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Identification and quantification of impurities in the industrial-grade sesamol

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ABSTRACT

Analysis of impurities in the industrial-grade sesamol (3,4-methylenedioxyphenol, $C_7H_6O_3$) was carried out. Sesamol, the main antioxidant in sesame oil and the principal chemical intermediate, is used to manufacture paroxetine, an antidepressant drug. Gas chromatography-mass spectrometry (GC-MS) analysis of a sesamol sample indicated the presence of four impurities. After further purification, these four impurities were obtained and characterized by nuclear magnetic resonance (NMR) and Fourier-transform infrared spectroscopy (FTIR). The four sesamol-derived impurities were 1,2-methylenedioxybenzene ($C_7H_6O_2$), sesamol formate ($C_8H_6O_4$), sesamol acetate ($C_9H_8O_4$), and 3,4-methylenedioxybenzaldehyde ($C_8H_6O_3$). Sesamol and its impurities were assayed by both gas chromatography (GC) and liquid chromatography (LC) for routine quality control. Correlation coefficients (r) in the LC method ranged from 0.9989 to 0.9997, and relative standard deviations (RSD) range from 1.76% to 3.32%. These values were higher than those by the GC method, where correlation coefficients were in the range of 0.9875 to 0.9981 and relative standard deviations in the range of 7.45% to 26.8%. Moreover, the LC method with the limit of detection (LOD) in the range of 0.013 to 0.045 μg/mL was more sensitive than the GC method, where the limit of detection was in the range of 0.067 to 3.103 μg/mL. Therefore, the LC method was more suitable for assay sesamol and its impurities during the in-process control of drug manufacture.

Keywords: Impurity analysis, Sesamol, 1,2-methylenedioxybenzene, Sesamol formate, Sesamol acetate, 3,4-methylenedioxybenzaldehyde, Piperonal, Chemical intermediate, Paroxetine.

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1. INTRODUCTION

Sesamol, sesamolin, and sesamin are lignans (non-fat constituents) in sesame seed oil. Sesamol has been regarded as the main antioxidative component in sesame oil (Fukuda et al., 1981; Florence, 1983; Kim et al., 2003; Joshi et al., 2005). Sesamol (< 0.01%) only exists in trace amounts in sesame seeds compared with two major components of sesamolin (~ 0.4%) and sesamin (~ 0.6%) (Beroza and Kinman, 1955; Kamal-Edlin and Appelqvist, 1994). However, it can be liberated from sesamolin during roasting or frying sesame seeds or bleaching sesame oil (Yoshida and Takagi, 1997; Fukuda et al., 1986; Budowski, 1964). Sesamol prevents oils' spoilage by acting as an antifungal (Wynn et al., 1997) and is a potential anti-microbial pesticide (Brooker et al., 2000). Sesamol can protect the body from free-radical damage (Ohsawa, 1991) and serves as an additive in food supplements and cosmetics, and is used in Ayur-Vedic medicine. Using sesamol, the overall vascular fibrinolytic capacity is enhanced to regulate plasminogen activator gene expression (Chen et al., 2005). Sesamol delays mortality and attenuates oxidative stress-associated liver injury by inhibiting nitric oxide production, at least partially, in septic rats (Hsu et al. 2006). Sesamol is sparingly soluble in water but miscible with

most oils. For sesamol with purity at greater than 99.9%, it remains as a colorless liquid at a temperature above 64°C (melting point). In contrast, it solidifies into flakes or chunks at room temperature, which can be crushed into white or light yellow powder with a pungent odor. The purity of industrial-grade sesamol is around 98%. It tends to be slowly oxidized into a brown or dark brown solid with the decreases of purity at room temperature after a few storage weeks. If sesamol is stored in a dark room at a temperature below -18°C, it can be kept over 24 months without decomposition.

Sesamol is also used as a chemical intermediate in the pharmaceutical drug paroxetine (Paxil). As the World Health Organization predicts, chronic depression remains one of the leading killers for the twenty-first century. With the increase of depression diseases, about 10 to 15 percent of the patients face the danger of committing suicide. Paroxetine is a selective serotonin reuptake inhibitor (SSRI), which has a higher therapeutic effect with fewer side effects for the patient (Barlow and Durand, 2009).

