

Fast micro thermal desorption combined with cryofocusing for ultra fast gas chromatography

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Abstract

In safety research, gas chromatography is a commonly used technique for the detection of hazardous substances in air samples for example. When public safety is at risk and decisions about protective measures must be made, the speed of sampling and analysis is a decisive factor. This demand for rapid results in combination with a high sample throughput is also important in industrial applications. In this context, time-saving methods also contribute to cost efficiency. The three investigations presented here focus on the step-by-step development of a rapid system designed to accelerated sample application.

In the initial study, a liquid CO₂ cryofocusing unit was developed to enable rapid refocusing of volatile analytes at the head of the separation column with low CO₂ consumption. A test mixture comprising four gases and 16 solvents was investigated, with the solvent analysis being particularly important for pharmaceutical quality control. The effect of cryofocusing on retention time, full width at half maximum (FWHM), and resolution was evaluated in comparison to measurements conducted without cryofocusing. The entire method, including system cool down, has a run time of less than 90 s.

In the second study, a thermal desorption unit (TDU) and corresponding micro thermal desorption tubes (μ TD-tubes) were developed as an alternative to the conventional split/splitless injector for the flow field thermal gradient GC (FF-TG-GC) system. The low thermal mass of this setup enables for exceptionally rapid heating and cooling cycles and thus a faster analyte desorption compared to existing systems. The study investigates the impact of the reduced μ TD-tube dimensions on parameters such as desorption time, FWHM, breakthrough volumes, tube flow rates (and thus linear velocities), porosity and back pressure. The system's functionality is demonstrated by measurements of an *n*-alkane standard ranging from *n*-pentane to *n*-eicosane.

In the next step, a rapid method was developed for analyzing a complex mixture containing six chemical warfare agent (CWA) simulants and ten explosives using the TDU in combination with cryofocusing. Due to the substantial differences in physicochemical properties among the target compounds, the analytical parameters had to be adjusted accordingly. The effects of desorption conditions, cryofocusing and the thermal gradient along the separation column were systematically examined and a cycle time of only 164 s was achieved.

Chapter 1

General Introduction

1.1 Gas Chromatography

1.1.1 Fields of Application

Gas chromatography (GC) is a widely used and versatile analytical technique commonly applied in fields such as food and cosmetic safety, environmental monitoring, forensic analysis or public security. Typical applications are the detection of pesticide residues in food, allergenic fragrances in cosmetics or polychlorinated biphenyls (PCBs) in environmental samples for example [1, 2, 3]. Especially in security-critical situations such as fires, chemical accidents or terrorist attacks instrumental analysis is essential for the rapid and reliable identification of hazardous substances in air, debris and other matrices [2, 4]. In this context, GC is employed for the detection of toxic industrial chemicals, the presence or absence of fire accelerants, chemical warfare agents and explosive residues for example [2].

1.1.2 Functional Principle

GC enables the separation of analyte mixtures that are either already in the gaseous state or can be vaporized without decomposition. The principle relies on the distribution of analytes between a mobile phase (carrier gas) and a stationary phase (mainly the coated inner surface of a separation column). The type and intensity of interactions and thus eventually the required time to pass the column (retention time, t_R) depend largely on the physico-chemical properties of the analytes and the separation column. The effective velocity of a substance is a fraction of the mobile phase velocity reduced by retention. After elution from the column, the analytes are detected and quantified separately.

The degree of separation between two peaks with different retention times ($t_{R,1}$ and $t_{R,2}$) is characterized by the resolution R_s [1, 3]:

$$R_s = 2 \cdot \frac{t_{R,2} - t_{R,1}}{w_{b,1} + w_{b,2}} \quad (1.1)$$

$$(1.2)$$

with $w_{b,1}$ and $w_{b,2}$, being the peak width at baseline level. Assuming a Gaussian peak shape, the resolution can also be calculated by the peak width at half height (full width at half maximum, FWHM) [3]:

$$R_s = 1.18 \cdot \frac{t_{R,2} - t_{R,1}}{FWHM_1 + FWHM_2} \quad (1.3)$$

A resolution value of $R_s > 1.5$ indicates baseline separation of two peaks [5].

1.1.3 Conventional and Flow Field Thermal Gradient GC

The structure of a GC consists of four functional units: the carrier gas supply (A), the injector (B), the GC oven housing a separation column (C), and the detector (D), Figure 1.1. In conventional oven GCs, the column, typically 10 m to 60 m meters long [1], is housed in an air-bath oven (Figure 1.1, C₁). Measurements can be carried out both isothermally and temperature-programmed with a temporal temperature rate. Due to the large oven volume and its high thermal mass, both the heating and cooling processes are relatively slow compared to a flow field thermal gradient GC (FF-TG-GC).

In a FF-TG-GC a thin, resistively heated stainless steel capillary is used as an oven, into which short separation columns with a length of only 2 or 4 m are inserted (Figure 1.1, C₂). The stainless steel capillary is coiled into a helix and a cylindrical flow resistance made of foam (F) is placed in its center. A flow field of decreasing intensity from bottom to top is generated by an air fan (H) underneath the foam. As a result air velocities are higher respectively temperatures are lower due to cooling by the air flow at the column outlet compared to the inlet. Thereby an additional spatial temperature gradient along the separation column is created. This enables peak focusing that counteracts diffusion, as the migration speed at the peaktail is higher than at the front, which pushes the analyte band together. Another advantage of the spatial temperature gradient, especially for thermolabile analytes, is the reduction of the elution temperature [6, 7, 8].

In general the high measurement speed resulting from the short separation column in combination with the rapid oven cool-down phase, shortens cycle times and enhances the system efficiency [6, 8].

1.1.4 Carrier Gas Flows at the FF-TG-GC

The configuration of the FF-TG-GC, with its purged connectors, offers several options for directing the carrier gas flows through the system. If both purged connectors are utilized, carrier gas is supplied via the two separate tubings (A) and (I), Figure 1.2.

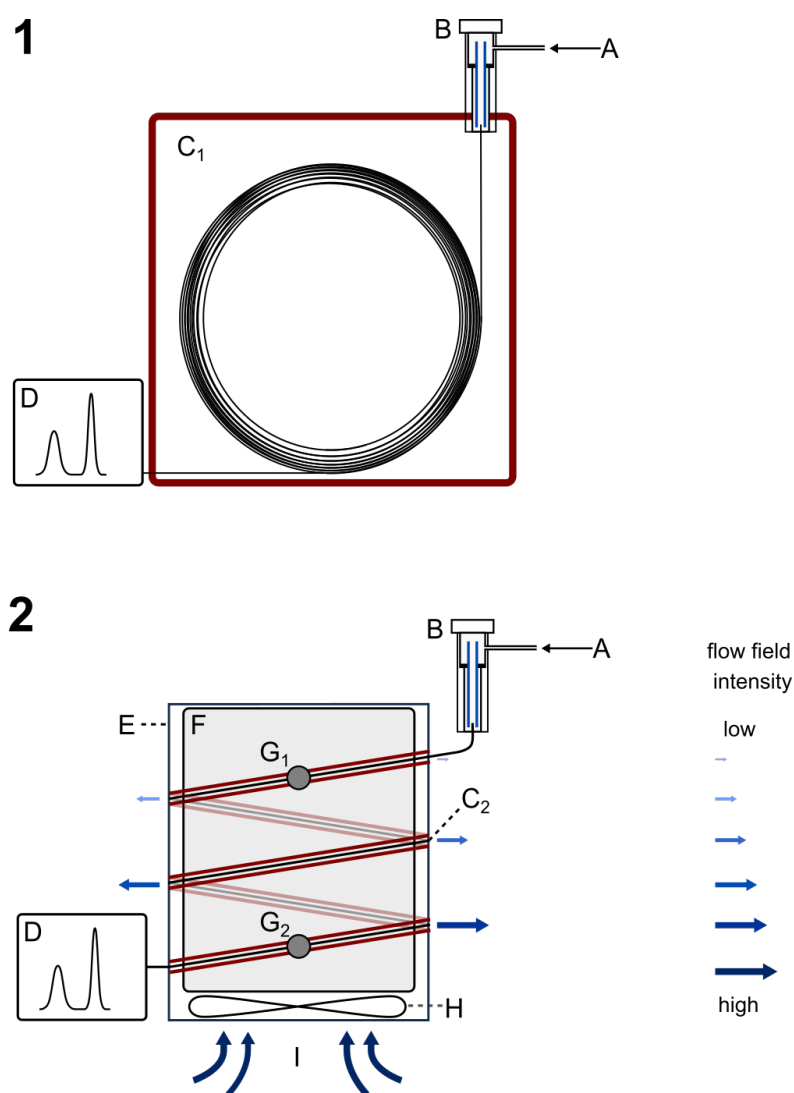


Figure 1.1. Schematic drawing of a conventional oven GC (1) and a FF-TG-GC (2).

A - carrier gas supply; **B** - injector; **C_1** - air bath oven containing the separation column; **C_2** - resistively heated capillary; **D** - detector; **E** - column fixture; **F** - flow resistance (foam cylinder); **$G_{1/2}$** - upper / lower IR-sensor for temperature control; **H** - air fan; **I** - air drawn in by the fan to cool the separating column; **blue arrows** - indicate the airflow induced by the fan, airflow intensity decreases and temperature increases from the bottom to the top.

For the injector-side carrier gas supply (A), Figure 1.2, a 3-way valve facilitates switching between the supply line to the injector (a_1) during sample injection and the supply line to the connector (a_2) once the sample has been transferred to the separation column completely. The flow direction of the carrier gas is shown in Figure 1.3 I and II for both options. The latter configuration via a_2 (Figure 1.3, II) has the advantage that it prevents the transfer of highly volatile sample components or impurities to the separation column. Simultaneously, it allows the back-flushing of the injector as well as the transfer line in the purged injector connector (F_1) in order

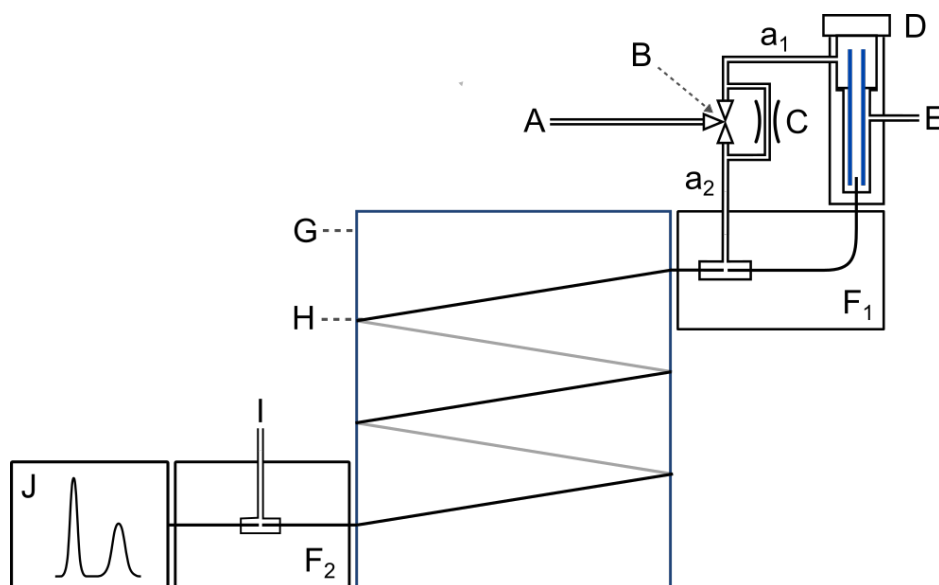


Figure 1.2. Flow diagram of a FF-TG-GC:

A - injector side carrier gas supply; **a_{1/2}** - tubing to the injector/ purged connector **F₁**; **B** - 3-way valve; **C** - bypass with flow restriction; **D** - injector; **E** - split outlet; **F_{1/2}** - transfer line oven with purged injector respectively detector connector; **G** - column fixture; **H** - separation column; **I** - detector side carrier gas supply; **J** - detector.

to remove impurities. Bypass (C) maintains a minimal carrier gas flow through the temporarily unused tubing (**a₁**) respectively (**a₂**), preventing sample components from being pushed in and causing carryover.

The carrier gas supply at (I) serves two purposes: firstly it flushes the dead volume in the detector connector (**F₂**). Secondly, depending on the detector type, make-up gases can be supplied or higher flow rates can be generated than those typically used during the analytical separation (usually 0.7 - 0.8 mL/min with a 0.1 mm I.D. separation column and approx 1.5 mL/min with a 0.25 mm I.D. separation column). This is advantageous for detection by an ion mobility spectrometer (IMS) [9, 10], for example. In addition, the carrier gas supply via (I) offers the possibility of backflushing the separation column (H) if the pressure at (I) is greater than at (A) (Figure 1.3, III).

In the case of a looped-through separating column (Figure 1.3, IV), the carrier gas is only supplied via the injector (Figure 1.2, **a₁**).

1.1.5 FID and TOF-MS

Flame ionization detectors (FID) and mass spectrometers (MS) are the most essential detectors in GC. In the present studies, both types of detectors were employed, with the MS being a time-of-flight (TOF-MS) instrument utilizing electron ionization (EI).

