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Bilayered buccal films as child-appropriate dosage form for systemic administration of propranolol

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ABSTRACT

Buccal mucosa has emerged as an attractive site for systemic administration of drug in paediatric patients. This route is simple and non-invasive, even if the saliva wash-out effect and the relative permeability of the mucosa can reduce drug absorption. Mucoadhesive polymers represent a common employed strategy to increase the contact time of the formulation at the application site and to improve drug absorption. Among the different mucoadhesive dosage forms, buccal films are particularly addressed for paediatric population since they are thin, adaptable to the mucosal surface and able to offer an exact and flexible dose. The objective of the present study was to develop bilayered buccal films for the release of propranolol hydrochloride. A primary polymeric layer was prepared by casting and drying of solutions of film-forming polymers, such as polyvinylpyrrolidone (PVP) or polyvinylalcohol (PVA), added with different weight ratios of gelatin (GEL) or chitosan (CH). In order to achieve unidirectional drug delivery towards buccal mucosa, a secondary ethylcellulose layer was applied onto the primary layer. Bilayered films were characterized for their physico-chemical (morphology, thickness, drug content and solid state) and functional (water uptake, mucoadhesion, drug release and permeation) properties. The inclusion of CH into PVP and PVA primary layer provided the best mucoadhesion ability. Films containing CH provided a lower drug release with respect to films containing GEL and increased the amount of permeated drug through buccal mucosa, thanks to its ability of interfering with the lipid organization. The secondary ethylcellulose layer did not interfere with drug permeation, but it could limit drug release in the buccal cavity.

1. Introduction

Regulatory initiatives in the United States and Europe over the last decades have stimulated the development of suitable medicines for children taking into consideration appropriate route of administration, dosage form, excipients, taste/palatability and delivery device. In fact many drugs are routinely prescribed by physicians although they are not approved by registration agencies for use in children (Van Riet-Nales et al., 2017; Ernest et al., 2007; Strickley et al., 2008).

Buccal mucosa has emerged as an attractive site for systemic administration of drug in paediatrics by reason of advantages such as the direct passage of drug into the systemic circulation through the jugular vein, thus bypassing the stomach environment and first-pass liver metabolism, fast onset of action and rapid decline after removing the dosage form, ease access for self-medication. It allows a significant improvement in patient acceptance and compliance (Lam et al., 2014; Patel et al., 2011). Delivery of drugs via the buccal mucosa may be achieved by using mucoadhesive dosage forms able to maintain an intimate and prolonged contact with mucosa and favor the drug absorption to improve the

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Table 1
Properties of primary polymeric layers and bilayered film: thickness, drug content, water-uptake ability and drug fractional amount released from the different formulations.

Polymeric mixtures	Polymer weight ratios	Thickness (mm)		Drug content (mg/cm^2)	WU after 60 min (%)	Mt/M0 released after 60 min (%)
		Primary layer	Bilayered film		Primary layer	
PVP:CH/GEL	10:0	0.25 ± 0.04	–	2.82 ± 0.08	–	100.22 ± 1.89
PVA:CH	10:0	0.22 ± 0.02	0.39 ± 0.03	2.63 ± 0.25	–	99.90 ± 2.25
PVP:GEL	0:10	0.23 ± 0.09	0.39 ± 0.01	2.89 ± 0.77	647.72 ± 31.49	51.06 ± 4.88
	7:3	0.23 ± 0.03	0.36 ± 0.05	2.80 ± 0.21	940.25 ± 45.68	34.57 ± 11.53
PVP:CH	5:5	0.24 ± 0.05	0.39 ± 0.08	2.53 ± 0.28	1335.91 ± 52.69	33.10 ± 14.80
	3:7	0.24 ± 0.05	0.35 ± 0.02	2.89 ± 0.53	1622.32 ± 78.48	32.98 ± 10.96
	7:3	0.26 ± 0.04	0.37 ± 0.05	2.98 ± 0.51	193.77 ± 10.08	97.95 ± 1.12
PVP:GEL	5:5	0.25 ± 0.04	0.36 ± 0.01	3.02 ± 0.12	429.52 ± 19.35	88.61 ± 3.23
	3:7	0.22 ± 0.04	0.34 ± 0.06	2.96 ± 0.26	602.21 ± 29.64	79.97 ± 4.87
	7:3	0.28 ± 0.05	0.39 ± 0.04	2.72 ± 0.13	697.36 ± 49.85	35.68 ± 10.25
PVA:CH	5:5	0.32 ± 0.07	0.43 ± 0.08	2.77 ± 0.32	997.91 ± 65.06	55.36 ± 12.36

bioavailability (Sudhakar et al., 2006). Among the different mucoadhesive formulations suitable for young children, buccal films ensure accurate dosing and compared to conventional buccal tablets they are thin, flexible, easily applicable and adequately strong to withstand breakage caused from mouth movements (Borges et al., 2015; Dixit and Puthli, 2009; Trastullo et al., 2016; Krampe et al., 2016).

