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Original article

Taste-masking assessment of orally disintegrating tablets and lyophilisates with cetirizine dihydrochloride microparticles

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ABSTRACT

Orally disintegrating tablets and oral lyophilisates are novel attractive dosage forms that disintegrate or dissolve in the buccal cavity within seconds without necessity of drinking. The major limitation in designing of these dosage forms is unpleasant taste of the drug substance. Cetirizine dihydrochloride is a H_1-antihistamine substance indicated for the treatment of allergy. It is characterized by extremely bitter taste, therefore in order to deliver cetirizine dihydrochloride using orodispersible formulations, effective taste-masking is required. The aim of this study was to investigate whether microparticles containing cetirizine dihydrochloride could be successfully used to formulate orally disintegrating tablets by direct compression method and oral lyophilisates by freeze-drying process. Taste masking of cetirizine dihydrochloride was achieved by the spray-drying technique using Eudragit® E PO as the drug agent carrier. Based on the preliminary studies, optimal compositions of microparticles, tablets and lyophilisates were chosen. Obtained dosage forms were characterized for drug content, disintegration time and mechanical properties. In order to determine whether the microparticles subjected to direct compression and freeze-drying process effectively mask the bitter taste of cetirizine dihydrochloride, the *in vivo* and *in vitro* evaluation was performed. The results showed that designed formulates with microparticles containing cetirizine dihydrochloride were characterized by appropriate mechanical properties, uniformity of weight and thickness, short disintegration time, and the uniform content of the drug substance. Taste-masking assessment performed by three independent methods (e-tongue evaluation, human test panel and the *in vitro* drug release) revealed that microparticles with Eudragit® E PO are effective taste – masking carriers of cetirizine dihydrochloride and might be used to formulate orally disintegrating tablets and oral lyophilisates.

1. Introduction

Unacceptable taste is an important problem encountered in the designing of orodispersible dosage forms which disintegrate or dissolve in the patient's oral cavity and drug has direct contact with the taste buds. In pharmaceutical applications, a wide variety of techniques is available for taste-masking of bitter drugs. The simplest and most common approach is using flavors or sweeteners (Hannan et al., 2016). However, their efficacy is limited in the case of very bitter or highly water-soluble drugs administered at high doses, and therefore this method is often used with other more advanced taste-masking techniques like: complexation, coating or granulation with hydrophilic polymers, melting and liquid extrusion and ion-exchange resins (Badgujar and Mundada, 2011; Pein et al., 2014; Kaushik and Dureja, 2014; Fu et al., 2004). One of the frequently used and the most effective taste masking method is microencapsulation by the spray-drying process, in which polymer barrier between bitter drug and the taste buds is creating (Szakonyi and Zelkó, 2012; Rogers and Wallick, 2012).

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Cetirizine dihydrochloride (CET) is a second-generation antihistaminic drug indicated for the treatment of allergies. CET is an extremely bitter drug requiring effective taste-masking, therefore it was chosen as a model drug (Drug bank Version 5.0; Chen, 2008).

In order to develop taste masked CET microparticles, preliminary studies have been done. Microparticles were obtained by the spray drying method with CET and Eudragit® E PO as a barrier coating. Eudragit® E PO is poly(butyl methacrylate-co-(2-dimethyla minoethyl) methacrylate-co-methyl methacrylate 1:2:1 copolymer (Nikam et al., 2011; Rogers and Wallick, 2012). Effective taste masking barrier was created with CET:polymer ratio (0.5:1) (Amelian et al., 2017) and this formulation was used for designing orally disintegrating dosage forms in this study.

Selection of excipients and their amounts depends on the properties of the active substance, target mass of the formulation and technological process used (Badgujar and Mundada, 2011). In order to develop the composition of orally disintegrating tablets via method of direct compression, placebo tablets with various multifunctional mixtures and various disintegrants were prepared. A number of preliminary studies were performed and formulation characterized by sufficient mechanical properties and short disintegration time was selected to obtain tablets with taste-masked CET microparticles (Amelian and Winnicka, 2012). The excipients used in the formulation of lyophilisates are binders (e.g. gelatin, sodium alginate, hypromellose) constituting the skeleton of the lyophilisate and providing appropriate hardness, and fillers (sugars and sugar alcohols, e.g. mannitol, sorbitol, glucose) (Ohrem et al., 2014). The choice of the optimal composition of oral lyophilisate was preceded by numerous studies in which the effect of various excipients on lyophilisates quality was examined. Lyophilisates were formulated by freeze-drying process using different concentration of gelatin, mannitol and sodium bicarbonate and formulation characterized by the most favorable physicochemical properties was selected.

