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Dynamic head-space extraction and estimation of Dimethyl fumarate using GC-TQ-MS

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ABSTRACT
Dimethyl fumarate (DMFu), a volatile fumaric acid ester, is often used in sachets or small pillow pouches in shoe boxes, and in the packaging of furniture, particularly in leather upholstered furniture, to prevent mould growth during long shipment periods and storage. However, its strong sensitising properties and cytotoxic effects have led to regulatory restrictions in consumer products to less than 0.1 mg/kg. Accurate determination of DMFu is essential for ensuring consumer safety. The regular analytical methods, including gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), and high-performance liquid chromatography (HPLC), often face challenges such as co-extraction issues, contamination from solvent extraction, while limitations associated with solid-phase microextraction (SPME), found to suffer from low extraction capacity, limited fibre lifespan, and selectivity constraints. A dynamic headspace (DHS) extraction method coupled with GC-TQ-MS was developed and validated to overcome these challenges. This is a solvent-free approach enhancing analyte sensitivity while minimising matrix interferences and environmental impact. The method employed C18 solid-phase sorbent material for efficient analyte capture and was optimised for key parameters, including temperature, extraction time, and sorbent bed size. Validation studies were demonstrated satisfactorily. This method offers a reliable, efficient, and environmentally friendly alternative for detecting DMFu in various consumer products

1. INTRODUCTION:

Dimethyl fumarate (DMFu) is a fumaric acid ester that sublimes at room temperature and has been applied in the oral treatment of psoriasis1, as well as reported to exhibit antibacterial and antifungal activity2,3. Despite these therapeutic applications, DMFu poses significant health risks, including allergic contact dermatitis, non-immune contact urticaria, and cytotoxic effects (epidermoid cell line A431, LD50: 5.04 g/ml)4,5. Industrially, DMFu is widely used as a biocide to inhibit mould growth in leather, footwear, textiles, and furniture during storage and transport under humid conditions. It is often incorporated into sachets with silica gel and enclosed within product packaging. Even at trace levels, DMFu has been identified as a potent sensitizer4,6 capable of inducing acute dermatitis. Outbreaks of DMFu-related dermatitis have been reported across Europe, including furniture dermatitis in Finland and the UK7-10, as well as footwear-associated cases in Spain, Portugal, Italy, and Finland6,11-14. These widespread incidents highlight the public health concern surrounding DMFu contamination in consumer products.

The European Union (EU) set a maximum limit of 0.1 mg/kg for DMFu in consumer products, which was made permanent by Commission Regulation (EU) No. 412/2012, published in the Official Journal on May 16, 201215.

Determining DMFu in consumer products, including textiles, leather, polymers, and silica gel pouches, is essential to safeguard consumer safety

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and ensure regulatory compliance. Several analytical methods have been developed for the determination of DMFu, including gas chromatography coupled with mass spectrometry (GC-MS, quadrupole and ion trap)16-22, gas chromatography with electron capture detection (GC-ECD)21,22, high-performance liquid chromatography with UV detection (HPLC-UV)20,23-25, and liquid chromatography with mass spectrometry (LC-MS)24,25. Among these, GC-MS is the most widely used due to its high sensitivity and specificity, compatibility with the volatility of DMFu, high chromatographic resolution, low matrix interference, and well-established regulatory methods. Other techniques have notable limitations: GC-ECD exhibits low selectivity, relatively poor sensitivity, and cannot provide structural confirmation; HPLC-UV detection at lower wavelengths (<230 nm) is susceptible to interference from matrix and mobile phase components; and LC-MS, although sensitive and selective, often requires more extensive sample preparation and method optimization. Moreover, this study focuses on optimizing sample preparation toward greener analytical techniques, minimizing solvent use and environmental impact.