To achieve an optimal mucoadhesion ability, but also a suitable drug release profile, it is important the selection of polymeric material (Salamat-Miller et al., 2005). Generally a single polymer may not possess adequate characteristics and polymeric blends prepared by physical mixing of two or more polymers often exhibit properties that are superior to any one of the component polymers (Munasur et al., 2006). Polyvinylalcohol (PVA) and polyvinylpyrrolidone (PVP) are synthetic and water soluble hydrophilic polymers available with different molecular weights, and have been widely used for decades in pharmaceutical and biomedical applications for their excellent mechanical, biocompatible, biodegradable, nontoxic properties. Moreover, they have been successfully employed as film-forming materials (Falath et al., 2017; Hifumi et al., 2016; Kumar et al., 2014). Chitosan (CH) and gelatin (GEL) are naturally occurring polysaccharides that have been proposed as ideal carrier in oral mucosal drug delivery due to their good mucoadhesive properties (Salamat-Miller et al., 2005; Kumar et al., 2016; Abruzzo et al., 2015). Moreover, since CH has been shown to be capable to interfere with lipid micelle organization in the intestine, Şenel et al. (2000) explained that it could enhance the absorption of drugs across the buccal mucosa by interfering with the lipid organization in the buccal epithelium. In fact, the buccal mucosa (thickness of approximately 500–800 μm) shows the important function of protection of the underlying tissue and a variety of barrier mechanism are integrated in this part. The first is represented by saliva that contains high molecular weights glycoprotein (MG1) able to adhere to the surface of the oral epithelium, constituting the mucus layer. This is a viscoelastic layer of varying thickness (approximately 70–100 μm) that affects drug absorption. Nevertheless, it is known that the main penetration barrier for the drug molecules lies in the superficial layer of the epithelium. This layer shows cells with increased size and more flattened shape as compared with the basal layer and in the 200 μm outermost part it contents lipophilic intracellular material derived from the membrane coating granules (MCGs) (Teubl et al., 2013). In this work, the use of relatively low molecular weight polymers is justified by the hypothesis that the rate-limiting step in buccal drug transport is the biological barrier itself and that the use of high molecular weight polymers can represent an additional obstacle (del Consuelo et al., 2007).

As regard the choice of drug, some classes may benefit from buccal administration include antihypertensives. Propranolol is a β-blocker used in pediatric patients primarily for the treatment or prevention of cardiac arrhythmias, hypertension, outflow obstructions in congenital heart disease, and hypertrophic cardiomyopathy. It is commercially available in different dosage forms, including oral tablets, extended-release capsules, and liquid solutions. In this work propranolol was chosen as a model drug for incorporation into a buccal formulation because is a potent drug which has suitable physicochemical properties (MW 259.3 g/mol, logP = 3.48, log $D_{pH6.8}$ = 1.20), and extensive and highly variable first pass metabolism following oral administration with only ~ 25% of oral drug reaching the systemic circulation (Amores et al., 2014). Moreover as some of the oldest β-blocker, propranolol falls into the category of off-patent drugs used in paetiatrics (Chu et al., 2014).

In the present study we developed new bilayered buccal films using synthetic film-forming polymers in combination with natural mucoadhesive polymers for the release of propranolol hydrochloride in paediatric. Briefly the main steps were: (a) prepare a polymeric matrix (primary polymeric layer) based on PVA or PVP added with different weight ratios of CH or GEL; (b) demonstrate whether the addition of CH or GEL was able to maximize the mucoadhesion properties and the control of drug release of the primary polymeric layer; (c) after identification of an ideal polymeric blend, apply a non-dissolvable backing layer onto the first one to achieve unidirectional release towards the oral mucosa (bilayered film), avoiding drug release in the oral cavity.

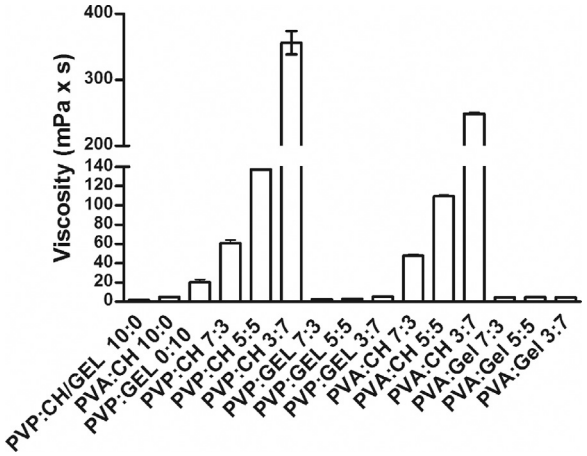

Fig. 1. Viscosity of polymeric solutions used for primary polymeric layer preparation.