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Original article

Coated dextrin microcapsules of amlodipine incorporable into orally disintegrating tablets for geriatric patients

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ABSTRACT

To improve oral absorption and patient compliance when using amlodipine, novel coated dextrin microcapsules incorporable into orally disintegrating tablets (ODT's) were investigated. Amlodipine-loaded dextrin microcapsules (ADM) were prepared by spray-drying a mixture of amlodipine free base dissolved in ethanol and aqueous dextrin solution. The ADM were suspended in Eudragit® EPO solution in ethanol and subsequently spray-dried to collect coated ADM (CADM). The ADM or CADM were blended with ODT excipients and then directly compressed into ODTs. The ADM and CADM used were both spherical with smooth surfaces and had mean particle sizes of 13.3 and 18.5 μm, respectively. Amlodipine was dispersed in an amorphous state and was readily encapsulated within ADM or CADM. Unlike the ADM, the tableted CADM remained intact without rupture during tableting, which was consistent with no loss of ethanol (0.82%) entrapped in the ODTs containing the CADM (ODTs-CADM). The amlodipine content appeared to be uniformly maintained as designed in all the dextrin microcapsules and ODTs. The ODTs-CADM compressed with 3kp of hardness showed acceptable ODT characteristics: fast disintegration time (29.8 s) and low friability (0.1%). Drug dissolution from the ODTs-CADM was much faster than that of amlodipine free base itself at both pH 1.2 and 6.8 over the tested time. CADM demonstrated significantly higher plasma concentrations (2.7 fold in $AUC_{0\text{-}24h}$ and 2.5 fold in C_{max}) in SD rats than did amlodipine free base. These results indicate that CADM substantially increased the oral absorption of amlodipine and can be incorporated into ODTs while maintaining their original physicochemical features. The dextrin microcapsules coated using Eudragit® EPO may be applied to the development of an amlodipine ODT formulation for improving geriatric patient compliance.

1. Introduction

Hypertension is a major risk factor for stroke, cardiovascular and renal diseases, affecting around 40% of the global adult population [1,2]. The prevalence of hypertension increases with age and is highest (65.0%) among U.S. adults aged 60 and over [2,3]. Since vascular complications of hypertension are the leading cause of morbidity and mortality in elderly patients, their blood pressure should be actively controlled using suitable antihypertensive medications [4–6]. Amlodipine, a long-acting dihydropyridine-type calcium channel blocker, is considered to be one of the most effective and tolerable agents in the elderly for reducing blood pressure and vascular morbidity and mortality [4–7]. Like other antihypertensive drugs used for chronic conditions in the geriatric population [8,9], amlodipine has been developed into orally disintegrating tablets (ODT's) that can enhance geriatric patient compliance and acceptance for long-term daily administration [10,11].

In the formulation of amlodipine ODT's, the besylate salt form used in marketed conventional tablets has primarily been used because of its increased aqueous solubility compared to the free base [10,11]. When, instead of salt forms, amlodipine free base is intentionally employed as an alternative active ingredient, its limited oral absorption and bioavailability as a result of the lower dissolution rate and permeability characteristics in the gastrointestinal tract are challenges that must be overcome for ODT development [12,13]. Amlodipine is light-sensitive and photodegraded to therapeutically ineffective derivatives [14,15]. In previous studies, enhanced oral absorption and photostability of

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amlodipine free base were achieved by dispersing and encapsulating the amlodipine into dextrin microcapsules formed through spray-dried solid dispersion or emulsion [16,17]. The approach is supported by gelatin or dextrin-based microencapsulation used to improve the oral bioavailabilty of poorly water soluble drugs [18–21]. Amlodipine also has a bitter taste, which may lead to poor medication adherence [22,23]. Encapsulation of bitter or unpleasant tasting agents into microcapsules or microspheres prepared with aminoalkyl methacrylate copolymers effectively masks taste and is potentially applicable to ODT's [24–27]. These taste-masked microparticles do not undergo rupture or significant deformation when incorporated into ODT's [24,25]. Furthermore, no or very few changes in drug release that could lead to non-bioequivalence to the reference listed tablet products have been shown in ODT's containing microparticles [25,26].

Here, we attempted to develop an appropriate ODT formulation for amlodipine free base. A dextrin-based microcapsule system was designed as a drug micro-carrier to enhance the oral absorption and photostability of amlodipine. Subsequently, a Eudragit® EPO coat on the microcapsule surface was devised as a carrier-combined layer, which was flexible, strong enough to mask its bitter taste, and able to withstand tablet compression. Dextrin is eligible as an immediate-release microcapsule forming polymer because it is non-toxic, biocompatible, and highly water soluble [16,17,20,21]. Eudragit® EPO is suitable for the taste-masking and coating of particles to be compressed into tablets since it is a pH-dependent, flexible film forming polymer that is insoluble in saliva but soluble in the stomach [28,29]. Therefore, to improve oral absorption and administration compliance of amlodipine for geriatric patients, novel Eudragit® EPO coated dextrin microcapsules were prepared using a consecutive spray-drying process and were incorporated into ODTs by direct compression. The particle properties, drug content, dissolution and pharmacokinetic profile of amlodipine-loaded dextrin microcapsules (ADM) and coated ADM (CADM) were characterized. The ODTs containing ADM or CADM were evaluated for tablet properties and performance.

