Development of A New Manufacturing Process for Oral Cladribine for the Treatment of Multiple Sclerosis

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Abstract

This work assessed the feasibility of replacing the lyophilization manufacturing process with fluid-bed coating as a new method for preparing a cladribine-cyclodextrin inclusion complex. The objective was to enhance the processing time, cost, and quality of the finished product by switching from poorly compressible lyophilized powder to coated pellets filled into capsules. The inclusion complex of cladribine and 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) dispersed in water was sprayed and deposited onto the surface of the microcrystalline pellets. Several factors were assessed in this study, including pellet particle size, drug to HP-β-CD complexation ratio, complexation temperature, and solution concentration. Various analytical testing tools were used to determine the optimum cladribine pellets. This includes dissolution testing using various media, Fourier transform infrared (FTIR), X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), scanning electron microscope (SEM), and stability study. The dissolution test revealed a profile similar to that of Mavenclad (reference listed drug of cladribine manufactured by Merck & Co., Inc.). Additionally, FTIR, XRPD, and DSC characterization techniques

suggested the conversion of free API to complex form. Furthermore, SEM micrographs demonstrated uniform pellets surface when using HPMC E5. The stability testing (including physical stability, water content, dissolution, and assay) of cladribine pellets at different storage conditions showed comparable results when compared to the initial data. Eventually, the batch prepared with pellets having a particle size of 350 µm, a 1:14 complexation ratio of cladribine to HP-β-CD, a solution temperature of 48°C, and an inclusion complex solution with 687.5mg/capsule of water demonstrated the most satisfactory outcomes. It is concluded that fluid-bed coating could be used as a new technique to prepare the cladribine cyclodextrin inclusion complex.

Keywords: Cladribine, dissolution, inclusion complex, physical characterization, 2-hydroxypropyl-b-CD.