linecaps®). Ibuprofen was selected as model drug to be loaded into the buccal formulation as a β-cyclodextrin complex. The produced films showed good physico-chemical and functional properties including homogeneous drug content, thickness, mechanical strength, mucoadhesion, thus guaranteeing suitable drug loading and applicability. *In vitro,* permeation studies of Ibuprofen buccal films were carried out using a synthetic biomimetic membrane, and rabbit mucosae tissue exhibited values of permeability fluxes in the same order of magnitude for the two tested membranes ($1.51 \times 10^{-2} \pm 0.33 \times 10^{-2}$ μg/cm^2*s *vs* $1.21 \times 10^{-2} \pm 0.18 \times 10^{-2}$ μg/cm^2*s).

The release of the drug from the buccal film, the taste-masking and permeation properties suggested that the proposed combination of polysaccharides represent a potential formulation of mucoadhesive buccal films.

1. Introduction

Natural-derived polysaccharides have attracted research attention for the development of buccal formulations due to their biocompatibility, film-forming capability and mucoadhesive properties (Guru et al., 2023; Yu et al., 2018). Buccal drug administration is an attractive route for the systemic delivery of drugs and one that presents a series of advantages over traditional oral administration (Nair et al., 2023; Shipp et al., 2022). Specifically, the use of this administration route in the pediatric population is continuously increasing due to the ease of administration and the substantial enhancement in patient compliance (Abruzzo et al., 2017; Montero-Padilla et al., 2017; Rathbone et al., 2015). Indeed, the buccal route avoids hepatic first-pass metabolism (Adhikari et al., 2010), and gastrointestinal (GI) enzymatic degradation, allows administration to a highly vascularized area without enzymatic activity, and displays rapid action onset and quick elimination after detaching the dosage form (Lam et al., 2014; Patel et al., 2011). Several formulations, such as capsules, lozenges, tablets, sprays, mouthwashes, gels and, recently, films have been designed for buccal drug delivery over the past decades (Lee et al., 2000; Montenegro-Nicolini and Morales, 2017). In this context, orally dissolving films (ODFs) have attracted particular attention as potential delivery systems for drug administration in the pediatric population (Ouda et al., 2020). Notably, the solid dosage forms specifically developed for administration to this population should comply with a series of requirements including acceptability, palatability, minimal dosing frequency, dose titration, possibility of weight-based dosing and easy administration. Furthermore, the excipients used should also be safe for the pediatric population (EMA, 2013; Ernest et al., 2010; Strickley et al., 2008; World Health Organization, 2005). Mucoadhesive buccal films are flexible, easily

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adaptable to the surface of mucosa, thin, soft and developed to offer both local and systemic drug effects, resulting in an extended duration of activity (Aframian et al., 2006; Shady et al., 2022). Moreover, these dosage forms can disintegrate and dissolve quickly without the need of water and can withstand the damage caused by mouth movements (Borges et al., 2015; Dixit and Puthli, 2009; Krampe et al., 2016), making them suitable for the use in children. Additionally, buccal administration can overcome the difficulties associated with swallowing conditions, such as dysphagia, that are observed with the use of tablets and capsules, as well as the unpleasant taste and inaccurate dosing observed with solution-based dosage forms (Ahmady and Abu Samah, 2021; Padhi et al., 2020). Furthermore, the buccal films can successfully ensure prolonged contact between the drug and the buccal epithelium due to the close interaction between the absorption site and the drug-rich surface of the film (Boddupalli et al., 2010; Sudhakar et al., 2006). The particular mucoadhesive properties of specific buccal films depend on the polymer/s employed (Bala et al., 2013; Ritu et al., 2014). Hydroxyethyl cellulose (HEC), hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) are examples of cellulose derivatives that are usually adopted in the preparation of buccal films (Priyanka and Senthil Prabhu, 2020). Moreover, polymer concentration is an additional important parameter to consider when developing films with successful mechanical properties, drug loading capacity and disintegration times (Borges et al., 2015). From a technological point of view, films containing polymeric matrices are fabricated to be rapidly disintegrated in the mouth (Mfoafo et al., 2021). There are several examples of this technology applied to the administration of different molecules for children. Mucoadhesive buccal films based on chitosan blended with HPMC, methylcellulose (MC), HEC and polyvinyl alcohol (PVA), containing cetylpyridinium chloride demonstrated high antimicrobial activity against *Streptococus mutans* for the treatment of dental caries, gingivitis, aphthous ulcers and periodontitis (Abouhussein et al., 2020). Similarly, a polymeric buccal film loaded with ondansetron hydrochloride, a selective inhibitor of the 5-HT3 receptor, is able to prevent and treat nausea and vomiting associated with postoperative cytotoxic chemotherapy and radiotherapy in the pediatric population (Trastullo et al., 2016). Furthermore, it was also found that buccoadhesive films of gliclazide are suitable for the treatment of type II diabetes in children (Gaber et al., 2022). Moreover, a buccal film composed of ethanolic and aqueous films using sodium alginate (SA), HPMC, MC and carrageenan (CA), containing omeprazole have been developed (Khan et al., 2015). Additionally, propranolol hydrochloride has been loaded on a bi-layered buccal films formed by a blend of polyvinylpyrrolidone (PVP), PVA, chitosan and gelatin, with a back layer of insoluble ethylcellulose, to avoid the release of the drug in the oral cavity (Abruzzo et al., 2017). Ibuprofen (IB) is a nonsteroidal anti-inflammatory molecule conventionally used to reduce pain, fever and inflammatory deceases, such as rheumatoid arthritis (Rainsford, 2007). IB belongs to Class II of the biopharmaceutical classification system (BCS). It is a weak acid (pKa = 4.4) with water solubility of around 20 μg/mL (Park and Choi, 2006; Stoyanova et al., 2016) and for this reason it was selected as model drug. The formation of complexes with cyclodextrins (CDs) is a viable approach to enhancing IB solubility and release rate (Frömming and Szejtli, 1994; Hussein et al., 2007). This, in turn, has the potential to increase bioavailability (Argenziano et al., 2019; Argenziano et al., 2023; Di Cagno et al., 2011; Pereva et al., 2020; Yang et al., 2016). Indeed, mucoadhesive buccal patches of IB have been proposed as a new therapeutic dosage form against buccal and dental diseases. The films were fabricated using the casting method with carboxymethylcellulose sodium salt (NaCMC) and PVP. The results show that no irritation occurred and that IB was detected in saliva for 5 h (Perioli et al., 2004). Similarly, Kianfar et al. (Kianfar et al., 2011) demonstrated that IB undergoes fast released from carrageenan- and poloxamer-based bioadhesive films). We propose the use of Linecaps®, a pea starch derivative consisting of linear and soluble amylose chains, containing α-helix structures (Fig. 1) that possess a hydrophilic external surface and a hydrophobic internal cavity able to complex lipophilic molecules showing taste-masking properties (Tannous et al., 2022). Linecaps® can be considered a "green" excipient, and its use might allow for the reduction of the amount of CD that present dose-limitation for pediatric use (EMA, 2017). The objective of the present work is therefore the development of pediatric buccal films for poorly soluble drugs delivery using natural components in a solvent-free manufacturing process. We hypothesize that a new buccal drug delivery system can be obtained by exploiting a novel combination of biocompatible, natural-derived polysaccharides and cyclodextrins. The feasibility of exploiting this hydrophilic matrix for the fast release of poorly water-soluble molecules, such as IB, is here investigated. For the buccal film preparation, a solvent-free manufacturing process based on freeze-thaw technique was developed using a combination of HEC and Linecaps®. Furthermore, we suggest that a thin, flexible film might be a more acceptable dosage form for children, improving compliance. The study focuses on the *in vitro* film characterization, including physico-chemical and functional properties, mucoadhesion, and drug permeation behavior. The drug transmucosal uptake from the newly formulated film was investigated *in vitro* using both a synthetic biomimetic membrane and rabbit buccal mucosa, while additional biological evaluations (*e.g. in vivo* studies, antimicrobial and thrombogenic activity) can be addressed in future investigations.

