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Original research

Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology

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ABSTRACT

The objective of this study was to enhance the solubility as well as to mask the intensely bitter taste of the poorly soluble drug, Mefenamic acid (MA). The taste masking and solubility of the drug was improved by using Eudragit® E PO in different ratios via hot melt extrusion (HME), solid dispersion technology. Differential scanning calorimetry (DSC) studies demonstrated that MA and E PO were completely miscible up to 40% drug loads. Powder X-ray diffraction analysis indicated that MA was converted to its amorphous phase in all of the formulations. Additionally, FT-IR analysis indicated hydrogen bonding between the drug and the carrier up to 25% of drug loading. SEM images indicated aggregation of MA at over 30% of drug loading. Based on the FT-IR, SEM and dissolution results for the extrudates, two optimized formulations (20% and 25% drug loads) were selected to formulate the orally disintegrating tablets (ODTs). ODTs were successfully prepared with excellent friability and rapid disintegration time in addition to having the desired taste-masking effect. All of the extruded formulations and the ODTs were found to be physically and chemically stable over a period of 6 months at 40 °C/75% RH and 12 months at 25 °C/60% RH, respectively.

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1. Introduction

The oral route of drug administration has many advantages over other routes (i.e. simple self-administration, painlessness compared to the parenteral route, and often excellent patient compliance) and, is generally considered to be the most important route for a drug delivery system [1–4]. However, some patients may find it difficult to swallow intact tablets or capsules. This is particularly true for both pediatric and geriatric populations, who have a tendency to suffer from dysphagia, or among those who suffer from certain mental disorders. These problems could be overcome, in part, by developing orally disintegrating tablets (ODT). These tablets have the capability to dissolve in the mouth rapidly without the need of additional water, or they can dispersed directly in water to make a suspension which is then administered as a liquid [5,6]. The U.S. FDA has defined ODTs as “A solid dosage form containing medical substance or active ingredient which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue” therefore the disintegration time for ODT's are limited from seconds up to a minute [7]. In addition to rapid disintegration concerns, ODT formulations must also provide sufficient taste masking as the tablet dissolves in the oral cavity thereby allowing the drug to come into direct contact with the patient's taste buds. The bitter taste of the drug could be prevented

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from coming in directly contact with the patient's tongue, via the formulation of a solid dispersion system [8].

According to the drug discovery field, more than 50% of the active pharmaceutical ingredients (APIs) belongs to class II of Biopharmaceutical classification system (BCS), characterized as poorly soluble compounds resulting in low bioavailability, which is a major disadvantage in oral drug delivery systems [9]. The bioavailability can be enhanced by increasing the apparent solubility of the API [10–12]. Various strategies for improving solubility of poorly water soluble drugs have been developed, such as micronization, chemical modification, pH adjustment, solid dispersion formation, complexation, co-solvency, micellar solubilization, hydrotropy etc [14]. Amorphous solid dispersion formulation is a technique that leads to the conversion of the crystalline lattice to the amorphous phase and disperses the drug molecules in a suitable carrier in order to enhance the solubility of the drug [15]. High drug load in the drug delivery system, especially in solid dispersion systems, is crucial when high dosing is required. Thus, the present study has employed hot-melt extrusion (HME) technology to improve the solubility and to mask the bitter taste of the API in the ODT formulations with maximized drug load.

Over the last decade, HME has been used as a processing technique in the pharmaceutical industry for the formulation of oral solid dosage forms. HME has multiple inherent advantages such as elimination of organic solvents and fewer processing steps compared to the other pharmaceutical technologies [13,16]. HME has been used to form solid dispersions in order to increase the bioavailability of many drugs by increasing their solubility. This is especially true for BCS class II drugs [17–19]. Also, HME has been utilized for taste masking purposes [20]. Mefenamic acid (MA) [2-(2,3-dimethyl phenyl) aminobenzoic acid], is a non-steroidal anti-inflammatory agent, which acts by inhibiting the activity of cyclo-oxygenase-2 and thereby the production of prostaglandin [21]. It is an odorless white or light gray powder with a melting point of 230°–231 °C, with an unpleasant taste, which could lead to patient compliance issues [22,23] was used as a model drug.

Based on our knowledge, there is no MA ODT available on the market. In addition, there are no taste masking studies reported in the literature regarding the bitter taste of MA. Therefore, the objectives of the present study were to mask the bitter taste and to enhance the solubility of MA using HME solid dispersion techniques, and to optimize the HME processing conditions to manufacture stable orally disintegrating tablets by incorporating milled extrudates. In this study, the authors selected Eudragit® E PO (aminoalkyl methacrylate copolymer) and explored its solubilizing and taste making potential for MA by HME.

