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Development of direct compression entecavir 0.5 mg-loaded tablet exhibiting enhanced content uniformity

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ABSTRACT

The aim of the present research was to develop direct compression entecavir 0.5 mg-loaded tablet (DCET) providing enhanced content uniformity. Various compositions and preblending methods were tested at lab-scale, and the optimum composition and method were applied to pilot-scale production for further confirmation of the entire process. The content uniformity, physical properties and dissolution behavior of the final film-coated DCET were compared to the commercial product. In lab-scale preparation, the method involving preblending, micronization of API ($d_{0.5}$ = 5.13 μm), addition of a larger quantity of colloidal silicon dioxide (1%) and sieving through smaller pores (300 μm) yielded an excellent acceptance value (AV) in the content uniformity criteria compared to a control method and composition (AV 1.0 vs. 9.8). In pilot-scale production, the film-coated DCET provided better content uniformity than the commercial product (AV 1.3 vs. 3.8). Furthermore, both products exhibited similar dissolution profiles in various media. Thus, direct compression entecavir 0.5 mg-loaded tablet developed in this study would be a promising dosage form with excellent content uniformity that may be bioequivalent to the commercial product.

1. Introduction

Hepatitis B virus (HBV) annually affects approximately 400 million people across the globe [1,2] and can lead to hepatic cirrhosis, hepatic failure and hepatocellular carcinomas [3]. These complications result in about 1 million deaths per year [1]. In long-term therapy of hepatitis B, one way is to inhibit replication of HBV [4]. Entecavir potentially and selectively inhibits HBV reverse transcriptase resulting in suppression of its DNA replication [5,6]. Entecavir at a dose of 0.5 mg once daily has resulted in remarkable reduction in DNA replication of HBV [7]. Baraclude® 0.5 mg tablet (Bristol-Myers Squibb, New York, USA) is the commercial product of entecavir which has been frequently prescribed for the treatment of HBV [8,9].

In low-dose tablet formulations, content uniformity, which is an essential quality criteria to produce safe, effective unit products consistently, remains a critical challenge [10]. To overcome the problems of the content uniformity, numerous approaches have been described [11–14]. Previously, the content uniformity for low-dose formulations has been achieved by homogeneous mixing with starch 1500 [14], sugar [15], maltose and dextrose [16]. The direct compression is the simplest method to prepare tablets [14,15]. The main procedures of direct compression method generally consist of blending and tableting, which can give the advantages such as cost effectiveness, stability, faster dissolution, and simplified process validation [14,15]. However, with decreasing doses of the drug, achievement of proper content uniformity also decreases [17]. Accordingly, special care is required for direct compression of formulations containing potent active pharmaceutical ingredients (APIs) [18].

The purpose of this study was to develop direct compression entecavir 0.5 mg-loaded tablet with improved content uniformity. The optimization of formulation and method was performed at lab-scale.

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Then, the formulation and method exhibiting the optimum content uniformity at lab-scale were chosen for making direct compression tablets at pilot-scale. The content uniformity, physical properties and dissolution of the final tablet were assessed in comparison with the commercial product.

2. Materials and methods

2.1. Materials

Entecavir monohydrate was obtained from Cipla Ltd. (Mumbai, Maharashtra, India). Aerosil® 200 (colloidal silicon dioxide), Kollidon® VA64 (copovidone), Kollidon® CL (crospovidone), Pharmatose® DCL11 (lactose monohydrate), Pharmatose® 200M (lactose monohydrate), CeolusTM PH102 (microcrystalline cellulose), and Pruv® (sodium stearyl fumarate) supplied by Whawon Pharm. Co., Ltd. (Seoul, Kangnam, South Korea) were of USP grade. Commercial entecavir tablets (Baraclude® 0.5 mg) were from Bristol-Myers Squibb (New York, USA). All other chemicals were of reagent grade and were used without further purification.

2.2. Particle size reduction of API

The drug was micronized using a Micro-Jet™ Size Reduction System (Fluid Energy Processing and Equipment Co., Telford, PA, USA) with nitrogen gas at a pressure of about 100 psi. The milled drug lot was compared with the non-treated lot in the particle-size distribution, microscopic examination and thermal analysis. The detailed characterization is described below.

2.3. Particle-size distribution of API

The particle size-distribution was determined using laser scattering particle size analyzer (Master sizer 2000®, Malvern Instruments Ltd., Malvern, UK) at an air pressure of 3 bar. The particle-size distribution was evaluated by cumulative distribution data ($d_{0.1}$, $d_{0.5}$ and $d_{0.9}$ measurements). The median diameter ($d_{0.5}$) was considered for comparing particle-size of the milled and non-treated API.

