European Journal of Pharmaceutics and Biopharmaceutics 105 (2016) 115–121

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

# Design and evaluation of buccal films as paediatric dosage form for transmucosal delivery of ondansetron

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ARTICLE INFO

*Article history:*
Received 31 March 2016
Revised 25 May 2016
Accepted in revised form 31 May 2016
Available online 4 June 2016

*Chemical compounds studied in this article:*
Hydroxypropylmethylcellulose (PubChem CID: 57503849)
Chitosan (PubChem CID: 71853)
Sodium hyaluronate (PubChem CID: 3084049)
Ondansetron hydrochloride dihydrate (PubChem CID: 59774)

*Keywords:*
Paediatric formulation
Buccal film
Polymeric mixture
Ondansetron hydrochloride
Permeation study

ABSTRACT

In the process of implementation and innovation of paediatric dosage forms, buccal films for transmucosal administration of drug represent one of the most interesting approach. In fact, films are able to provide an extended duration of activity allowing minimal dosage and frequency and offer an exact and flexible dose, associated with ease of handling. The objective of the present study was to develop polymeric films for the sustained release of ondansetron hydrochloride, a selective inhibitor of 5-$HT_3$ receptors indicated in paediatrics for the prevention and treatment of nausea and vomiting caused by cytotoxic chemotherapy or radiotherapy and postoperatively. Films were prepared by casting and drying of aqueous solutions containing different weight ratios of hydroxypropylmethylcellulose (HPMC) with chitosan (CH) or sodium hyaluronate (HA) or gelatin (GEL) and characterized for their physico-chemical and functional properties. The presence of HA, GEL and CH did not improve the mucoadhesive properties of HPMC film. The inclusion of GEL and CH in HPMC film increased in vitro drug release with respect to the inclusion of HA, although films containing HA showed the highest water uptake. Moreover in agreement with the release behaviour, the inclusion of CH and GEL provided higher drug permeation through porcine buccal mucosa with respect to HPMC film and ensured linear permeation profiles of drug.



## 1. Introduction

The extensive changes into the regulatory environment for paediatric medicines, designed to better protect the health of children, have stimulated the research into child-appropriate dosage forms. These dosage forms should satisfy important requisites: easy administration, possibility of weight-based dosing and dose titration, acceptability and palatability, and finally minimum dosing frequency. Moreover, excipients should be safe in the target age group [1–4].

One approach in the process of implementation and innovation of paediatric dosage forms for young children is represented by the use of buccal films for transmucosal administration of drug [5]. Buccal films are relatively new dosage form intended to deliver drug substances through the oral mucosa directly onto the systemic circulation, avoiding the hepatic first pass metabolism and similarly, the drug degradation along the gastrointestinal tract, thus allowing the reduction of the dose necessary to achieve the therapeutic action. Compared to conventional buccal tablet formulation, they are thin, flexible and better adaptable to the mucosal surface, and therefore more acceptable to younger patients. Moreover, buccal films are safe and convenient unit dosage systems since they can be easily applied or removed from the application site, even during a state of patient unconsciousness or when swallowing is impaired [6–8].

From the technological point of view, buccal films are matrices fabricated using mucoadhesive and film forming polymers and

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http://dx.doi.org/10.1016/j.ejpb.2016.05.026
0939-6411/

loaded with the active ingredient(s). The use of mucoadhesive polymers is essential to maintain an intimate and prolonged contact of the formulation with the oral mucosa allowing a longer duration of absorption [9]. Polymers that are commonly used in the development of buccal films include cellulose derivatives, chitosan, gelatin, hyaluronic acid, carrageenan, pectin, sodium alginate and acrylic polymers [10].

Effective design of such delivery system, requires careful consideration of other relevant parameters, including the choice of the active substance [11,12]. These involve good lipophilicity and water solubility at physiological pH, as well as high potency. Ondansetron (ODS), a selective inhibitor of serotonin (5-hydroxytryptamine) subtype 3 (5-$HT_3$) receptors indicated in paediatrics for the prevention and treatment of nausea and vomiting caused by cytotoxic chemotherapy or radiotherapy and postoperatively, represents a suitable candidate for buccal delivery (octanol/water log P at pH 7.4: 2.4, water solubility at pH 7.4: 2.42 mg/mL, small molecular size) [7,8,13]. ODS is commercially available as injection, oral liquid and solid oral dosage form. All these formulations are indicated for administration in multiple daily dosing, potentially for a series of days (recommended oral maintenance dose for children of 4–11 years: 4 mg every 4–8 h). This is due to the pharmacokinetic profile of ondansetron, which has a half-life of approximately 3–6 h and a time to peak plasma levels of approximately 2 h. This profile is often associated with alternating periods of increased side effects and lacking efficacy and therefore, there is a need to develop sustained release formulations able to maintain a constant drug concentration for a specific period of time with minimum side effects [14–17].

The objective of this study was to: (1) implement paediatric dosage forms for young children with buccal films intended for ODS systemic absorption through the buccal mucosa over a prolonged period of time; (2) prepare mucoadhesive films based on non-toxic, biocompatible and hydrophilic polymers as hydroxypropylmethylcellulose (HPMC), chitosan (CH), sodium hyaluronate (HA) and gelatin (GEL), and by using an easy and economic method as solvent casting method; (3) investigate the influence of preparative parameters on the physico-chemical properties of drug; and (4) study the influence of polymeric composition (different polymer blends and different weight ratio) on the drug loading, mucoadhesion potential, water uptake properties, and drug release and permeation ability.

