Spontaneous Carbonate Formation in an Amorphous, Amine-Rich, Polymeric Drug Substance: Sevelamer HCl Product Quality

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ABSTRACT: Spectral differences among multiple manufacturers/lots of sevelamer HCl were observed by Fourier transform infrared spectroscopy, and further characterization was performed to identify the cause for these differences. The drug substance is a polymer that possesses a large molecular weight, is amorphous, and is practically insoluble in both water and organic solvents. Thus, solid-state characterization methods (spectroscopic and thermal) were required to identify and characterize differences among the samples to assess possible differences in product quality. ^{13}C cross-polarization–magic-angle-spinning nuclear magnetic resonance spectroscopy of sevelamer HCl substances demonstrated the presence of a carbonyl-containing species, which was attributed to a carbonate impurity among samples. Stability studies demonstrated that this carbonate impurity formed spontaneously upon exposure of the drug substance to atmospheric water vapor and carbon dioxide, even under ambient conditions. Mechanistically, this behavior likely arises from the large number of primary and secondary amine groups, the hygroscopicity of the HCl salt, and a high degree of molecular mobility due to the amorphous nature of the drug substance. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:2681–2685, 2012

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INTRODUCTION

Sevelamer is administered orally as a solid-dosage form to patients with end-stage kidney disease to reduce serum phosphate levels.[1] The drug substance is a high-molecular-weight, insoluble polymer that binds dietary phosphate to prevent gastrointestinal absorption. Sevelamer drug substance is an amorphous solid, marketed as either a hydrochloride (HCl) or carbonate salt.[2] The molecular structure of sevelamer HCl (SH) is shown in Figure 1.[3]

The comparison of Fourier transform infrared (FTIR) spectra of SH drug substances from different manufacturers/lots indicated differences in the intensity of a peak at approximately 1300 cm^{-1}. To understand the reason for these spectral differences, further analyses were performed. Sevelamer's insolubility in both water and organic solvents prevented the use of typical solution-based methods such as liquid-state nuclear magnetic resonance (NMR) spectroscopy or high-performance liquid chromatography—mass spectrometry (HPLC–MS). Instead, sevelamer samples were analyzed by solid-state characterization methods, including spectroscopic [^{13}C solid-state NMR (SSNMR) and FTIR] and thermal methods [thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC)].

Additional Supporting Information may be found in the online version of this article. Supporting Information

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The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

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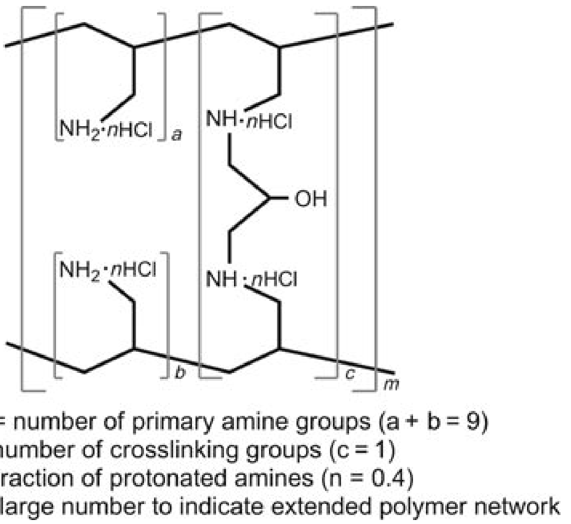

Figure 1. Molecular structure of sevelamer HCl. Redrawn from Ref. 3.

Initial studies of SH using ^{13}C cross-polarization–magic-angle-spinning (CP–MAS) NMR demonstrated the presence of a peak at 165 ppm (location typical for a carbonyl carbon) within some of the samples. The ^{13}C CP–MAS NMR spectrum of the corresponding carbonate-counterion substance (SC) contained a peak (although possessing a much greater intensity) at the same position. Thus, the 165-ppm peak in the spectrum of the HCl salt was identified as a carbonate impurity. The differences in the 1300-cm^{-1} peak observed in FTIR spectra among SH samples were attributed to the presence of the carbonate counterion and its interactions with primary amine groups within the sevelamer molecule. This assignment is supported by the observation that a strong peak at 1300 cm^{-1} exists within bulk sevelamer carbonate drug substance (Supplementary Information).

