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Statistical Optimization of Evaporative Light Scattering Detection for Molten Sucrose Octaacetate and Comparison With Ultraviolet Diode Array Detection Validation Parameters Using Tandem HPLC Ultraviolet Diode Array Detection/Evaporative Light Scattering Detection—Specific Stability-Indicating Method

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ABSTRACT

A sucrose octaacetate (SOA) gradient HPLC evaporative light scattering detection (ELSD) and low-wavelength UV-diode array detection (UV-DAD)-specific stability-indicating method development and validation comparison is reported. A central composite response surface design and multicriteria optimization was used to maximize molten SOA area-under-the-curve response and signal-to-noise ratio. The ELSD data were also analyzed using multivariate principal component analysis, analysis of variance, and standard least squares effects modeling. The method suitability and validation parameters of both methods were compared. To the authors' knowledge, this is the first report that validates an ELSD method using a molten analyte. SOA exhibited a low molar absorptivity of 439 absorption units/cm/M in water at 210 nm requiring low-wavelength UV-DAD detection. The low-wavelength UV-DAD method provided substantially better intraday and interday precision, intraday and interday goodness-of-fit, detection limit, and quantitation limit than ELSD. ELSD exhibited a 60-fold greater area-under-the-curve response, better resolution, and 58% more theoretical plates. On balance, the UV-DAD method was chosen for SOA chemical kinetic studies. This study illustrates that ELSD may not always be the best alternative to gradient HPLC low-wavelength UV detection.

Introduction

Sucrose octaacetate (SOA) is a compendia material having a monograph in the United States National Formulary.[1] SOA has a number of uses in several disciplines. It is used as an indirect and direct food additive and synthetic flavoring in bitters, spices, and ginger ale beverages.[2-5] SOA was used for many years as a nailbiting and thumbsucking deterrent in over-the-counter products until 1993 when the U.S. Food and Drug Administration (FDA) issued a final rule stating that SOA and other nailbiting and thumbsucking agents are not drugs.[6] It has been used in clinical studies to understand the effect of sweeteners on bitter taste in young and elderly subjects and as a bitter standard for taste mechanism studies.[7-10] SOA has also been used as a bitter tasting control for blinded clinical trials of bitter tasting drugs.[11,12]

Even though SOA has been used and studied over many decades, a validated stability-indicating method and pH-rate profile has not been reported. Therefore, the general program aim was to develop a specific stability-indicating method for SOA. This method would be used to generate a pH-rate profile over both an acidic and basic pH range.

Several interesting SOA physicochemical properties pose challenges to the development of a stability-indicating separation and

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detection method. SOA has 8 acetate groups, which can form a myriad of potential degradation products. SOA could form 255 possible isomers.[13] SOA ultraviolet (UV) detection is limited due to lack of a strong chromophore. Thus, it has a very low UV absorptivity requiring low UV wavelength detection. Our laboratory results showed that SOA molar absorptivity in water was 439 and 442 absorption units/cm/M in 30:70 acetonitrile (ACN):water at 210 nm. Low UV wavelength detection is problematic due to solvent interferences, potential solvent impurities, interference by low levels of degradation products, and shift in baseline during gradient elution. Low wavelength analysis also suffers from decreased signal-to-noise (S/N) ratio, which can affect quantitation limits (QLs) and precision.

Evaporative light scattering detection (ELSD) has been introduced as a favored alternative to low wavelength UV analysis.[14,15] ELSD has been referred to as a universal detector. It uses mass detection as its mode of analysis, which does not depend on the drug or analyte chemical structure.[16-18] The mass detector is solvent-insensitive compared to UV. It can be used with volatile solvents having strong chromophores. In addition, ELSD gives flat gradient baselines. However, ELSD response is significantly affected by the organic composition of the mobile phase. There is a nonlinear increase in peak area with increasing proportion of organic solvent in the mobile phase.[19,20] As the proportion of organic solvent is increased, the efficiency of analyte transport in the nebulizer is increased, allowing more particles to reach the detector and thereby increasing detector response. The detector measures the light intensity scattered by the analyte remaining after the mobile phase has been evaporated. Therefore, analyte detection requires a significantly higher vapor pressure of the solvent or mobile phase as compared to the vapor pressure of the solute or analyte.[17] Analytes that are thermosensitive, sublime, have low melting point, or are volatile in the solvent at the evaporative temperatures limit ELSD as a truly universal detector. Thus, ELSD has been referred to as a "quasi universal" detector.[21] SOA melts at about 83°C to 85°C (see Results and Discussion section). Analytes in the solid state scatter light more efficiently than in the liquid or molten state. An underlying assumption is that the analyte melting point needs to be substantially higher than the evaporation chamber temperature for better ELSD response.[15,22]

ELSD offers an advantage compared to low-wavelength UV and refractive index detectors, which exhibit baseline drift and instability with gradient HPLC. ELSD involves 4 critical processes: nebulization of the HPLC effluent to form a uniform aerosol, evaporation of the volatile aerosol components in a heated drift tube, generation of scattered light from the dried sample, and detection of the scattered light. A number of articles have evaluated potential problematic effects of low melting point and low molecular weight compounds on the suitability of ELSD.[15,21,23,24] In general, the utility of ELSD for low melting and low molecular weight compounds is suspect that requires a case-by-case evaluation.

