Solid State ^{13}C NMR Analysis of Patiromer

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Abstract

Purpose: VELTASSA (patiromer sorbitex calcium oral powder) is a drug product approved for the treatment of hyperkalemia. The active moiety of the drug product, patiromer, is a cross-linked polymer consisted of three monomers: 2-fluoro-2-propenoate (m), diethenylbenzene (n) and octa-1,7-diene (p). However, the composition information about the polymer was not fully disclosed in the reference listed drug (RLD) labeling (m : (n+p) = 0.91 : 0.09, the ratio/amount of n and p is not listed). To facilitate the development of generic patiromer, we conducted research to develop a convenient and effective analytical method to characterize the chemical structure of patiromer.

Methods: To characterize the chemical structure and quantify the relative amounts of each monomer in the patiromer polymer, we employed solid-state Nuclear Magnetic Resonance (SSNMR) spectroscopy. Carboxylate, aromatic and aliphatic groups were first identified, evaluated, and quantified using cross polarization (CP), magic angle spinning (MAS) and other ^{13}C SSNMR techniques to provide structural information of the polymer. Then, seven lots of patiromer (VELTASSA, purchased from pharmacy) were compared to investigate lot-to-lot variations and changes that may occur during the shelf-life of the drug.

Results: Various ^{13}C-SSNMR techniques were used to account for cross polarization dynamics and ensure that quantitative data were acquired. It was found that the average patiromer sample contained 90.9 ± 0.4% carboxylate group (m), 7.6 ± 0.3% aromatic group (n), and 1.5 ± 0.4% aliphatic group (p) (mean ± SD, N=7). The resulting values agree well with values reported in the drug labeling while providing previously unpublished data on the relative amounts of n- and p-block rather than the sum of these two monomers. Seven different patiromer lots were compared. Little to no differences were observed between lots; neither as a function of dosage strength or time to expiration.

Conclusion: Our research demonstrates that SSNMR is a valuable and practical tool for analyzing polymeric materials like patiromer. The patiromer structure can be determined by evaluating the monomer components in the polymer. The quantitative data obtained from this study agree well with literature values. Comparison of the composition showed little to no lot-to-lot variability.

Introduction

Patiromer is the active moiety of the drug product VELTASSA (patiromer sorbitex calcium oral powder) used in the treatment of hyperkalemia. It is a cross-linked polymer consisting of three monomers: 2-fluoro-2-propenoate (m), diethenylbenzene (n), and octa-1,7-diene (p). However, the composition information about the polymer was not fully disclosed in the reference listed drug (RLD) labeling (m : (n+p) = 0.91 : 0.09, the ratio/amount of n and p is not listed) (Figure 1). The lack of detailed monomeric composition in patiromer becomes an obstacle in the development of generic patiromer drug products. Structural analysis of the cross-linked polymeric materials is very challenging because of their poor solubility in various solvent systems. To facilitate the development of generic patiromer, we developed a solid state ^{13}C NMR-based method to characterize the chemical structure of patiromer. This method proved to be very convenient and effective, and it can provide quantitative monomer information that enables determination of the polymer structure.

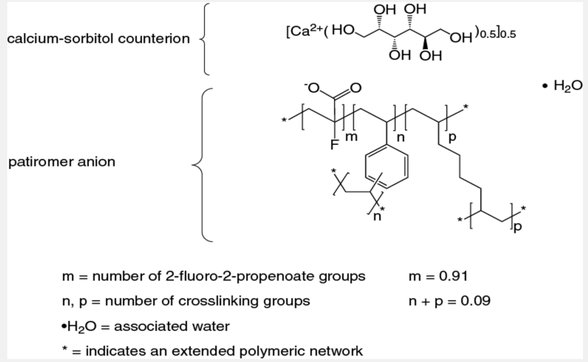

Figure 1. Patiromer chemical structure (excerpt from VELTASSA labeling)

Materials and Methods

Seven lots of patiromer drug product were analyzed, including three lots of different strengths and four expired lots at the time of the study. All SSNMR experiments were acquired using a Tecmag Redstone HF3 2RX spectrometer (Tecmag, Inc., Houston, TX) operating at 75.48 MHz for ^{13}C. All experiments were acquired using cross polarization (CP), magic angle spinning (MAS), SPINAL64 decoupling with a ^{1}H decoupling field of approximately 64 KHz and performed using a 7.5 mm double-resonance MAS probe (Varian, Palo Alta, CA) at 20°C. 3-Methylglutaric acid (MGA) was used as an external standard to optimize the spectrometer parameters. The methyl peak was referenced to 18.84 ppm. Initial SSNMR experiment was run to identify patiromer functional groups and set parameters for quantitative data acquisition (Figure 2). Then, study parameters were further optimized to ensure quantitative data collection and quantitation of the carbonyl, aromatic and aliphatic carbons in the patiromer sample (Figure 3). In the third stage, the relative monomer ratios in different lots of patiromer were compared to investigate lot-to-lot variations and see if there are any compositional changes during the shelf-life of the drug product (Figure 4 and Table 1).