## 2. Materials and methods

### 2.1. Materials

Hydroxypropylmethylcellulose (MW 250 kDa, methoxyl content 19–24%, hydroxypropyl content 7–12%) was purchased from Eigenmann & Veronelli (Milan, Italy); chitosan (MW 150 kDa, deacetylation degree 97%) was commercially obtained from Fluka (Milan, Italy); sodium hyaluronate (MW 1800–2300 kDa, D-glucuronic acid > 42%) was provided by ACEF (Piacenza, Italy); type B Gelatin from bovine skin (MW 50 kDa, 100–115 mmol of free carboxyl groups per 100 g of protein, isoelectric point in the range of pH = 4.7–5.2) and ondansetron hydrochloride dihydrate (MW 365.85 g/mol) were commercially obtained from Sigma-Aldrich (Milan, Italy). All other chemicals and solvents were of analytical grade and supplied by Carlo Erba (Milan, Italy). Release and permeation studies were conducted in NaCl solution (0.9% w/v); mucoadhesion studies were carried out in aqueous buffer with the following composition: 33.9 mM $KH_2PO_4$, 46.8 mM $Na_2HPO_4 \cdot \times 12H_2O$ adjusted with hydrochloric acid to pH = 6.8 [18] (healthy saliva pH = 6.7–7.4 [19]); buccal tissue was stored after excision in Krebs Ringer bicarbonate buffer with the following composition: 115.5 mM NaCl, 4.2 mM KCl, 2.5 mM $CaCl_2$, 1.6 mM $NaH_2PO_4$, 0.8 mM $MgSO_4$, 4.0 mM HEPES, 17.3 mM $Na_2CO_3$, and 12.2 mM glucose [20].

### 2.2. Preparation of buccal films

Buccal films were prepared by casting-solvent evaporation method. An aqueous solution of GEL, an aqueous solution of HA and an acid solution (acetic acid 1% v/v) of CH were separately added to an aqueous solution of HPMC at different weight ratios (10:0, 9:1, 7:3, 5:5, 0:10 HPMC:GEL or HPMC:HA or HPMC:CH), in order to obtain 1% w/w polymeric mixtures. All mixtures were stirred at room temperature for 2 h and allowed to stand overnight to eliminate the air bubbles. 15 g of each polymeric solution was spread on a Petri dish (diameter = 5 cm) and oven-dried at 50 °C for 6 h (heating oven FD series; Binder, Tuttlingen, Germany). Loaded films were prepared by the same procedure, adding to each mixture 17.45 mg of ODS. Circles of 1.3 cm in diameter (surface area = 1.33 $cm^2$) were cut to obtain a child-appropriate dosage form and were used for the studies described below. Each circle contains theoretically 1.18 mg of drug.

Different films were named in this work as follows: HPMC:CH 10:0, HPMC:HA 10:0, HPMC:GEL 10:0, films based on HPMC (they are also reported as HPMC:CH(GEL,HA) 10:0); HPMC:CH 0:10, HPMC:HA 0:10, HPMC:GEL 0:10, films based on CH, HA and GEL, respectively; HPMC:CH (or HPMC:HA or HPMC:GEL) 9:1 (or 7:3 or 5:5), films based on HPMC mixtures with CH or HA or GEL at different weight ratios.

### 2.3. Solution viscosity

The viscosity of the polymeric solutions used for the preparation of loaded and unloaded buccal films was measured at room temperature with an Ubbelohde capillary viscometer equipped with an electronic time-measuring unit ViscoClock (capillary tubes I and II; Schott, Mainz, Germany) for CH and GEL solutions (1% w/w) and with a rotational viscometer (spindle TR8-TR9, RPM 60-200; Visco Star, Fungilab S.A., Barcelona, Spain) for all the others.

### 2.4. Characterization of buccal films

#### 2.4.1. Scanning electron microscopy (SEM)

SEM analysis was performed to evaluate the morphologic characteristics. Films were cut with a razor blade, fixed on supports and coated with gold–palladium under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. Samples were then observed with LEO 420 (LEO Electron Microscopy Ltd., Cambridge, UK) using secondary electron imaging at 15 kV in order to examine their surface morphology and their internal structure.

#### 2.4.2. Thickness and drug content

Each film obtained from a Petri dish (diameter = 5 cm) was accepted as a single batch in these studies and for each formulation three batches were prepared. Thickness of loaded film was measured as mean of three batches. The thickness of films was determined by means of a Mitutoyo pocket thickness gauge (Mitutoyo Mfc. Co. Ltd., Tokyo, Japan). Drug content was assessed by dissolving one circle (diameter = 1.3 cm) from each batch in 20 ml of 0.9% (w/v) NaCl solution. The system was stirred for 2 h until complete release and the amount of drug in solution was evaluated. The results were expressed as milligrams of drug for square centimetre (mg/$cm^2$).

In these tests as well as in subsequent experiments the ODS concentration was determined by HPLC equipped with a UV detector. The HPLC system consisted of Shimadzu (Milan, Italy) LC-10ATVP chromatographic pump and a Shimadzu SPD-10AVP