Only a minor quantity of sesamol can be extracted from sesame oil since the total content of sesamol and sesamolin, which can liberate sesamol by dilute mineral acids or by hydrogenation, are only about 0.4% in sesame oil. The limited natural source of sesamol is unable to satisfy the mass consumption in many uses. At present, the primary source of seasmol is manufactured by chemical synthesis. It is commonly prepared from piperonal or 3,4-methylenedioxy acetophenone by chemical oxidation followed by hydrolysis reaction. These synthetical methods are simple and easy, with around 70% yield (Nikaido et al., 1984).

Concepts of setting impurity limits in bulk drug substances are complex and major concerns of the regulatory and compendia agencies and the pharmaceutical industry. The basic tenet for setting limits is that impurities in a drug substance must be controlled to ensure its safety and quality. The bulk pharmaceutical chemicals' purity profile constructed from experiments using several analytical methods is the ultimate goal. It has been suggested that impurities should be identified when these exceed some set amount, e.g., 0.1, 0.3, or 0.5%, and the total impurities should not exceed 2.0%, in general. It is more rational to identify impurities and set limits based on manufacturers' scientific judgments, the compendia, and regulators to arrive at sets of acceptable limits for identified and unidentified impurities. The goal is to make available to the public high-quality and reasonable-cost products that are safe and effective (Anonymous, 2006; Fuh and Wu, 1999).

The industrial-grade sesamol produced by Sinon Corporation of Taiwan, a sesamol and paroxetine supplier, was used for this study. There are two purposes of this investigation. First, the identification and quantification of the sesamol impurities would help monitor chemical reactions to improve production costs. Second, by comparing two analytical methods of gas chromatography (GC) and liquid chromatography (LC), one of the two methods can hopefully be selected to monitor sesamol's routine production.

There are several reports related to the identification and quantification of sesamol and its relatives using LC-UV, GC-FID, LC-MS, or GC-MS. Determination of sesamolin, sesamol, and sesamol dimer by reversed-phase liquid chromatography was carried out using a ZORBAX ODS column. The mobile phase was a mixture of methanol and water (70:30, v/v). The detector wavelength was set at 300 nm (Kikugawa et al., 1983). The determination of sesamol, sesamolin, and tocopherol by RP-LC was carried out using a Waters C18 column. The mobile phase was a mixture of methanol and water (70:30, v/v). The detector wavelength was set at 288 nm (Lee et al., 2008). Determination of sesamol and tocopherol homologues by normal-phase liquid chromatography was carried out using a Shim-pack CLC-SIL column. The mobile phase was a mixture of *n*-hexane and ethyl acetate (90:10, v/v). The fluorescence detector was set at an excitation wavelength of 296 nm and an emission wavelength of 320 nm (Yoshida and Takagi, 1999). The antioxidants in sesame seed were purified by preparative LC using methanol-water (70:30, v/v) as the solvent system, monitoring the absorbance at 280 nm. The instruments of UV, IR, NMR, and MS were used for the structural elucidation of antioxidants (Fukuda et al. 1985). Semipreparative RP-LC was used to separate the sesamin and sesamolin constituents in high purity (> 99%). The identities of the separated compounds were confirmed by GC-MS (Amarowicz et al., 2001). A Luna C18 column performed separation of the unbound sesamol from various biological fluids. The mobile phase was a mixture of methanol and 1% acetic acid buffer, pH 6.0. The UV detector was set at a wavelength of 290 nm. Identification of sesamol and sesamol metabolites was carried out by LC-MS/MS equipped with electrospray ionization. Selected reaction monitoring was used to monitor the transition of the deprotonated molecule *m/z* 137 $[M - H]^-$ to the product ion 138 for sesamol analysis (Jan et al., 2008). Determination of 3,4-methylenedioxyphenyl derivatives by GC-FID was carried out using a 3% Carbowax 20M column (Zielinski and Fishbein, 1966). Antioxidants on the volatiles of roasted sesame seeds were identified by GC-MS equipped with a 3% SE 30 on the chromosorb column (Soliman et al., 1985).