Various solvent systems extract DMFu from leather, textiles, and non-leather footwear components which has been contaminated with DMFu from silica gel pouches. These include acetone16,17,26-28, diethyl ether16, dichloromethane (DCM)17, hexane17, methanol16,17,19,21,23, acetonitrile17,22,25, ethyl acetate17-20,23,29,30, water21, and trichloroethylene21. The extraction methods employed included ultrasonic-assisted solvent extraction (UAE)16-22,25-28, as well as accelerated solvent extraction and vortex-assisted liquid-liquid microextraction (ASE-VALLME)21. Solvent-free extraction methods, such as solid-phase microextraction (SPME)16-18 and headspace solid-phase microextraction (HS-SPME)17-21, have also been employed. In solvent extraction techniques, controlling co-extraction remains a significant challenge. Co-extraction leads to a complex chromatogram of the target analyte due to the introduction of impurities, which adversely affects the accuracy, recovery, and overall efficiency of the extraction process. The presence of co-extracted impurities, particularly non-volatile and non-polar compounds, could contaminate chromatography columns and detectors such as mass spectrometers. To prevent these issues, additional clean-up steps are necessary to ensure the removal of contaminants and protect analytical systems, thereby enhancing the reliability and efficiency of the overall analytical approach. Similarly, solid-phase microextraction (SPME) is a popular technique for analysing volatile and semi-volatile analytes. While SPME offers several advantages, such as being inherently quantitative and requiring minimal solvents, it has its own set of limitations. These include low extraction capacity18, and the potential degradation of the fibre, which can compromise its performance and longevity. To address these challenges, a dynamic headspace (DHS) technique31,32 is probed as an alternative sample preparation method. This approach can potentially overcome the limitations of solvent extraction and SPME by offering enhanced efficiency of analyte extraction, allowing for more effective isolation and concentration of volatile compounds.

DHS extraction is proposed for DMFu for the following points: DMFu is a volatile fungicide released by controlled heating from solid samples; unlike liquid-liquid extraction, DHS reduces matrix interferences like fats, oils, and polymers from samples and enables the enrichment of DMFu vapour onto the absorbent and improves sensitivity.

2. MATHEMATICAL MODEL:

Chemicals and reagents:

Different sorbent masses of solid phase extraction (SPE) material, Strata C18-E 100 mg in 3 mL tube, Strata C18-E 200 mg in 3 mL tube, Strata C18-E 500 mg in 3 mL tube, Strata C18-E 500 mg in 6 mL tube, Strata C18-T 1g in 6 mL tube, Strata C18-E 2g in 12 mL tube used to capture DMFu in vapour phase were procured from Phenomenex, CA, United States. HPLC-grade acetone and n-hexane were obtained from Avantor Performance Materials, Thane, Maharashtra, India. DMFu and dimethyl maleate (DMMa) were procured from Dr Ehrenstorfer, Burgermeister-Schlosser-Strasse, 86199 Augsburg, Germany. Nitrogen gas of 99.99% purity was used to carry the vapour phase and collision gas, and Helium, with a purity of 99.99%, was used as the carrier gas for the gas chromatography-mass spectrometer and was procured from Praxair India Private Limited, Bangalore, India. PTFE Syringe filter of 13 mm diameter with pore size 0.2 micron was procured from Axiva Sichem Pvt Ltd, Haryana, India.

Instrumentation:

The GC-TQ-MS consisted of an Agilent 8890A GC equipped with a 7693A autosampler featuring a 150-vial capacity sample tray. The mass spectrometer model used was 7010 Triple Quadrupole (7010TQ), and it was procured from Agilent Technologies, Stevens Creek Blvd, Santa Clara, United States, and was utilised for method development. A DB-17MS analytical column was employed for GC-TQ-MS analyses, with a length of 30 m, and an i.d of 0.25 mm with a film

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thickness of 0.25 µm. The carrier gas flow rate was maintained at 1 mL/min. Additionally, a digital oil bath with a temperature controller was procured from Equitron, Mumbai, India.

Preparation of a Reference Standard for Analysis:

A 1000 µg/mL stock solution of DMFu was prepared in acetone. A secondary stock solution of 100 µg/mL was obtained through serial dilution. Further dilutions were performed to prepare 10 µg/mL and 1.0 µg/mL solutions. The 1.0 µg/mL solution was then used to prepare working standard solutions for assessing linearity at the following concentrations: 0.001 µg/mL, 0.002 µg/mL, 0.005 µg/mL, 0.01 µg/mL, 0.025 µg/mL, 0.050 µg/mL, 0.10 µg/mL and 0.250 µg/mL.