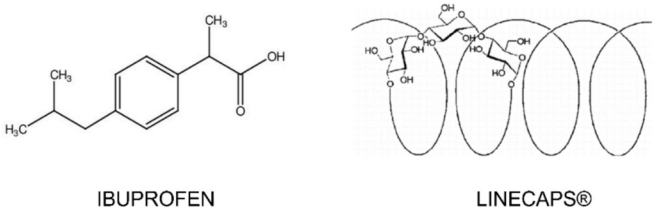

Fig. 1. Chemical structure of IB and Linecaps®.

2. Material and methods

2.1. Materials

All solvents were HPLC grade. Methanol and ethanol were purchased from VWR Chemicals (BDH Prolabo®, Europe). IB, potassium dibasic phosphate, potassium dihydrogenphosphate, glycerol and sorbitol were obtained from Sigma-Aldrich (St. Louis, Missouri, USA). Deionized and MilliQ® water were produced using a Millipore system. Beta-cyclodextrin (β-CD) and KLEPTOSE® LINECAPS 17 pea maltodextrin (LC) (Mw = 11,500 g/mol, viscosity in water 0.25 Pa.s for 50 g of dry substance/100 g of solution) were a kind gift from Roquette Frères S.p.a (Lestrem, France). Hydroxyethylcellulose (HEC) Mw = ~250.000 g/mol, viscosity 90–160 cP, 5 % in H_2O (25 °C) was obtained from Serva, Feinbiochemica-Heidelberg (Germany). The synthetic biomimetic membranes (Permeapad®) were provided by Phabioc InnoME GmbH (Espelkamp, Germany).

2.2. IB and β-cyclodextrin inclusion complex preparation

β-CD was dissolved in water and IB was added at a stoichiometric molar ratio of 1:1 in order to give 0.5 g of complex. The complex (IB-β-CD) was agitated under magnetic stirring for 48 h at room temperature. The samples were then centrifuged at 60000 rpm for 20 min and the supernatant was collected and freeze-dried. The lyophilized IB-β-CD complex was stored in a closed glass container at 25 °C (room temperature).

2.3. Development of IB buccal Films

The new polysaccharide-based buccal films were fabricated using the

freeze-thaw technique; specifically using hydroxyethyl cellulose (HEC) and Linecaps®, a pea starch derivative. Aqueous solutions of Linecaps® (1.8 % *w/v*) and HEC (1.5 % w/v) were separately dispersed and stirred slowly using a magnetic stirrer to obtain homogenous systems. The HEC aqueous mixture was heated at 90 °C for 2 h until a clear a viscous solution appeared. Then, 0.5 % (*w/v*) of glycerol or sorbitol (used as plasticizers), were added to each polymer solution under continuous stirring. The resultant solutions were mixed, sonicated for 15 min and left to stand at room temperature for 30 min to avoid the presence of air bubbles. Subsequently, 15 mL of each polymeric solution was spread onto a Petri dish (diameter = 8.5 cm), frozen at −20 °C for 20 h and then thawed for 4 h at 25 ± 1 °C (Sarheed et al., 2015). The freeze-thaw cycle was repeated twice. After the freeze-thaw cycles, films were dried at 25 °C for 48 h. The drug-loaded films were developed using the same procedure, but with the addition of 100 mg of the IB-β-CD complex solution to Linecaps®. Then, in order to formulate a child-appropriate dosage form, circle samples (surface area = 2 cm^2) were cut and stored at room temperature for a period of 6 months. Film composition is listed in Table 1.

2.4. Characterization of IB buccal films

2.4.1. Variation in weight

For the evaluation of film weight, three films of 2 cm^2 were individually weighed using a digital balance (AG245, Mettler Toledo). The average weights were calculated.

2.4.2. Film thickness

A micrometer screw gauge (Mitutoyo MMO-25DS) was employed for the thickness measurements of three different sections (upper, middle and lower part).

2.4.3. Uniformity of IB content

To guarantee even IB distribution in the developed films, content uniformity was measured. In these studies, each film was obtained from a Petri dish (diameter = 8.5 cm) and considered as a single batch. Three different batches were then prepared for each formulation. The dissolution of one circle (2 cm^2) from each batch in 25 mL of MeOH was performed in order to calculate IB content. To support the complete solubilization of the polymer matrix and the drug, the sample was sonicated for 2 h and then left to rest overnight. The IB amount inside the prepared film was quantified using a UV spectrophotometer at λ = 270 nm. The theoretical amount of drug in each circle was 0.80 mg/cm^2. The experimentally determined amounts of the active ingredients in formulations A and B were 0.78 ± 0.06 mg/cm^2 and 0.74 ± 0.11 mg/cm^2, respectively.

2.4.4. IB-film flexibility

Three films with a surface area of 2 cm^2 were selected randomly and folded until cracking occurred at the same position. Folding endurance is expressed as the number of folds before a film broke (Preis et al., 2012).

2.4.5. IB-film disintegration time

The disintegration time for all of the prepared films was evaluated using a method mentioned by Rawas et al. (Rawas-Qalaji et al., 2006) with a slight modification. The disintegration medium consisted of simulated saliva solution (pH 6.8). A 2 cm^2 section of film of each formulation was placed on a Petri dish with 1 mL of simulated saliva solution. Complete disintegration of the film was observed visually and was recorded using a stop watch. Three repetitions were performed.

Table 1
Formulation composition (% w/v), experimental amounts of ingredients used for the preparation of the tested buccal films.

FORMULATION	HEC (%w/v)	Linecaps® (%w/v)	Glycerol (%w/v)	Sorbitol (%w/v)	IB-β-CD (%w/v)
Buccal Film A	1.5	1.9	1.0	/	0.3
Buccal Film B	1.5	1.9	/	1.0	0.3

2.4.6. IB-film swelling capacity

A portion of the films with a surface area of 2 cm^2 and predetermined mass (m_1) was placed in a Petri dish, immersed in 1 mL of simulated saliva (pH = 6.80) at RT and allowed to swell. After 10 min the excess of simulated saliva on the film surface was removed and the film mass (m_2) was measured. The swelling capacity (%) represents the mass gained in respect to the mass of a dry film and was calculated according to following equation: Swelling (%) $= \frac{(m_2 - m_1)}{m_1} \times 100$.

The experiment was performed in triplicates.

2.4.7. In vitro adhesion test

A texture analysis of IB formulations was performed using an *in vitro* adhesion assay with mucin as the adherent substrate. The surface tension of samples was evaluated using a tensiometer (du Noüy interfacial tensiometer). Instrument calibration using distilled water was performed prior to use. During the test, samples were set at 25 °C. Measurements were repeated three times. Briefly, a mucin solution (10 mg/mL) was prepared, spread on a 50 cm × 10 cm glass support and the surface tension of the medium was determined. Afterwards, 0.5 mL of each IB sample solution that was prepared for film formulation was mixed with 10 mL of mucin solution and placed onto a glass support. The surface tension of these mixtures was then measured.

2.4.8. Stability studies

The IB-films were stored up to 6 months at room temperature in a Petri dish and characterized over time by determining film weight, thickness, folding endurance, erosion time and drug content. In addition, the morphology of the films was evaluated after 6 months by scanning electron microscopy (SEM) using a FESEM Tescan S9000G microscope. The samples were mounted onto stubs using double sided adhesive tape and observed after Au metallization.