2. MATERIALS AND METHODS

2.1 Reagents

Purified standard (99.9%) and industrial-grade sesamol (98.0%) were obtained from Sinon Corporation (Taiwan). 1,2-Methylenedioxybenzene reagent grade was purchased from TCI Corporation (Japan). 3,4-Methylenedioxy-benzaldehyde (99.0%) industrial-grade was purchased from Hebei Haili Fragrances Co., Ltd. (China). Acetic anhydride (ACS grade) was purchased from Tedia Company, Inc., Fairfield (USA). Dried methanol and 50% hydrogen

peroxide (aqua) (reagent grade) were purchased from Riedel-deHaën (UK). Dichloromethane and acetonitrile (HPLC/SPECTRO grade) were purchased from Tedia Company, Inc.

2.2 Instrumentation

A GC-MS (HP 5890 MSD) consisted of a GC (HP 5890) coupled with a quadrupole mass spectrometer (HP 5989A). The column was HP-FFAP (30 m × 0.25 mm i.d., film thickness 0.25 μm). The temperatures of injection and detection ports were set at 250°C. The injection volume for GC-MS was 0.4 μL, and the split ratio was 1:50. The oven temperature of GC-MS was initially at 200°C (remaining 5 min) and 25°C/min until reaching the final 240°C (remaining 18.4 min). The flow rate of helium in GC-MS was 0.5 mL/min with constant pressure. A GC (HP 6890) coupled with a flame ionization detector and split/splitless injector was used. The injection volume for GC was 1.0 μL, and the split ratio was 1:20. The type of column, temperature programming, and injection/detection port temperatures were the same as for GC-MS. The flow rates of GC were 0.5 mL/min for N_2 (column), 20 mL/min for N_2 (makeup), 45 mL/min for H_2, and 450 mL/min for air. An LC (HP 1100) with a UV-Vis detector was used. A column of Prodigy C8 (25 cm × 4.6 mm) with a pore size of 5 μm was used. The mobile phase constituted of 60% water and 40% acetonitrile with the isocratic condition. The injection volume for LC was 20 μL. The flow rate was 1 mL/min. The detector wavelength was set at 220 nm. All of these chromatographic devices were equipped with Chemstation software from HP.

An NMR (Varian Mercury-300), and FTIR (Perkin Elmer 1600), and a preparative LC (ASI, HyperQuan 501) were used. A Karl Fisher titrator (Mettler Toledo DL38) was used to determine the samples' water content.

2.3 Synthesis of Sesamol Formate

36.0 g (33.3 mL) of acetic anhydride was charged into a 3-necked 100 mL round bottom flask equipped with a stirrer and a condenser. The acetic anhydride was preheated to a temperature of about 40°C. 8.3 g (7.0 mL) of 50% hydrogen peroxide was dropped into the flask within 10 min, and the reaction mixture was stirred for 3 hours at a temperature of about 40°C. 10.0 g of 3,4-methylenedioxybenzaldehyde was added to the flask, and the reaction mixture was stirred for 2.5-3.0 hours at a temperature of 25-28°C. It was subsequently concentrated via a rotary evaporator to yield a brown liquid. The brown liquid was then subjected to vacuum distillation, which operated at a temperature of about 80-95°C and a vacuum pressure of 2-5 mmHg to yield a pale yellow liquid product with a yield of 82%. The purity of the product was determined by liquid chromatography was greater than 98% of sesamol formate (Nikaido et al., 1984).

2.4 Synthesis of Sesamol Acetate

13.8 g of sesamol and 100 mL of dichloromethane were charged into a 3-necked 300 mL round bottom flask equipped with a stirrer and a condenser. 11.8 g of acetic anhydride was dropped into the flask, and the reaction mixture was stirred for 3 hours at room temperature. Afterward, the reaction mixture was concentrated via a rotary evaporator to yield a brown liquid. It was subsequently subjected to vacuum distillation at a temperature of about 100-105°C and a vacuum pressure of 2-5 mmHg to yield a pale brown liquid product with a yield of 75%. The purity of the product was determined by liquid chromatography was greater than 98% of sesamol acetate.

Nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy, and gas chromatography-mass spectrometry were used to confirm the prepared impurity standards' structures and purities (Beroza, 1956; Alexander et al., 1958).

