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Solid dispersion of dutasteride using the solvent evaporation method: Approaches to improve dissolution rate and oral bioavailability in rats

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ABSTRACT

The aim of this study was to develop a dutasteride (DUT) solid dispersion (SD) using hydrophilic substances to enhance its dissolution (%) and oral bioavailability in rats. DUT-SD formulations were prepared with various co-polymers using a solvent evaporation method. The physical properties of DUT-SD formulations were confirmed using field emission scanning electron microscopy (FE-SEM), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and attenuated total reflectance Fourier transform infrared (ATR-FT-IR) spectroscopy. The toxicity and oral bioavailability of DUT-SD formulations were evaluated. Tocopheryl polyethylene glycol-1000-succinate (TPGS) was chosen as the solubilizer; and methylene chloride, and Aerosil® 200 or microcrystalline cellulose (MCC) were chosen as the solvent and carrier, respectively, based on a solubility test and pre-dissolution study. The dissolution levels of DUT-SD formulations were 86.3 ± 2.3% (F15) and 95.1 ± 1.9% (F16) after 1 h, which were higher than those of the commercial product, i.e., Avodart® (75.8 ± 1.5%) in 0.1 N HCl containing 1% (w/v) sodium lauryl sulfate (SLS). The F16 formulation was found to be stable, after assessing its dissolution (%) and drug content (%) for 6 months. The DUT-SD formulations resulted in relative bioavailability (BA) values of 126.4% (F15) and 132.1% (F16), which were enhanced compared to that of Avodart®. Dissolution (%) and relative BA values were both increased by hydrogen interaction between TPGS and DUT. This study might contribute to a new formulation (powder) whose oral bioavailability is greater than that of Avodart® (soft capsule), which could facilitate to the use of the SD system during the production process.

1. Introduction

In order to improve the oral bioavailability of poorly water-soluble drugs, many researchers have developed methods to improve the solubility and dissolution of drugs. In particular, poorly water-soluble drugs comprise 40% of the top 200 oral drugs in the US and Europe [1]. The improvement of the inherent solubility (low water solubility) of drugs is a challenge during the development of drug formulation strategies. Several systems have been used to increase the solubility of drugs, such as solid dispersion (SD) [2–6], complexation [7,8], nanocrystals [9–12], self-micro (nano) emulsification drug delivery systems (SM[N]EDDS) [13–16], emulsion [17,18], and co-crystals [19]. Among them, the solid dispersion (SD) system has been widely used to enhance the solubility and dissolution (%) of poorly water-soluble drug in pharmaceutical fields [20]. Several processes are involved in the SD system, such as melting [21,22], solvent evaporation [23], spray drying [24], supercritical anti-solvent process [25], and freeze-drying [26,27].

Dutasteride (DUT), i.e. (1S,3aS,3bS,5aR,9aR,11aS)-N-[2,5-bis(trifluoromethyl)phenyl]-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide, is a chemical inhibitor of 5-α reductase [28]. It is used for the treatment of benign prostatic hyperplasia (BPH), prostate cancer, and male pattern baldness [29]. The commercial product, Avodart® (formed soft gelatin capsule), contains 0.5 mg of DUT in mono-di-glycerides of caprylic/capric acid to improve its solubility [28]. The level of solubility of DUT is low (< 0.038 ng/mL), and it is composed of a single commercial formulation (lipid formulation in soft gelatin capsule).

Many formulations have been developed to obtain new DUT formulations having a high solubility and dissolution (%). The DUT/Eudragit E (1:10) SD formulation, which was prepared by spray drying increased the solubility to 79.1 μg/mL [28], and the DUT/HP-β-CD/

Abbreviations: DUT, dutasteride; SD, solid dispersion; DW, distilled water; FE-SEM, field emission scanning electron microscope; DSC, differential scanning calorimetry; PXRD, powder X-ray diffraction; ATR-FT-IR spectroscopy, attenuated total reflectance Fourier transform infrared spectroscopy; SLS, sodium lauryl sulfate; DMEM, Dulbecco's modified Eagle medium; MCC, microcrystalline cellulose; relative BA, relative bioavailability; TPGS, tocopheryl polyethylene glycol-1000-succinate

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HPMC 2910 (1:26.6:13.3) nanostructures formed by a supercritical antisolvent (SAS) process increased the solubility to 47.1 μg/mL. The in vitro dissolution rate of the nanostructures was higher than that of Avodart® [30]. Moreover, the dissolution rate of DUT-gelatin microparticles (containing a self-microemulsifying formulation, G13 [DUT:-Gelatin:Capryol™ 90:Cremophor EL:Transcutol HP: Soluplus® = 0.5:75:31.5:17.5:21:25]) was significantly higher (> 90%) than that of PM-G13 (physical mixture-G10) (< 10%), in DW at pHs of 1.2, 4.0, and 6.8 [31]. However, the development of a powder-type formulation is insufficient, especially if it is possible to develop powder-type formulations using specific spray drying and supercritical antisolvent (SAS) methods.

The goal of the present study was to prepare powder-type of DUT-SD formulations with solubilizers to improve solubility, dissolution (%), and oral bioavailability in rats by using a simple method of preparation. The hydrophilic solubilizers used were hydroxypropyl-β-cyclodextrin (HP-β-CD), polyethylene glycol-6000 (PEG6000), poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol) (Kolliphor® P188 and P407), tocopheryl polyethyleneglycol-1000-succinate (TPGS), and poly(vinyl pyrrolidone-covinyl acetate; VP 60% and VA 40%) (PVP/VA S-630). The carriers used were hydrophilic fumed silica (Aerosil® 200), mannitol (SD200), lactose (Flowlac® 100), and microcrystalline cellulose (MCC; Avicel® PH-102). The carriers used in SD formulation play a role in inhibiting the recrystallization of drug and stabilizer, and enhancing wettability and dispersibility [2,32,33].