Figure 1.4 shows the structure of a TOF-MS with EI ionization source. In EI, electrons are emitted from a filament (B) and accelerated by an electric field. These electrons collide with the compounds eluting from the separation column respectively transfer line (A), causing their

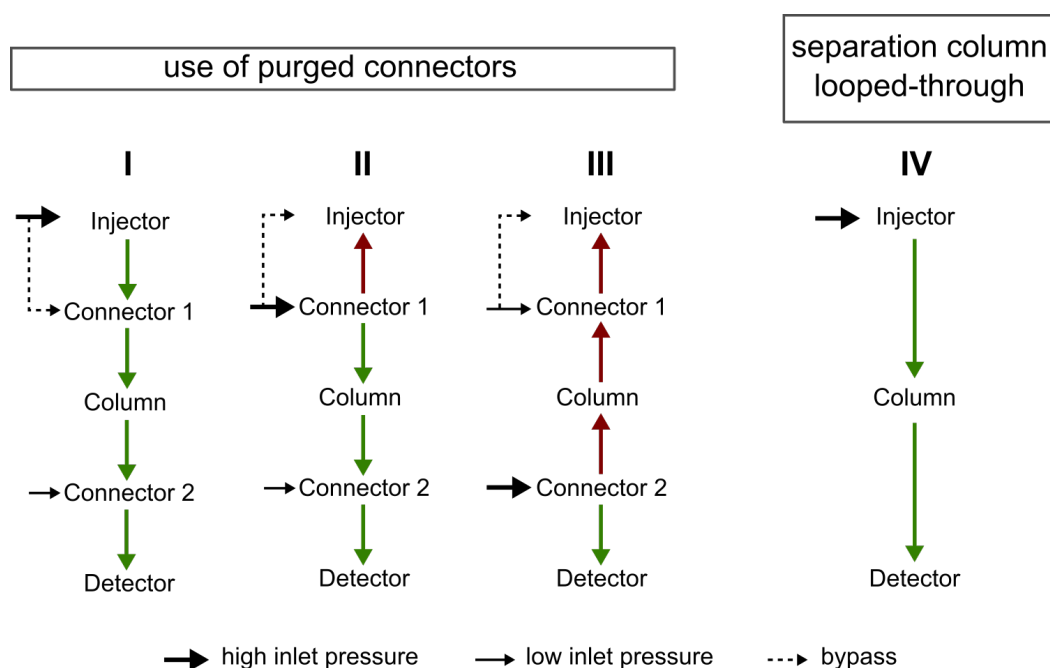


Figure 1.3. Overview of three settings for the carrier gas supply using purged connectors (I-III) and a looped-through separation column (IV). The carrier gas is mainly supplied in I via the injector, in II via the connector 1 (injector connector) and in III via the connector 2 (detector connector).

Description of the arrows:

green - flow direction towards the detector
red - flow direction towards the injector

black - inflow of carrier gas

fragmentation and ionization. The resulting charged species are then focused and accelerated towards the flight tube (E) by apertures (C). During acceleration, the ions receive the same kinetic energy but exhibit different velocities due to their varying masses, resulting in a time delay as they reach the detector (G). With a TOF-MS, the mass of a compound ion can be determined via the flight time through the flight tube, which is proportional to the mass-to-charge ratio (m/z). The mass-to-charge ratio of all fragment ions of a compound in combination with their respective abundance are characteristic and therefore enable identification by comparison with reference spectra in mass spectra databases. This also enables the identification of unknown compounds [11].

In a FID (Figure 1.5), components eluting from the GC column (A) are carried by a makeup gas (e.g. N_2) and introduced through a jet (B) into a hydrogen-air flame (C). Within the flame, the organic molecules in the eluate undergo a cascade of reactions that result in the formation of carbon-containing cations and free electrons. The movement of these ions generates an electrical current which is measured between a usually negatively charged circular collector electrode (D) and the grounded jet located underneath the flame. This current is then amplified and digitized.

The FID is a destructive, mass-sensitive detector. Its response is proportional to the mass of carbon converted per unit of time. Major advantages of the FID include its stability despite moder-

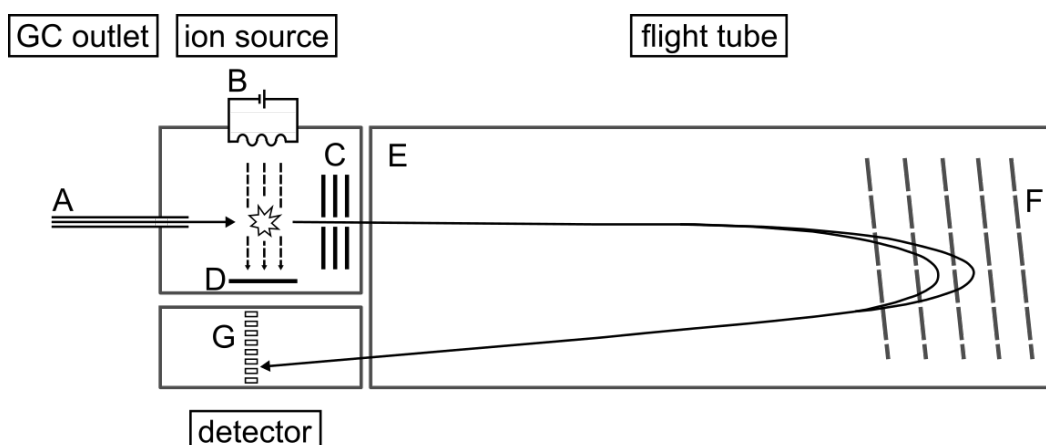


Figure 1.4. Scheme of a time of flight mass spectrometer (TOF-MS) with electron ionization (EI).
A - separation column/ transfer line; **B** - filament; **C** - apertures; **D** - anode for electron discharge, **E** - flight tube, **F** - reflectron, **G** - multi channel plates.

ate variations in flow, pressure, and temperature, as well as its exceptionally large linear dynamic range of 10^7 . Therefore it is the detector primarily used for quantification [1, 2, 3].

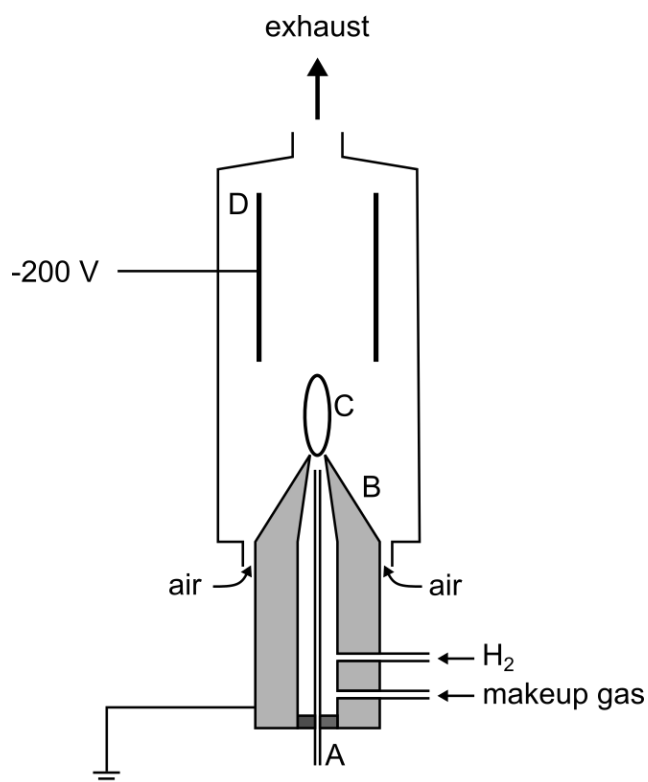


Figure 1.5. Scheme of a flame ionization detector (FID).
A - separation column/ transfer line; **B** - grounded jet; **C** - hydrogen air flame, **D** - circular collector electrode, usually negatively charged.

1.2 Sample Introduction

In GC, various sample introduction techniques are available to ensure an efficient transfer of analytes into the system. The choice of method depends on the properties of sample and the specific analytical requirements. This flexibility enables the injection of diverse sample types ranging from gases and liquid samples to wipe sampling from surfaces. However, sample introduction is a critical step in quantitative analysis where even small mistakes can lead to serious errors that compromise the reliability of the results [2, 3].

In principle, all sample introduction techniques must meet the following requirements: When sampling and sample introduction constitute a single process, the injected sample must serve as a representative subset of the original material to ensure accurate and reliable analysis. Fundamentally, reliable results cannot be achieved without a reliable sample introduction. Ideally, the sample should be introduced into the separation column as a sharp, symmetrical band. The amount of sample should be large enough to obtain a signal distinguishable from the background noise, but at the same time neither overload the column nor the detector. Further, the conditions during injection must be adjusted so that losses due to decomposition and adsorption on surfaces are avoided as far as possible. Consistent measurement results with high reproducibility are also a prerequisite for data evaluation [2].

1.2.1 Liquid Sample Injection

A common method for sample introduction is the injection of naturally liquid or dissolved samples, usually 0.5 μL - 10 μL , with a microliter syringe into an either hot or initially cold injector. A programmable temperature vaporizing (PTV) injector combines both operating modes as the inlet liner is programmatically heatable and coolable [2].

Depending on the method, samples can be injected with and without split. The split has two functions: firstly, only a fraction of the injected sample is applied to the column avoiding column and detector overload. Secondly, higher carrier gas flows reduce the residence time of the sample gas in the liner resulting in narrow bandwidths and sharp peaks. Split injections can be used with almost all sample introduction techniques. As an alternative to vaporizing the sample in the injector, the liquid sample can also be injected directly onto the separation column or an uncoated precolumn (on-column injection). Advantages include the complete sample transfer to the column. Mass discrimination caused by vaporisation effects in the injector is further avoided [1, 2].

1.2.2 Gaseous Sample Injection

In headspace sampling, the gas phase above a liquid or solid sample within a sealed container, such as a vial is analyzed. The vial is heated to a predetermined temperature until equilibrium is reached between the sample and its vapor phase.

There are two main types of headspace sampling [1, 2]:

- **Static Headspace Extraction (SHE):**

In this method, an aliquot of the gas phase is extracted using a gas-tight syringe or a sample loop positioned between the vial and the GC inlet. Additionally, analytes can be trapped on an adsorbent material and subsequently desorbed within the injector. Sorptive extraction is commonly employed with techniques such as solid-phase microextraction (SPME) or thermal desorption tubes.

- **Dynamic Headspace Extraction (Purge and Trap):**

Here, a carrier gas is passed through the liquid phase inside the vial, whereby the volatile components are continuously vaporized and removed.

1.2.3 Thermal Desorption

There are various techniques that are summarized under the broad term “thermal desorption” (TD), including solid phase microextraction (SPME), stir bar sorptive extraction (SBSE) or thermal desorption of adsorbent packed tubes (TD-tubes) for example. In the following chapter, I will focus exclusively on TD-tubes.

1.2.3.1 Thermal Desorption of Adsorbent Packed Tubes

TD is a versatile technique combining sampling, sample preparation, analyte extraction and transfer to the GC [12, 13]. It is used in particular for trace analysis of volatile and semi-volatile organic compounds (VOCs and SVOCs) in air, gas or sample headspace [12, 14]. The application includes both continuous online monitoring and sampling in the field with mobile laboratories as well as offline analysis [12]. Multi-sorbent tubes, which contain different sorbents, are used for samples with a wide volatility range [13, 15]. Within the tube, the sorbents are arranged in sampling direction in order of increasing sorbent strength [15]. For various reasons, such as increased sensitivity, reduced exposure risk and high automatability the previously widely used solvent extraction method typically using carbon disulfide (CS_2) is now largely replaced by TD [12].

A thermal desorber consists of two basic components: adsorbent-filled TD-tubes and the thermal desorption unit connected to the GC for releasing the trapped sample by heating the TD-tube in a flow of carrier gas. A TD-tube is typically a 89 mm (3.5”) long glass or metal tube, with an O.D. of 6.4 mm (1/4”) or 6 mm. The I.D. varies depending on the material: 5 mm for stainless or inert coated steel and 4 mm for glass. Within the tube, an adsorbent packing is present, usually containing between 200 mg and 1 g adsorbent depending on its density, the tube’s I.D. and the specific application [2, 14, 13].

There are three strategies for sorbent tube/ trap sampling [12, 14]:

- **Active sampling**

A defined volume of air is drawn through the tube using a pump at a constant flow of 20 - 200 mL/min (optimum 50 mL/min for 1/4” TD-tubes). Alternatively, grab samples with a volume of a few hundred milliliters can also be taken using bellows pumps or large gas syringes.

- **Passive sampling**

Adsorption occurs solely through diffusion, without the need for active airflow. Depending on the sampling direction, a distinction is made between radial and axial samplers. For axial diffusive samplers, the sampling period is 1 - 8 h for short term monitoring and 3 days to 4 weeks for long term monitoring. Radial diffusive samplers are suitable for short term monitoring (0.5 - 6 h), only.

- **Whole-Air sampling**

An on- or offline air sampling method for ultra-volatile organic compounds such as N_2O , H_2S , SF_6 or C_2 - C_9 hydrocarbons (ozone precursors) for example emitted from vehicle exhaust in urban air. The target compounds are directly trapped on cooled focusing traps, a TD-tube is not used.

After sampling, the analytes are released by controlled heating of the TD-tube within a thermal desorption unit. The desorbed compounds are then transferred to the GC by an inert carrier gas flow, such as helium. Typically, a two-stage desorption process is applied: primary desorption occurs within the TD-tube, followed by a secondary focusing step on an either cryogenically (liquid N_2 or CO_2) or electrically cooled (Peltier) trap. This approach reduces the bandwidth of the injected compounds and enhances analyte concentration up to a factor of 10^6 [12, 13, 14].

