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Short Communication

Determination of sorbitan trioleate in metered-dose inhalers by supercritical-fluid chromatography

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Introduction

Sorbitan esters are non-ionic surface active agents used in the preparation of various pharmaceutical formulations and as additives in foods, beverages, drugs, textiles and plastics. Sorbitan trioleate (SPAN 85®), a partial ester of oleic acid derived from sorbitol, is commonly used in many drug products (Fig. 1). It is used in metered-dose inhalers to keep the drug dispersed in the propellant and to lubricate the actuator valve. Published oral and dermal toxicity studies label sorbitan trioleate as relatively non-toxic by oral administration and causes only slight irritation when administered topically [1, 2]. However, good product design dictates that the amount of sorbitan trioleate used be compatible with achieving optimum performance characteristics and be within the industry-accepted quantities. Although listed as an ingredient in several commercially available aerosol formulations, the level in each dose is not reported. Consequently, an assay procedure for the measurement of sorbitan trioleate in four marketed aerosol preparations and an experimental formulation was developed.

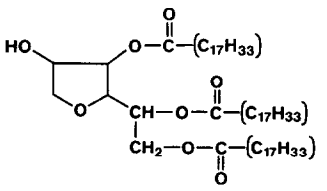

Figure 1
Sorbitan trioleate.

Supercritical fluid chromatography (SFC) with flame-ionization detection lends itself to the analysis of polymeric materials with no chromophore. SFC employs a compressed fluid above its critical pressure and temperature as the mobile phase. Supercritical fluids possess higher solute diffusivities and lower viscosities than liquids leading to faster analysis times and higher chromatographic efficiencies [3, 4]. Supercritical carbon dioxide has a high critical pressure and low critical temperature suitable for the analysis of high molecular weight, thermally labile materials. These unique features of SFC make it ideally suited for the analysis of sorbitan trioleate in metered-dose inhaler formulations.

Experimental

Instrumentation

A model 5890 gas chromatograph (Hewlett–Packard, Palo Alto, CA) was equipped with a Microgradient System Syringe Pump (Applied Biosystems Inc., Santa Clara, CA) to pressurize and pump the supercritical fluid mobile phase. SFC-grade carbon dioxide (Scott Specialty Gases, Plumsteadville, PA) was used for all experiments. Samples were introduced onto the column via a Rheodyne injection valve with a 0.5-μl sample rotor. Separations

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were performed on a Rexchrom 300 Å C-18 column (5 μm, 100 × 2.1 mm) (Chromatographic Sciences Co., St. Laurent, PQ, Canada). A fused silica integral restrictor, constructed in-house, maintained the supercritical conditions. Eluents were monitored with a flame-ionization detector set at 350°C. All experiments were conducted at constant pressure (2400 psi) and constant temperature (40°C). Solvents were all HPLC grade and were used as received. Sorbitan trioleate was obtained from ATLAS Chemicals (lot No. A17297; Newark, NJ).

Sample preparation

Each aerosol canister was immersed in liquid nitrogen for 20 min to liquefy the contents. The canister was opened with a pipe cutter and the contents poured into a beaker. After all the propellant had evaporated, the dry residue was vortexed with a known quantity of dichloromethane to dissolve the sorbitan trioleate. The sample was then centrifuged (Eppendorf Centrifuge 5415, Brinkmann Instruments, Westbury, NY) at 12,000 rpm for 15 min and the supernatant is filtered (0.45 μm) prior to injection. A calibration curve was prepared by dissolving appropriate amounts of sorbitan trioleate and an internal standard (pyrene 0.2 mg ml^{-1}) in dichloromethane.

Results and Discussion

The separation of sorbitan trioleate was achieved on a reversed-phase column with supercritical carbon dioxide mobile phase at comparatively low temperature and pressure. The retention of the surfactant decreased with increasing pressure at constant temperature, suggesting that the retention mechanism was governed by the analyte solubility in the supercritical fluid phase. Under isobaric and isothermal conditions, sorbitan trioleate eluted as one major and two minor components (Fig. 2). The larger peak with a capacity ratio of 1.7 was used to quantitate the sorbitan trioleate.

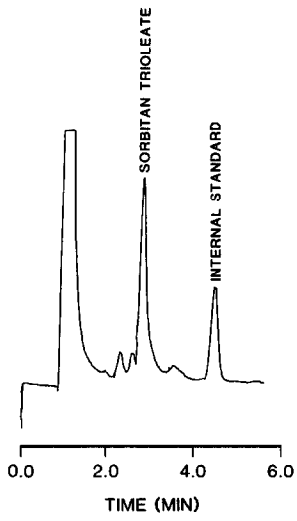

Figure 2
Chromatogram of sorbitan trioleate standard (3.2 μg). Column: Rexchrom 300 Å C-18 (2.1 × 100 mm; 5 μm). Mobile phase: supercritical carbon dioxide. Pressure: 2400 psi. Temperature: 40°C. Detection: FID at 350°C.

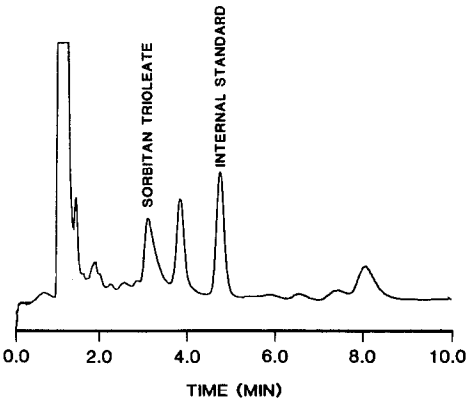

Figure 3
Chromatogram of Medihaler ISO® sample (1.5 μg). For chromatographic conditions refer to Fig. 2.

Table 1
Sorbitan trioleate in drug products used for inhalation

Product	Supplier	Amount per dose (μg)	RSD* (%)
Experimental		123	1.4
Duo-Medihaler®†		214	1.6
Medihaler ISO®†		267	1.7
Medihaler EPI®†		160	1.2
Alupent®‡		212	1.8

*Relative standard deviation for $n = 5$.
†RIKER Canada Inc.
‡Boehringer Ingelheim Canada Ltd.

The sorbitan trioleate was well separated from other components of all the formulations tested (Fig. 3). Values for each product have been reported as the average of five canisters and ranged between 123–267 μg/burst (Table 1). The amount per dose was calculated by dividing the total weight of sorbitan trioleate per canister by the label claim number of bursts. The in-house formulation was designed to deliver 120 μg of sorbitan trioleate per dose which agreed well with the amount found, 123 μg/burst. For both standards and samples, four injections were averaged. A linear calibration curve for peak height as a function of weight of sorbitan trioleate was obtained between 0.5–10 μg injected on column. The detection limit calculated as three times the peak-to-peak baseline noise was 50 ng per injected volume. Retention times were recorded with RSD values ($n = 5$) below 0.5%, and peak height values have RSDs between 1.0–2.0%. This method is currently being used to determine sorbitan trioleate droplet size and distribution in metered-dose inhaler plumes.

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