Sample Preparation of the Proposed Method:

The initial sample was cut into pieces of approximately 2–3 mm² in size. One gram of the sample cut pieces was accurately weighed and placed into a 50 mL amber glass bottle, which featured a lid with inlet and outlet tubes for gas flow. The inlet was connected to a carrier gas source, while the outlet was linked to a C18 sorbent cartridge pre-conditioned with acetone before use. The sample bottle was then positioned in an oil bath, maintained at 70 °C, and allowed to equilibrate for 10 minutes. Following this, the carrier gas was introduced at a flow rate of 500 mL/min. The resulting vapours were passed through the C18 cartridge for 15 minutes, facilitating the absorption of compounds onto the C18 material. The absorbed compounds were then eluted from the C18 solid-phase extraction (SPE) cartridge using 2 mL of acetone. The eluted acetone was filtered through a 0.2 µm PTFE filter before being analysed using GC-TQ-MS.

Chromatographic Condition:

The total analytical time was approximately 16 minutes. **Table 1** presents the operational conditions for the GC-TQ-MS analysis of the proposed method.

Table 1. Operational conditions for the GC-TQ-MS analysis of the proposed method:

GC-MS/MS Analytical parameter for the proposed method			
GC parameters		**Oven programme**	
Carrier gas	Helium	Initial temperature 1	60 °C
Flow rate	1 ml/min	Hold time	4 min
Inlet mode	Multimode inlet, split less	Temperature 2	260 °C
Inlet liner	4 mm single taper, with glass wool	Rate	30 °C/min
Inlet temperature	230 °C	Hold time	3 min
Injection volume	1 µL	Total GC runtime	16 min
Column	Agilent DB-17 MS (30 m × 250 µm × 0.25 µm)		
MS parameters			
Transfer line temperature	280 °C	Acquisition mode	Multiple Reaction Monitoring (MRM)
Source temperature	250 °C	Collision gas	Nitrogen
Source	Electron Impact (EI)	Collision energy	6 eV
Electron energy	70 eV	Qualifier ion (m/z)	144 → 113 and 85
Quadrupole temperature	230 °C	Quantifier ion (m/z)	113 → 113 and 85
Solvent delay	6 min		

3. RESULTS AND DISCUSSION:

Selection of SPE materials for the recovery of DMFu:

Various solid-phase extraction (SPE) materials, including silica, Florisil, octadecylsilane (C18), and octylsilane (C8), are widely in general. Among these, C18, a reverse-phase SPE material, is found particularly effective for capturing DMFu in the vapour phase due to its strong hydrophobic interactions and high affinity for non-polar compounds. For method optimisation, including temperature and extraction time, a sorbent mass of 1 g in a 6 mL tube of C18 SPE material was employed, ensuring efficient analyte retention and reproducibility.

Optimization of desorption gas flow for the recovery of DMFu:

This study investigated the influence of nitrogen desorption flow rate on the recovery of DMFu at a constant extraction temperature of 80 °C over extraction times ranging from 15 to 60 min. Flow rates of 200, 500, and 1000 mL/min were evaluated using spiked samples at 1.0 µg/mL. At 200 mL/min, recoveries increased progressively with time, from 69.9% at 15 min to 98.2% at 60 min. At 500 mL/min, recoveries were consistently high, reaching 99.1% at 15 min but gradually declining to 82.8% at 60 min. In contrast, recoveries at 1000 mL/min decreased steadily with time, from 92.9% at 15 min to 75.3% at 60 min. Overall, a desorption flow rate of 500 mL/min was identified as the optimal condition for DHS extraction. Although 200 mL/min yielded slightly higher recovery at 60 min, it required extended extraction to reach maximum efficiency, making it less practical for routine applications. By comparison, 500 mL/min achieved the highest recovery (99.1%) within only 15 min, highlighting its suitability for rapid analyte enrichment. The slight decline in recovery at longer extraction times is likely attributable to analyte breakthrough at elevated flow rates. Nevertheless,

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for routine analysis, shorter extraction times at 500 mL/min minimize analyte loss, reduce total analysis duration, and improve sample throughput. Thus, 500 mL/min represents the most favourable compromise between recovery efficiency and operational practicality, as illustrated in **Fig.1**.