The DUT-SD formulations were prepared using the solvent evaporation method in an SD system. The physical properties of DUT-SD formulations were evaluated by field emission scanning electron microscopy (FE-SEM), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and attenuated total reflectance Fourier transform infrared (ATR-FT-IR) spectroscopy. In addition, the solubility, dissolution, cytotoxicity, stability, and oral bioavailability of the DUT-SD formulations were tested in rats.

2. Materials and methods

2.1. Materials

Dutasteride (DUT) was obtained from MSN Laboratories Limited (Hyderabad, India). Avodart® soft gelatin capsules (containing 0.5 mg dutasteride) were purchased from GlaxoSmithKline (Middlesex, UK). HP-β-CD was purchased from Sigma-Aldrich (St. Louis, MO). Kolliphor® (P188 and P407), TPGS, and PEG6000 were obtained from BASF (Ludwigshafen, Germany). PVP/VA S630 was purchased from ISP Technologies Inc. (Wayne, NJ). Ethyl alcohol and methylene chloride were purchased from Samchun Pure Chemical Co., Ltd. (Pyeongtaek, Korea). Aerosil® 200 was obtained from Evonik (Essen, Germany). Mannitol (200SD) was purchased from Roquette Frères (Lestrem, France). Lactose (Flowlac® 100) was purchased from DFE Pharma (Goch, Germany). Microcrystalline cellulose (MCC, Avicel® PH-102) was obtained from Whawon Pharm (Seoul, Korea). Dimethyl sulfoxide (DMSO), tert-butyl ether and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma-Aldrich. Caco-2 cells were purchased from the Korean Cell Line Bank (KCLB) (Seoul, Korea). Fetal bovine serum (FBS), antibiotics, and Dulbecco's modified Eagle medium (DMEM) were obtained from Hyclone (Logan, UT). Acetonitrile and methyl alcohol were purchased from Burdick & Jackson (Honeywell, NJ).

2.2. Screening of solubilizers

The solubility testing of DUT was performed as described in a previously published report [34]. Approximately 5 mg of DUT was added into an aqueous solution (1 mL) in 2-mL microtubes containing 1% (w/v) of a hydrophilic carrier, which was HP-β-CD, P188, P407, TPGS, PEG6000, or PVP/VA S630, and distilled water (DW). These samples were shaken at 200 rpm at 37 ± 0.5 °C for 24 h in an incubator (LSI-3016A, Daihan Lab Tech Co., Ltd., Namyangju, Korea), and insoluble DUT was filtered through a 0.45-μm nylon syringe filter (Whatman, International Ltd., Maidstone, UK). All samples were evaluated by using high-performance liquid chromatography (HPLC) (n = 3).

2.3. Preparation of DUT-SD formulations

The preparation of DUT-SD formulations was based on solvent evaporation in an SD system [2]. TPGS was used for solubilization, based on the results obtained after screening the solubilizers. Briefly, TPGS (DUT vs TPGS; 50 mg [1:5], 100 mg [1:10], 150 mg [1:15], 200 mg [1:20], or 250 mg [1:25]) was dissolved in 5 mL of an organic solvent, such as acetonitrile, ethyl alcohol, or methylene chloride for 10 min, while stirring at 500 rpm. DUT (10 mg) was added into the TPGS solution, and then stirred at 500 rpm for 10 min. A filler (300 mg) such as Aerosil® 200, MCC, Mannitol, or Flowlac® 100 was added into the solution, while stirring at 500 rpm for 40 min. The organic solvents in the DUT-SD formulations were removed using a vacuum desiccator for 3 days (Table 1). All processes were performed at room temperature. Physical mixtures (PM) were prepared using the above method without organic solvents. The obtained solid powders were then passed through a 20-mesh sieve (0.841 mm).

2.4. Pre-dissolution test

We have developed a simplified pre-dissolution test, because it is difficult to test the dissolution of many formulations [2,4]. The pre-dissolution test was performed using a multi-channel stirrer (MS-53MH, JEIO TECH, Daejeon, Korea) in 0.1 N HCl with SLS solution (1%, w/v) at 37 ± 1 °C. The DUT-SD formulations (equivalent to 0.5 mg of DUT) were added into 250 mL of SLS solution (1%, w/v), while stirring at 500 rpm for 1 h. Samples were withdrawn at 5, 15, 30, 45, and 60 min, and then filtered through a 0.45-μm nylon syringe filter. The DUT content in the samples was determined using HPLC (n = 3).

2.5. Morphology of DUT-SD formulations

The morphologies of DUT (pure), DUT-SD formulations (F15 and F16), and DUT-PM formulations (PM-F15 and PM-F16) were evaluated using a field emission scanning electron microscope (FE-SEM) (LYRA3 XMU, TESCAN, Czech Republic). The powdered samples were placed on

Table 1
Composition of DUT-SD formulations (mg, 1 batch).

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
DUT	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
TPGS	50	100	150	200	250	50	100	150	200	250	50	100	150	200	250	250	250	250
Aerosil	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	–	–	–
MCC	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	300	–	–
Mannitol	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	300	–
Flowlac	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	300
Solvents	Acetonitrile					Ethyl alcohol					Methylene chloride							