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Improvement of bioavailability and photostability of amlodipine using redispersible dry emulsion

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ABSTRACT

To improve the bioavailability and photostability of poorly water-soluble and photosensitive amlodipine, dry emulsion (DE) was prepared by spray-drying the oil-in-water emulsion of amlodipine. Labrafil M 1944 CS and dextrin were employed as oil phase and matrix material, respectively. Dispersing DE in distilled water formed an emulsion with a mean droplet size 1.4-fold larger than that of the homogenized amlodipine emulsion before spray-drying ($0.24 \pm 0.30\,\mu m$ versus $0.17 \pm 0.02\,\mu m$). The mean droplet size of DE remained unchanged during 6-month storage at room temperature. 94.4% versus 33.1% of amlodipine remained intact after 24-h UV irradiation of amlodipine as DE formulation or as powder. These data suggest that DE formulation greatly improved the photostability of amlodipine, as well as increasing the physical stability of emulsion systems. *In vitro* release of DE was higher than that of amlodipine powder (66% versus 48% release at 60 min). Consequently, DE formulation resulted in 2.6- and 2.9-fold higher C_{max} and $AUC_{0-24\,h}$ of amlodipine compared after oral administration of amlodipine powder in rats. Our data suggest that the DE may be a potential oral dosage form for amlodipine to improve its bioavailability.

1. Introduction

Dissolution rate is the limiting factor for the drug absorption for both class II and class IV drugs according to the biopharmaceutics classification system (Löbenberg and Amidon, 2000). Emulsion has been reported to be one of the efficient methods to improve the dissolution rate and increase bioavailability of poorly water-soluble drugs (Tarr and Yalkowsky, 1989). However, the instability of an emulsion such as creaming, flocculation, coalescence, and phase separation was often mentioned (Floyd, 1999; Welin-Berger and Bergenståhl, 2000).

Dry emulsion (DE) has been suggested as one way to circumvent such disadvantage of conventional emulsions (Vyas et al., 1992; Molina and Cadorniga, 1995; Shively and Thompson, 1995). It has been successfully applied as a potential oral drug delivery system for lipophilic and poorly soluble drug substances (Dollo et al., 2003) as well as drug substances needing protection against light (Takeuchi et al., 1992) or oxidation (Heinzelmann and Franke, 1999). Solid carriers such as sugar, trehalose, mannitol (Hansen et al., 2004), magnesium alumino metasilate (Hansen et al., 2004), hydroxypropylmethylcellulose (Hansen et al., 2005; Christensen et al., 2001)

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and maltodextrin (Dollo et al., 2003) have been implemented as a matrix material to render conventional emulsions to powdery, lipid-based formulations.

Amlodipine is a dihydropyridine calcium antagonist and its besylate salt (Norvasc® manufactured by Pfizer) is one of the most frequently prescribed antihypertensive drugs in the world (Humphreys and Boersig, 2003). In present study, amlodipine was used as a model drug with poor aqueous solubility and photostability. It has been reported that the dissolution rate of amlodipine is low due to its limited solubility in water (McDaid and Deasy, 1996). Amlodipine is also known as photosensitive since light catalyzes oxidation of amlodipine to pyridine derivatives that are therapeutically ineffective (Yeung et al., 1991; Marinkovic et al., 2000; Ragno et al., 2002).

The purpose of this study was to develop spray-dried DE of amlodipine, without utilizing any milling method or chemical modification, in order to enhance the bioavailability and photostability of amlodipine. To the best of our knowledge, no information is currently available on the improvement of photodegradation, dissolution and bioavailability of amlodipine by DE formulation. We used dextrin as a matrix material since the formulation with dextrin derivative has been reported to improve the solubility, dissolution and absorption of certain types of drugs (Te Wierik et al., 1994; Palmieri et al., 1998), and was proven to be suitable for solid dosage form due to their free-flowing property in our previous study (Lee et al., 2001).

2. Materials and methods

To minimize the photodegradation of amlodipine, all experiments were carried out under restricted illumination of a red lamp (60 W), kept at a distance of about 2 m.