During the course of these initial studies, growth of the 165-ppm peak was observed. Figure 2 shows repeated ^{13}C CP–MAS NMR analyses of a single lot of SH following storage in a closed vial under ambient conditions over an extended period of time. This peak growth suggested that the initially observed carbonate impurity was not simply due to contamination, but potentially due to instability of the drug substance. Further studies were performed to assess the stability of SH and confirm the spontaneous formation of the carbonate counterion impurity within these SH samples. Currently, there is no USP monograph that would provide a purity specification for sevelamer.

RESULTS AND DISCUSSION

Conditions of Carbonate Formation

The studies reported here were designed to test the hypothesis that sevelamer HCl absorbs both atmospheric water vapor and carbon dioxide to form a carbonate counterion. Samples of SH from a single lot were monitored for weight change by dynamic vapor sorption (DVS) analysis under isothermal (40°C) and constant relative humidity (0% or 60% RH) conditions for 96 h, using CO_2 or N_2 as the purge gas (Table 1). To identify physicochemical changes, each sample was further analyzed by SSNMR, TGA, DSC, and FTIR following DVS analysis.

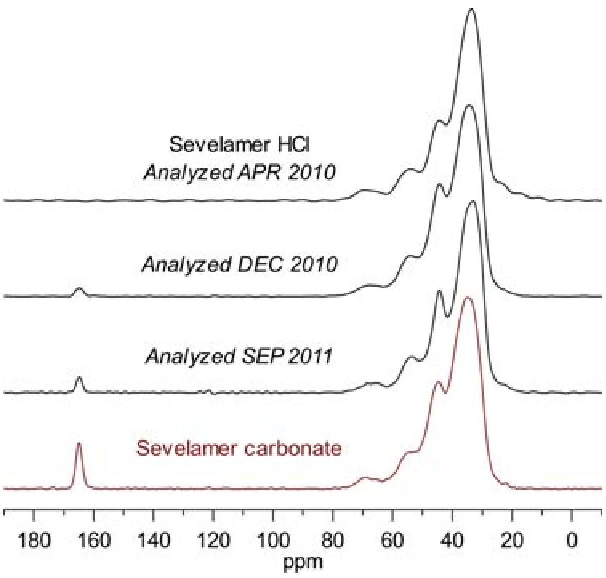

Figure 2. ^{13}C CP–MAS NMR spectra of a single lot of sevelamer HCl that was analyzed at different time points while stored under ambient conditions in a closed container. The spectrum of sevelamer carbonate is included for reference.

Table 1 contains the weight-change results for SH samples held under different conditions during DVS analysis. Upon exposure to high RH and nitrogen gas, the SH-sample weight increased 27.8%. This significant weight gain is not unexpected, as amorphous materials, as well as HCl salts, tend to be hygroscopic. When SH was held under CO_2 gas at 0% RH, no significant weight change was observed, suggesting that the sample did not sorb any CO_2 gas in the absence of water vapor. However, exposure to both high RH and CO_2 resulted in a weight increase of 43.1%. This weight gain is 15.3% greater than under the same RH conditions in the absence of CO_2 (presence of N_2). This suggests the cosorption of CO_2 and H_2O. The samples were further analyzed to correlate this cosorption of CO_2 and H_2O to carbonate formation within the SH samples.

Figure 3 contains ^{13}C CP–MAS NMR spectra for the SH samples following DVS analyses. Differences are observed in both the carbonyl and aliphatic regions among all spectra. All spectra possess a small peak in the carbonyl region at approximately 165 ppm; however, the peak size is significantly larger