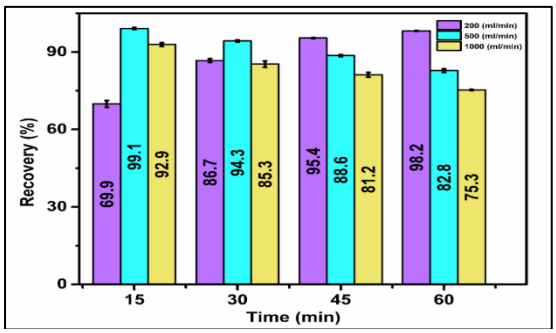

Fig. 1. Optimization of desorption gas flow on recovery of DMFu at 1.0 µg/mL.

Optimization of extraction temperature for the recovery of DMFu:

The effect of extraction temperature on DMFu recovery was evaluated over 30–80 °C using spiked samples at 0.1 and 1.0 µg/mL (Fig. 2). Recovery exhibited a pronounced temperature dependence at both concentration levels. At 30 °C, poor recoveries (29.1% and 23.5%) were obtained, indicating inadequate volatilisation of DMFu. Increasing the temperature to 40–50 °C led to a moderate enhancement in recovery (57.2–62.1% at 0.1 µg/mL; 53.7–61.7% at 1.0 µg/mL), reflecting partial improvement in headspace transfer. A marked increase in extraction efficiency was observed at 60 °C, with recoveries of 84.3% and 77.1% for 0.1 and 1.0 µg/mL, respectively. Near-quantitative and reproducible recoveries were achieved at 70 °C, reaching 99.6% and 99.2%, as confirmed by low standard deviations. Further elevation of the temperature to 80 °C did not yield any significant gain (99.1–98.9%), indicating saturation of the extraction process. Consequently, 70 °C was selected as the optimal extraction temperature, providing maximum and consistent DMFu recovery while minimising unnecessary thermal exposure. This condition was applied in all subsequent analyses.

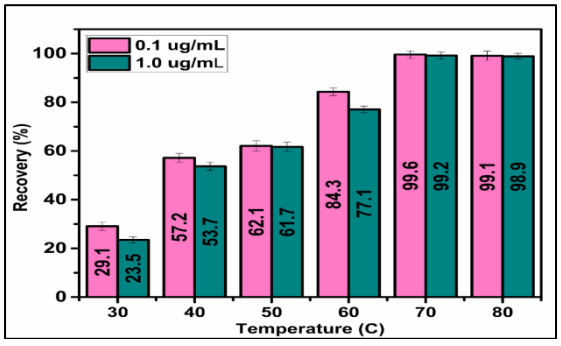

Fig. 2. Optimisation of temperature for recovery of DMFu at 0.1 µg/mL and 1.0 µg/mL.

Optimization of extraction time for the recovery of DMFu:

The effect of extraction time on dimethyl fumarate (DMFu) recovery was evaluated at 70 °C using dynamic headspace extraction. Spiked samples at 0.1 and 1.0 µg/mL were subjected to extraction times of 5–30 min following a 10 min equilibration period, after which carrier gas flow was initiated (Fig. 3). At 5 min, recoveries were low for both concentrations (13.9% and 13.8%), indicating insufficient analyte transfer. Recovery increased markedly at 10 min (65.6% and 63.9%) but remained incomplete. Near-quantitative extraction was achieved at 15 min, with recoveries of 99.4% (0.1 µg/mL) and 99.9% (1.0 µg/mL). Extending the extraction time to 20–30 min did not result in any statistically significant improvement (recoveries >98%), indicating that extraction equilibrium was reached within 15 min. Accordingly, an extraction time of 15 min was selected as optimal, providing quantitative recovery with improved analytical throughput.

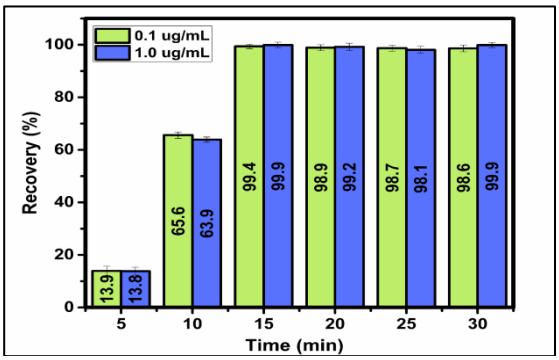

Fig. 3. Optimisation of extraction time for recovery of DMFu at 0.1 µg/mL and 1.0 µg/mL.