2.5. Physico-chemical properties

2.5.1. ATR fourier transform infrared spectroscopy

The ATR Fourier Transformed Infrared (ATR-FTIR) spectra of IB, the IB-β-CD complexes and the films were carried out using a Perkin Elmer Spectrum 100 FTIR, equipped with software version 10.03.05 (Perkin Elmer Corporation). The analyzed range was 4000–650 cm^{-1}.

2.5.2. Differential scanning calorimetry

To determine the thermal characteristics of the polysaccharide films, differential scanning calorimetry (DSC) analysis was performed on a Perkin Elmer DSC/7 differential scanning calorimeter equipped with a TAC 7/DX instrument controller. Indium was used for instrument calibration for melting point and heat of fusion measurements. Thermal analyses were performed under a nitrogen purge at a heating rate of 10 °C min between 25 and 150 °C. Samples (about 10 mg) were placed in a standard aluminum sample pan. The thermal peaks are the mean of three measurements.

2.5.3. Determination of buccal film pH value

The circle samples were soaked with 1.0 mL artificial saliva in a beaker and pH was determined after 30 min using an Orion pHmeter.

2.6. In vitro permeation studies

2.6.1. Permeation profiles of IB buccal films using the biomimetic barrier

Franz cells with a receptor chamber of 9.0 mL and an exposed area of 2 cm^2 were used for the permeation studies of IB buccal films. The

biomimetic membrane was placed with the filter side facing the donor chamber and the regenerated-cellulose side facing the receptor chamber. Potassium phosphate buffer (1 M, pH 6.5) was freshly prepared by dissolving 47.50 g of KH_2PO_4, and 26.25 g of K_2HPO_4 into 500 mL of MilliQ water (final pH = 6.5) and was used as receptor fluid (RF) and agitated under magnetic stirring. The temperature of the water bath was 37 ± 1 °C. Firstly, IB buccal films (the experimental amount of the active ingredient in each film is given in section 2.4.3) were applied as donors to the Franz cell before the two Franz cell compartments were sealed and fastened together using a clamp. This corresponds to $Q_0 = 0.80$ mg/cm^2 (theoretical applied dose). At a predetermined time (0, 5, 10, 15, 20, 30, 45, 60, 120, 180, 240 min), 9.0 mL was withdrawn from the receptor chamber and replaced with fresh RF in order to maintain sink conditions. Experiments were conducted in six replicates. The contents of IB present in the receptor compartment, as well as in the synthetic barriers, were analyzed by HPLC, as described in paragraph 2.6.4.

2.6.2. Retention and permeation studies of IB films through rabbit buccal mucosa

The buccal mucosa of rabbits was adopted to study the absorption of IB from the buccal films and the residence time. The permeation assays were conducted following the same procedure, as reported above (see section 2.6.1.), but with the biomimetic membrane being replaced by the rabbit buccal tissue. The buccal mucosal membrane was isolated from buccal cavity of died rabbits received as waste from a local slaughterhouse. The surrounding tissue was removed from the buccal mucosa using a sharp scalpel, and the specimens (surface area 2 cm^2) were frozen at −20 °C. Mucosae with any visual damage at the surface were discarded. On the day of the experiment, the mucosae tissue was defrosted and thawed, in physiological solution, for 15 min at room temperature. The mucosae tissue (2.8 mm thick) was fixed between the two chambers (surface area = 2 cm^2). At time 0, films loaded with IB (the experimental amount of the drug in each film formulation is reported in section 2.4.3) were attached to the rabbit mucosa. Potassium phosphate buffer at pH = 7.4 was adopted as receptor fluid and the temperature of the water bath was 37 ± 1 °C. A 9 mL sample was withdrawn from the receptor chamber at fixed time points for analysis (0, 5, 10, 15, 20, 30, 45, 60, 120, 180, 240 min) and immediately replaced with fresh RF to maintain sink conditions. The experiments were performed in triplicate. The contents of IB observed in the receptor compartment and those retained in the mucosae tissue were determined by HPLC (paragraph 2.6.4). To evaluate the film retention the time required for the removal of the buccal film from the rabbit mucosa after the addition of artificial saliva solution was determined.

2.6.3. Treatment of samples

The Franz cells were dismantled after 4 h of contact time and the receptor fluid was collected. The artificial membrane surface and the mucosae tissue were washed with 3.0 mL of MilliQ water. The samples were then transferred to a Falcon and 5.0 mL MeOH was added. The mucosae tissues were cut to leave only the exposed surface area (2 cm^2). The explant of mucosae tissue was cut with a scalpel, immersed in 10 mL of MeOH, stirred for 2 h and centrifuged at 60000 rpm for 10 min. Before HPLC analysis, the supernatant was diluted 1:10 in MeOH. The mucosae tissue was homogenized with 5.0 mL of MeOH for 20 min, sonicated for 30 min and stirred overnight (15 h) at room temperature. Then, centrifugation at 60000 rpm was performed for 10 min to separate the supernatant, which was collected and diluted 1:20 in MeOH for HPLC quantification. Three extractions of the tissue were performed. Aliquots were collected, filtered using a 0.45 μm polypropylene filter and quantified by HPLC. The experiments were performed in three replicates. Alternatively, biomimetic membranes were cut and immersed in 2.0 mL of MeOH. Afterward, the samples were incubated overnight and diluted 1:10 in MeOH. The extraction of IB from the synthetic barriers was performed at room temperature overnight, and IB contents were subsequently analyzed by HPLC.

2.6.4. HPLC determination of IB

The quantification of IB was performed using an HPLC system consisting of a PerkinElmer PUMP 250B, equipped with a Flexar UV/Vis LC spectrophotometer detector. The analysis was performed using an Agilent TC C18 reversed phase column (150 mm × 4.6 mm, pore size 5 μm) at a column temperature of 23 °C. The mobile phase consisted of 0.1 % phosphoric acid, water and acetonitrile (40:60, *v*/v) at a flow rate of 1.0 mL/min and the detection wavelength was 270 nm. The IB retention time was 4.8 ± 0.02 min. The IB calibration curve was linear (R^2 = 0.999) in 0.1–15 μg/mL (concentration range).

2.6.5. Permeability calculations

The steady-state flux was determined from the cumulative contents of IB that permeated through the membrane divided by the time and the membrane surface area, as in Eq. 1 (Hopf et al., 2020):

$$J = \frac{dQ}{A*dt} \quad (1)$$

The apparent permeability coefficient (P_{app}) (cm/s) was obtained from flux J (μg/cm^2*s) and the drug concentration in the donor compartment (μg/cm^3), as shown in Eq. 2:

$$P_{app} = \frac{J}{C_d} \quad (2)$$

The resistivity to permeation (R) (s/cm), was determined utilizing Eq. 3:

$$R = \frac{1}{P_{app}} \quad (3)$$

2.7. In vitro cytocompatibility assay of IB films

Keratinocyte cells (HaCat) were used to determine the cytotoxicity and biocompatibility of the IB films. Cells were cultured in a 6-well-plate at a density of 0.5× 10^6 cells/mL and incubated at 37 °C using 5 % CO_2 in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10 % fetal bovine serum (FBS), 1 % antibiotics and 2 mM glutamine. After overnight incubation, cells were exposed to IB film solutions at different concentrations for 24 h. Cell viability was evaluated by MTT assay. The experiments were repeated in triplicate and analyzed using a microplate reader at 570 nm.

2.8. Hemolytic activity determination of IB films

The biocompatibility of IB film solutions was evaluated using hemolysis tests. The determination of hemolytic activity was performed using rat blood that was diluted (1:10 v/v) with PBS pH 7.4. Notably, the samples at different ratios (1:25, 1:50, 1:100, v/v) were incubated at 37 °C using 1 mL of diluted blood for 90 min and subsequently centrifuged for 10 min at 2000 rpm. Due to hemolysis, the hemoglobin content in the supernatant was spectrophotometrically measured at 543 nm. The hemolytic activity was measured comparing negative control and hemolyzed samples (induced through the addition of Triton X-100 1 % *w/v* to the blood, adopted as positive control).