Key method parameters during desorption are the desorber temperature, the desorption time as well as the carrier gas flow rate, which must be carefully optimized, especially for thermolabile analytes [12].

1.2.3.2 μ TD-tube

In the present study, a miniaturized thermal desorption tube (μ TD-tube) was developed. With an outer diameter of 1/16" (~ 1.6 mm), as a measure commonly used in analytics, and a wall thickness of 0.1 mm, it possesses only a fraction of the mass¹ and volume² of a conventional TD-tube. Furthermore, the adsorbent quantity has been significantly reduced to just 10 mg.

The primary objective of this development was to minimize the thermal mass of the tubes and the desorption unit, thereby enabling substantially faster heating and cooling. Due to the small μ TD-tube volume in combination with the reduced amount of adsorbent, shorter desorption times are facilitated, further accelerating sample introduction. Moreover, the adsorbed compounds can be released into a very small carrier gas volume (low injection volume) with the aim to avoid a secondary focusing step.

1.2.3.3 Sorbent Materials

The effectiveness of thermal desorption tubes depends to a large extent on the properties of the adsorbent(s) used. For high sampling and desorption efficiency, the sorbent(s) must be strong

1. Mass ratio μ TD-tube/conventional TD-tube: 3.3 % (glass), 7.3 % (metal)

2. Volume ratio μ TD-tube/conventional TD-tube: 7.0 % (5 mm I.D.) and 11.0 % (4 mm I.D.)

enough to retain the analytes of interest but weak enough to release them efficiently at elevated temperatures during desorption [15]. Sorbent strength describes the affinity between analytes and a particular sorbent, whereby it is measured in terms of breakthrough volumes (section 1.2.3.4). Strong analyte-sorbent interactions are associated with a high sorbent strength [14, 15]. A sufficient temperature stability of the sorbent is required for desorption [15, 16]. Furthermore, high mechanical stability and low friability are essential to prevent particle breakage during manual packing. Such breakage leads to the formation of fines and an increase in back pressure [15]. This is particularly important for μ TD-tubes, as manual packing is more prone to excessive compression, resulting in an irregular packing density. Other important properties are a high inertness to avoid decomposition of the analytes and a low ability for artifact formation as well as a low affinity to water [16]. Humidity is an issue to be considered, as hydrophobicity decreases with increasing sorbent strength. Thus sampling at high relative humidity can lead to a reduction of sorbent strength for hydrophilic sorbents like carbonised molecular sieves. Dry purging is the method of choice to remove adsorbed water prior to desorption avoiding further adverse effects like ice blockages or damage to the separation column [15].

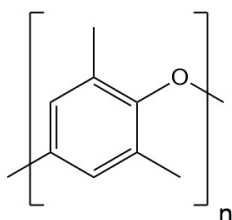


Figure 1.6. Structural formula of poly(2,6-diphenyl-p-phenylene oxide) also known as Tenax TA.

The sorbent Tenax TA 80/100 mesh was used to fill the μ TD-tubes in this study. Tenax TA (poly(2,6-diphenyl-p-phenylene oxide), Figure 1.6) is a weak, hydrophobic sorbent with a thermal stability up to 350 °C. Its inability to retain methanol makes it particularly well suited for spiking tubes with liquid standards [15, 17, 18].

1.2.3.4 Breakthrough and Porosity

As a measure of the capacity of a sorbent packing, the breakthrough volume (BTV, measured in L/g, Equation 1.4) can be used. It represents the volume of gas that can pass through an adsorbent bed until the relevant analytes begin to elute. Exceeding the BTV results in incomplete recovery [14, 19]. For this reason, the safe sampling volume (SSV) should not be exceeded during sampling. It corresponds to 2/3 of the BTV [13]. The counterpart of the SSV is the safe elution volume which corresponds to twice the BTV. It is the minimum volume that must be flushed through a TD-tube for complete elution of an analyte. Whereas the SSV refers to the temperature during sample collection, the safe elution volume corresponds to the higher temperatures applied for desorption [20].

The BTV is always specified for a particular temperature and also depends on the tube flow rate:

$$BTV = \frac{t'_R \cdot F_c}{1000 \cdot w_a} \quad (1.4)$$

$$F_c = 60 \cdot \pi \cdot r^2 \cdot u \cdot \epsilon \quad (1.5)$$

with the reduced retention time t'_R [min], the tube flow rate F_c [mL/min], the weight of adsorbent w_a [g] the tube radius r [cm], the linear velocity u [cm/s] and the interparticle porosity ϵ which is given as 0.4 for conventional TD-tubes [18, 20, 21]. A reduction of tube I.D. results in an increase of linear velocity at constant flows [18]. To avoid breakthrough, samples should be taken at lower tube flow rates for TD-tubes with reduced dimensions.

Due to the different dimensions compared to conventional TD-tubes and the manual filling, the determination of porosity ϵ and back pressure ($p_i - p_o$) is additionally relevant for in-house manufactured μ TD-tubes. The porosity may deviate from the above-mentioned value due to the formation of cavities or too much compression of the packaging during filling. The use of TD-tubes with lower I.D. and thus an extended adsorbent packaging or adsorbent materials with increased mesh sizes is accompanied by an increase in back pressure [18, 22]. It must be taken into account that the back pressure capacity of battery-operated air sampling pumps is not exceeded.

To calculate the porosity, equation 1.6 was resolved to ϵ (Equations 1.7 and 1.8):

$$F_c = \frac{\pi}{2160} \cdot \frac{d^2 \cdot d_p^2}{L \cdot \eta} \cdot \frac{\epsilon^3}{(1 - \epsilon)^2} \cdot \frac{p_i^2 - p_o^2}{p_o} \quad (1.6)$$

$$\epsilon = \frac{\sqrt[3]{2x^3 - 18x^2 + 3\sqrt{3}\sqrt{27x^2 - 4x^3} + 27x}}{3\sqrt[3]{2}} - \frac{\sqrt[3]{2}(6x - x^2)}{3\sqrt[3]{2x^3 - 18x^2 + 3\sqrt{3}\sqrt{27x^2 - 4x^3} + 27x}} + \frac{x}{3} \quad (1.7)$$

with:

$$x = F \cdot \frac{2160}{\pi} \cdot \frac{L \cdot \eta}{d^2 \cdot d_p^2} \cdot \frac{p_o}{p_i^2 - p_o^2} \quad (1.8)$$

with the flow rate F_c [m³/s], the μ TD-tube I.D. d [m], the particle size d_p^2 [m], the μ TD-tube length L [m], the viscosity η [Pa/s] and the pressures at the TD-tube inlet p_i [Pa] as well as the TD-tube outlet p_o [Pa] [21].

1.3 Cryofocusing

In the case of slow sample introduction, such as the headspace injection of large gas volumes or the desorption of tubes, the initial bandwidth at the top of the separation column is wide [12, 13, 23, 24]. It is not possible to reduce this initial width during analyte separation on the column which inevitably leads to a deterioration in resolution and separation efficiency. Cryofocusing is used to overcome this problem. By significantly lowering the temperature at the head of the separation column, analyte migration speed is temporarily reduced. This enables the re-concentration of analytes into a sharp band prior to separation. Then, the cryospot is heated abruptly and the sample is ideally released as a narrow band to the separation column [12, 24, 25]. The required temperature drop can among others be generated electrically by Peltier cooling [26] as well as by liquid nitrogen [25, 27, 28] or expanded liquid carbon dioxide [29, 30].

1.3.1 Carbon Dioxide Cooling

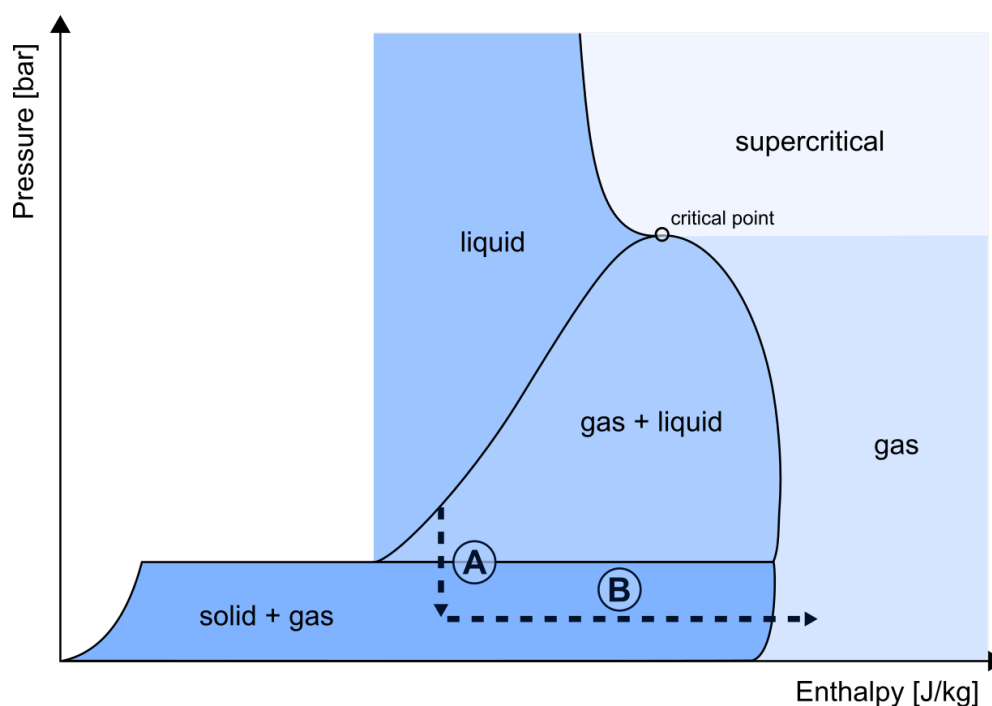


Figure 1.7. The CO₂ phase diagram shows the isenthalpic expansion of liquid CO₂ creating CO₂ gas and dry ice particles in step **A** as well as the subsequent isobaric sublimation of solid dry ice particles to gaseous CO₂ in step **B**. Modified from [33, 34].

In carbon dioxide (CO₂) spray cooling, the temperature drop results from the sudden expansion of liquid CO₂ from 57.3 bar (storage conditions at 20°C) to atmospheric pressure. This abrupt pressure drop causes a decrease in its boiling point. The liquid CO₂ enters a superheated state when it is released through an orifice, since its temperature exceeds the new boiling point. To achieve equilibrium conditions again, a portion of the meta-stable overheated liquid undergoes

an almost instantaneous vaporization (flash evaporation) in the expansion zone. The energy required for this phase transition is extracted from the remaining liquid CO₂, leading to a significant temperature drop and the formation of CO₂ ice particles (dry ice) [31, 32]. The sudden expansion of liquid CO₂, illustrated in Figure 1.7 (A), constitutes an isenthalpic process, that produces both gaseous CO₂ and dry ice particles [31, 33]. In the subsequent isobaric process (Figure 1.7, B), the dry ice sublimates, further cooling the cryospot through natural convection [33]. As long as the liquid level in the gas cylinder is above the dip tube opening, the internal pressure remains almost constant due to continuous vaporization [33, 35]. In addition, the spray pattern of liquid CO₂ is determined by various other factors such as nozzle dimensions, internal surface roughness, flow rate or bubble concentration at the nozzle exit [31, 36]. In particular, changes in the bubble concentration at the nozzle outlet can lead to fluctuations in the mass flow during release [37].

1.3.2 Selection of Suitable Nozzles

The main objective in developing the cryofocusing unit was to achieve constant CO₂ spraying conditions and uniform temperatures at the cryospot. The main influencing factor here was the choice of the right nozzle. Pieces of a transfer line or cut-off cannula tips with varying I.D. glued into stainless steel capillaries (Figure 1.8, A and B) had a poor reproducibility. The temperatures between individual spraying cycles fluctuated significantly (Figure 1.9, A). Sufficiently reproducible conditions could be achieved by using screw in sapphire nozzles (Figure 1.8, C₁, C₂ and Figure 1.9, 2a, 2b).

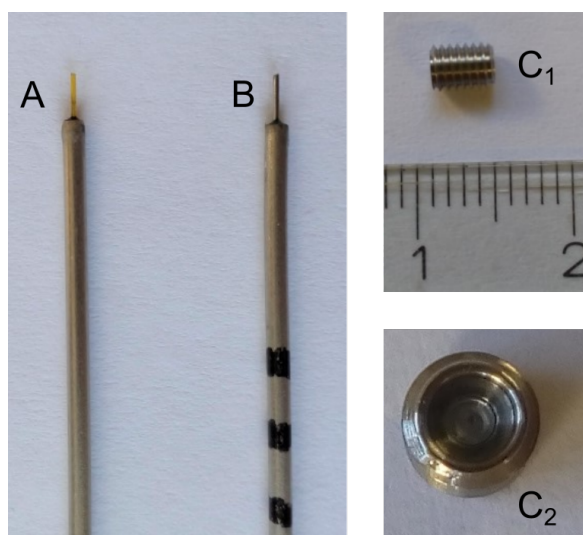


Figure 1.8. Nozzles tested for cryofocusing:

A - in a stainless steel capillary glued in transfer line piece, **B** - cut-off cannula tip, **C_{1/2}** screw in sapphire nozzle.