Optimization of the sorbent quantity for the recovery of DMFu:

The effect of sorbent quantity on DMFu recovery during dynamic headspace extraction was evaluated using SPE cartridges with different configurations (0.5 g/3 mL, 0.5 g/6 mL, 1.0 g/6 mL, and 2.0 g/12 mL) at fortification levels of 0.01, 1.0, and 10.0 µg/mL (Fig. 4). Sorbent loading significantly influenced trapping efficiency. The 0.5 g/3 mL cartridge provided high recoveries at low and medium levels (97.3% and 95.9%), but recovery decreased at the highest level (83.1%), indicating limited sorbent capacity. In contrast, the 0.5 g/6 mL configuration yielded consistently lower recoveries (82.6–84.4%), likely due to reduced effective bed length and diminished analyte–sorbent interaction. Near-quantitative recoveries were achieved with 1.0 g/6 mL across all concentration levels (98.5–99.8%), reflecting an optimal balance between sorbent capacity and

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dynamic flow. Increasing sorbent quantity to 2.0 g/12 mL did not provide further improvement (98.4–99.6%). Accordingly, 1.0 g/6 mL was selected as the optimal condition and applied for all subsequent validation and sample analysis.

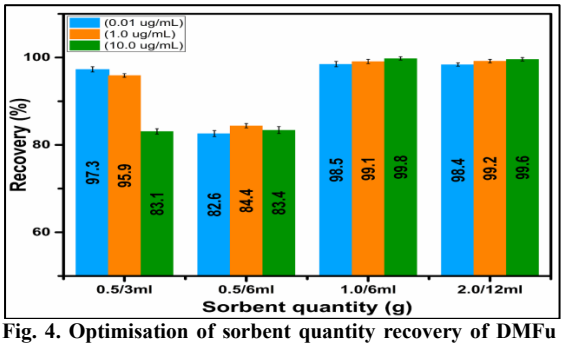

Fig. 4. Optimisation of sorbent quantity recovery of DMFu at 0.01 µg/mL, 1.0 µg/mL and 10.0 µg/mL.

Validation of the Method:

Method validation scientifically confirms that an analytical method is appropriate for its intended use. It supports the development of methods that exhibit high specificity, linearity, accuracy, sensitivity, and precision. The necessary validation parameters differ based on the analytical procedure employed. The optimisation of method validation was achieved through the following parameters, which represent **Table 2**.

Table 1. Method validation data for the proposed method

S. No	Parameter			Result	Acceptance criteria
1	Linearity		R^2	0.99951	≤ 0.990
2	LOD		µg/mL	0.001	--
3	LOQ		µg/mL	0.003	--
4	Accuracy				
	30% Less LOQ		Recovery (%)	87.7	80-120%
	100% LOQ			93.9	80-120%
	200% LOQ			83.8	80-120%
5	Precision				
	Repeatability	30% Less LOQ	RSD (%)	3.8	≤ 20.0%
		100% LOQ		2.4	≤ 20.0%
		200% LOQ		1.6	≤ 20.0%
	Intermediate precision			6.5	≤ 20.0%
6	Specificity		Min	0.5	--
7	Measurement uncertainty		µg/mL	±0.006@0.133	--

Linearity:

The linearity and analytical range for DMFu were established using 7 standard concentration levels from 0.001 µg/mL to 0.250 µg/mL, and the observed correlation coefficients is $R^2 > 0.99951$, as shown in **Fig. 5.**

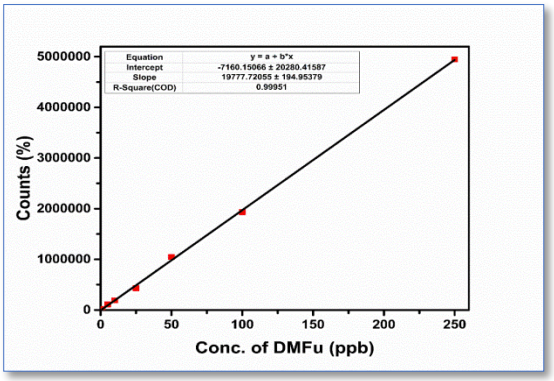

Fig. 5. Linearity graph for DMFu.

