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Fast releasing oral electrospun PVP/CD nanofiber mats of taste-masked meloxicam

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ABSTRACT

Fast release and taste masking of meloxicam (MX)-loaded polyvinylpyrrolidone (PVP)/cyclodextrin (CD) nanofiber mats were developed using an electrospinning process. CDs were blended to improve the stability of the mats. The morphology and diameter of the mats were determined using scanning electron microscopy (SEM); physical and mechanical properties were also studied. The MX content, disintegration time, MX release and cytotoxicity of the mats were investigated. *In vivo* studies were also performed in healthy human volunteers. The results indicated that the mats were successfully prepared with fiber in the nanometer range. MX was well incorporated into the mats, with an amorphous form. The mats showed suitable tensile strength. CDs improved the physical stability by their cage-like supramolecular structure to protect from humidity and moisture, and create bead free nanofiber mats. The nanofiber mats with CDs were physically stable without any hygroscopicity and fusion. A fast disintegration and release of MX was achieved. Moreover, this mat released MX faster than the MX powder and commercial tablets. The cytotoxicity test revealed that mats were safe for a 5-min incubation. The disintegration studies indicated that *in vivo* disintegration agreed with the *in vitro* studies; the mat rapidly disintegrated in the mouth. The less bitter of MX was occurred in the mats that incorporated CD, menthol and aspartame. In addition, this mat was physical stable for 6 months. The results suggest that these mats may be a good candidate for fast dissolving drug delivery systems of bitter drugs to increase the palatability of dosage forms.

1. Introduction

Among the delivery routes, oral drug delivery is the most acceptable according to patients. Recently, new strategies for oral drug delivery have gained increasing interest. One such new approach is an oral disintegrating dosage form, a solid dosage form that quickly dissolves or disintegrates in the oral cavity. Oral disintegrating tablets (ODTs) are tablets containing medicinal substances that disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue (Hirani et al., 2009). These tablets hold advantages for geriatric and pediatric patients. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short dissolution and disintegration time. Therefore, oral disintegrating films (ODFs) are developed (Nagar et al., 2001). Essentially, ODFs can be considered to be a thin film containing one or more drugs that are intended to be placed on the tongue for rapid disintegration or dissolution in the oral cavity, resulting in the enhancement of drug solubility, release, onset of action and bioavailability (Dixit and Puthli, 2009; Li et al., 2013). They combine the advantages of tablets along with those of liquid dosage forms. The larger surface area leads to rapid disintegration and dissolution, and their flexibility allows for simple transportation, consumer handling and storage. ODFs can be prepared with hydrophilic polymers, by either the film casting or hot melt extrusion method. The film casting process involves the casting of a solution to yield the films. Alternatively, hot melt extrusion is a process that forces the blend of melted polymers to create films (Douroumis, 2011).

Currently, the polymer fiber materials or nanofiber mats with diameters in the nano-range are attractive. Their remarkable

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characteristics, such as large surface area to volume ratio and high porosity, make the nanofiber mats optimal candidates for ODF formulation. A number of processing techniques including drawing, template synthesis, phase separation, self-assembly, electrospinning, *etc*. have been used to prepare these nanofiber mats (Huang et al., 2003). Electrospinning has been shown to be a viable technique to produce nanofibers that can be further developed into a continuous production of nanofiber mats from polymer solution. Thus, this technique is a good choice for developing nanofiber mats as ODFs. The desired characteristics of these nanofiber mats for ODFs are to have a fast disintegration/dissolution time and a pleasant taste in the oral cavity. To achieve rapid disintegration, dissolution and drug release, an appropriate water soluble polymer is necessary. Polyvinylpyrrolidone (PVP) is a water-soluble polymer that can provide these features. Nonetheless, its hygroscopic nature induces water absorption up to 40% of its weight in atmospheric conditions and may subsequently result in unstable nanofiber mats (Haaf et al., 1985). Cyclodextrins (CDs) are cyclic oligosaccharides that have the ability to form an inclusion complex by taking up an entire molecule or some non-polar part into their cavity (Brewster and Loftsson, 2007). This cyclodextrin inclusion complex can be applied for the enhancement of drug solubility and stability. A previous report illustrated that PVP containing β-cyclodextrin (βCD) successfully prepared the nanofiber mats *via* electrospinning technology (Bai et al., 2008a). Thus, blending CDs with PVP are of particular interest to improve PVP stability. Moreover, CDs may have potential for reducing the unpleasant taste by encapsulating the drug molecules at the molecular level (Loftsson and Brewster, 1996). Additionally, sweeteners and flavors are used for taste masking.