The purpose of the present study was to prepare orally disintegrating tablets and oral lyophilisates containing taste masked microparticles with CET. Designed formulations were examined in terms of mechanical properties, and uniformity of weight and thickness. Morphology of formulations was determined by scanning electron microscopy. Disintegration time and sensory evaluation of the tablets and lyophilisates were measured *in vivo* and *in vitro*. The primary method for the taste measurement is human sensory evaluation. Taste-sensing by human taste panel has some difficulties due to high variability and subjectivity, therefore particularly important aspect of this work was the evaluation of taste masking efficacy by a multichannel taste detector (e-tongue), which is promising and useful tool to evaluate pharmaceutical formulations (Ahn et al., 2016; Nakamura et al., 2015; Latha and Lakshmi, 2012).

2. Materials and methods

2.1. Materials

Ludiflash® and crospovidone (Kollidon® CL-SF - superfine) were obtained from BASF, Ludwigshafen, Germany. Magnesium stearate was a product of POCH, Piekary Śląskie, Poland. Gelatin (type B), sodium bicarbonate, mannitol and glycerol were purchased from Sigma Aldrich, Steinheim, Germany. Water was distilled and passed through a reverse osmosis system Milli-Q Reagent Water System (Billerica, MA, USA). Polivinyl chloride (PCV) blisters (diameter of 13 mm and a depth of 5 mm) were obtained from Fagron, Kraków, Poland. Cetirizine dihydrochloride (CET) was a gift from ZF Polfa S.A., Warszawa, Poland. Polyvinyl chloride (PVC), plasticizers, lipophilic salts, ionophores were obtained from Fluka (Sigma-Aldrich, Saint Louis, MO, USA).

2.2. Microparticles

Based on the preliminary studies, microparticles formulation with acceptable taste and appropriate release profile was chosen (Amelian et al., 2017). Microparticles were obtained by the spray drying method using Mini Spray Dryer B-290 (Buchi Labortechnik AG, Flawil, Switzerland). CET/polymer ratio of 0.5:1 and 10% Eudragit® E PO was used for microparticles formulation.

2.3. Preparation of orally disintegrating tablets

Orally disintegrating tablets (composition per tablet: 150.8 mg Ludiflash, 5.4 mg Kollicoat® CL-SF, 1.8 mg magnesium stearate and microparticles with CET in the amount corresponding to 10 mg of CET) were prepared by direct compression method using a single punch tablet machine (Type XP1, Korsch, Berlin, Germany) equipped with 8 mm diameter flat-faced punches. In order to set the appropriate parameters of the direct compression, different tensile force values were tested. The tensile force at which no damage of the surface of microparticles was observed, was applied for the process of tableting.

2.4. Preparation of oral lyophilisates

Oral lyophilisates (composition per lyophilisate: 5.0 mg gelatin, 50.0 mg mannitol, 1.25 mg sodium bicarbonate and microparticles with CET in the amount corresponding to 10 mg of CET) were obtained by the freeze-drying method. Gelatin, mannitol and sodium bicarbonate were dissolved in distilled water at the temperature about 40 °C, then microparticles were suspended in the find solution. Obtained suspensions were dosed into PCV blisters, frozen at −20 °C for 10 min and freeze-dried (Lyophilizer FreeZone System, Labconco, Kansas, MO, USA). After number of preliminary tests, the following conditions were chosen: primary drying for 4 h at −48 °C, pressure of 0.08 mbar with gradually increasing the temperature to 20 °C. In the second drying step, the temperature was set to 20 °C for 1 h and vacuum pressure of 0.08 mbar.

2.5. Uniformity of weight and thickness

Weight and thickness of obtained formulations were evaluated according to the pharmacopoeial requirements (European Pharmacopoeia, 2010). Thickness was measured using calibrated digital caliper (Beta 1651 DGT, Milan, Italy). Each formulation was weighed individually using an electronic balance (XA 60/220, Radwag, Radom, Poland).

2.6. Uniformity of drug content

The amount of CET was examined using the HPLC system Agilent Technologies 1200 and Zorbax Eclipse XDB–C18, 4.6 × 150 mm, 5 μm column (Agilent Technologies, Waldbronn, Germany). Data collection and analysis were conducted with Chemstation 6.0 software. Acetonitrile/water solution (40:60, v/v) with addition of 0.1 mol L^{-1} triethylamine (pH 3.5) was used as the mobile phase. The flow rate was 1.0 mL min^{-1} and ultraviolet detection was done at 215 nm (Paw et al., 2002; Jelińska et al., 2000). CET retention time was 3.5 min. Standard calibration curve was linear over the range of 1–100 μg/mL with the correlation coefficient $R^2 = 0.999$. The studies were carried out in triplicate.

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