Limit of Detection (LOD) and Limit of Quantification (LOQ):

The limit of detection (LOD) and the limit of quantification (LOQ) were calculated using the linear regression equation established during method validation. The LOD was determined by taking the standard deviation of the y-intercept, multiplying it by 3.3, and dividing the result by the average slope and LOQ was calculated by multiplying the standard deviation of the y-intercept by 10 and then dividing by the average slope. LOD found to be 0.001 µg/mL, while the LOQ was found to be 0.003 µg/mL.

Accuracy:

The accuracy of DMFu was evaluated using the standard addition method at three levels: 30% of LOQ, 100% of LOQ, and 200% of LOQ. A known amount of analyte was added to the pre-analysed sample, and the percentage recovery was calculated using this method; the recovery rates were found to be 87.7% at 30% LOQ, 93.9% at 100% LOQ, and 83.8% at 200% LOQ.

Precision:

Repeatability:

The repeatability of DMFu was determined using three different concentration levels: 0.001 µg/mL (30% of LOQ), 0.003 µg/mL (100% of LOQ), and

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0.006 µg/mL (200% of LOQ). The RSD values were measured using an average area from six injections with each level, and the RSD in each level was obtained as follows: 3.8% at 30% LOQ, 2.4% at 100% LOQ, and 1.6% at 200% LOQ. These values were within the acceptable limits.

Intermediate precision:
For DMFu, intermediate precision was determined by assessing six injections of concentration levels at 100% of LOQ by the same analyst using another GC-MS equipment. The %RSD values were determined and reported (6.4% RSD), confirming acceptability.

Specificity:
This characteristic parameter assures the reliability of analyte measurement without interference. To assess specificity, the retention times of the isomers DMFu and DMMa were determined both individually and in a mixture. The individual retention times were 8.399 minutes for DMFu and 8.957 minutes for DMMa. In the standard mix, these retention times remained unchanged, with DMFu eluting at 8.399 minutes and DMMa at 8.957 minutes. This consistency confirms the method's capability to distinguish the two close isomers by 0.5 minutes without interference. which is shown in **Fig. 6.**

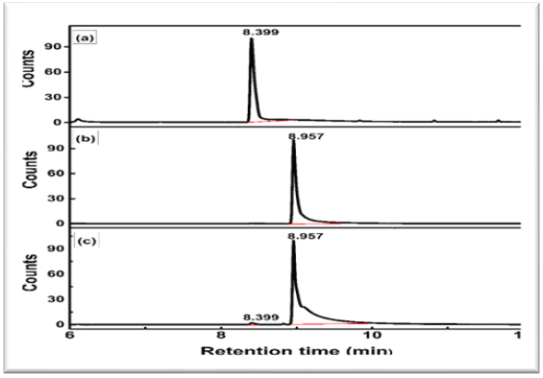

Fig. 6. Specificity for (a) chromatogram for DMFu, (b) chromatogram for DMMa, (c) chromatogram of DMFu and DMMa.

Evaluation of Measurement uncertainty:
A fundamental concept in metrology is a measurement of uncertainty, which quantifies the level of uncertainty associated with any given measurement. The evaluation relied on non-statistical sources, such as instrument specifications and literature data. The uncertainty values for the balance, micropipettes, and volumetric flasks utilised in the method were sourced from calibration certificates, while the uncertainty value for DMFu-certified reference materials was derived from certificates of analysis. Ultimately, the combined measurement uncertainty for the proposed method, reported at a 95% confidence level, was determined to be 0.133 ± 0.006 µg/mL.

Analysis of Real Samples:
The DMFu-spiked leather sample, processed at the tannery for interlaboratory comparison, was initially analyzed using the official method, yielding a DMFu concentration of 17.85 mg/kg with an RSD of 3.4%. The same sample was analysed using the proposed method, which yielded a DMFu concentration of 18.00 mg/kg with an RSD of 3.0%. The RSD values obtained for both the official and proposed methods were presented in **Table 3**. The values obtained for DMFu using the proposed method were well within the acceptable limits, demonstrating its reliability and precision. The chromatogram and the mass spectrum analysis of DMFu using GC-TQ-MS are shown in **Fig. 7.**