2.5 Preparation of Calibration Curves

1. GC calibration curves: four-impurity standard solutions were prepared as a calibration set, at concentrations of 2.82, 5.64, 8.46, 11.28 and 14.10 μg/mL for 1,2-methylenedioxybenzene, at concentrations of 3.18, 6.36, 9.54, 12.72 and 15.90 μg/mL for sesamol formate, at concentrations of 2.94, 5.88, 8.82, 11.76 and 14.70 μg/mL for sesamol acetate, and at concentrations of 1.94, 3.88, 5.82, 7.76 and 9.70 μg/mL for 3,4-methylenedioxybenzaldehyde.
2. LC calibration curves: four-impurity standard solutions were prepared as a calibration set, at concentrations of 0.604, 1.21, 1.81, 2.42 and 3.02 μg/mL for 1,2-methylenedioxybenzene, at concentrations of 0.246, 0.492, 0.738, 0.984 and 1.23 μg/mL for sesamol formate, at concentrations of 0.842, 1.68, 2.53, 3.37 and 4.21 μg/mL for sesamol acetate, and at concentrations of 0.204, 0.408, 0.612, 0.816 and 1.02 μg/mL for 3,4-methylenedioxybenzaldehyde. The calculations were carried out using the peak height, calibration curve equations, and the determination of coefficients (r^2) for each analyte in the six different samples. The calibration curves were constructed without including the origin point.

2.6 LOD and LOQ Determination

From the relative standard deviations of repeatability at each lowest concentration level of the 11 target analytes, the instrument LOD and LOQ were determined. The LOD was calculated three times the relative standard deviation from the six replicate injections at the lowest or detectable concentration level, using the formula: LOD (μg/mL) = 3 × RSD% × concentration. The LOQ was defined as 10× RSD% × concentration, that is, LOQ = 3.3 × LOD (Shrivastava and Gupta, 2011).

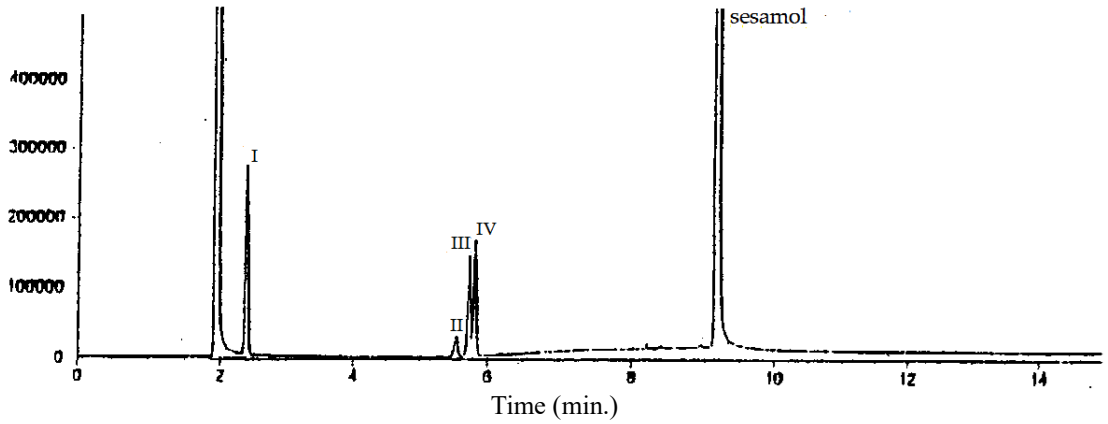


Fig. 1. Typical GC-MS chromatogram of technical sesamol

3. RESULTS AND DISCUSSION

3.1 Identification of Sesamol and its Impurities

The technical grade sesamol manufactured by Sinon Corporation of Taiwan was used for this study. Beginning with the analysis of GC-MS, there was a prominent peak along with four small detectable peaks (Fig. 1). On the other hand, the mass spectra database library (Agilent, GC Chem Station G1701AA) could recognize only two of the four impurities. These two impurities were initially considered as 1,2-methylenedioxybenzene and 3,4-methylenedioxy benzaldehyde, purchased from TCI Co. (Japan) and Hebei Haili Fragrances Co., Ltd. (China), respectively. After refinement for this impurity profile, the PLC technique (Preparative Liquid Chromatography) was applied to collect the impurities one by one. According to the NMR, FTIR, and GC-MS spectra of each impurity and the previous results, the rest of the two unknown impurities were identified as sesamol formate and sesamol acetate. Therefore, the other two remaining impurities unavailable commercially were synthesized and purified by our laboratory. After the four impurity standards were obtained, it was found that their NMR, FTIR, and GC-MS spectra were identical with those of collected impurities. The chemical structures and spectrum data of the impurities have been shown in Fig. 2. During the running of GC and LC, technical sesamol was spiked with the four purified impurity standards whose peaks were overlapped and retention times were consistent.