2.4. Thermal characterization

Thermal analysis was performed using differential scanning calorimetry (DSC-Q10, TA Instruments; New Castle, Delaware, USA) and thermal gravimetric analysis (TGA-Q50, TA Instruments; New Castle, Delaware, USA). For DSC, about 4 mg of each sample was sealed in an aluminum pan and heated from 25 to 250 °C at a rate of 10 °C/min. For TGA, about 4 mg of each sample was heated up to 800 °C at a rate of 10 °C/min.

2.5. Microscopic examination

Polarized microscopic images of jet-milled drug and non-treated API were captured at 400-fold magnification using an optical microscope (Olympus BX51, Olympus Optical Co., Tokyo, Japan) to examine particle size and homogeneity.

2.6. High performance liquid chromatography (HPLC) assay

For the HPLC analysis of entecavir in the standard and sample solutions, Agilent 1200 HPLC system (Agilent Technologies, Santa Clara, CA, USA) outfitted with a C18 column (Symmetry®, Waters, 5 μm, 100 mm × 4.6 mm i.d.) and UV detector (Model L-7450, Agilent Technologies, Santa Clara, CA, USA) was used. The injection volume was 75 μl. The mobile phase (water/acetonitrile, 92/8, v/v) eluted at the rate of 1.0 ml/min was monitored at 254 nm for entecavir concentration measurement.

Table 1
Compositions of entecavir 0.5 mg-loaded core tablet in the divided four steps.

Ingredients in each step	F1	F2	F3
	Amount (mg)		
Preblending I			
Entecavir monohydrate	0.503	0.503	0.503
Aerosil® 200 (colloidal silicon dioxide)	0.000	0.500	1.000
Pharmatose® 200M (lactose monohydrate)	20.000	20.000	20.000
Preblending II			
Pharmatose® DCL11 (lactose monohydrate)	99.497	98.997	98.497
Blending			
Ceolus™ PH102 (microcrystalline cellulose)	65.000	65.000	65.000
Kollidon® VA64 (copovidone)	5.000	5.000	5.000
Kollidon® CL (crospovidone)	8.000	8.000	8.000
Final blending			
Pruv® (sodium stearyl fumarate)	2.000	2.000	2.000
Total (mg/tablet)	200.000	200.000	200.000

2.7. Lab-scale preparation of DCET

The composition of each formulation and the characteristics of each batch are summarized in Tables 1 and 2, respectively. The batch size for lab-scale preparations was 1000 tablets. The entire blending method for B2–B8 consisted of four steps: preblending I, preblending II, blending and final blending. However, B1 was prepared using only the latter two steps.

In step 1 (preblending I), entecavir monohydrate and Pharmatose® 200M, with or without Aerosil® 200, were mixed together in a cube mixer (AR403 equipped with KB15, Erweka, GmbH, Frankfurt, Germany) for 5 min at 60 rpm (Table 1). Subsequently, the mixture was sieved through a specific screen diameter (Table 2) and poured into the cube mixer again. In step 2 (preblending II), Pharmatose® DCL11 was added to each preceding mixture as shown in Table 1 and mixed for 5 min at 60 rpm. The sieving after preblending II was performed for B3, B5, B6, B7 and B8 only (Table 2). In step 3 (blending), Ceolus™ PH102, Kollidon® VA64 and Kollidon® CL were added, and further mixed for 20 min at 60 rpm. In step 4 (final blending), Pruv® pre-sieved through 50 mesh was incorporated into the blended mixture and further blended for 3 min at 60 rpm. For the control batch (B1), all constituents (except Pruv®) were mixed in the cube mixer for 20 min at 60 rpm, and Pruv® was added and mixed for further 3 min at 60 rpm.

The entecavir 0.5 mg-loaded core tablets with a triangular shape and 5–6 KP hardness were directly compressed with the above-mentioned each final blend using ERWEKA tablet machine (GmbH, Frankfurt, Germany) [19].

2.8. Pilot-scale production of film-coated DCET

At pilot-scale production, batch size was 10,000 tablets. The composition of the formulation was exactly the same as F3 (Table 1). Moreover, the preparation method was the same as for B8 (Table 2).

Table 2
Summary of preparation characteristics for the lab-scale batches.

Batch number	Composition[a]	API particle size ($d_{0.5}$, μm)	Screen-hole diameter (μm)	Sieving times
B1	F1	17.72	N/A	N/A
B2	F1	17.72	600	1
B3	F1	17.72	600	2
B4	F2	17.72	600	1
B5	F2	17.72	600	2
B6	F3	17.72	600	2
B7	F3	5.13	600	2
B8	F3	5.13	300	2

[a] The composition given in Table 1.