DEVELOPMENT OF BUCCAL FILMS AS NOVEL DOSAGE FORM FOR PAEDIATRIC USE

It is estimated that in European Union 50% of the medicines employed in children has actually been studied only in adult population and not necessarily for the same indication and the same disease. The general lack of information, coupled with the absence of pharmaceutical formulations suitable for the administration in children, can result in unwanted side-effects or underdosing that preclude the efficacy of the treatment. The aim of this study is the development of innovative formulations, suitable for buccal administration, to meet the needs, in terms of safety, effectiveness and acceptability of children. In particular, we prepared and characterized mucosal adhesive polymeric films for transmucosal drug delivery of ondansetron hydrochloride (ODS), a serotonin 5-HT3 receptor antagonist widely used in the management of post-operative nausea and vomiting and concomitantly with chemotherapy and radiotherapy.

An aqueous solution of sodium hyaluronate (HA, MW=2000 kDa) and an acidic solution (acetic acid 1 % v/v) of chitosan (CH, MW=180 kDa) were separately added to an aqueous solution of hydroxypropylmethylcellulose (HPMC, MW=150 kDa) at different weight ratios (10:0, 9:1, 7:3, 5:5, 0:10). HPMC:HA and HPMC:CH) and stirred at room temperature for 24 hours. 15 g of each mixture were spread on a Petri-dish (Ø=5 cm) and dried at 56°C for 6 hours. Loaded films were prepared by the same procedure, adding 14,79 mg of ODS. Circles of 0,65 cm in diameter were cut from each film to obtain a child-appropriated dose (ODS oral dose for children 4-11 years of age: 4 mg/3 l.i.d.; ODS oral bioavailability: 58 %).

The viscosity of the polymeric solutions used for films preparation was measured at T=25°C with a rotational viscometer (Visco Star, Fungilab S.A., Barcelona, Spain).

Increasing amounts of HA in the HPMC:HA mixture improved solution viscosity, while HPMC:CH solution viscosity proportionally decreased with increasing the amount of CH in the mixture. This behaviour can be mainly attributed to the different molecular weight of HPMC, HA and CH.

The morphological structure of buccal films was studied by SEM analysis (LEO 420, LEO Electron Microscopy Ltd., England). Polymeric films showed an uniform and smooth surface, and a dense and homogeneous cross-section.

XRPD analysis (X’Pert PRO, PANalytical’s, Netherlands) was conducted to study the crystalline or amorphous state of the drug in loaded polymeric films.

In vitro water uptake studies were performed in 0.9% w/v sodium chloride solution, measuring the increase of weight with a gravimetric method.

Water uptake ability of HPMC film was strongly increased by the presence of CH and HA. In particular, HPMC:HA film showed an higher water uptake than HPMC:CH film, but a lower hydration ability than HA and CH films. At the expected conditions (pH=6,3), HA (pKa=2,9) was highly negatively charged while CH (pKa=6,3) presented lower charge density, allowing greater entry of water for HPMC:HA film with respect to HPMC:CH film.

The mucoadhesion properties were measured with an adapt tensiometer (Krüss 132889, Hamburg, Germany) in terms of the force needed to pull out a freshly excised porcine buccal mucosa from polymeric film.

Increasing amounts of CH in HPMC:CH films decrease mucoadhesive ability of HPMC film, while HPMC:HA films showed the same mucoadhesive properties of HPMC film. Despite both HA and CH present good water uptake ability, low mucoadhesion properties of HPMC:CH films can be attributed to their inability to entangle with mucus due to their low viscosity in the gel state.

Release studies were performed in a Vision Classic 6 Dissolution Tester (Hanson, CA, USA), using as a dissolution medium a volume of 70 ml of 0.9% w/v sodium chloride solution stirred at 80 rpm and maintained at 37 °C.

Despite HPMC:HA and HPMC:CH films presented an higher water uptake ability than HPMC film, a lower drug release was obtained. This behaviour can be correlated with drug diffusibility in differently viscous networks.

In vitro permeation studies through porcine buccal mucosa were conducted in a Static Franz Cell, equipped with a VSA stirrer (PermeGear Inc, Helfertown, Pennsylvania, USA), using as a receptor medium 0.5% w/v sodium chloride solution (12 ml) maintained at 37 °C.

HPMC:CH 5:5 film provided higher permeated drug amount at each time with respect to HPMC film. This behaviour indicated that the addition of CH to HPMC film facilitated drug diffusion through buccal mucosa. Moreover, HPMC:CH 5:5 was able to provide an high and sustained permeation of drug within 6 hours (MW/M % = 82 %).

This study indicated that HPMC can be mixed with HA and CH to obtain buccal film for the administration of ODS. The selection of suitable polymer, associated with appropriate preparative conditions, allowed the modulation of film water uptake behaviour, mucoadhesion properties, and ODS release and permeation at the administration site.

REFERENCES:  

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