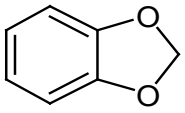
Impurity-1, 1,2-Methylenedioxybenzene (1,3-benzodioxole) with a boiling point of 172°C at normal pressure appeared clear to light yellow liquid with an aromatic odor were stable under ordinary conditions.

Impurity-4, 3,4-methylenedioxybenzaldehyde (Piperonal, heliotropine) is an aromatic aldehyde that comes as transparent crystals, $C_8H_6O_3$, and has a floral odor. It is used as a flavoring agent and in perfume. Melting point was 35-37°C, and boiling point 264°C at normal pressure.

3.2 Analytical Results of GC and LC Method

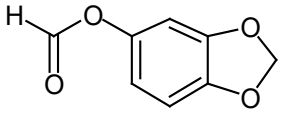
Due to solute volatilities, the order of retention times in GC is: 1,2-methylenedioxybenzene < sesamol formate < sesamol acetate < 3,4-mthylenedioxybenzaldehyde < sesamol shown in Fig. 3. However, due to solute polarities, the order of retention times in reversed-phase LC is sesamol < 3,4-mthylenedioxybenzaldehyde < sesamol formate < sesamol acetate < 1,2-methylenedioxybenzene shown in Fig. 4.

For separating the polar species of sesamol and its impurities in GC, the polar stationary phase of HP-FFAP (Polyethylene Glycol Terephthalic acid Modified) was chosen to achieve a satisfactory resolution between the eluting peaks. The results of GC-FID analyses have been summarized in Table 1. The sensitivity of sesamol formate was about fifty times lower than the other three impurities. In other words, the limit of detection about fifty times higher. Besides, its correlation coefficient (r) was equal to 0.9875. As a result of the relatively strong polar interaction between sesamol formate and HP-FFAP stationary phase, the GC analyses' results were not ideal. The sensitivity and linearity correlation of the polar purity analyses by LC-UV techniques were superior to GC-FID results, as shown in Table 2. The ultraviolet absorption of 3,4-mthylenedioxybenzaldehyde at 220 nm was much higher than those of the other three impurities, owing to the effect of conjugated chromophore on the substituted position of the aromatic ring. The developed GC and LC methods quantified the impurities of technical sesamol. GC determined 1.35% of total impurities with a coefficient of variation in the range from 7.45 to 26.8, and LC determined 1.27% of total impurities with a coefficient of variation in the range from 1.76 to 3.32, shown in Table 3. The CV data (26.8%) of sesamol formate could not meet the acceptability criteria (European Union, SANCO/2007/3131) of RSD (≤ 20%).



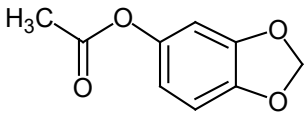
I. 1,2-Methylenedioxybenzene (Formula: $C_7H_6O_2$; MW: 122.12)

- ^{1}H-NMR (300 MHz, $CDCl_3$): δ5.94 (2H, s), 6.83 (4H, s)
- ^{13}C-NMR (75 MHz, $CDCl_3$): δ100.84 (CH_2), 108.91, 121.88, 147.62 (Ph)
- IR(ν): 3064.80, 2890.58 (C-H), 1501.03 (C=O), 1478.77, 1360.74 (C = C), 1232.75, 1041.23 (C-O) cm^{-1}
- MS(m/z): 121(M^+), 107(M^+-CH_2)



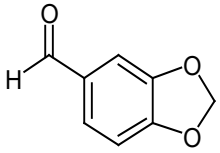
II. Sesamol formate (Formula: $C_8H_6O_4$; MW: 166.13)