2.9. Taste-masking evaluation by electronic tongue

The samples (ibuprofen solution, buccal film A and buccal film B) at IB concentration of 0.1 mg/mL, were analyzed with an IoT compliant low power portable e-tongue exploiting Wi-Fi connection for data transfer (Stighezza et al., 2025). The system was preliminarily validated using a placebo formulation. Metrohm DropSens DRP-110GNP screen printed electrodes were used. A Differential Pulse Voltammetry (DPV) was used for scanning: the potential was varied between 0 V and 1.3 V, with the IoT potentiostat set with a pulse amplitude of 50 mV, a step potential of 2 mV, a pulse time of 400 ms, an interval time of 500 ms. A

preconditioning time of 1 s was applied before starting the scan.

2.10. Statistical analysis

The data sets related to the absorption tests are shown as mean ± standard error of the mean (SEM) and normalized to the thickness of the biomimetic membrane. Statistically significant differences were determined between two groups using the Student *t*-test with probability (*p*) values <0.05. No ANOVA or multiple comparison corrections were applied, as only pairwise comparisons were performed.

3. Results and discussion

3.1. Formation and evaluation of buccal films

This study presents an investigation into a new combination of polysaccharides that can be used to produce mucoadhesive buccal films for the delivery of a hydrophobic drug to pediatric patients. We selected IB as model drug due to its low water solubility and pediatric use. In order to enhance the water solubility IB was complexed in β-CD and incorporated in the film matrix. Two non-irritant and non-toxic natural-derived polysaccharide polymers, HEC and Linecaps®, which is a pea starch derivative, were explored (Fig. 1).

The combination of Linecaps® and β-CD could be a strategy to produce taste-masked buccal films for children. Cyclodextrin capability to reduce the taste perception of bitter drugs is well-known (Guo et al., 2017). Indeed, CD can form inclusion complexes with guest molecules modifying their properties. The IB complexation in the β-CD cavity can create a barrier around the drug avoiding the interaction with taste buds. The extent of taste masking is related to the amount of free drug available in the formulation. We speculated that Linecaps® might complex the amount of free IB. Indeed, Linecaps® datasheet from Roquette reports the taste-masking capability of this pea starch derivative (Kleptose Linecaps DataSheet, 2025). The use of two excipients with taste-masking properties may produce a greater modulation of the drug taste than the β-CD complex. A formulation with a good taste-masking capability can play a crucial role in the development of pediatric buccal films (Walsh et al., 2014). HEC is a non-ionic polysaccharide derivative of cellulose and is a compendial excipient largely used in the pharmaceutical industry as a coating agent, suspending agent, tablet binder and thickener. It's a polysaccharide with a linear chain of glucose subunits linked by β(1–4) glycosidic bonds. Furthermore, buccal films containing HEC combined with other polymers have previously been reported (Arslan et al., 2022; Senta-Loys et al., 2017). Interestingly, the α-helix architecture combined to the short chain length of Linecaps® might favor the entanglement of the polymer chains and thus increase the cohesion of the polymer matrix. Supporting our hypothesis, the two-polymer combination produces flexible

and mucoadhesive buccal films. The freeze-thaw technique, also known as cryo-gelation has been adopted to formulate buccal films, while avoiding the use of any solvents. Indeed, the safety and biopharmaceutical problems of commonly used solvents represent a key point for the development of pediatric formulations. This preparation technique is based on three steps; the mild freezing of a polymer solution, storage in the frozen state and its thawing (Anowaar et al., 2020; Szekalska et al., 2019). Polymeric combinations provide film formulations that are easy to handle without any damage from the support, as well as showing good storage stability. Additionally, two humectants and plasticizers, namely glycerol and sorbitol, were incorporated into the films, and these excipients led to higher homogeneity and flexibility in film formulations compared to the films without these excipients, while helping to maintain moisture content (Malik et al., 2022). The addition of glycerol and sorbitol as plasticizer in buccal film formulations has been previously reported, showing improved matrix performance (Alrimawi et al., 2021; Paolicelli et al., 2018). Indeed, glycerol and sorbitol can affect mechanical and swelling properties of the formulation. Here, sorbitol was compared to glycerol to evaluate the effect of increased number of hydroxyl groups of sorbitol (6 *vs* 3, respectively) on the hydration and swelling capability of polysaccharide film, as well as the drug release kinetics. Placebo films were initially produced for preliminary tests and the most promising formulations were selected to be loaded with IB incorporation as β-CD inclusion complexes. The complexation of IB with several β-cyclodextrins has been well documented, in the literature, to improve the water solubility and quicken the dissolution of such molecules (Di Cagno et al., 2011; Pereva et al., 2016; Salústio et al., 2011; Upadhyay et al., 2023).

Buccal film compositions are summarized in Table 1 (see paragraph 2.3), whereas the results as to the characteristics of the prepared films loaded with the IB-β-CD complex are reported in Table 2.

The presence of β-CD complex did not affect the physico-chemical properties of the films.

The data demonstrate that the weight values of films were not significantly different ($p > 0.05$), exhibiting the good repeatability of the preparation technology employed (Begum et al., 2021; Nair et al., 2013). Film thickness is an important parameter affecting the mechanical properties of, and drug release from, films (Iqbal et al., 2023). In the present study, the two formulations exhibited similar thickness values of around 150 ± 0.5 μm (Table 2). The thinness of films makes them suitable for the buccal cavities of the pediatric population, meaning that they are less obtrusive, more tolerable and thus may increase compliance in younger patients (Montero-Padilla et al., 2017; SeviNç Özakar and Özakar, 2021). The film size can be modulated according to the patient's age. Importantly, our results demonstrate that the experimental drug content measured from each film was found to be close to the theoretical value (0.8 mg/cm^2 see Table 2), suggesting that the selected preparation method is effective for creating homogenous drug distribution in the formulation. These results are in line with the amounts of IB for cm^2 obtained with polysaccharide-based buccal films prepared by solvent casting (Bolko Seljak et al., 2025). Moreover, the measurement of IB content in the formulated films allowed us to calculate the recovery percentage, which ranged from 92.5 ± 1.3 % for film B to 97.5 ± 1.6 % for film A. The pH values of the two buccal films are about 7.0. The elasticity and mechanical strength of the films were determined by the folding endurance (Nair et al., 2013). The folding endurance value indicates the number folds that can be performed before a film breaks. It is a key parameter in the formulation process and one that evaluates the durability and pliability of the designed films. Our data shows that the two buccal films retained high endurance values (>100 times), exhibiting good flexibility (Table 2) (Bîrsan et al., 2018). Notably, they exhibited similar values; 137 ± 0.2 for film A (containing glycerol) and 139 ± 0.1 for film B (containing sorbitol) (Table 2). A mechanically strong film should be able to resist tearing and detachment from the site to which it is applied. Subsequently, the disintegration time of the films was also monitored using the simulated saliva, which imitates the conditions in the human mouth. This parameter is a crucial characteristic and affects drug release. Indeed, when the film comes into contact with saliva, it is immediately hydrated, starting release *via* diffusion through the polymeric matrix and film erosion (Irfan et al., 2016). The results reported in Table 2 suggest that film B possesses a slightly higher erosion time than film A (136 ± 0.3 min *vs* 128 ± 0.5 min). Table 2 also summarizes the results of film surface-tension measurements. It should be noted that low surface tension can lead to improved formulation spreading. The surface tension of the investigated films ranged from 52 mN/m for film A to 54 mN/m for film B, and was slightly lower than that measured for the mucin solution (56.9 mN/m, Table 2). This result was expected because the ingredients used in the preparation of films can interact with mucin and decrease the surface tension, confirming the film mucoadhesion capability. Both the films showed swelling capacity when exposed to simulated saliva. In particular, a swelling degree of 325 and 950 % for film A (containing glycerol) and film B (containing sorbitol), respectively was observed. The higher swelling capacity of film containing sorbitol in respect to the glycerol film may be attributed to

Table 2
Characterization of buccal films: film weight; thickness, folding endurance; erosion time, surface tension and drug content.