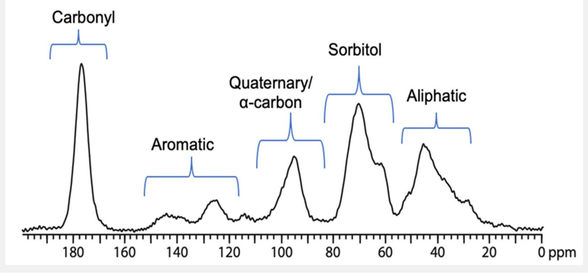

Figure 2. Initial CP-Total sideband suppression (TOSS) spectrum of patiromer acquired at 4 kHz MAS with labeled functional group ranges

Results and Discussion

Initial CP-MAS spectra confirmed the presence of carboxylate, aromatic, and aliphatic groups present in patiromer, along with the sorbitol. Various ^{13}C SSNMR techniques were used to account for cross polarization dynamics and ensure that quantitative data were acquired. From this, a quantitation procedure was developed which accounted for all spinning sidebands. Analysis of different lots of the drug product showed that all patiromer lots contain approximately the same relative amounts of each block copolymer. The average patiromer sample contained 90.9 ± 0.4% m-block, 7.6 ± 0.3% n-block, and 1.5 ± 0.4% p-block (mean ± SD, N=7, Table 1). The resulting values agree well with values reported in the labeling while providing more detailed information on the relative amounts of n- and p-block. Lot-to-lot comparison of the composition showed little to no differences as a function of dosage strength or expiration date and only slight variations existed between the relative amounts of each block copolymer present in each lot.

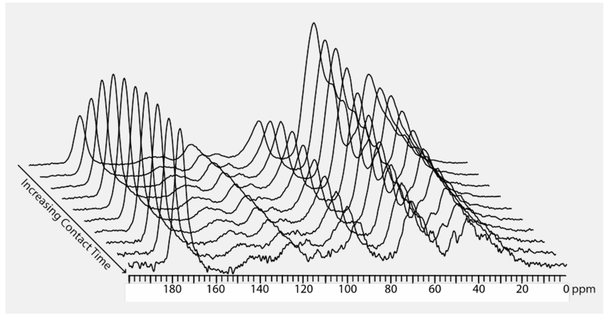

Figure 3. Stacked patiromer spectra as a function of contact time

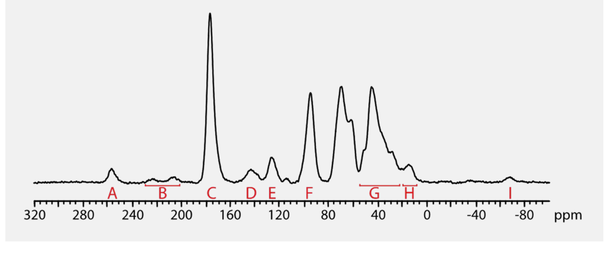

Figure 4. Patiromer lot 1 spectrum with peak labels for quantitative procedure (Relative amount of each block copolymer in lot 1: m-block: 90.8%; n-block: 7.7%; p-block: 1.5%)

During the study, extensive care was taken to ensure the temperature of the spectrometer was consistent between runs. Each sample was given adequate time to equilibrate to 20°C prior to spectral acquisition. The spectrometer was calibrated prior to each sample change to ensure experimental conditions were consistent between each lot. Therefore, the observed variations in Table 1 are likely due to the uncertainty of measurement and natural lot-to-lot variation.

Table 1. Relative amount of each monomer in different patiromer lots

Lot	Dose	Expiration	m-block (%)	n-block (%)	p-block (%)
1	8.4	2021	90.8	7.7	1.5
2	16.8	2021	90.2	7.9	1.9
3	25.2	2020	90.9	7.7	1.4
4	8.4	2017	91.2	7.2	1.7
5	8.4	2018	90.4	7.7	1.9
6	16.8	2018	91.4	7.4	1.2
7	25.2	2017	91.2	8.0	0.9
Average			90.9 ± 0.4	7.6 ± 0.3	1.5 ± 0.4

Conclusion

We have developed and validated a novel SSNMR method to characterize the structure of patiromer and quantify the relative amount of each monomer present in different lots of patiromer. This research demonstrates that SSNMR is a valuable and practical tool for analyzing complex polymeric materials like patiromer. The patiromer structure can be determined by evaluating the monomer components in the polymer. The quantitative data obtained from this study agreed well with literature values. Comparison of the composition showed little lot-to-lot variability. Adaptation of this method can be used to establish active ingredient sameness during generic drug development or as a tool for the advanced characterization and analysis of other complex polymeric drug products.

Disclaimer

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