The aim of this study was to use the design of experiments (DOEs) and other statistical methods consistent with Analytical Quality by Design concepts[25] to evaluate and optimize an SOA ELSD-specific stability-indicating method. Furthermore, the validation parameters of SOA ELSD-specific stability-indicating method were compared with the validation parameters of low-wavelength UV-diode array detection (UV-DAD). To the authors' knowledge, this is the first report that validates an ELSD-specific stability-indicating method using a molten analyte. The developed, specific stability-indicating method used a coupled HPLC UV-DAD/ELSD tandem analysis technique. Principal component analysis (PCA), analysis of variance, standard least squares effects modeling, and response surface multicriteria analysis was used to determine the relationship and effect of SOA concentration, drift tube temperature, and nebulizer gas flow rate on ELSD area-under-the-curve (AUC) response and S/N ratio.

Materials and Methods

Materials

Two lots of SOA (99% wt/wt) (Lot no. SU104 and Lot no. WS0277, United States Pharmacopeia National Formulary [NF]) and ACN (Lot no. 50144046, HPLC Grade) were purchased from Spectrum Chemical Mfg. Corporation (New Brunswick, NJ). Trifluoroacetic acid (TFA) (Lot no. 50144046, HPLC Grade) was bought from EMD Chemical (Gibbstown, NJ). United States Pharmacopeia deionized reverse osmosis water was provided by an in-house water system. It was filtered through a 0.2-μm nylon filter (GE Water and Process Technologies, Trevose, PA) at the point of use.

ELSD Statistical Optimization and Analysis

A 3-factor central composite response surface design with 2 center points was implemented to study the effect of SOA concentration (0.006-0.100 mg/mL), tube temperature (105°C-110°C), and gas flow rate (0.8-1.2 L/min) on analyte peak area and S/N response. JMP® DOE software (JMP 8; SAS Institute, Cary, NC) was used to design the experimental trials and analyze the data using analysis of variance, standard least squares effects modeling, and response surface multicriteria analysis. DOE supports the simultaneous evaluation of a number of variables. It can provide statistically significant quantitation of the main variables, interaction of variables, and curvilinear quadratic effects. Interactions of the main variables occur when a change in the level of one variable leads to change in the effect of another variable. Multivariate qualitative PCA was also performed using The Unscrambler® 10.3 (Unscrambler; CAMO AS, Trondheim, Norway).

Instrumentation

Differential scanning calorimetry (DSC) was used to determine the melting point and purity of SOA using a DSC Q1000 (TA Instruments, New Castle, DE). The melting points of SOA lots were determined by weighing approximately 5 mg into a nonhermetically sealed aluminum pan. Samples were heated at 10°C/min from 30°C to 105°C. A nitrogen purge of 40 mL/min was employed. DSC purity analysis was performed on both lots. Sample weights were about 1.7-1.8 mg. The heating ramp was 0.5°C/min from 75°C to 92°C.

Thermal gravimetric analysis (TGA Q500; TA Instruments) was performed on SOA Lot SU104 to determine the weight loss of molten SOA when held at 105°C and 110°C for 10 min. The sample size was about 30 mg. The nitrogen purge rate was 60 mL/min. DSC and TGA data analysis was performed using the Universal Analysis software version V4.5A (TA Instruments).

The molar absorptivity of SOA at 210 nm was determined using a GENESYS 10S UV/Vis spectrophotometer (Thermo Scientific, Waltham, MA) at room temperature in water and 30:70 ACN:water mixture. The SOA concentration range was 0.045-0.725 mM and 0.045-1.436 mM for water and 30:70 ACN:water mixture, respectively.

Liquid chromatographic separation was achieved using an 1100 series HPLC (Agilent Technologies, Santa Clara, CA) equipped with an Agilent 1100 series UV/Vis DAD (Model G1315A) set at 210 nm. The Agilent system included a binary pump (Model G1312A), autosampler (Model G1376A) set at 4°C, and a thermostated column compartment (Model G1316A) set at 40°C. The mobile phase was degassed inline (Model G1379) at room temperature prior to use. Data were collected and analyzed on a ChemStation version B.01.01 (Agilent Technologies).