Formulation	Weight (mg)	Thickness (μm)	IB content (mg/cm^2)	Folding Endurance (times)	Erosion Time (min)	Surface Tension (mN/m)
Buccal Film A	49.8 ± 0.2	150 ± 0.5	0.78 ± 0.06	137 ± 0.2	128 ± 0.5	52 ± 0.1
Buccal Film B	39.2 ± 0.7	150 ± 0.3	0.74 ± 0.11	139 ± 0.1	136 ± 0.3	54 ± 0.1

the different water uptake capability of the two excipients. Indeed, sorbitol having increased number of hydroxyl groups compared to glycerol can lead to greater hydration capability of polysaccharide film.

Stability studies were carried out storing the two buccal films at room temperature in Petri dishes up to 6 months. The IB content did not change over time, but a 10 % weight decrease was observed for both the films, probably due to water evaporation. This behavior suggested that a suitable packaging avoiding water loss from the films is required. Fig. 2 reports the SEM images of the two buccal films after 6 months of storage.

3.2. Physico-chemical properties

To assess the stability of the IB-β-CD complex during film formulation, ATR-FTIR and DSC analyses were carried out. Fig. 3 presents the IB, IB-β-CD complex and buccal film ATR-FTIR spectra. The ATR-FTIR analysis of the drug displays characteristic IB peak around 1706 cm^{-1} (carbonyl stretching C═O). Meanwhile, in IB-β-CD, the peak was absent (band at 1706 cm^{-1}), suggesting the presence of interactions between IB and β-CD cavity. Interestingly, in the buccal film the IB peak was not detected as well, showing that the IB-β-CD complex stability is maintained during the film manufacturing process.

The thermal behavior of IB, the inclusion complex and films was determined using DSC, and the thermograms are reported in Fig. 4. The thermogram of IB displayed a sharp endothermic peak at about 80 °C, which can be attributed to the melting of the drug, indicating its crystalline nature in its raw form. Conversely, no specific thermal events were observed in the DSC thermograms of the buccal films and of the inclusion complex. The absence of peaks here reveals that IB was molecularly dispersed into the film matrices.

3.3. In vitro permeation assays of IB films through the biomimetic membrane

The permeation profiles of IB from optimized films are reported in Fig. 5. The data revealed that the amount of IB released from the buccal film and permeated through the biomimetic membrane constantly increases over time. The release profile is probably ascribable to the polymeric matrix composition that affect the time-dependent diffusion of the drug.

Interestingly, the drug content that permeated from film B after four hours of exposure is higher than that obtained for film A. Specifically, the mean contents of IB registered in RF for film A and film B were 226 ± 22.1 μg/cm^2 and 303.6 ± 26.3 μg/cm^2, respectively. These statistically significant ($p < 0.05$) differences between the two films can be explained by the different hydration capacity of film B. Moreover, the steady state flux of IB from film B was also found to be higher ($1.51 \times 10^{-2} \pm 0.33 \times 10^{-2}$ μg/cm^2*s) than that for film A ($0.93 \times 10^{-2} \pm 0.13 \times 10^{-2}$ μg/cm^2*s), as reported in Table 3. Film B exhibited a higher value of P_{app} ($2.72 \times 10^{-4} \pm 0.66 \times 10^{-4}$ cm/s) than film A ($1.68 \times 10^{-4} \pm 0.24 \times 10^{-4}$ cm/s), as listed in Table 3.

3.4. Ex vivo permeation and retention study of IB films through rabbit mucosa

It is generally well accepted that rabbit mucosa is a suitable membrane model for oral-delivery studies thanks to their similarity to human buccal mucosa (Macartney et al., 2025; Nair et al., 2020). Alternatively, synthesized artificial membranes can be used for permeation tests (de Souza Teixeira et al., 2020; Hedge and Bergström, 2020; Torlak et al., 2024). In the present work, a biomimetic membrane was explored alongside animal mucosa in the evaluation of the transmucosal uptake of IB. Formulation B was selected due to its higher drug release rate of IB. The concentrations of the drug from film B that were registered in the receptor fluid were normalized to the synthetic barrier thickness, as described in one of our previous works (Magnano et al., 2022) (see Eq. 4 below).

$$\text{X value}^* \left(\frac{h\ rabbit\ mucosa}{h\ Permeapad®} \right) \tag{4}$$

where X represents the IB concentration measured in the receptor compartment (μg/cm^2), and h is membranes thickness (cm). The biomimetic membrane exhibited a thickness of 0.02 cm, while rabbit mucosa has a thickness of 0.28 cm. After four hours, the mean contents of IB that were registered in the receptor compartment using the synthetic barrier were similar to those measured for rabbit mucosa samples, reaching values of 303.6 ± 26.3 μg/cm^2 and 228.3 ± 57.6 μg/cm^2, respectively (Fig. 6).

The permeation profile obtained in both membranes (biomimetic membrane and rabbit mucosa) were found to be similar. The values the steady states flux were 1.51*10^{-2} μg/cm^2*s and 1.21*10^{-2} μg/cm^2*s,

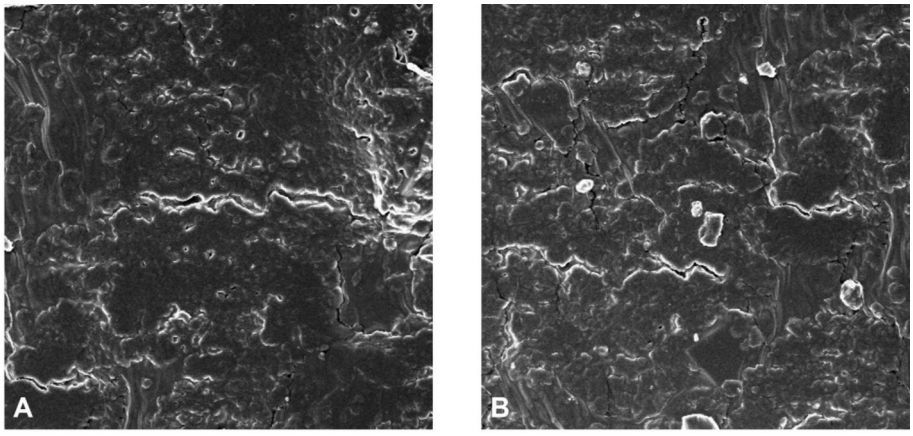

Fig. 2. SEM images of IB-film containing glycerol (A) and sorbitol (B) after 6 months of storage (Magnification 3 kX).