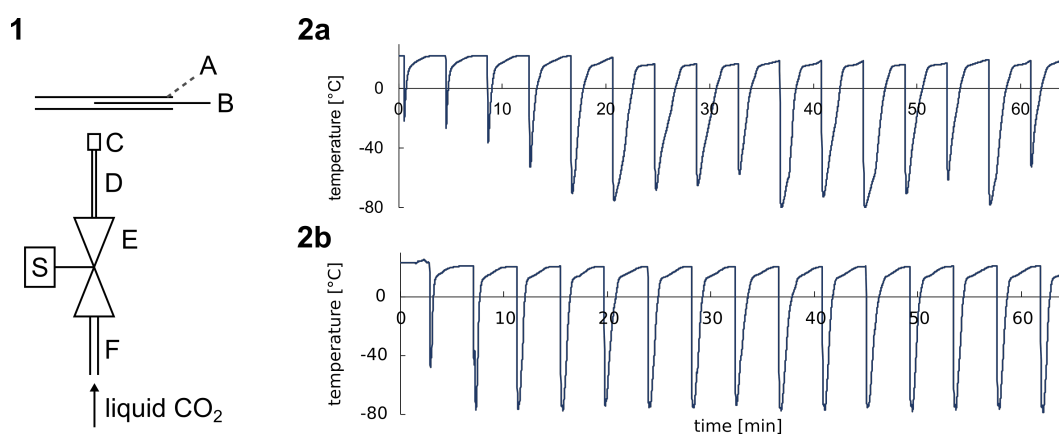


Figure 1.9. Experimental setup (1) for measuring the temperature change within the stainless steel capillary during cryofocusing:

A - stainless steel capillary (not heated), **B** - Type-K thermocouple for temperature measurement, **C** - cannula resp. nozzle for CO₂ release, **D** - CO₂ transfer line, **E** - solenoid valve, **F** - liquid CO₂ supply line.

Subfigures (2a) and (2b) illustrate the temperature changes during a repeated release of liquid CO₂ through a cannula (0.22 mm I.D.) that is glued into a stainless steel capillary and a sapphire nozzle (0.15 mm I.D.), respectively.

1.4 Investigated Groups of Analytes

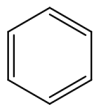
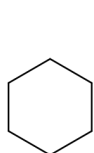
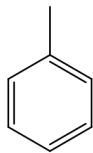
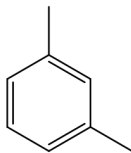
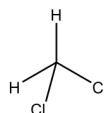
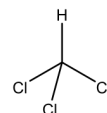
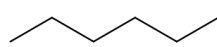
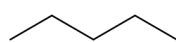
The focus of this study was primarily on the technical development of the described cryofocusing and thermodesorption unit. To access their performance, measurements were carried out with analyte groups selected in cooperation with the project partners. My research was part of two projects: first, the 'GC-Plasma-TOF' project (Grant 13N14890) funded by the Federal Ministry of Education and Research (BMBF). This project focused on combining fast GC with a novel plasma ionization technique for TOF-MS, aimed at the mobile detection of hazardous substances. The second project 'Kopplung FAST-GC-IMS' (Grant E/E590/MZ006/ HF069) was funded by the German Federal Ministry of Defense. The main objectives were the development of a fast sample introduction using TD as well as the coupling of the FF-TG-GC with an IMS for the detection of hazardous substances from air and surfaces.

1.4.1 Residual Solvents

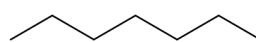
According to the ICH guideline Q3C (R9) *Guideline on impurities: guideline for residual solvents*, residual solvents (RS) are a group of organic volatile compounds that are used or produced in the manufacture of pharmaceuticals, excipients or in the preparation of drug products [38]. The use of these solvents is indispensable in the manufacturing process or its formation cannot be avoided [38]. A complete removal by practical manufacturing techniques like drying at high temperatures under vacuum or freeze-drying is impossible, so residues may remain in drug substance materials [38, 39]. Analyzing these solvents is an important part in pharmaceutical quality control because of potential health risks. Depending on their toxicity, three classes of RS are distinguished [38]:

- **Class 1** solvents cause unacceptable toxicities and should be avoided, e.g. known or strongly suspected human carcinogenes.
- **Class 2** solvents e.g. neurotoxic or teratogenic substances have a less severe toxicity and their use should be limited.
- **Class 3** solvents are less toxic and should be used if possible, e.g. solvents with low toxic potential to humans.

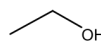
For class 1 and 2 solvents, substance dependent concentration limits are stipulated. Class 3 solvents may generally be used up to a concentration limit of 5 000 ppm per solvent. However, an exceedance is acceptable as long as it remains realistic in the context of good manufacturing practice and manufacturing capability [38]. The European Pharmacopoeia recommends using static HS-GC with FID or MS detection to verify compliance with concentration limits. Alternatively, detection using an electron capture detector (ECD) is also permitted for chlorinated class 1 solvents [40]. If only Class 3 solvents are present, the content may also be determined by loss on drying [38]. The solvents analyzed in the present study as well as their class assignment and the respective concentration limit are shown in Figure 1.10.

Class 1Benzene
2 ppm**Class 2**Cyclohexane
3380 ppmToluene
890 ppmm-Xylene
2170 ppmDichloromethane
1870 ppmTrichloromethane
60 ppmMethanol
3000 ppmn-Hexane
290 ppm**Class 3**

n-Pentane



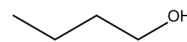
n-Heptane



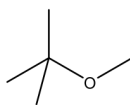
Ethanol



2-Propanol



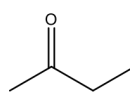
1-Butanol



Methyl tert-butyl ether



Acetone



2-Butanone

Figure 1.10. Structural formulas of the residual solvents investigated in the present study, divided into classes 1, 2 and 3 according to the ICH guideline Q3C. The respective concentration limits (ppm) are given for the solvents of classes 1 and 2. For Class 3 solvents, the concentration limit is 5 000 ppm [38].

1.4.2 Explosives

A potential explosive is a chemical compound or mixture of substances in a metastable state that allows chemical reactions without additional reactants such as atmospheric oxygen [4]. During an explosion high temperatures and large quantities of gas develop rapidly, creating shock waves in the surrounding medium [41]. Based on their ignitability, explosives are divided into primary, secondary and tertiary types. Primary explosives such as diazodinitrophenol (DDNP) are highly sensitive and can detonate easily when exposed to sparks, flames or weak mechanical impacts for example. The resulting heat or shock wave is required to initiate the detonation of a less sensitive secondary explosives. Most of the examined compounds are assigned to this category (Table 1.1), the respective structural formulas are shown in Figure 1.11. Tertiary explosives (e.g. ammonium nitrate) are relatively insensitive materials and need the boost of a preceding detonation of a secondary explosive [4, 41].

Explosive compositions generally consist of an oxidizer and fuel. The oxidizer serves as the oxygen source, while fuel reacts with it under the release of heat [41].

Table 1.1. Information on explosive compounds analyzed in the present study including abbreviation, name, structural information and type.

Analyte	Structural classification	Type
EGDN	ethylene glycol dinitrate	nitrate ester
2-MNT	2-nitrotoluene	nitroaromat
4-MNT	4-nitrotoluene	nitroaromat
PETN	pentaerythritol tetranitrate	nitrate ester
NG	nitroglycerin	nitrate ester
DNT	2,4-dinitrotoluene	nitroaromat
TNT	2,4,6-trinitrotoluene	nitroaromat
DNAN	2,4-dinitroanisole	nitroaromat
Tetryl	N-methyl-N,2,4,6-tetranitroaniline	nitroaromat,
RDX	hexogen	nitramine
		secondary explosive ^[41]

taggant: marker added to the explosive to facilitate detection^[43].

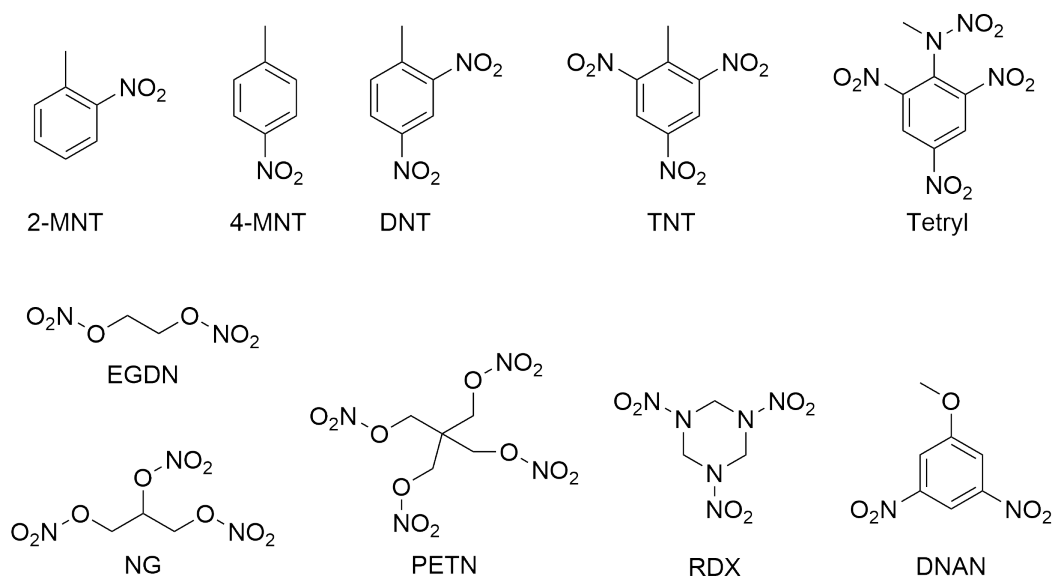


Figure 1.11. Structural formulas of investigated explosives.

Sample type and target compound determine which analytical techniques work best for explosive detection. In addition analyzing liquid standards, either pipetted directly into a TD-tube [44, 45] or injected via a split/splitless injector [7], explosive detection from the gas phase [46, 47, 48, 49] and swipe sampling [50, 51, 52] are widely used methods. Gas phase detection is an ongoing trend, as it allows quick and easy identification of explosives [47, 48, 49]. Techniques

used for vapor-phase detection include headspace measurements using SPME [48], diverse types of sensors [53], TENAX filters [49] and thermal desorption tubes [46]. Since most explosives are low volatile, it is possible to heat samples such as post-determination dust or debris in a closed container to increase the gas phase concentration [46].

A wide range of technologies are used to detect explosives, including GC-MS and GC-ECD (electron capture detector), ion mobility spectrometry (IMS), raman spectroscopy, further spectroscopy based methods as well as animal olfactoring with detection dogs for example [42, 54].

1.4.3 Chemical Warfare Agents and Their Simulants

Chemical warfare agents (CWAs) are toxic substances used in the military that damage the human body in such a way that the fighting ability of soldiers is drastically reduced or death occurs [55]. According to their type and location of action, CWAs are classified as blood, lung, skin, nerve or psychotoxic agents, among others [55, 56]. Due to the high toxicity of CWAs, simulants that mimic the chemical and physical properties are used for study purposes instead [57, 58]. The nerve agents sarin, soman, tabun, VX and the novichoks were replaced by the following CWA simulants for analysis in the present study: DMMP (dimethyl methylphosphonate), DEMP (diethyl methylphosphonate), TEP (triethyl phosphate), TBP (tributyl phosphate), Malathion ([[(Dimethoxyphosphinothioyl)thio]-butanedioic acid diethyl ester) and TEHP (tris(2-ethylhexyl) phosphate). The structural formulas as well as the assignment of the simulants to the respective CWAs is shown in Figure 1.12.

Nerve agents affect the nerve signal transmission by irreversibly inhibiting the acetylcholinesterase enzyme (AChE). This prevents the breakdown of the neurotransmitter acetylcholin, causing it to accumulate in the synaptic cleft. As a result nerves become overstimulated, leading to muscle cramps, paralysis and ultimately respiratory failure [56].

Based on their physicochemical properties and their toxicity, three groups of nerve agents are distinguished [56]:

- **G-series** (first generation):
These nerve agents contain fluorine or nitrile substituents and are liquid in their pure form, e.g., Sarin, Soman, Tabun.
- **V-series** (second generation):
Significantly more toxic and persistent than G-series agents, they often contain sulfur and exist as viscous liquids, such as VX.
- **A-series** (third generation):
Known as Novichok agents, these substances are extremely toxic and can exist in both liquid and solid forms.