2.1. Materials

Micronized amlodipine powder (mean particle size, 20 μm; particle size range, 5–30 μm) was kindly supplied by CJ Corp. (Seoul, Korea). Amlodipine besylate, ethanol, diethylether and dextrin were purchased from Pfizer Pharmaceutical (Tokyo, Japan), Aldrich Chemical Co. (Milwaukee, WI, USA), Merck (Darmstadt, Germany) and Hanawa Chemical Co. (Osaka, Japan), respectively. Isopropyl myristrate, soy bean oil, mineral oil, castor oil, cotton seed oil, corn oil, tocopherol acetate, carboxymethyl cellulose and desipramine were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Labrafac® CC, Labrafil® M 1944 CS and Plurol® Oleique CC 497 were obtained from Gattefosse (St. Priest, France). All other chemicals used were of reagent grade.

2.2. Determination of amlodipine solubility in oil

The solubility of amlodipine in various oils, e.g. isopropyl myristrate, soybean oil, mineral oil, castor oil, cotton seed oil, corn oil, Labrafac® CC, Labrafil® M 1944 CS, Plurol® Oleique CC 497 and tocopherol acetate, was determined. After adding excess of amlodipine into 1 ml of each oil in polypropylene vial, the mixture was shaken by a rotating mixer at 30 rpm, 25 °C for 72 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble amlodipine was removed by filtration using a 0.2 μm syringe filter (National Scientific, USA). The concentration of amlodipine dissolved in oil was measured at 356 nm using UV spectrophotometer (Beckman DU-600, Beckman, USA).

Table 1 – The composition of the dry emulsion admixture studied

Component	Quantity
Amlodipine	100 mg
Labrafil® M 1944 CS	4 ml
Dextrin	5 g

2.3. Preparation of dry emulsions

Four ml of amlodipine in Labrafil® M 1944 CS (25 mg/ml, concentration approaching the solubility of amlodipine in Labrafil® M 1944 CS at 25 °C) was added to 16 ml of distilled water and dispersed by magnet stirring. The coarse emulsion was further homogenized in a high pressure homogenizer (Emulsiflex C5, Avestin, Canada) at 2000 bar. The homogenized emulsion was blended with dextrin (1.25 g/ml Labrafil® M 1944 CS) as the matrix material. The resulting mixture was spray-dried using Buchi mini spray dryer B-190 apparatus (Buchi, Switzerland) under the following conditions: inlet temperature, 150 °C; aspiration, 100%; drying air flow, 800 N l/h; feeding rate of the emulsion, 7 ml/min. The condition was chosen according to the spray-drying feasibility, yield and reconstitution properties. The composition of the DE admixture is shown in Table 1.

2.4. Reconstitution of dry emulsions

In a 30-ml vial, the spray-dried powder was dispersed with the same volume of distilled water as that of the homogenized emulsion before drying (e.g. 16 ml distilled water per 100 mg amlodipine) by brief hand-shaking (10 s). After 2 h of rotation at 40 rpm using a rotating mixer (Glas-col, USA), samples were withdrawn for further characterization.

2.5. Physical stability of dry emulsions

The reconstitution properties for the DE were determined at the predetermined time intervals after being stored in a sealed bottle protected from light at room temperature. The droplet size of reconstituted DE was measured for 6 months.

2.6. Droplet and particle size measurement

The droplet size distribution of the emulsions before spray drying or after reconstituting the DE was determined by photon correlation spectroscopy using a submicron particle sizer (Nicomp 370, Particles Sizing Systems, USA). All results were recorded as volume distributions. The width of the droplet size distribution was expressed by the SPAN value: 10% volumetric $d(v,0.1)$; median $d(v,0.5)$; 90% volumetric $d(v,0.9)$ diameters.

$$\text{SPAN} = [d(v, 0.9) - d(v, 0.1)]/d(v, 0.5)$$

The particle size distribution of the DE was measured by a laser particle size analyzer (CILAS 1064, CILAS, France) after