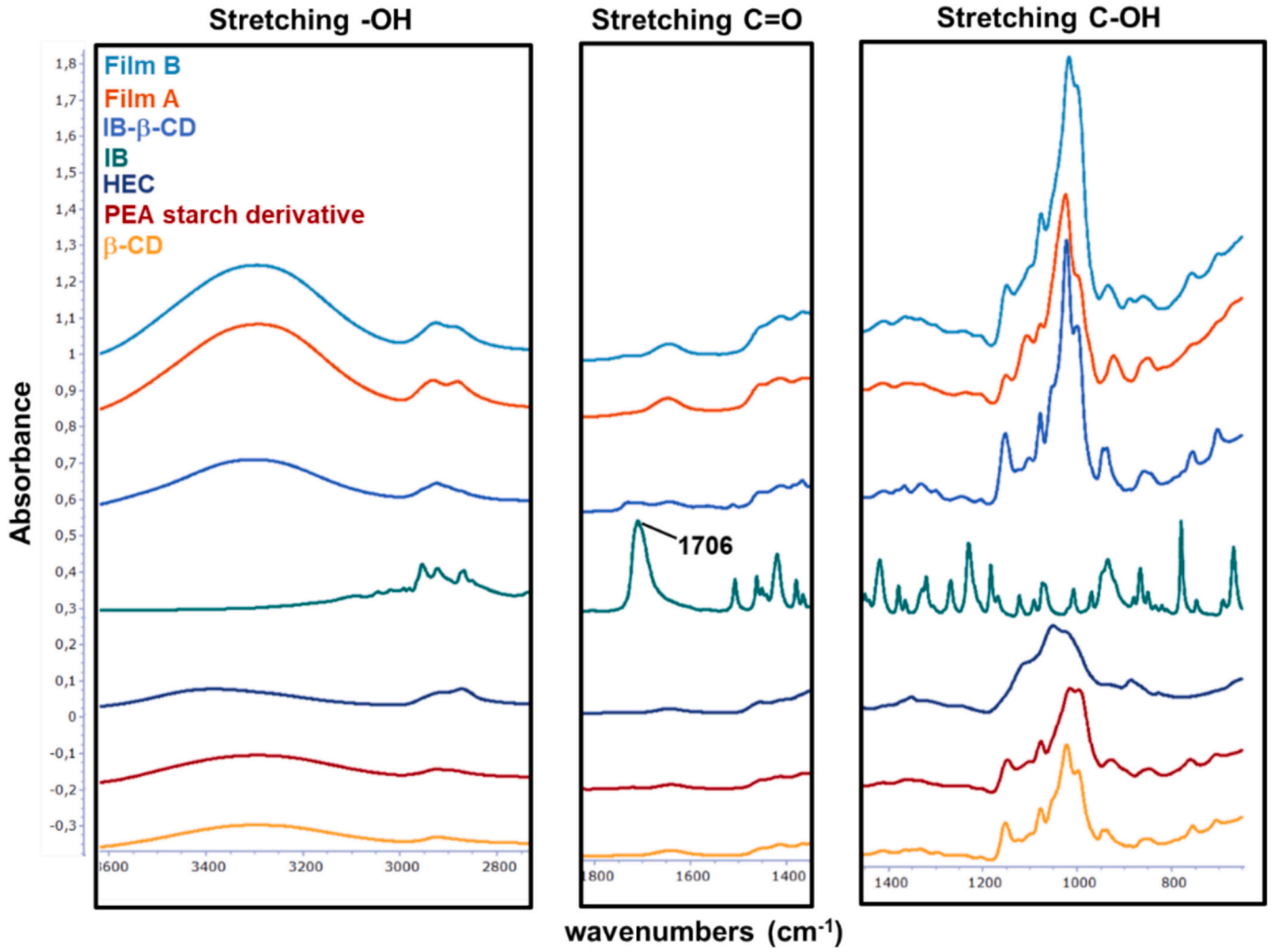

Fig. 3. ATR-FTIR analysis of IB, IB-β-CD complex, and films.

respectively (Table 4). Moreover, both permeability systems exhibited a similar order of magnitude P_{app} $2.72*10^{-4}$ cm/s and $2.18*10^{-4}$ cm/s, respectively. No statistically significant differences were found, demonstrating that the two tested membranes are comparable ($p = 0.276$). A probable explanation for this behavior can be found in the structure of the biomimetic barrier, which possesses a similar permeation profile and permeability coefficient values to the mucosal tissue (Bibi et al., 2016; di Cagno et al., 2015). Notably, the artificial biomimetic barrier used in this study possesses a particular structure characterized by the presence of a lipid layer containing only phosphatidylcholine S-100, which mimics the mucosa lipids. This layered structure prevents any interaction between the lipid layer and formulation components, allowing only the free fraction of the drug to penetrate.

To further confirm the comparability between the artificial biomimetic barrier and rabbit buccal mucosa membrane, the resistance (R) to IB permeation of the two systems was measured and the data obtained were compared. Our results, summarized in Fig. 7, demonstrate that the resistance measured using the rabbit mucosa was in the same order of magnitude as those measured in the synthetic barrier, reaching values of $3.33 \times 10^3 \pm 1.52 \times 10^2$ s/cm and $4.82 \times 10^3 \pm 1.08 \times 10^2$ s/cm, respectively.

Furthermore, the amount of IB retained by the mucosa tissue and by the entire biomimetic barrier was also quantified (Fig. 7). As described in our previous study (Magnano et al., 2022), the values were normalized over the membrane thickness (Eq. 4). The results reported in Fig. 8 suggest that the total content of the drug that penetrated through rabbit buccal mucosa is significantly higher (604 ± 144.2 μg/cm^2) than for the biomimetic barrier (42.8 ± 8.4 μg/cm^2) after four hours of exposure.

3.5. *Biocompatibility test of IB films*

The cytocompatibility of the IB-film solutions prepared for the realization of film formulations was evaluated using human keratinocyte cells (HaCat). Cell viability was determined using an MTT assay which estimates the ability of living cells to reduce thiazolyl blue tetrazolium bromides (Ghasemi et al., 2021). Cell-viability tests (Fig. 9) demonstrated that IB film solutions did not affect cell survival, indicating that the selected film formulations are safe for buccal applications.

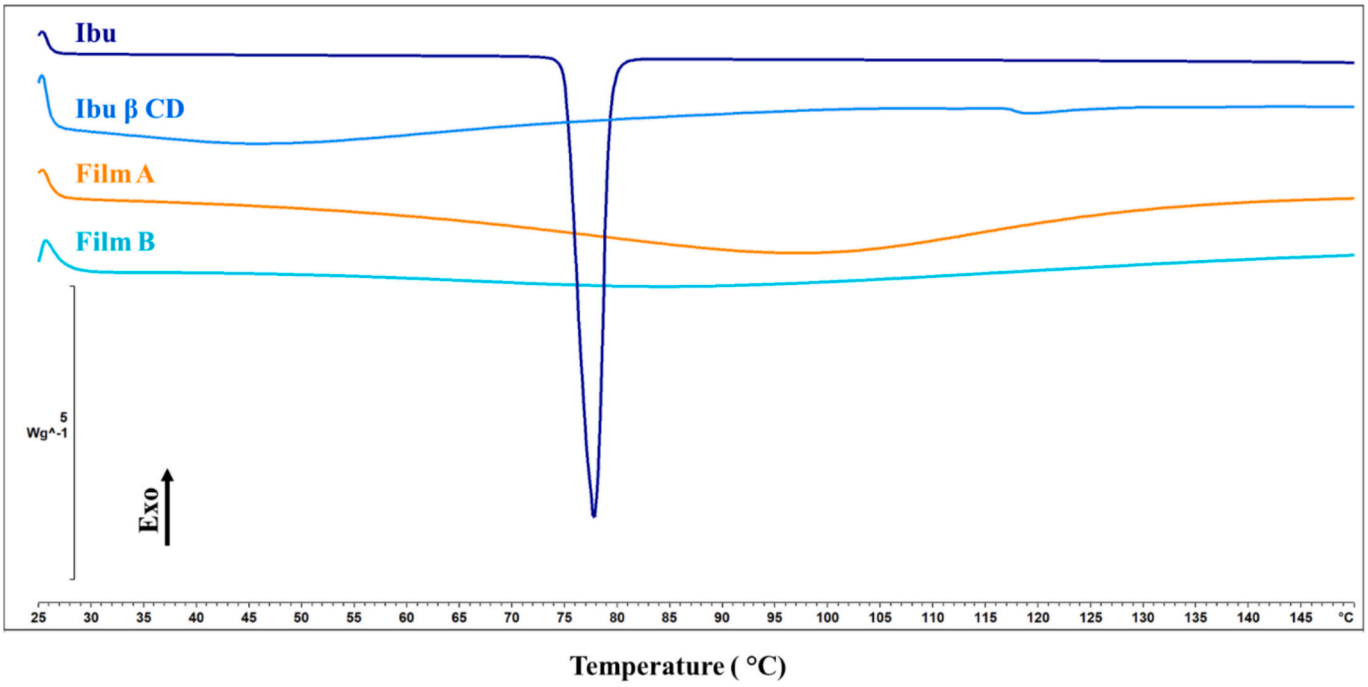

Fig. 4. DSC thermograms of IB, IB-β-CD complex and films.

