Kinetic Model for Solid-State Degradation of Gabapentin

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ABSTRACT: Gabapentin degrades directly to gabapentin-lactam (gaba-L) in the solid state. The objective of this study was to formulate a drug degradation model that accounted for the environmental storage conditions and mechanical stress (prior to storage) on lactamization kinetics. The effects of mechanical stress on drug degradation kinetics were determined by milling gabapentin in a FRITSCH Planetary Micro Mill for 0 and 60 min. The resultant gabapentin powder was stored at 40°C–60°C and 5%–30% relative humidity. The rate of gaba-L formation was measured by high-performance liquid chromatography. An irreversible two-step autocatalytic reaction scheme was fit using nonlinear regression methods. The resultant kinetic model was used to predict the time-dependent concentration of degradant of gabapentin tablets prepared under various exemplary manufacturing conditions, thereby demonstrating the ability of the model to link manufacturing variation and chemical stability in solid-state gabapentin formulations. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:2123–2133, 2012

Keywords: chemical stability; crystal defects; dehydration; milling; physical stability; solid-state stability; mathematical model

INTRODUCTION

The use of gabapentin as a model for studying the connection between manufacturing-related stress and solid-state oral drug product has been the subject of a US Food and Drug Administration (FDA)-supported, multiyear project involving researchers at nine universities working collaboratively with industrial and governmental scientists.[1] The overarching objective of this multi-institutional project was to incorporate stability and unit operation scaling issues into a quality-by-design paradigm for manufacturing quality control. Gabapentin is an ideal model compound for this project because of its proclivity to exist in various physical forms, its propensity to undergo structural disorder when subjected to mechanical stress, and the susceptibility of the disordered material to chemical degradation by intramolecular cyclization.

This manuscript represents one of a series of reports on the underlying physical chemistry of gabapentin that provides the scientific foundations for underlying the manufacturing–product performance relationships described in the final statistical design space models. The complete reports on additional scientific foundations and applications leading to and including the design space and product performance prediction models are currently being prepared for publication.

Gabapentin, a γ-aminobutyric acid, was originally developed to treat epilepsy. Its major chemical degradation pathway is intramolecular cyclization to form gabapentin-lactam (gaba-L) by nucleophilic attack of the amine on the carboxylate carbonyl followed by dehydration. We have previously reported that the formation of lactam is irreversible in solution and solid state under mild pH and temperature conditions associated with gabapentin formulations.[1] Gaba-L has a reported toxicity of 300 mg/kg (DL_{50}, mouse) compared with 8000 mg/kg for gabapentin.[2,3] The US Pharmacopeia has a limit on gaba-L to be no more than 0.4% in gabapentin tablets.[4] Thus, minimizing lactamization is a critical product quality attribute.

Gabapentin has been reported to exist in three polymorphs (forms II, III, and IV) and in a monohydrate (form I).[5,6] All polymorphs are described by intermolecular hydrogen bonds between amino and carboxyl groups from neighboring molecules; intramolecular hydrogen bonds have been reported for form III.[6] Form II is the most physically stable anhydrous form and is the predominant form present in solid pharmaceutical dosage forms. Forms III and IV have been reported to transform into form II under a variety of

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conditions including exposure to elevated humidity (e.g., 50% relative humidity or RH).[7] Thermal treatment and mechanical stress (e.g., milling) have been reported to induce interconversion between the polymorphic forms.[7–9]

We have previously reported that gabapentin undergoes physical changes during milling and upon subsequent storage under various environmental conditions that can affect its degradation kinetics. We have hypothesized that milling induces crystal disorder, which results in an observed increase in the rate of chemical degradation. Additionally, we have reported that the subsequent exposure to high humidity decreases the apparent lactamization rate, and we have hypothesized that this apparent moisture "stabilization" is likely due to the competitive recovery of crystallinity wherein milling-induced crystal defects were lost upon exposure to high moisture, thereby stabilizing the milling-damaged drug substance.[1]

The objective of the work reported herein is to develop quantitative kinetic model that accounts for the effect of milling stress and environmental storage conditions on lactamization rate. This model forms the basis for connecting manufacturing-related effects on the physical integrity of the model drug substance to its subsequent chemical stability under a range of environmental conditions.