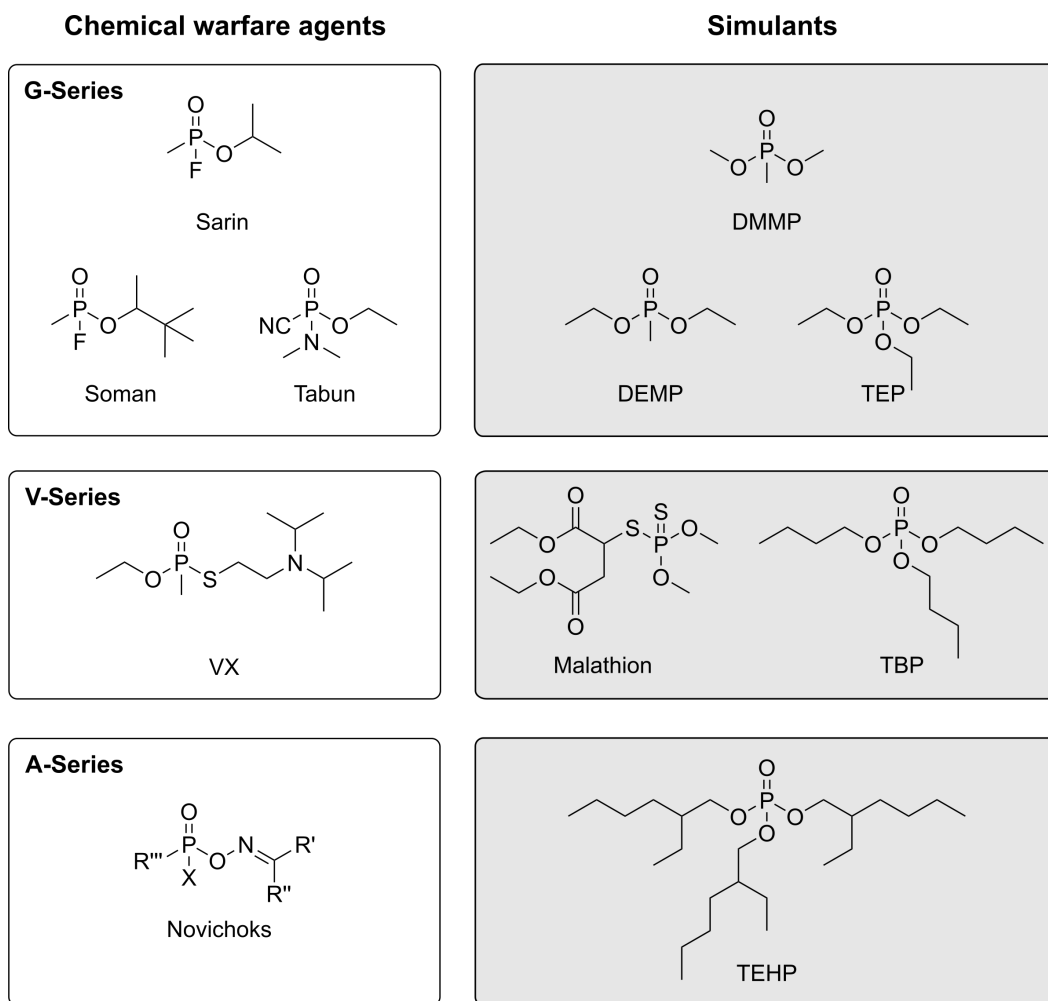


Figure 1.12. Structural formulas of investigated chemical warfare agents and the corresponding simulants.

1.5 Objective of the Thesis

The aim of this study is to develop a technique for the rapid and efficient application of gas samples using thermal desorption combined with cryofocusing. This involves both, the necessary technical engineering of the experimental setups and the subsequent development of suitable analytical methods.

For cryofocusing, liquid CO₂ is sprayed onto the head of the separation column, creating a temperature drop to -50 to -60 °C through the combined effects of cold gas flowing around the capillary and dry ice deposition on it. The temporary analyte retention at low temperatures reduces initial band broadening and improves peak resolution during separation. Efficient CO₂ usage is ensured by employing a small nozzle diameter and targeted pulses rather than continuous release. To evaluate the system, comparative measurements were conducted with and without cryofocusing, using a mixture of five permanent gases and 16 residual solvents regulated by the ICH guideline (**Chapter 2**).

Sample introduction via a conventional thermal desorber typically takes 5–15 min [59, 60, 61], making it the rate-limiting step in hyper-fast GC analyses, which last only tens of seconds to a few minutes [6, 7, 8]. To maintain system efficiency, accelerating the sample introduction process is essential. The principle of rapid thermal desorption is based on two factors: the low thermal mass of the entire setup enables extremely fast heating rates and very rapid cooling, which is additionally accelerated by switching on two PC fans. In addition, the small amount of adsorbent, only 10 mg, enables faster desorption. The entire packing also heats up faster and more evenly. Proof of concept measurements were conducted in 82 s via TD-FF-TG-GC-FID using an *n*-alkane mixture (C₅ - C₂₀) (**Chapter 3**).

In the last step, a validated method for the complex analysis of six CWA simulants and ten explosives was developed with rapid thermal desorption and liquid CO₂ cryofocussing via TD-FF-TG-GC-TOF-MS within 164 s (**Chapter 4**).

Chapter 2

Residual solvent analysis with hyper-fast gas chromatography-mass spectrometry and a liquid carbon dioxide cryofocusing in less than 90 s

The research summarized in this chapter has been published as

Miriam D. Chopra, Peter J. Müller, Jan Leppert, Matthias Wüst, Peter Boeker, J. Chromatogr. A 1684 (2021) 462179, <https://doi.org/10.1016/j.chroma.2021.462179>.

A reprint of this publication is given in **Appendix A** of this thesis.

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2.1 Author's contributions

My contribution to this project is the optimization of the experimental setup, the planning and execution of the experiments as well as the entire data analysis and writing of the publication. I also programmed the Arduino controller with the help of Roland Lutz and Peter Faust and optimized the timing of the signal output of the Chronos software together with Patrik Kursawe. The initial idea of a liquid carbon dioxide cryofocusing came from Peter Boeker. In cooperation with Wilfried Berchtold, Michael Marr and Knut Ockenfels, we developed and manufactured the setup. Peter Boeker further acquired the funds, did the project administration, supported the experimental design and gave writing assistance. Jan Leppert helped with maintenance of the laboratory equipment and made important suggestions. Matthias Wüst, did project administration, provided guidance and gave writing assistance.

2.2 Summary

In headspace sample introduction using a syringe, injection volumes are typically 1 mL [3]. The extended injection time required for this volume results in broadened peaks for highly volatile compounds when combined with the short analysis times of hyper-fast GC [3, 8]. The main objective of this study was the development of an efficient cryofocusing unit using liquid CO₂ for the refocusing of analyte bands at the head of the separation column. In contrast to conventional instruments, the separation column in a FF-TG-GC is not housed within a column oven but instead consists of a resistively heated stainless steel capillary. This has the advantage of being easily accessible. For cryofocusing, liquid CO₂ from a gas cylinder with a dip tube is directly sprayed onto a 1–2 cm long section of the sheath capillary. Neither the valve nor the CO₂ supply line need to be installed inside the column oven and can instead be mounted externally on the FF-TG-GC.

The use of small nozzle diameters enables an efficient release of liquid CO₂, which expands from 57.3 bar (at 20 °C) to atmospheric pressure. This expansion generates both cold CO₂ gas which flows around the outer capillary and solid CO₂ (dry ice) that deposits on the outer capillary surface. Dry ice has a temperature of -78.5 °C [33]. During cryofocusing, temperatures of -50 °C to -60 °C are achieved within the sheath capillary. However, unexplained fluctuations in the amount of dry ice escaping from the nozzle were observed during successive spraying cycles. It is assumed that these variations are influenced by the fill level in the gas cylinder and the temperature of the liquid CO₂ it contains as well as the nozzle temperature. During release, the boiling of the CO₂ in the gas cylinder also leads to a reduction of its temperature [35].

A measurement can be divided into the following three steps: First, the cryospot is pre-cooled with a long spray pulse of 4 s. During the injection of the gas sample, the temperature at the cryospot is stabilized with short CO₂ pulses (0.3 s pulse, 0.2 s pause). At the start of the FF-TG-GC temperature program, the CO₂ release is finished, and the cryospot is thawed by resistively heating the sheath capillary. This releases the analytes as a narrow band, which is then separated via gas chromatography. For reproducible results and stable retention times, precise timing of the cryofocusing initiation and sample injection is crucial.

To test and evaluate the performance of the developed cryofocusing setup, a method for the analysis of four gases and 16 solvents was developed in this study. The solvents analyzed are commonly used in pharmaceutical manufacturing, and their residual levels are regulated by threshold values listed in the *ICH Q3C (R9) Guideline on impurities: guideline for residual solvents* of the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [38]. The use of cryofocussing leads to a decrease in the full width at half maximum (FWHM) and an improvement in the resolution of most eluting analytes. A chromatogram and detailed results are shown in Figure 2.1 and Table 2.1.

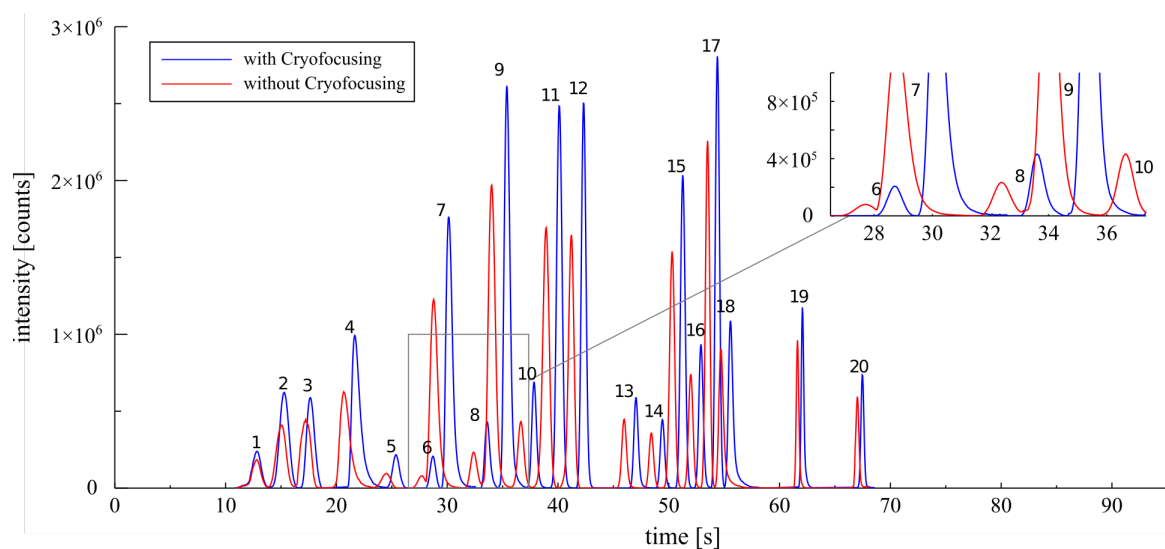


Figure 2.1. Overlay of two chromatograms recorded with the application of liquid CO₂ for cryofocusing (blue line) and without cryofocusing (red line). The DMSO solvent peak is not shown in the chromatograms.

1 - Propane, 2 - 2-Methylpropane, 3 - n-Butane, 4 - Methanol, 5 - 2-Methylpentane, 6 - n-Pentane, 7 - Ethanol, 8 - Acetone, 9 - 2-Propanol, 10 - Dichloromethane, 11 - Methyl tertbutyl ether, 12 - n-Hexane, 13 - 2-Butanone, 14 - Trichloromethane, 15 - Cyclohexane, 16 - Benzene, 17 - n-Heptane, 18 - 1-Butanol, 19 - Toluene, 20 - m-Xylene

Table 2.1. Retention time (t_R), full width at half maximum (FWHM) and resolution (R) of permanent gas and residual solvent measurement with (On) and without cryofocusing (Off) and the relative change of the respective value in relation to the corresponding value without cryofocusing.

No.	Analyte	t_R [s]		Δ [%]	FWHM [s]		Δ [%]	Resolution		Δ [%]
		On	Off		On	Off		On	Off	
1	Propane	12.8	12.8	0.1	0.97	0.94	3.8			
2	iso-Butane	15.3	15.1	1.2	0.97	1.04	-7.4	1.52	1.39	9.4
3	n-Butane	17.6	17.2	2.8	0.86	1.19	-35.2	1.50	1.07	39.2
4	Methanol	21.7	20.7	4.6	0.82	0.98	-17.0	2.82	1.93	46.2
5	iso-Pentane	25.4	24.5	3.4	0.71	0.93	-24.1	2.86	2.36	21.4
6	n-Pentane	28.7	27.7	3.6	0.58	0.78	-22.0	3.06	2.17	41.2
7	Ethanol	30.1	28.8	4.6	0.68	0.79	-12.1	1.35	0.83	61.6
8	Acetone	33.6	32.4	3.6	0.53	0.69	-17.0	3.36	2.86	17.5
9	2-Propanol	35.4	34.0	3.9	0.63	0.75	-12.7	1.81	1.33	36.0
10	DCM	37.8	36.7	3.1	0.49	0.63	-15.0	2.59	2.26	14.7
11	MtBE	40.1	39.0	3.0	0.57	0.66	-10.4	2.54	2.07	22.7
12	n-Hexane	42.3	41.2	2.7	0.48	0.56	-8.7	2.47	2.15	14.8
13	2-Butanone	47.0	46.0	2.3	0.45	0.49	-4.0	5.97	5.34	11.8
14	TCM	49.4	48.4	2.1	0.45	0.47	-2.2	3.12	3.02	3.4
15	Cyclohexane	51.3	50.3	1.9	0.49	0.52	-3.7	2.31	2.23	3.7
16	Benzene	52.9	52.0	1.8	0.46	0.47	-1.4	2.04	1.98	2.7
17	n-Heptane	54.4	53.5	1.7	0.44	0.45	-0.8	1.94	1.94	-0.2
18	1-Butanol	55.6	54.7	1.6	0.46	0.46	-0.3	1.54	1.55	-0.8
19	Toluene	62.1	61.6	0.7	0.26	0.27	-0.5	10.57	11.14	-5.1
20	m-Xylene	67.5	67.0	0.7	0.31	0.31	0.6	11.08	11.04	0.4

Chapter 3

A fast thermal desorption unit for micro thermal desorption tubes, Part I: Development of the system and proof of concept measurements with hyper-fast gas chromatography

The research summarized in this chapter has been published as

Miriam D. Chopra, Florian A. Menger, Benny Duong, Matthias Wüst, Peter Boeker, J. Chromatogr. A 1730 (2024) 465039, <https://doi.org/10.1016/j.chroma.2024.465039>.