2. Materials and methods

All experiments were performed under limited illumination (30-watt red lamp, kept at a distance of about 1.5 m) to minimize the possible photo-degradation of amlodipine.

2.1. Materials

Amlodipine free base powder was donated by CJ Corp. (Seoul, Korea). Dextrin and sodium lauryl sulfate (SLS) were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). Aminoalkyl methacrylate copolymer (Eudragit® EPO), microcrystalline cellulose (Avicel® PH-102), and crospovidone (Kollidon® CL-F) were purchased from Evonik Röhm GmbH (Darmstadt, Germany), FMC BioPolymer (Philadelphia, PA, USA), and BASF (Ludwigshafen, Germany), respectively. Spray-dried mannitol (Pearlitol 200 SD) and sodium stearyl fumarate were provided as generous gifts by Roquette (Lestrem, France) and Edward Mendell Co. (New York, NY, USA), respectively. All other chemicals were of reagent grade and used without any further refinement.

2.2. Preparation of amlodipine-loaded dextrin microcapsules (ADM) and coated ADM (CADM)

ADM were prepared by a spray-drying method. Dextrin (84 g) and sodium lauryl sulfate (1 g) were dissolved in distilled water (100 g), and amlodipine free base (5 g) was dissolved in ethanol (80 g). Both solutions were pre-warmed and mixed at 55–60 °C, and the resulting mixture was spray-dried using a Büchi B-290 mini spray dryer (Flawil, Switzerland) equipped with a 0.7 mm diameter nozzle under the following conditions: inlet air temperature of 150–155 °C, outlet air temperature of 100–110 °C, spray flow control of 800 Nl/h; feed spray rate of 5 mL/min, and aspirator level of 100%. The spray-dried powdered ADM were collected and kept in a tightly sealed container at 4 °C.

ADM (82.5 g) was added to the coating solution prepared by dissolving Eudragit® EPO (17.5 g) in ethanol (600 g) with continuous stirring. The ADM-suspended coating solution was then spray-dried to collect CADM by maintaining an inlet air temperature of 90–100 °C, a feed spray rate of 7 mL/min, and an aspirator level of 100%.

2.3. Characterization of ADM and CADM

The shape and surface of ADM and CADM were observed using a Hitachi S-4800 scanning electron microscope (SEM, Tokyo, Japan) at an acceleration voltage of 3.0 kV after sputtering with platinum. The size distribution of the microcapsules was measured using a Mastersizer 2000 laser diffraction particle size analyzer (Malvern, Worcestershire, UK). Particle size was evaluated as volume-weighted mean diameter and distribution width expressed by the SPAN, which was calculated from [d (v, 0.9) – d (v, 0.1))]/d (v, 0.5) with 10% d (v, 0.1), median d (v, 0.5), and 90% d (v, 0.9) volumetric diameter data.

The thermal transition of amlodipine free base, dextrin, Eudragit® EPO, physical mixture of amlodipine with all excipients used, ADM, and CADM were examined using a Perkin Elmer 4000 differential scanning calorimeter (DSC, Norwalk, CT, USA). Approximately 7 mg from each sample was placed in an aluminum pan and scanned from 25 to 200 °C at a heating rate of 10 °C/min under a nitrogen flow of 15 ml/min. The X-ray diffractograms for the same samples were generated using a Rigaku D/MAX 2500 powder X-ray diffractometer (Rigaku, Japan), and the X-ray patterns were collected over a range of 10° to 70° on 2θ scale at room temperature.

2.4. Preparation of ODTs incorporating ADM and CADM

The ODTs containing ADM (ODTs-ADM) or CADM (ODTs-CADM) were prepared by direct compression. Microcrystalline cellulose (40 g), crospovidone (10 g), spray-dried mannitol (25 g), aspartame (3 g) and menthol (2 g) sieved through 40 mesh screens were added to the ADMs (118 g) or CADMs (118 g) and blended using a turbula mixer (Daemyoung DM-T2, Gwangmyeong, Korea) at 60 rpm for 5 min. Sodium stearyl fumarate (2 g) was added as a lubricant to the above blend and uniformly mixed for an additional 5 min. The final powder blend was compressed into ~200 mg targets using a Sejong GRC-7S rotary press (Sejong Pharmactech, Incheon, Korea). A round standard concave tooling with 9 mm diameter set was used, and the compression force was adjusted to obtain tablet hardness of 3.0 kp.

2.5. Characterization of ODTs

Weight, thickness, and hardness of randomly selected ODTs were individually measured; hardness was measured using an Erweka TBH 125 hardness tester (Heusenstamm, Germany).

Friability testing for ODTs was conducted using a Copley scientific FR 1000 friability tester (Nottingham, UK). Thirty de-dusted tablets were accurately weighed and placed in the tester drum. After 100 revolutions at speed of 25 ± 1 rpm, the tablets were re-weighed and the % friability was calculated according to the USP 35 <1216> tablet friability test method.