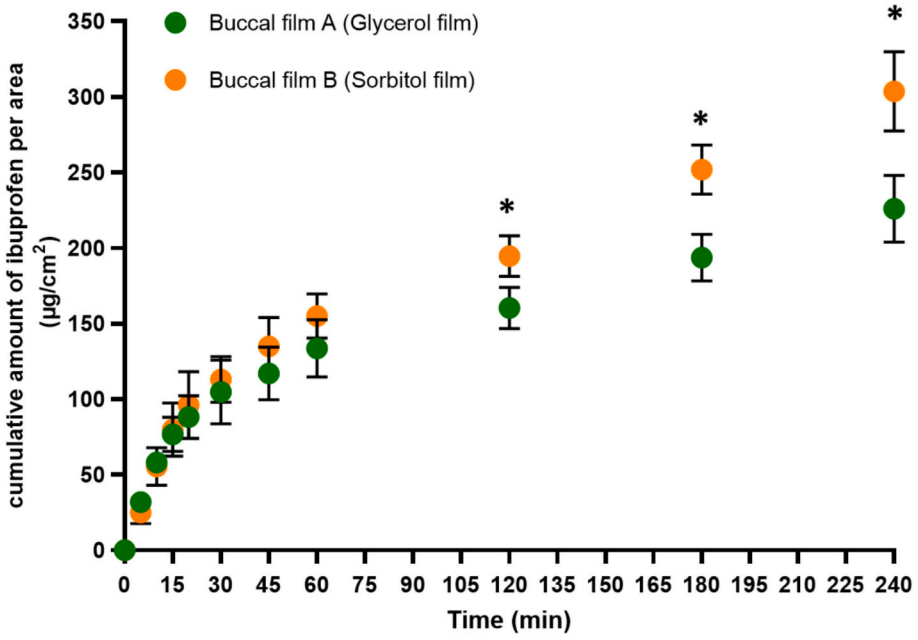

Fig. 5. Permeation profiles of IB from the tested films over 4 h. Values are shown as mean ± SEM ($n = 6$). (*) statistically significant ($p < 0.05$) between the two films.

Table 3
Flux values (J), permeability coefficients (Papp), and IB amounts obtained for each tested film. Values are presented as mean ± SEM (n = 6). (*) statistically significant ($p < 0.05$) between the two films.

Formulation	J (μg/cm²*s)	P_{app} (cm/s)	IB amounts in RF at 4 h (μg/cm²)
Buccal Film A	$0.93 \times 10^{-2} \pm 0.13 \times 10^{-2}$ *	$1.68 \times 10^{-4} \pm 0.24 \times 10^{-4}$ *	226 ± 22.1*
Buccal Film B	$1.51 \times 10^{-2} \pm 0.33 \times 10^{-2}$	$2.72 \times 10^{-4} \pm 0.66 \times 10^{-4}$	303.6 ± 26.3

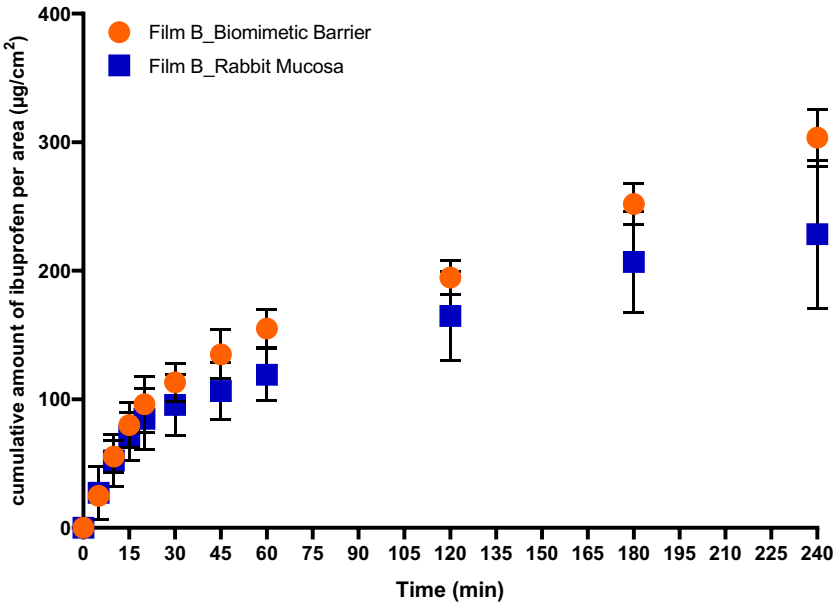

Fig. 6. IB amount (µg/cm2) from film B that permeated into the receptor fluid through the biomimetic membrane and rabbit mucosa. Values are normalized and shown as mean ± SEM ($n = 3$).

Table 4
Flux values (J), permeability coefficients (Papp), and IB amounts. Values are normalized and presented as mean ± SEM (n = 3).

Formulation	J (µg/cm^2*s)	P_{app} (cm/s)	Normalized IB amounts in RF at 4 h (µg/cm^2)
Film B-Biomimetic membrane	$1.51 \times 10^{-2} \pm 0.33 \times 10^{-2}$	$2.72 \times 10^{-4} \pm 0.66 \times 10^{-4}$	303.6 ± 26.3
Film B-Rabbit Mucosa	$1.21 \times 10^{-2} \pm 0.18 \times 10^{-2}$	$2.18 \times 10^{-4} \pm 0.32 \times 10^{-4}$	228.3 ± 57.6

Moreover, IB film solutions demonstrated no hemolytic activity, confirming the biocompatibility of these films.

3.6. Electronic tongue analysis

Three replicate readings for each type of samples (ibuprofen solution, buccal film A and buccal film B), was performed with a DPV technique. In Fig. 10 mean and standard deviation for each type of sample are reported. The DPV peak currents were found to be 1.186 ± 0.149 µA, 2.849 ± 0.32 µA, 1.899 ± 0.115 µA, 2.306 ± 0.102 µA for the ibuprofen solution, the buccal film A, the buccal film B and placebo, respectively. The measured peak potentials were 1.046 ± 0.015 V, 1.125 ± 0.002 V, 1.145 ± 0.006 V and 1.135 ± 0.003 V.

As it can be seen from Fig. 10 the samples are clearly distinguishable in both current and voltage domains, confirming that it is possible to

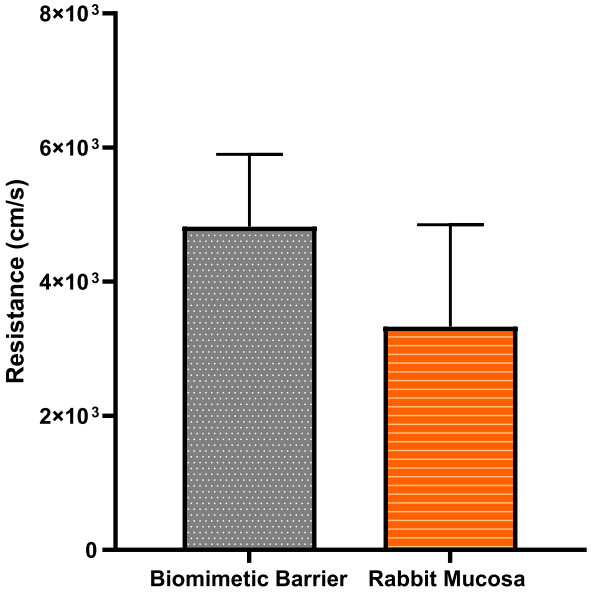

Fig. 7. Resistance values (R) of the biomimetic barrier and rabbit mucosa to permeation of IB.