Meloxicam (MX), a non-steroidal anti-inflammatory drug, is produced commercially in various dosage forms (suspensions and tablets). However, these dosage forms have received poor acceptance because of their bitter taste and difficulty swallowing, especially in children (Mennella et al., 2013). In addition, incomplete drug absorption after oral administration has occurred due to its low solubility (Hörter and Dressman, 2001; Martinez and Amidon, 2002). Thus, the objectives of this study are to improve upon these limitations and prepare fast releasing and taste masking formulations of this drug. The MX-loaded PVP nanofiber mats as ODFs were developed by an electrospinning process. The creation of PVP nanofibers and incorporation of CDs and sweeteners were conducted to enhance MX solubility, disintegration time, MX release, and the taste and palatability of dosage forms. The nanofiber mats were evaluated for MX content, disintegration time, MX release characteristics, cytotoxicity and stability. *In vivo* studies were also conducted to investigate the disintegration time and texture of the MX-loaded nanofiber mats in healthy human volunteers.

2. Materials and methods

2.1. Materials

MX was received from Siam Pharmaceutical Co., Ltd., Thailand. PVP (MW ~~ 1,300,000), β-cyclodextrin (βCD), 2-hydroxypropyl-β-cyclodextrin (HPβCD) with molar substitution 0.6 and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) were purchased from Sigma Chemical Co., USA. Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), Trypsin–EDTA, L-glutamine, penicillin, streptomycin and amphotericin B were purchased from Gibco BRL (Grand Island, NY, USA). Menthol and aspartame were used as received. All other reagents and solvents were analytical grade. Only deionized water was used in this work.

2.2. Solubility studies of MX

The solubility of MX was determined using the shaken flask method. Excess MX was added to a microcentrifuge tube containing the selected solvents. The solution was mechanically shaken in a horizontal shaker (30 rpm) for 72 h at 25 °C and then centrifuged to analyze the dissolved MX. The absorbance of the MX test solutions at 362 nm was determined using a UV–vis spectrophotometer (PG Instrument, Oasis Scientific Inc., USA). MX solubility studies were carried out in various single solvents (USP buffer solution pH 3, 6 and 8, PEG 400, dimethylformamide (DMF) and benzyl alcohol (BzOH)), binary solvent mixtures of USP buffer solution pH 3, 6 and 8 with ethanol at 1:1 volume ratio and ternary solvent mixtures (USP buffer solution pH 8/ethanol (1:1) with PEG 400, DMF and BzOH from 0 to 100% v/v). The experiments were performed in triplicate. Absorbance was correlated using a calibration curve in order to determine the amount of MX.

2.3. Electrospinning of PVP/CD nanofiber mats

The 10% w/v PVP solution was prepared by dissolving PVP in DMF, followed by stirring for 24 h at room temperature. To determine the optimum amount of CDs for developing stable and uniform PVP/CD composite nanofibers, various amounts of HPβCD (0–150 mM) were added into the PVP solution. The viscosity, conductivity and surface tension of these mixed solutions were determined using a Brookfield viscometer (Model DV-III ultra, Brookfield Engineering Laboratories, Inc., Massachusetts, USA), a EUTECH ECtestr11+ conductivity meter (Eutech Instruments Pte Ltd., Singapore) and a Drop shape analyzer (FTA 100, USA), respectively. The solution was contained in a 5 ml glass syringe connected with a 20-gauge, stainless steel needle (external diameter = 0.9 mm and internal diameter = 0.6 mm) at the nozzle. The needle was connected to the emitting electrode of positive polarity of a Gamma High Voltage Research device (Ormond Beach, Florida, USA). The electric potential was fixed at 15 kV. The nanofiber mats were collected as-spun on an aluminum foil that was covered on a rotating collector. The rotating diameter and speed were 6 cm and 400 m/min, respectively. The electrospinning process was conducted at 25 °C ± 2 °C, 60 ± 5% relative humidity (RH), and the collection distance was fixed at approximately 15 cm. The solution feeding rate was fixed at 0.50 ml/h using a syringe pump (Model: NE-300, New Era Pump Systems Inc.) during processing.

The morphology and diameter of PVP/HPβCD nanofiber mats were examined using a scanning electron microscope (SEM, Camscan Mx2000, England). A small section of the nanofiber mats was attached to aluminum stubs with double sided adhesive carbon tape then gold coated with a sputter coater before observation by a SEM. The average diameter of nanofiber mats was determined using image analysis software (JMicro Vision V.1.2.7, Switzerland); fifty measurements were collected from the SEM image for each sample. The morphology and diameter of each nanofiber mat was examined on day 0 and kept at room temperature for 1 month.

2.4. MX-loaded PVP/CD nanofiber mats

MX was loaded into a 10% w/v PVP solution containing 110 mM βCD or HPβCD at the intrinsic solubility concentration (25 mg/ml) and stirred by magnetic stirrer for 24 h. After stirring process, the solutions were centrifuged and filtrated. Menthol and aspartame were used as a flavoring agent and sweetening agent, respectively. The viscosity, conductivity and surface tension of the solution was measured before preparing the nanofiber mats *via* the electrospinning process as described in Section 2.3.