- ^{1}H-NMR (300 MHz, $CDCl_3$): δ5.99 (2H, s), 6.58 (1H, d, J = 8.4 Hz), 6.65 (1H, s), 6.80 (1H, d, J = 8.4 Hz), 8.25 (1H, s)
- ^{13}C-NMR (75 MHz, $CDCl_3$): δ102.11 (CH_2), 103.52, 108.34, 113.81, 144.37, 146.06, 148.46 (Ph), 159.80 (OCHO)
- IR(ν): 2907.94 (C-H), 1736.65 (C = O), 1484.33 (C = C), 1254.95, 1173.95, 1035.04(C-O) cm^{-1}
- MS(m/z): 166(M^+), 137(M^+-CHO), 121(M^+-OCHO)



III. Sesamol acetate (Formula: $C_9H_8O_4$; MW.: 180.16)

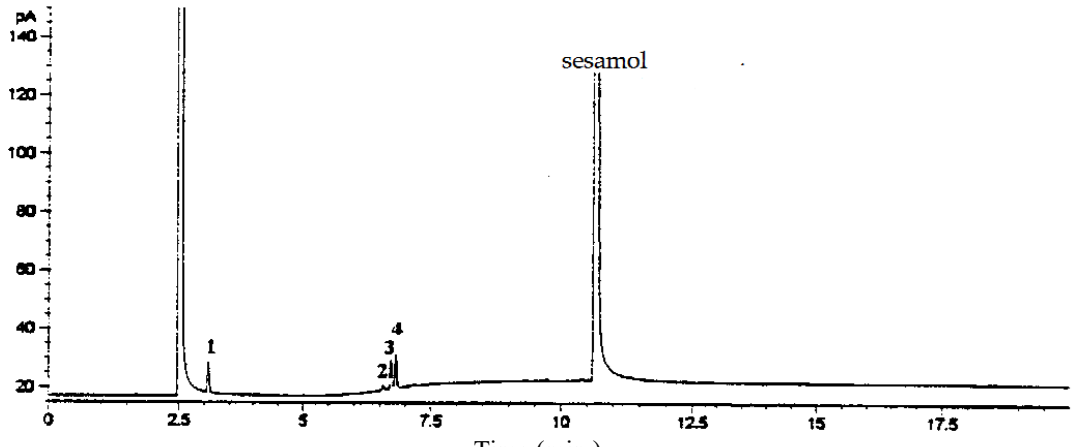
- ^{1}H-NMR (300 MHz, $CDCl_3$): δ2.26 (3H, s), 5.97 (2H, s), 6.52 (1H, dd, J = 8.4 Hz, 2.4Hz), 6.60 (1H, d, J = 2.4 Hz), 6.77 (1H, d, J = 8.4 Hz)
- ^{13}C-NMR (75 MHz, $CDCl_3$): δ21.21 (CH_3), 101.92, 103.95, 108.18, 114.13, 145.22, 145.58, 148.22 (Ph), 170.02 (OCOR)
- IR(ν): 2899.20 (C-H), 1761.72 (C = O), 1483.75 (C = C), 1170.62, 1121.16, 1095.31 (C-O) cm^{-1}
- MS(m/z): 180(M^+), 149(M^+-CH_3O), 121(M^+-$OCOCH_3$)



