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Orodispersible films and tablets with prednisolone microparticles

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ABSTRACT

Orodispersible tablets (ODTs) and orodispersible films (ODFs) are solid oral dosage forms disintegrating or dissolving rapidly when placed in the mouth. One of the main issues related to their preparation is an efficient taste masking of a bitter drug substance. Therefore, the aim of this study was to prepare and evaluate the microparticles intended to mask a bitter taste of the prednisolone and use them in further preparation of two orodispersible dosage forms. Microparticles based on the Eudragit E PO or E 100 as a taste-masking agent were prepared with spray-drying technique. Tablets containing microparticles, co-processed ODT excipient Pharmaburst, and lubricant were directly compressed with single-punch tablet press. Orodispersible films were prepared by casting polymeric solutions of hydroxypropyl methylcellulose containing uniformly dispersed microparticles. Physicochemical properties of microparticles were evaluated, as well as mechanical properties analysis, disintegration time measurements and dissolution tests were performed for prepared dosage forms. Both formulations showed good mechanical resistance while maintaining excellent disintegration properties. The dissolution studies showed good masking properties of microparticles with Eudragit E 100. The amount of prednisolone released during the first minute in phosphate buffer 6.8 was around 0.1%. After incorporation into the orodispersible forms, the amount of released prednisolone increased significantly. It was probably the effect of faster microparticles wetting in orodispersible forms and their partial destruction by compression force during tableting process.

1. Introduction

The most popular form of administering a drug is still the oral route, due to the non-invasive, simple and most convenient application, which causes the highest patient acceptability and leads to the high therapy compliance. The majority of registered medicines available on the market are oral solid dosage forms. Their advantages include the dose accuracy, relatively high stability, and possibility to modify the drug release profile in order to delay or sustain the therapeutic effect, as well as to speed it up. However, the application of solid oral dosage forms in drug therapy is still associated with many challenging problems. One of them is difficulty with swallowing, mostly encountered in pediatric or geriatric populations, but also in the case of handicapped or bedridden patients. It is estimated that some swallowing issues associated with solid dosage forms are experienced by between 20% and up to 50%, of all patients. They can involve only a little discomfort when administering large sized tablets or capsules as well as more serious problems such as a drug sticking to the throat mucosa, irritation of the pharyngeal region, coughing or choking (Stegemann et al., 2012).

One of the solutions for eliminating the problems associated with swallowing solid dosage forms was the development of orodispersible formulations (orally disintegrating tablets, ODT, fast-disintegrating tablets, FDT). In the late 80s and the beginning of 90s, they were only available in a very friable and moisture-sensitive lyophilized form, but since that time the other technologies, such as molding or direct compression, have been applied to the ODT manufacturing, leading to the production of more stable forms (Yapar, 2014). The most important advantage of the ODT is their quick disintegration after contact with saliva in the mouth, which facilitates their swallowing. Another one is the ease in application, high dose accuracy, and no need of water to wash down the drug, which increases patient compliance. Quick disintegration of ODTs, in case of some drugs (e.g. selegiline, apomorphine, buspirone) can also lead to the rapid onset of action due to the pre-gastric absorption. It can significantly increase bioavailability, but on the other hand can cause toxic effects if the dose is not reduced (Seager, 1998).

Apart from the ODTs, another novel form of orodispersible drug formulation, that was introduced to the therapy in recent years, is orodispersible film (ODF, oral wafer, fast-dissolving film). It comes in the form of a thin strip and can be produced by solvent casting method, hot melt extrusion, electrostatic spinning, inkjet or

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flexographic printing. The main advantages of the ODFs are similar to the ODTs. Their disintegration time is usually shorter, due to their lower thickness, but the dose of the drug that can be incorporated into the film is strongly limited (usually not more than 60 mg). Moreover, they are more resistant to humidity and less brittle than the lyophilized ODTs.

One of the main issues related to all orodispersible dosage forms is the necessity of efficient taste-masking of a bitter drug substance. There is a wide spectrum of taste-masking technologies, including the addition of sweeteners and flavors, forming complexes with cyclodextrins, binding to ion exchange resins, cross-linking with polymers, chemical modification of drug particles or using flavor enhancers and modifiers. The drug particles can also be microencapsulated, coated with lipids, waxes or polymers with pH-dependent solubility, as well as formulated to the solid dispersion systems (Ayenew et al., 2009; Kawano et al., 2010). The addition of sweeteners or flavors in order to overwhelm the bitter taste of drugs appears to be insufficient in the majority of drugs. Therefore the most popular method of taste enhancement is to form a physical barrier between the drug and the taste buds. Microparticles can be produced by spray drying, spray congealing, spray chilling, extrusion-spheronization, hot melt extrusion, solvent evaporation, fluidized bed coating or coacervation (Gittings et al., 2014).