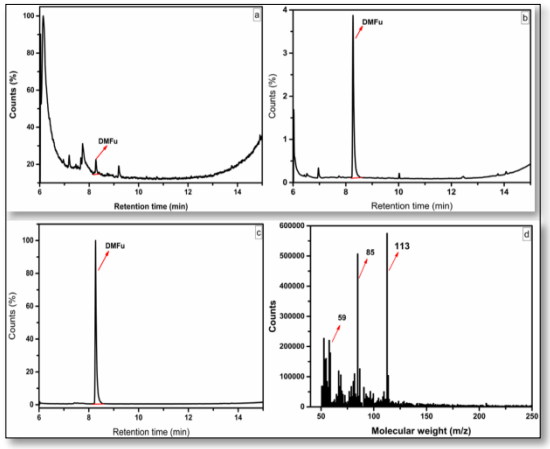

Fig. 7. The GC-TQ-MS chromatogram and mass spectrum of the DMFu analysis using the proposed method (a) chromatogram of Full scan mode (b) chromatogram of selective ion chromatogram (c) chromatogram of MRM (d) Mass spectrum of Full scan mode.

Table 3. RSD data for proposed and official method

Trail	Method	1	2	3	4	5	6	RSD (%)
DMFu (mg/kg)	Official Method	18.5	18.7	17.7	17.8	17.4	17.1	3.4
	Proposed Method	17.6	18.6	18.5	17.5	17.5	18.3	3.0

Comparative study of extraction techniques with Ultrasonication and Dynamic headspace for real samples:
The study demonstrated that during the solvent

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extraction of DMFu using the ultrasonication technique, the leather sample was fully immersed in the solvent throughout the sonication process. Leading to the extraction of matrix as well. The inactive ingredients that get in to the extract can could interfere with the column chemistry, potentially causing irreversible damage that diminishing the column's lifespan and adversely affecting resolution and sensitivity. In contrast, dynamic headspace analysis almost cut out these impurities by employing only vapour-phase extraction of the analyte. This distinction is illustrated in the chromatogram presented in **Fig. 8.**

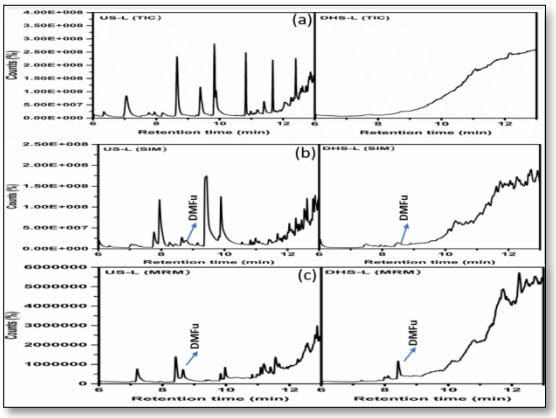

Fig. 8. Comparative chromatogram of ultrasonic and DHS extraction of DMFu (a) Full scan mode or Total ion chromatogram-(TIC) (b) Selective ion monitoring-(SIM) (c) Multiple reaction monitoring-(MRM

4. CONCLUSIONS:

This study successfully developed and validated a dynamic headspace (DHS) extraction method coupled with GC-TQ-MS for the determination of dimethyl fumarate (DMFu) in diverse matrices. The solvent-free, automated, and reproducible nature of DHS provided a green analytical approach, eliminating the need for labour-intensive sample preparation and minimizing analyte loss associated with multiple transfer steps. The method demonstrated high specificity and sensitivity, with well-resolved chromatographic peaks and minimal matrix interference, ensuring accurate qualitative and quantitative determinations.

A key achievement of this work is the extension of the DHS extraction technique, which can be applicable beyond conventional leather products to include textiles and polymeric materials such as PVC, PU, and EVA. This versatility enhances its utility for industries where product safety and regulatory compliance are critical. The method was further validated through the calculation of measurement uncertainty (±0.006 µg/mL), underscoring its accuracy, precision, and reliability. Identification of DMFu was confirmed by retention time matching in combination with full-scan and MS/MS spectral analysis, providing a high level of confidence in the results. The developed DHS-GC-TQ-MS method is rapid, cost-effective, sensitive, and environmentally friendly. Its robustness and broad applicability make it a valuable tool for routine monitoring of DMFu in consumer products and for supporting regulatory and environmental safety assessments.

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CONFLICT OF INTEREST:

The authors declare that they have no conflicts of interest.

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