Development of a Sustained-Release Donepezil Hydrochloride Formulation with Improved Drug Content and Tablet Content Uniformity via Hot-Melt Extrusion Technology

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Purpose
The objective of this study was to develop a sustained-release donepezil hydrochloride (DH) formulation with improved drug content and tablet content uniformity by hot-melt extrusion (HME).

Methods
DH is a highly water-soluble drug and is a centrally acting reversible inhibitor of acetylcholinesterase. Aricept® is the commercial product of DH and in this study it was used as a control formulation. Thermal stability of DH and the hydrophobic carrier matrix (Compritol® 888 ATO) at processing temperatures was determined by thermogravimetric analysis (TGA, Pyris 1 TGA Perkin Elmer). DH and the hydrophobic carrier (1:2) were blended with or without microcrystalline cellulose (65%) as a tablet diluent using a V-shell blender (MaxiBlend™, GlobePharma, North Brunswick, NJ, USA) at 25 rpm for 15 min. These two physical mixtures were extruded using a co-rotating twin-screw extruder (16 mm Prism Euro Lab, Thermo Fisher Scientific) at 50-100 rpm. The extrudates were obtained in the form of rods and further pulverized using a comminuting mill (Model L1A, Fitzpatrick, Perth Amboy, NJ). The milled extrudates were compressed on single punch tablet press (MCTMI, Globepharma Inc., New Brunswick, NJ), by using an 8 mm flat round punch. Magnesium stearate (1%) was added as a lubricant just before the direct compression process and each compressed tablet weighed 200 mg. Differential scanning calorimetry (DSC, Diamond DSC, Perkin Elmer) and PXRD (Bruker AXS, Madison, MI) were utilized to determine the physical properties of API in each blend and extrudates. In-vitro release studies were performed using a USP dissolution apparatus-II, in pH 6.8 phosphate buffer maintained at 37°C and a paddle speed of 50 rpm for 10 hours. All dissolution samples were analyzed using a Waters HPLC-UV system (Waters Corp).

Results
Thermal stability of DH, Compritol® 888 ATO, and microcrystalline cellulose was confirmed by the TGA. DSC and PXRD demonstrated the crystalline status of the drug based on processing temperatures. The formulation with Compritol® 888 ATO along with microcrystalline cellulose was extrudable at the lowest processing temperatures (60-70°C). Drug content and tablet content uniformity analysis displayed that the drug was uniformly distributed within the tablets with a standard deviation of <4%, indicating a good formulation and process. The extrudates with microcrystalline cellulose exhibited a 102.4% drug content compared to those without microcrystalline cellulose, which was approximately 71.4%. The premixed microcrystalline cellulose formulation containing a mixture of DH, Compritol® 888 ATO and microcrystalline cellulose, exhibited a more sustained drug release as compared to the marketed Aricept® formulation.

Conclusion
Highly water-soluble drugs such as DH can be prepared as a sustained release formulation, with improved drug content and content uniformity while maintaining the drug’s crystallinity, using a twin-screw extrusion process employing the extrusion of premixed microcrystalline cellulose embedded within a hydrophobic matrix and a relatively low processing temperature profile.

Acknowledgments
This project was partially supported by Grant Number P20GM104932 from the National Institute of General Medical Sciences (NIGMS), a component of NIH.