A reprint of this publication is given in **Appendix B** of this thesis.

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3.1 Author's contributions

My primary contributions to this research project included the experimental design, data evaluation and writing the publication. Benny Duong, Florian Menger and I collected the data together. I was also involved in developing the μ TD-tubes and the TDU. Peter Boeker acquired the funding, managed the project, supported the experimental design and assisted in writing. He originally developed the concept of the micro thermal desorber. The final version, along with several prototypes, was designed in cooperation with Wilfried Berchtold and manufactured by Michael Marr and Knut Ockenfels. The Arduino-based injector control was programmed by Roland Lutz and Florian Menger. Matthias Wüst is my supervisor, he did project administration, offered guidance and supported the writing process.

3.2 Summary

The aim of this study was to optimize sample introduction by thermal desorption to enable an efficient use of this technique in combination with a hyper fast GC. Conventional thermal desorber require usually approx. 10 min [60, 61, 59] for the release of analytes. This duration is too long compared to the very short cycles times of a hyper fast GC, which typically range from tens of seconds to a few minutes [6, 7, 8]. For this purpose, a faster thermal desorber consisting of a thermal desorption unit (TDU, Figure 3.1, 1 and 2) and suitable micro thermal desorption tubes (μ TD-tubes, Figure 3.1, E) was developed. Unlike

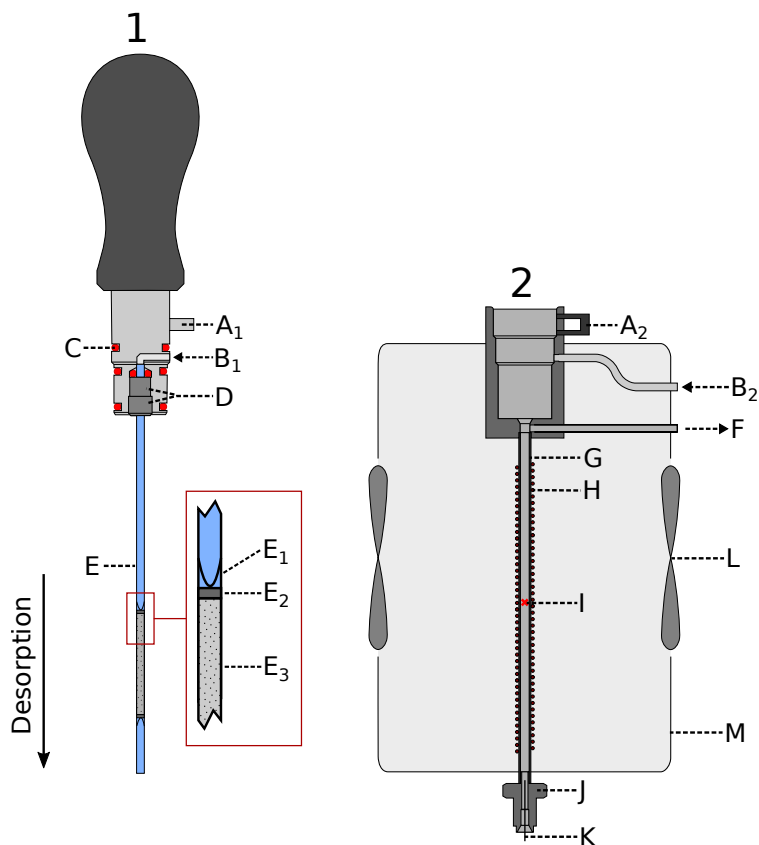


Figure 3.1. Scheme of the thermal desorption unit (TDU) with inserted micro thermal desorption tube (μ TD-tube):

1 - handpiece; **2** - TDU base; **A_{1/2}** - bayonet lock; **B_{1/2}** - carrier gas supply (Helium); **C** - O-ring; **D** - sleeve and grub screw for holding the μ TD-tube; **E** - micro thermal desorption tube (μ TD-tube) with **E₁** - spring wire, **E₂** - volumetric mesh disk and **E₃** - Tenax-bed (10 mg); **F** - split; **G** - injector tube; **H** - heat winding; **I** - temperature control point; **J** - transfer line connection; **K** - transfer line; **L** - PC fans; **M** - polymer housing.

conventional systems, the new setup is characterized by a significantly lower thermal mass and adsorbent quantity. This enables much faster heating and cooling rates. At just 0.33 g, the μ TD-tubes are 14 respectively 30 times lighter than conventional TD-tubes made of glass (4.5 g) or metal (10 g). In contrast to the commonly used 100 - 600 mg adsorbent [14], the μ TD-tubes only contain 10 mg.

The analysis of a μ TD-tube can be divided into the following three phases:

- I Desorption
- II a. μ TD-tube Conditioning
 - b. Separation of analytes
- III Cool down

Figure 3.2 shows the conversion of the individual phases into temperature programs for the TDU (A) and the FF-TG-GC (B).

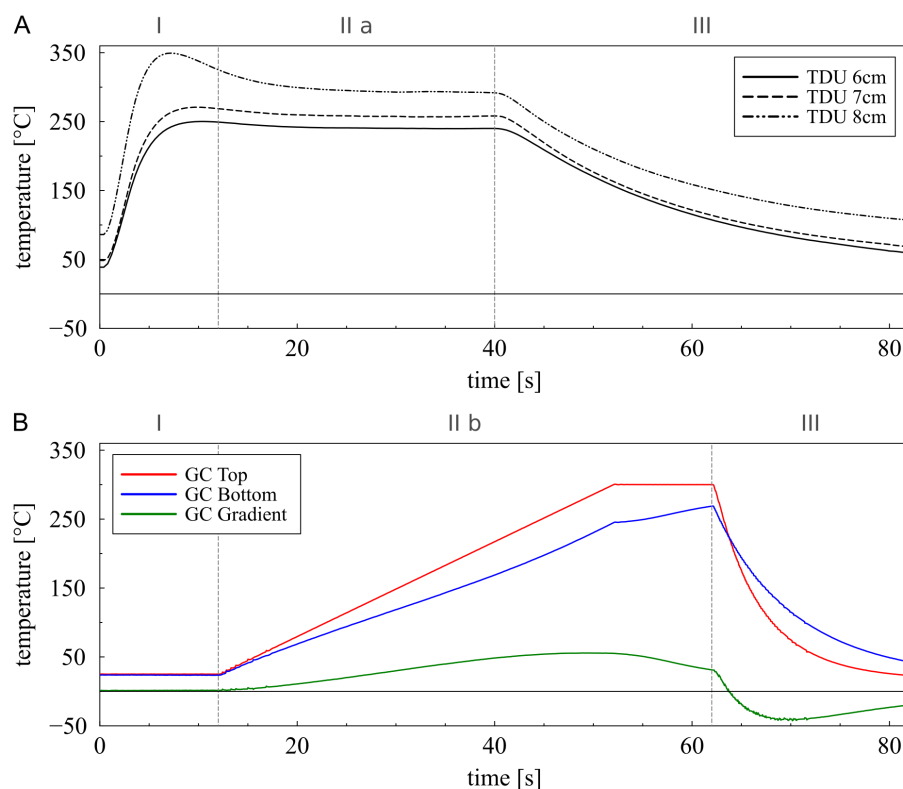


Figure 3.2. Temperature program of the TDU (A) and the FF-TG-GC (B). The indicated positions in A refer to the upper end (6 cm), the middle (7 cm) and the bottom (8 cm) of the Tenax-TA packaging in the μ TD-tube. GC Top and GC bottom refer to the temperatures measured by the upper and lower IR-sensors (Figure 1.1, subfigure 2, G_1 and G_2). The gradient is calculated as the temperature difference between GC top and GC bottom.

Proof of concept measurements were carried out with the developed TDU and FF-TG-GC/FID using an *n*-alkane standard in methanol containing *n*-pentane to *n*-icosane to evaluate the setup. Good precision with relative standard deviations between 0.4 % and 3.5 % of repeatability experiments (fivefold determination) as well as linearity with $R^2 \geq 0.995$ were achieved from *n*-octane to *n*-icosane. Due to the lack of analyte refocusing after thermal desorption, coelution occurs with methanol, *n*-pentane, *n*-hexane and *n*-heptane. A respective chromatogram is presented in Figure 3.3, red line.

The changed dimensions of a μ TD-tube compared to conventional TD-tubes have an effect on various parameters concerning thermal desorption such as breakthrough volumes, tube flow rates respectively linear velocities, porosity and back pressure that were also evaluated in this study.

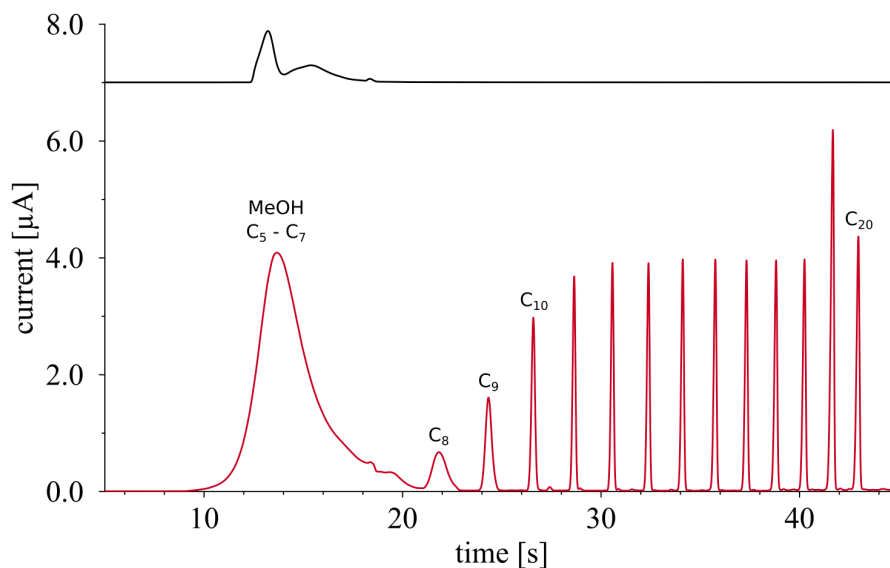


Figure 3.3. Two μ TD-tubes were connected in series during loading with 100 mL of analyte gas containing an *n*-alkane mixture (*n*-pentane to *n*-icosane). The red line shows the chromatogram of the first, directly loaded μ TD-tube and the black line shows the chromatogram of the backup μ TD-tube. The black line has an offset of $7 \cdot 10^6$.

To assess the comparability of individual μ TD-tubes, repeated measurements must be carried out and statistically evaluated. Differences between tubes cannot be explained solely by their previously determined porosities.

In part I of this publication, the initial development of the TDU as well as proof of concept measurements are presented. The second part focuses on the method development and validation for a complex analyte mixture containing ten explosives and six chemical warfare agent simulants with substantially differing physicochemical properties.

Chapter 4

A fast thermal desorption unit for micro thermal desorption tubes, Part II: Method development and validation for explosives and chemical warfare agent simulants

The research summarized in this chapter has been published as

Miriam D. Chopra, Benny Duong, Florian A. Menger, Thomas M. Klapötke, Matthias Wüst, Peter Boeker, J. Chromatogr. A 1739 (2024) 465537, <https://doi.org/10.1016/j.chroma.2024.465537>.

A reprint of this publication is given in **Appendix C** of this thesis.

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4.1 Author's contributions

In this research project, I designed the experiments, validated the method, analyzed the data statistically and wrote the resulting publication.

Florian Menger and Benny Duong carried out the measurements and signal integration. Florian Menger also programmed the Arduino control of the TDU and determined the limits of detection and quantification. Prof. Thomas Klapötke has provided the explosives standards. Peter Boeker acquired the funds, did the project administration, supported the experimental design and gave writing assistance. Prof. Matthias Wüst, provided guidance and gave writing assistance.

4.2 Summary

The need for rapid detection of explosives and CWAs has become increasingly important in view of their use in recent armed conflicts [62, 63]. Quick detection of these substances is crucial for public safety. Based on the TDU setup introduced in part I, a fast TD-FF-TG-GC/TOF-MS method was developed for the analysis of explosives and CWA simulants. The investigated analytes are a heterogeneous group of substances containing ten explosives and six CWA simulants with strongly differing physico-chemical properties (Table 4.1). The 183 °C temperature gap between the decomposition temperature of the most thermolabile and the boiling point of the most volatile analyte highlights this diversity.

Table 4.1. Abbreviation and retention time (t_R) in the chromatogram of the explosives and CWA simulants analyzed. Furthermore boiling point (T_{bp} , unless otherwise stated at 1013 hPa), decomposition temperature (T_{dec}) and vapor pressure (p_{sat} , at 25 °C) of the analytes are provided.