Among the latest approaches to taste-masking in orodispersible formulations, worth of notice is the work of Preis et al. (2012). They incorporated dimenhydrinate to the hydroxypropyl-β-cyclodextrin (Kleptose HPB oral grade), maltodextrin (Kleptose linecaps) or sulfobutylether-β-cyclodextrin (Captisol). Taste assessment was evaluated by using two electronic taste sensing systems. Formulation with Captisol presented the most effective taste-masking properties. Prepared orodispersible films were homogenous, and what is more, no recrystallization of the drug compound was observed. Dinge and Nagarsenker (2008) also incorporated active substance to the hydroxypropyl-β-cyclodextrin (Cerestar). However, the aim was not only to mask the unpleasant taste, but also to improve the solubility. Additionally, eugenol was used to improve the palatability of the films, because it masks the bitter aftertaste of the drug due to its mild local anesthetic effect. The addition of this excipient had no effect on the disintegration properties of orodispersible films. Cilurzo et al. (2011) prepared ODF containing sodium diclofenac. They utilized sweeteners: sucralose, saccharine or xylitol, and/or mint, licorice, and soft fruits flavors to mask the unpleasant taste of the active substance. A human taste panel and electronic taste-sensing systems were employed for the taste assessment. The addition of the mint and licorice flavors and sucralose mixture to the film was most appropriate to mask sodium diclofenac bitterness.

Nakano et al. (2013) compared the physical taste masking of ODT, i.e. the coating of the inactive core granules with a mixture of pioglitazone and Eudragit E PO, followed by mixing the granules with aspartame and other excipients to form the tablet with a gustatory masking procedure, including blending pioglitazone with sodium chloride and aspartame, followed by mixing the blend with other excipients to form the tablet. The visual analog scale analysis used to measure taste-masking efficiency in vivo showed that both methods efficiently suppressed the bitter taste of pioglitazone, but only gustatory masking decreased the drug astringency. Guhmann et al. (2012) used electronic taste sensors to evaluate the efficiency of the taste-masking formulations of diclofenac, prepared either by fluid bed coating of the pure drug particles or granulation of the drug and other excipients with Eudragit E PO dispersion. They proved that taste sensors are valuable tools allowing the elimination of in vivo tests, especially during entry level development studies.

Besides the many different approaches to evaluate the efficiency of taste-masking in orodispersible forms, there is still no official compendial method for this purpose. The literature reports in vitro methods such as application of electronic taste-sensing systems, dissolution studies with early stage sampling (2–5 min) or online monitoring of drug release, as well as in vivo tests conducted on humans or animals. FIP/AAPS proposed in 2003 the dissolution threshold of API usually providing efficient taste masking as a 10% of drug release within the first five minutes of the dissolution test. However, this value has only theoretical meaning and is strongly dependent on the drug substance and the individual taste sensibility (Siewert et al., 2003).

The aim of the present study was to prepare and evaluate the microparticles intended to mask a bitter taste of the prednisolone and use them in further preparation of two orodispersible dosage forms, i.e. orodispersible tablets (ODTs) and orodispersible films (ODFs).

2. Materials and methods

2.1. Materials

Pharmaburst 500 (SPI Polyols, USA), Pruv – sodium stearyl fumarate (JRS Pharma, Germany), prednisolone base (Henan Lihua, China), Eudragit E PO, Eudragit E 100 (Degussa, Germany), Aerosil 200 – colloidal silicon dioxide (Evonik, Germany), Pharmacoat 606 – hydroxypropyl methylcellulose (ShinEtsu Chemical Co., Japan), polyethylene glycol 200 (PEG 200, Roth, Germany), glycerol (PharmaCosmetics, Poland).

2.2. Methods

2.2.1. Preparation of spray dried microparticles

Two different kinds of microparticles were prepared: one based on the water dispersion of Eudragit E PO, and one based on organic solution of Eudragit E 100. The spray drying was performed with a Büchi Mini Spray Dryer B-191 equipped with a two-fluid pressure nozzle with 0.7 mm internal diameter. Based on the preliminary studies, the optimal 1:2 drug to polymer ratio was chosen for both formulations.

The water dispersion of prednisolone and Eudragit E PO was mixed with Ultra-Turrax for 45 min at 10,000 rpm, and spray dried. In the case of Eudragit E 100, acetone-isopropanol solution (1:2) was used as a solvent. The prednisolone solution in acetone was added to the dissolved polymer and the mixture was spray dried.

The experiment was carried out under the following conditions: inlet air temperature – 70 °C for the Eudragit E PO suspension and 40 °C for the E 100 solution, aspirator setting 100%, nozzle air flow – 800 NL/h, peristaltic pump setting 10–20%, giving flow of about 3–5 mL/min. The dried products were carefully removed from the product vessel after the process, and weighed in order to determine the process yield.

2.2.2. Preparation of tablets

Orodispersible tablets containing 15% of microparticles, i.e. 10 mg of prednisolone, were directly compressed with a single punch tablet press Korsch EK0 (Germany). They contained ready-to-use co-processed excipient for direct compression of ODTs – Pharmaburst 500 (82.5%) and sodium stearyl fumarate as a lubricant (2.0%). Silicon dioxide (0.5%) was added to achieve the better flowability of tablet mass necessary for the tableting process. The tablets' diameter was 9 mm and mass 200 ± 10 mg.

2.2.3. Preparation of films

In order to evaluate the effect of microparticles on the properties of the thin films, two kinds of films were prepared by casting method (Table 1). The hydroxypropyl methylcellulose (HPMC)