MATERIALS AND METHODS

Gabapentin was obtained from Hangzhou Starshine Pharmaceutical Company, Ltd. (Hangzhou, China), and gaba-L was purchased from Sigma–Aldrich (St. Louis, Missouri). All other chemicals, solvents, and water used were high-performance liquid chromatography (HPLC) grade.

X-Ray Powder Diffraction

X-ray powder diffraction (XRPD) was used to identify polymorphic changes in gabapentin samples. The analysis was conducted as follows: samples were filled in a glass holder and exposed to Cu Kα radiation (45 kV × 40 mA) in an X-ray diffractometer (Shimadzu LabX XRD-6000; Shimadzu) at ambient temperature. The instrument was operated in a step-scan mode, in 0.05° 2θ increments, and counts were accumulated for 1.0 s at each step over the angular range of 5°–40° 2θ. Data analyses were performed with commercially available software (JADE, version 5.0, MDI Inc, Livermore CA).

Chromatographic Methods

The mole fraction of gaba-L was determined by HPLC, as has been previously reported.[1] In brief, the HPLC system consisted of a Thermo SpectraSystem P4000 pump (Fisher Scientific, Pittsburg, PA), AS3000 auto injector, and UV 6000 LP photodiode array detector. The column was a 3.9 × 300 mm^2 μBondapak Cyano column (Water Corp. Milford MA). Mobile phase was composed of 95 parts buffer (10 mM KH_2PO_4/10 mM K_2HPO_4) and five parts acetonitrile. The mobile phase was filtered through 0.2 μm filter before using. Analysis was carried out using an isocratic method with a flow rate of 1.0 mL/min and an analytical wavelength of 210 nm. Retention volumes for gabapentin and gaba-L were 3.8 and 7.6 mL, respectively. As reported previously, limit of quantitation for gaba-L was 0.5 μg/mL.

Milling Stress

Aliquots (2.0 g) of gabapentin were placed in 45 mL milling chamber with four stainless steel balls (25 mm), and milled in a planetary mill (Pulvisierette 7, Planetary Micro Mill, FRITSCH GmbH, Idar-Oberstein, Germany) for 0, 15, 45, 60 min with speed setting 5 or for 60 min using a speed setting of 7. Speed settings of 5 generated motor and grinding bowl speeds of 1800 and 760 rpm, respectively; whereas a speed setting of 7 generated motor and grinding bowl speeds of 2400 and 1000 rpm, respectively. All milling operations were conducted at ambient environmental conditions.

X-ray diffraction (XRD) was used to confirm that the drug substance was form II upon receipt. Milled gabapentin samples were analyzed by XRD for crystal form changes and also assayed by HPLC to measure chemical changes. At mill speed setting of 5 using milling durations of 15–60 min, no polymorphic changes were observed; however, using a speed setting of 7 and milling duration of 60 min, XRD changes were observed that were consistent with the formation of form III.

Degradation Kinetics

Lactamization kinetics was determined using either aliquots of unmilled gabapentin or gabapentin that had been milled for 15, 45, or 60 min at a speed setting of 5. Gaba-L appearance profiles were measured by placing aliquots of milled gabapentin (15 mg) in glass vials, and then storing them in desiccators containing anhydrous calcium sulfate (Drierite®, Sigma-Aldrich, Co., St. Louis, MO) or saturated salt solutions to control the RH at the following values 5% (Drierite®), 11% (LiCl), 31% ($MgCl_2$), and 50% [$Mg(NO_3)_2$] at various isothermal conditions (40°C–60°C). Periodically samples were removed from stability chamber and dissolved in 1.0 mL 5% acetonitrile, and assayed for gaba-L and gabapentin. The gaba-L concentration was calculated as a molar percentage of the sum of gaba-L and gabapentin in the sample. Mass balance was 100%(±2%) of the initial amount of substrate at all time points.