2. Materials and methods

2.1. Materials

Mefenamic acid (MA) was purchased from Sigma Aldrich (Bellefonte PA. USA); Eudragit® E PO and Aerosil® was gifted by Evonik (Evonik Industries, Germany); Avicel® 200 was gifted by FMC Biopolymers (Philadelphia, PA. USA); Polyplasdone™ crospovidone was gifted by ISP Technologies (ISP Technologies, Inc., Wayne, NJ, USA); Magnesium stearate was purchased from Mallinckrodt (St. Louis, MO, USA). All other chemicals used were of analytical grade.

2.2. Preparation methods

2.2.1. Preparation and evaluation of hot-melt extrudates

2.2.1.1. Thermal gravimetric analysis (TGA). The thermal stabilities of Eudragit® E PO, Mefenamic acid and the physical mixtures, were determined in the temperature range of 30 °C–250 °C, at heating rate of 20 °C/min by TGA (Pyris 1 TGA, Perkin Elmer) using Pyris manager software (PerkinElmer Life and Analytical Sciences, 719 Bridgeport Ave., CT, USA). The analysis was performed on samples of approximately 3–5 mg and evaluated as a function of weight loss.

2.2.1.2. Preparation of hot melt extrudates. Mefenamic acid was blended with Eudragit® E PO at drug loadings of 20%, 25%, 30%, and 40% using a V-shell blender (GlobePharma, Maxiblend®, New Brunswick, NJ). The binary mixtures of drug and polymer were extruded using a co-rotating twin-screw extruder (16 mm Prism Euro Lab, ThermoFisher Scientific) at 110 °C with a screw speed of 100 rpm. The extrudates were further processed using a comminuting mill (Fitzpatrick, Model L1A), which was sieved by USP mesh (#35).

2.2.1.3. Determination of drug loading using differential scanning calorimetry (DSC). DSC (Diamond DSC, Perkin Elmer) equipped with Pyris manager software, was utilized to determine the physical properties, stability and miscibility of binary mixture of MA with the Eudragit® E PO in each physical mixture and the extrudates. Samples were prepared by weighing 2–4 mg each in hermetically sealed aluminum pans and analyzed at a heating rate of 20 °C/min under an inert nitrogen atmosphere at a flow rate of 20 ml/min, over a temperature range of 30 °C–250 °C.

2.2.1.4. Powder X-Ray diffraction (PXRD). PXRD measurements were used to study the crystallinity of the MA in melt extrudates. The PXRD studies were performed using a powder X-ray diffraction apparatus (Bruker AXS, Madison, MI) at room temperature using CuKα radiation at 15 mA and 30 kV, 4°/min, and diffraction angles (2θ) of 1–40°.

2.2.1.5. Fourier transform infrared spectroscopy (FT-IR). FT-IR spectroscopic analysis was performed on the extruded samples to study the drug–polymer interactions and corroborate the miscibility results obtained by DSC. FT-IR was conducted on a Cary 660 bench (Agilent Technologies, Santa Clara, CA.). The bench was equipped with an ATR (Pike Technologies MIRacle ATR, Madison, WI), which was fitted with a single bounce diamond coated ZnSe internal reflection element.

2.2.1.6. Scanning electron microscope (SEM). The surface morphology of the pure drug and milled extrudates were evaluated and studied using SEM. Samples were mounted on adhesive carbon pads placed on aluminum stubs prior to sputter coating. A Hummer® 6.2 sputtering system (Anatech LTD, Springfield, VA) in a high vacuum evaporator were used to sputter-coated the samples with gold. SEM (JEOL JSM-5600) operating at an accelerating voltage of 10 kV was used for imaging. Three magnificent (500×, 1000×, 1500×) were used to give more accurate and clear results comparing each blend with pure MA.

2.2.1.7. Quantitative evaluations on extrudates. All of the prepared extrudates were evaluated for content uniformity and dissolution profiles. The milled extrudates were filled into hard HPMC capsules for *in vitro* drug release studies, each capsule containing the equivalent amount of 100 mg MA. The capsule dissolution tests were conducted in 500 ml of acetate buffer (pH 5.5) dissolution medium utilizing a USP apparatus II (Hanson SR8) at 37 ± 0.5 °C for 120 min with a rotation speed of 100 rpm (n = 3) [24]. All of the samples from the content uniformity test and dissolution studies were analyzed using a Waters HPLC-UV system.

2.2.1.8. HPLC method. A Waters HPLC (Waters Corp, Milford, MA,