IV. 3,4-Mthylenedioxybenzaldehyde (Formula: $C_8H_6O_3$; MW: 150.13)

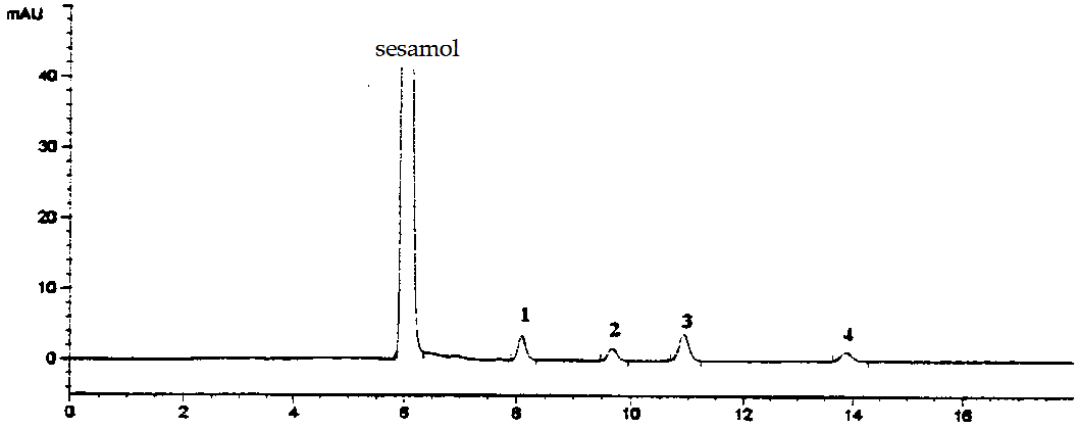
- ^{1}H-NMR (300 MHz, $CDCl_3$): δ6.07 (2H, s), 6.92 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 1.5 Hz), 7.40 (1H, dd, J = 8.0 Hz, 1.5Hz), 9.80 (1H, s)
- ^{13}C-NMR (75 MHz, $CDCl_3$): δ102.33 (CH_2), 107.12, 108.60, 128.89, 132.10, 148.93, 153.34 (Ph), 190.52 (CHO)
- IR(ν): 2996.26, 2916.78 (C-H), 1673.43 (C=O), 1494.10, 1449.36 (C=C), 1260.42, 1093.39, 1036.37 (C-O) cm^{-1}
- MS(m/z): 149(M^+), 121(M^+-CO)

Fig. 2. The four sesamol-derived impurities and characterization data



1. 3,4-Methylenedioxybenzaldehyde **2.** Sesamol formate
3. Sesamol acetate **4.** 1,2-Methylenedioxybenzene

Fig. 3. Typical GC chromatogram of technical sesamol



1. 3,4-Methylenedioxybenzaldehyde **2.** Sesamol formate
3. Sesamol acetate **4.** 1,2-Methylenedioxybenzene
Fig. 4. Typical LC chromatogram of technical sesamol

Table 1. Linearity, correlation (r), the limit of detection (LOD) of sesamol impurities analyzed by GC-FID method

Impurities	Linearity	Correlation (r)	LOD (μg/mL)
MDB[a]	y = 5.383x - 1.962	0.9915	0.067
Sesamol formate	y = 0.116x + 0.179	0.9875	3.103
Sesamol acetate	y = 4.078x - 0.826	0.9939	0.088
MDBA[b]	y = 4.885x - 0.387	0.9981	0.074

[a]MDB: 1,2-Methylenedioxybenzene
[b]MDBA: 3,4-Mthylenedioxybenzaldehyde
All values are averages of three measurements

Table 2. Linearity, correlation (r), the limit of detection (LOD) of sesamol impurities analyzed by LC-UV method

Impurities	Linearity	Correlation (r)	LOD (μg/mL)
MDB	y = 21.81x + 0.221	0.9996	0.033
Sesamol formate	y = 19.35x - 0.132	0.9989	0.037
Sesamol acetate	y = 15.97x + 0.195	0.9995	0.045
MDBA	y = 56.53x - 0.547	0.9997	0.013

All values are averages of three measurements

Table 3. Quantification of impurities in technical sesamol using GC and LC methods

Method	Sesamol[a]/ (CV)%	MDB/ (CV)%	Sesamol formate/ (CV)%	Sesamol acetate/ (CV)%	MDBA/ (CV)%	Total impurities %
GC	98.38 (5.82)	0.35 (7.45)	0.39(26.8)	0.36 (7.72)	0.25 (13.6)	1.35
LC	98.25 (1.18)	0.25 (2.09)	0.17 (3.32)	0.43 (1.76)	0.42 (3.01)	1.27

[a]Water content: 0.12% (Karl Fischer titration)
All values are averages of six measurements

In principle, the developed GC method could be partially improved via internal standard, temperature programming, and using a medium polar column instead of better precision, resolution, and method sensitivity. Since the developed LC-UV method was desirable with the precision, detection limit, linearity, resolution, sensitivity, and even robustness of assay, it was strongly recommended as the standard sesamol analytical method for quality control.

4. CONCLUSIONS

GC-FID or LC-UV methods could efficiently analyze sesamol and its derived impurities. Four significant impurities of the technical sesamol were characterized by GC-MS, NMR, and FTIR spectrometry. For the assays of polar sesamol impurities, the LC method was superior compared to the GC method.

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