Analyte	t_R [s]	T_{bp} [°C]	T_{dec} [°C]	p_{sat} [hPa]
Explosives				
EGDN	66.1	197.5 [64]	110 [65]	1.02E-01 [66]
2-MNT	72.6	222 [65]	232 [43]	1.91E-01 [66]
4-MNT	75.1	238 [65]	234 [43]	6.52E-02 [66]
PETN	76.6	-	157 [43]	1.54E-08 [66]
NG	79.6	245 [64]	167 [43]	6.41E-04 [66]
DNT	85.4	-	>250 [65]	3.51E-04 [66]
TNT	89.9	-	306 [43]	7.33E-06 [66]
DNAN	91.5	206 ^a [67]	-	3.40E-06 [68]
RDX	94.2	-	208 [43]	3.49E-09 [66]
Tetryl	99.1	-	190 [43]	8.68E-09 [66]
CWA simulants				
DMMP	58.9	181 [69]	-	1.11E+00 [69]
DEMP	65.3	192 [69]	-	5.59E-01 [69]
TEP	70.5	215 [65]	-	4.0 E-01 [70]
TBP	88.4	293 [65]	140 [65]	1E-3 [70]
TEHP	107.7	215 [64]	190 - 233 [71]	2.1E-07 [72]

dec: decomposition is observed at the stated boiling point.

^a: at 12 mm Hg.

^b: at 0.7 mm Hg.

In terms of method development, the decomposition temperatures, vapor pressures and polarities of the analytes are particularly important. Besides carefully optimizing the desorption conditions (temperatures, desorption times and flows), the influence of μ TD-tube deactivation via a SilcoNert coating, the spatial temperature gradient along the separation column and the effect of cryofocusing to refocus the analytes on the peak area were tested in the course of method development. With the method used, the analysis of a μ TD tube can be divided into the following four phases:

- 0 Inserting the μ TD-tube
- I Pre-cooling
- II Desorption and analyte refocusing

III Separation of analytes/ TDU cool-down

IV GC cool down

Figure 4.1 shows both the individual phases and the respective temperature programs of cryofocusing, thermal desorption and analytical separation.

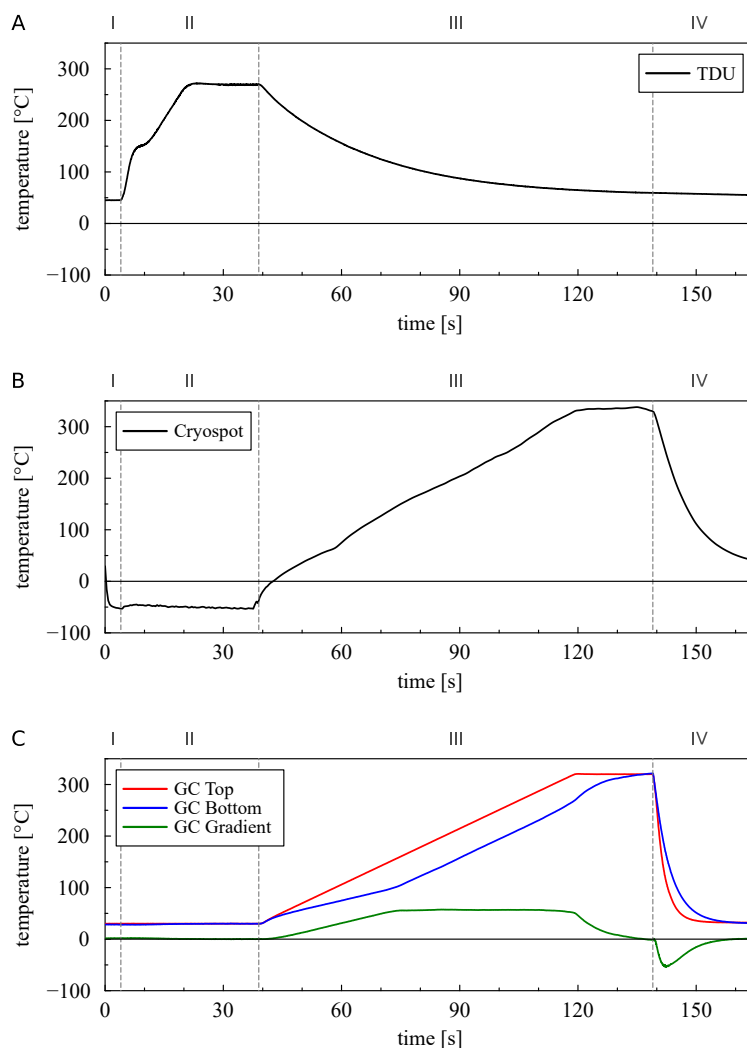


Figure 4.1. Temperature program of the TDU (A) the Cryospot (B) and the FF-TG-GC (C). GC Top and GC bottom refer to the temperatures measured by the upper and lower IR-sensors (Figure 1.1, subfigure 2, G_1 and G_2). The gradient is calculated as the temperature difference between GC top and GC bottom.

The deactivated μ TD-tube surface reduces the probability of chemical reactions and adsorption [73] while the temperature gradient leads to a reduction in the elution temperature by an average of 42.2 °C in the present study. Both the use of the SilcoNert coating and the spatial temperature gradient have led to an improvement in sensitivity, particularly for the thermolabile analytes EGDN, PETN and NG, as well as for RDX, Teteryl and TEHP. A respective chromatogram is shown in Figure 4.2. Cryofocusing only affects the FWHM of the first eluting and therefore most volatile analytes DMMP and DEMF, which was reduced by 39% and 8% respectively. For all other analytes, it led to a broadening of the signals, which

was most pronounced for NG, TBP and RDX at 181.7%, 253.5% and 209.1%. The reason for this is the slow heating rate when thawing the cryospot. Method validation included the determination of detection limits, calibration and inter- and intra-day repeatability tests.

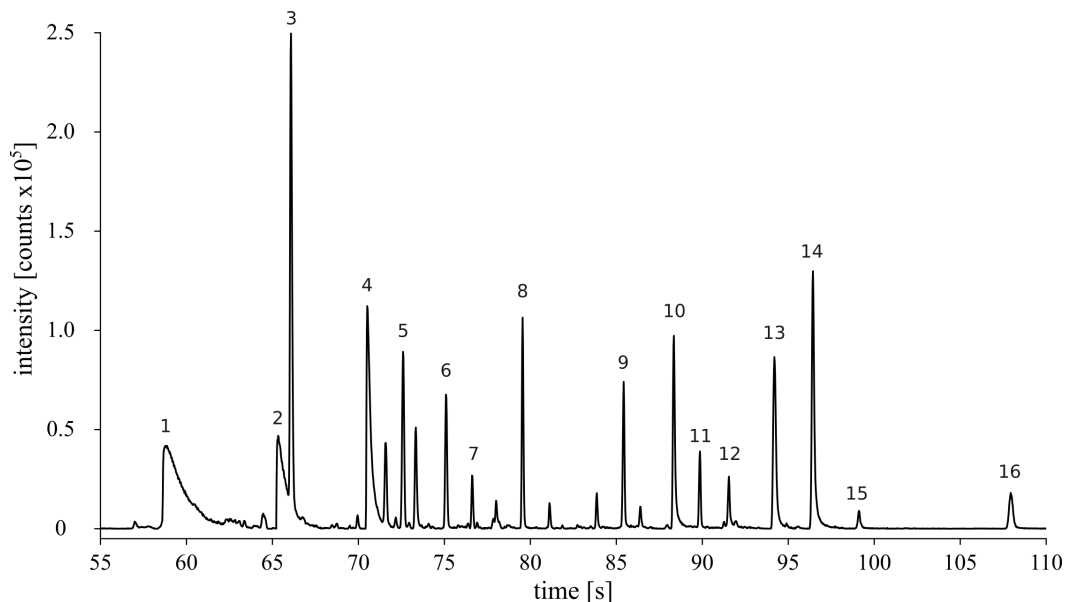


Figure 4.2. TIC chromatogram of an explosive and CWA simulant mixture. The chromatogram was recorded using a spatial temperature gradient but without cryofocusing. 1 - DMMP; 2 - DEMP; 3 - EGDN; 4 - TEP; 5 - 2-MNT; 6 - 4-MNT; 7 - PETN; 8 - NG; 9 - DNT; 10 - TBP; 11 - TNT; 12 - DNAN; 13 - RDX; 14 - malathion; 15 - tetryl; 16 - TEHP.

Chapter 5

Concluding remarks and outlook

In recent years, the demand for rapid, high-throughput analytical methods has grown significantly [74], especially in fields such as quality control of chemical or pharmaceutical production, environmental monitoring and security screening. Hyper-fast gas chromatography (e.g. via a FF-TG-GC) is one of the many analytical tools to meet this demand by reducing total run times while maintaining adequate resolution and sensitivity. However, the speed advantages of hyper-fast GC can only be realized if the sample introduction step is equally fast and the initial injection band of the introduced analytes is narrow. This requires adapting conventional sample introduction systems, originally designed for slower GC methods, to meet the specific requirements of hyper-fast separations.

This thesis describes the associated development, application and validation of three setups and corresponding methods for an accelerated sample introduction:

1. Headspace injection combined with cryofocusing using liquid CO₂ to reduce injection band broadening
2. Fast thermal desorption using a low thermal mass TDU and miniaturized μ TD-tubes
3. Combination of fast thermal desorption with cryofocusing for a sample with heterogeneous physico-chemical properties

In the first approach a cryofocusing setup was designed to counteract peak broadening by narrowing initial bandwidths resulting from the prolonged injection duration of large gas volumes (typically 1 mL [3]) in headspace analysis compared to the short analysis time of a hyper-fast GC. For this purpose, liquid CO₂ was expanded through a sapphire screw-in nozzle and sprayed onto the sheath capillary of the FF-TG-GC. The pressure drop caused a phase transition, dry ice and cold CO₂ gas were formed and used for cooling. This simple setup was facilitated by the open design of the FF-TG-GC, which, unlike conventional systems, required no modifications for the application of cryofocusing. The use of a small internal nozzle diameter (0.15 mm), the precise timing of the CO₂ release, and the fact that the cryofocusing unit operated outside a heated air-bath oven, thus avoiding the need to cool against the oven's heat, resulted in low liquid CO₂ consumption. A reproducible and effective cooling reaching temperatures of -50 to -60 °C was thereby enabled. Since the analytes were focused within the separation column, no additional trap was required. The release of trapped compounds was achieved upon resistively heating the sheath capillary during the GC temperature program.

Using this setup, a novel analytical method for the rapid and efficient detection of four permanent gases and 16 pharmaceutically relevant solvents was developed and validated with a total runtime of less than 90 s. Cryofocusing resulted in a reduction of the FWHM for almost all analytes investigated. This method addresses critical industry demands for speed, sensitivity and compliance with regulatory guidelines (e.g.

ICH R9 Q3C [38]). The minimal technical modifications required to implement the cryofocusing system make the approach practical for routine use.

Conventional TD-setups often require long heating and desorption cycles due to their high thermal mass. In addition, their relatively large dimensions demand high purging volumes to ensure complete sample transfer from the TD tube to the separation column. These factors make an efficient coupling with a hyper-fast GC impractical. To address this, the second study focused on developing a low thermal mass TDU and corresponding μ TD-tubes to enable a substantially faster sample introduction. The μ TD-tubes were made of stainless steel and filled with only 10 mg Tenax TA. Their reduced dimensions (1.4 mm I.D.) and low thermal mass allowed short heating and cooling cycles and a fast thermal desorption within 12 s for the investigated *n*-alkanes (*n*-pentane to *n*-icosane). Baseline separation was achieved for analytes ranging from *n*-octane to *n*-icosane. In combination with the FF-TG-GC, chromatographic separation was completed within a total cycle time of approximately 90 - 100 s, including the manual loading of the μ TD-tubes and final oven cool down. Proof-of concept measurements using the novel TDU setup demonstrated high linearity ($R^2 \geq 0.995$) and repeatability with RSD < 5 %. The study also examined how the reduced μ TD-tube dimensions affect parameters such as breakthrough, back pressure, porosity, linear velocity and FWHM of analyte signals.

Based on the results of the first two research projects, the applicability of the TDU in combination with the cryofocusing unit was demonstrated for the detection of ten explosives and six CWA simulants in the third study. These analytes are relevant in security contexts such as screenings at airports, border control or military applications for example. Their strongly differing physicochemical properties, especially the large difference of 183 °C between the lowest decomposition temperature ($T_{dec,min}$ (EGDN) = 110 °C) and the highest boiling point ($T_{bp,max}$ (TBP) = 293 °C) make a gradual increase in temperature during TD necessary. To reduce the peak broadening of the volatile analytes associated with the relatively slow desorption (35 s desorption duration), a combination of TD and cryofocusing is used. However, the results of the study have shown that the heating process of the cryo-spot is too slow and leads to a broadening of the FWHM with the exception of the first two analytes. The heat input of the resistively heated sheath capillary is not sufficient for a sudden increase in temperature and thus the release of analytes as a sharp band. Therefore, a separate heating of the cryospot is required.

Applying a spatial temperature gradient along the separation column as well as the use of SilcoNert-coated and thereby deactivated μ TD-tubes, reduced the decomposition of thermolabile analytes such as PETN, NG, EGDN or RDX, and further improved peak area reproducibility. Limits of detection ranged between 0.17 ng/ μ L (2-MNT) and 9.18 ng/ μ L (tetryl). Linearity with $R^2 \geq 0.983$, within-day precision of < 15 % and between-day precision of < 20 % were reached for most analytes. The total cycle time is 164 s, including 4 s for cryospot cooling, 35 s for thermal desorption, 100 s for analytical separation and 25 s for system cooldown.