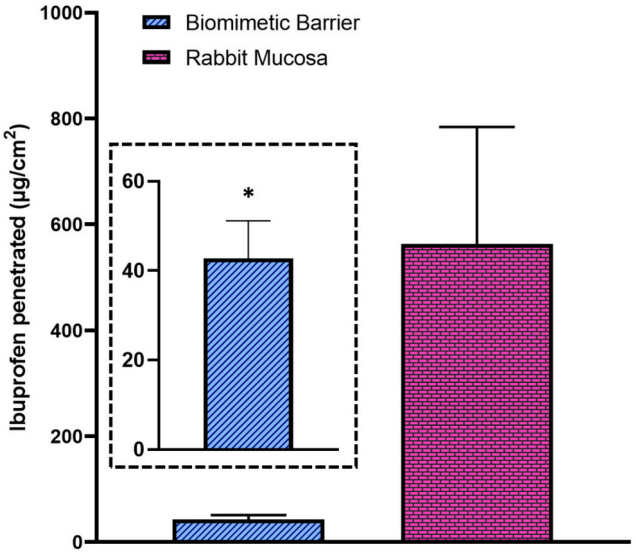

Fig. 8. IB concentration found in the mucosa tissue and in the whole biomimetic barrier after 4 h of contact. Values are normalized and shown as mean ± SEM (n = 3). (*) statistically significant differences ($p < 0.05$) between the membrane and rabbit mucosa.

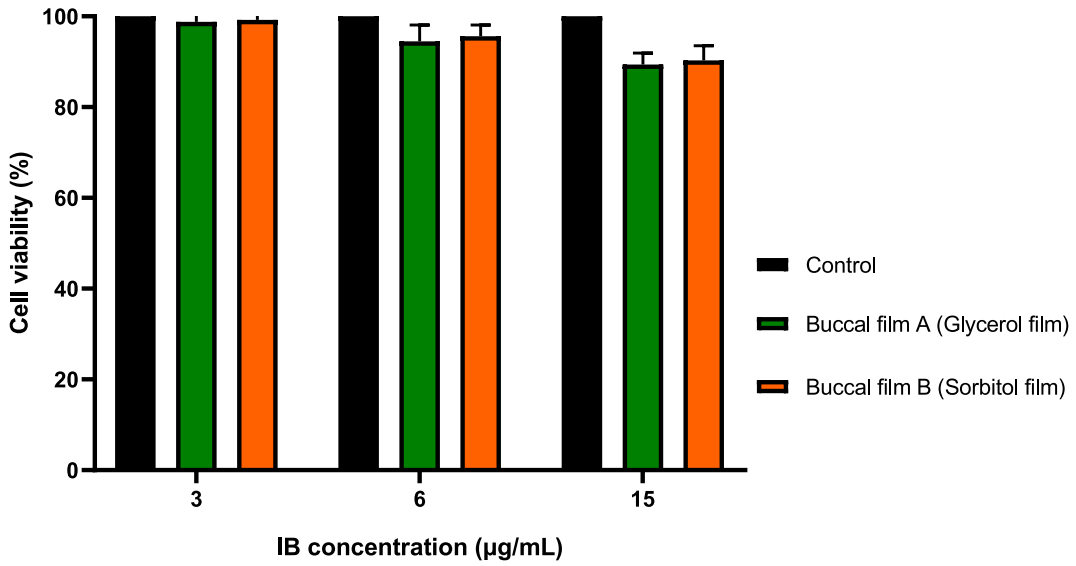

Fig. 9. *In vitro* cytotoxicity evaluation. Cell viability (%) of Hacat cells after incubation with IB-films for 24 h determined by MTT assay.

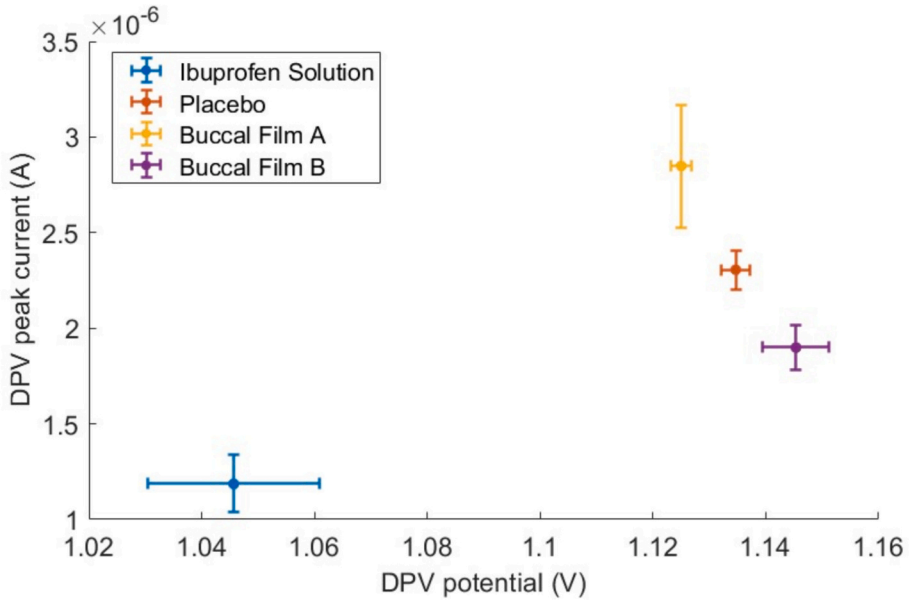

Fig. 10. DPV readings results, considering three replicates for each type of sample.

easily discriminate a type of sample from the others. The DPV measurements consistently discriminated ibuprofen solution from the buccal films and placebo, confirming a significant modification of the sensorial profile.

4. Conclusion

Two buccal films have been successfully prepared for the delivery of IB using a new polysaccharide combination, containing natural derived components and exploiting a "green", solvent-free, manufacturing method. To the best of our knowledge, it is the first time that the combination of HEC and Linecaps® has been applied to form a film. The polymer combination bestowed mucoadhesion, biocompatibility and physico-mechanical characteristics to form films appropriate for child-friendly buccal use. *In vitro* permeation studies through the rabbit mucosa showed the transmucosal uptake of IB released from the films. Additionally, our findings demonstrate that the data obtained using the artificial biomimetic barrier shows good correlation, in terms of similar permeation kinetics and permeability coefficients, with the results obtained from the rabbit mucosa, suggesting that the biomimetic membrane is a valid substitute for animal models for evaluating the permeability. Taken together, our results indicate that Linecaps® can be a promising excipient for the development of polysaccharide-based buccal films for pediatric population.

CRediT authorship contribution statement

Greta Camilla Magnano: Writing – original draft, Investigation, Data curation. **Anna Scomparin:** Writing – review & editing, Supervision. **Monica Argenziano:** Writing – review & editing, Supervision. **Rita Spagnolo:** Investigation. **Elisabetta Muntoni:** Investigation. **Dario Voinovich:** Writing – review & editing. **Dritan Hasa:** Writing – review & editing. **Valentina Bianchi:** Writing – original draft, Investigation. **Ilaria De Munari:** Writing – review & editing, Supervision. **Roberta Cavalli:** Writing – review & editing, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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