In summary, the three studies demonstrate that optimizing the sample introduction systems enables an efficient coupling with a hyper-fast GC, allowing the full potential of this analytical technique to be realized. In addition to speed, high reproducibility of the system is essential to ensure reliable results. The use of cryofocusing and the developed low thermal mass desorption system reduce analyte degradation, increases sensitivity and most importantly broadens the range of applications for hyper-fast GC. The developed setup represents an important contribution to the field of high-throughput analysis and enables frequent quality control in GMP-regulated production environments.

Nevertheless, there is potential to further improve the developed setups. In cryofocusing, faster heating of the cryospot is necessary to further reduce the initial bandwidth of the investigated analytes and to prevent a peak broadening caused by the slow release. This can be achieved by applying an additional resistive heating of the cooled sheath capillary piece. Another option to accelerate analyte release is to reduce the temperature difference between the cooling- and the release temperature. Since extremely

low temperatures in the range of -50 to -60 °C are not always required, temperatures between -10 and -30 °C are probably sufficient to focus less volatile compounds at the head of the separation column. An automated temperature control system for cryofocusing, in which the released amount of CO₂ is regulated by adjusting the pulse duration based on the actual temperature, can simplify method development and facilitates the adjustment of alternative cooling temperatures. Alternatively to cryofocusing, temperatures in this range can also be achieved using a Peltier element. The Peltier technology offers the additional advantage of more reproducible cooling conditions, avoiding the unpredictable temperature fluctuations that can occur when using liquid CO₂.

The conducted studies using the TDU have shown that the use of deactivated μ TD-tubes significantly improves reproducibility, especially for analytes prone to thermal degradation. A logical next step would now be the use of a deactivated injector tube (Figure 3.1, G) as well as deactivated spring wire segments (Figure 3.1, E₁) for attaching the Tenax packaging in the μ TD-tube. In the case of particularly thermally labile compounds, the use of deactivated purged connectors may contribute to a further reduction in analyte decomposition.

So far, only two sorbents have been tested: Tenax TA 60/80 mesh and 80/100 mesh. Tenax has the advantage of being non-polar, which means that it barely retains water. To extend the applicability of the setup, it would be advantageous to fill the μ TD-tubes with alternative sorbents. As polar sorbents accumulate water, it is therefore important to evaluate the possibility of dry-purging the μ TD-tubes within the injector via the split outlet. In addition, the use of multi-sorbent traps could be tested in order to broaden the range of analytes that can be effectively retained and released. One major disadvantage of the TDU system is the current lack of automation. Without it, the system is unsuitable for the use in high-throughput laboratories, real-time process monitoring in continuous manufacturing environments or for routine analysis.

Another project that has not yet been finished is the development of a miniaturized soil probe, designed to locally heat a small surface area, enabling the evaporation of compounds that are then sampled into a μ TD-tube with the aid of a pump.

These results underline the crucial role of sample introduction methods adapted to the requirement of hyper fast GC in unlocking its full analytical potential. Overall the methods and setups developed demonstrate the feasibility of fast, sensitive and reproducible analyses and thus provide a solid basis for future innovations. Further development can help to expand their application in practice, e.g. for additional analyte groups or automated analyses as part of routine analysis.

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Appendix A

First Publication

Residual solvent analysis with hyper-fast gas chromatography-mass spectrometry and a liquid carbon dioxide cryofocusing in less than 90 s



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Residual solvent analysis with hyper-fast gas chromatography-mass spectrometry and a liquid carbon dioxide cryofocusing in less than 90 s

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ABSTRACT

A new hyper-fast gas chromatography method with less than 90 s runtime including the column cool down was developed for the analysis of four gases and 16 residual solvents, combining a CO₂ cryofocusing with a flow-field thermal gradient gas chromatograph (FF-TG-GC) and ToF-MS. The extremely low analysis time can be achieved by combining the new FF-TG-GC and a very short Rxi-624 Sil MS separation column with a small inner diameter and small film thickness (2.05 m × 0.1 mm × 1.0 μm).

The column is inserted into a low thermal mass, resistively heated stainless steel capillary. This enables fast temperature programs with heating rates up to 3000 °C/min and a column cool down within a few seconds. In addition to temporal temperature gradients, the FF-TG-GC can generate a spatial temperature gradient that leads to an improved peak shape. Further, an external liquid CO₂ cryo-trap was designed in order to reduce the injection bandwidths of analytes and to take full advantage of the resolving power of the separation column. No modifications are required to the FF-TG-GC for the use of the cryogenic trap, as the cooled spot is heated by the resistively heated stainless steel capillary during the temperature program. With cryofocusing, analyzed residual solvents are baseline separated. *R*² values over 0.99 for calibration curves and low relative standard deviations (mainly < 3%) for repeatability tests were obtained.

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1. Introduction

A flow-field thermal gradient gas chromatograph (FF-TG-GC) is a new type of instrument for the hyper-fast analysis of diverse samples. Its operating principle was published in 2015 by Boeker and Leppert for the first time [1]. The set-up is fundamentally different from conventional GCs. In contrast to high-thermal mass air bath ovens and column length of ten to one hundred meters a resistively heated stainless steel sheath capillary acts as an oven. Commonly used fused silica capillaries of two or four meters length are inserted into the stainless steel capillary. By applying different voltages to it, temporal temperature gradients can be generated. An additional spatial temperature gradient along the length of the separation column is generated via a controlled forced external air flow. As the cooling capacity increases along the separation column, lower temperatures occur at the end of the column

than at the beginning [1]. The new FF-TG-GC design results in the following advantages for chromatography [1,2]:

1. Hyper-fast measurements in a range of 20 s to less than five minutes.
2. Extremely short oven cool-down phases of a few seconds.
3. High chromatographic resolutions due to the peak focusing effect.
4. Decreased elution temperatures based on the combination of temporal and spatial gradients.

In addition to the analysis of thermally unstable analytes, the short analysis time facilitates the performance of frequent checks in production processes as part of good laboratory practice or work in high-throughput laboratories.

In order to improve the chromatographic separation efficiency an external liquid carbon dioxide cryofocusing unit was developed. The temperature drop slows down the analyte velocity and thereby reducing the width of the analyte band transferred to the column. This allows the resolving power of the separation column to be fully utilized [3,4]. In general it is distinguished between separate

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cold traps and the direct focusing on the separation column, whereas it is possible to freeze the whole column or just a single piece of it [4]. Further, different coolants like liquid nitrogen [3,5,6], nitrogen gas chilled in liquid nitrogen [4,7], expanded liquid carbon dioxide [8,9] or electrical cooling via an Peltier element [10] can be applied.

A big advantage of the new FF-TG-GC is the good accessibility of the stainless steel capillary and thus the separation column. This enables the application of a technically simple set-up for the cryofocusing unit outside the oven without any modifications at the FF-TG-GC. Due to the low thermal mass of the stainless steel capillary, a temperature drop in a range of -50 to -60 °C can be obtained at a 1 - 2 cm long capillary piece, with a low carbon dioxide consumption.

The residual solvent and permanent gas sample mixture was analyzed in order to show fast measurements with the FF-TG-GC and the improvement of chromatography through the application of cryofocusing. A mix of four permanent gases and 16 organic solvents with a wide volatility range was analyzed. All 16 solvents are routinely used in the production process of drug substances. Since they often cannot be completely removed, residues may remain in the end product. As some of them show unacceptable toxic effects, it is important to ensure contents lower than the acceptable limits stipulated in worldwide regulations [11–13]. All analyzed solvents are included into the guideline for residual solvents of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use [14]. The residual solvents are divided into three classes by the guideline regarding to their toxicity. Class 1 solvents should be avoided because of unacceptable toxicity or deleterious environmental effects. Benzene for example is carcinogen and has a concentration limit of 2 ppm. Class 2 solvents are the solvents that should be limited due to inherent toxicity e.g. Methanol, Chloroform or Hexane. The toxicity of solvents in class 3 (e.g. Acetone, 1-Butanol or Ethanol) is considered as less toxic and of lower risk to human health low.

Amounts of 5000 ppm are considered acceptable without justification [14].

2. Material and method

2.1. Solvents and gases

Dimethyl sulfoxide (DMSO), n-Pentane, m-Xylene and Benzene were purchased from Sigma Aldrich (Steinheim, Germany). n-Heptane, Methyl tert-butyl ether (MtBE) and 2-Butanone are obtained from Merck (Darmstadt, Germany); Methanol, n-Hexane, Cyclohexane and Toluene were supplied by VWR (Darmstadt, Germany). Acetone, Dichloromethane (DCM) and 2-Propanol were obtained from Fischer (Schwerte, Germany). Trichloromethane (TCM) was supplied by Aldrich Chemicals (Milwaukee, USA) and 1-Butanol was purchased from Carl Roth (Karlsruhe, Germany). All solvents were either analytical grade or of a higher purity.

Liquid Carbon dioxide (99.7 vol. %) and Helium (99.999 mol %) were supplied by Air Liquide (Düsseldorf, Germany). The liquid carbon dioxide cylinder was equipped with a dip tube.

Further a gas mixture of Ethane (12.50 mol %), Propane (7.00 mol %), iso-Butane (3.02 mol %), n-Butane (3.00 mol %), iso-Pentane (0.503 mol %), n-Pentane (0.469 mol %), Carbon dioxide (0.506 mol %), Nitrogen (9.03 mol %) in Methane was supplied by Supelco (Bellefonte, USA).

2.2. Instrumentation

2.2.1. Flow-field thermal gradient GC (FF-TG-GC)

The principle of the flow-field thermal gradient GC (FF-TG-GC, Fig. 1) is based on a resistively heated capillary, into which a conventional fused-silica column is inserted (I). In addition to the usual temporal temperature gradient (temperature program), it is possible to create a spatial temperature gradient along the column. For this purpose, a forced external air flow from the lower

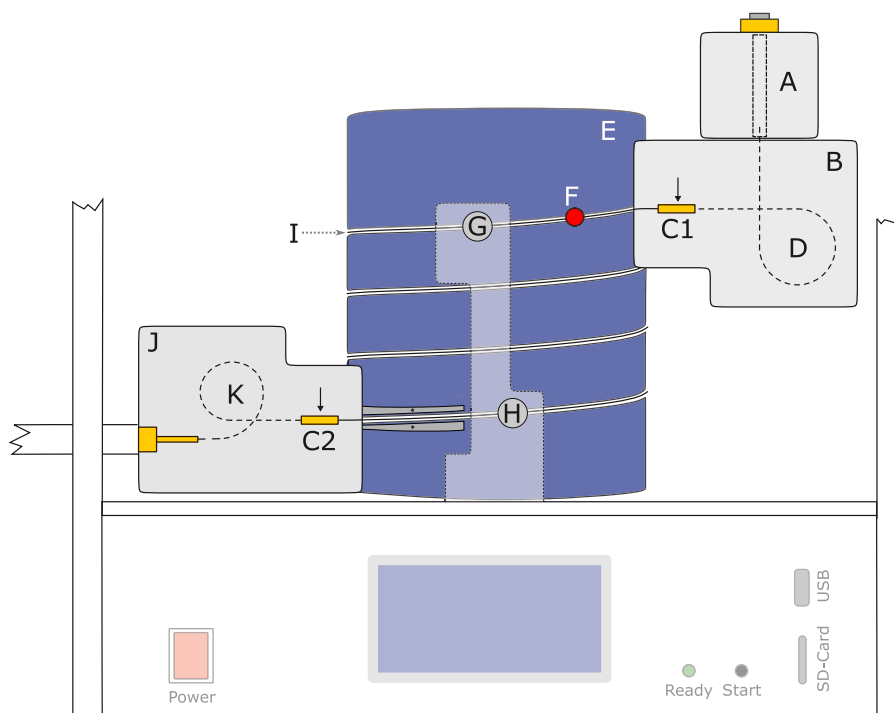


Fig. 1. Schematic drawing of the front side of the FF-TG-GC.

A - injector; B - transfer oven 1; C - purged connectors, the arrow marks the additional Helium supply; D - transfer line; E - column fixture; F - cryospot; G, H - upper and lower IR-sensors; I - resistive heated capillary; J - transfer oven 2; K - transfer line to the detector.

to the upper end of the column fixture (E) is generated. This leads to lower temperatures at the end of the column compared to the column inlet [1]. The column temperature is monitored by two IR-sensors (G, H). An advantage of negative spatial temperature gradients is the peak focusing effect, whereby the peak tail is accelerated due to higher temperatures and the peak front is slowed down due to lower temperatures [1].

Oven 1 (B) as well as oven 2 (J) serve to heat the transfer lines from the injector (A) to the column inlet (D) as well as from the column end to the detector (K). Transfer line and column are attached via purged connectors (C). The Helium purge flow into the connector flushes the remaining dead volumes and thereby reduces peak deformations caused by diffusion of the analytes into the dead volume. Furthermore, it is possible to switch the carrier gas supply from the injector (A) to the connector (C1) via a valve during a GC run, after completed transfer of the analytes to the separation column. This diversion of the carrier gas flow has three decisive advantages: On the one hand the separation column is protected from low volatile matrix components that might be transported with the normal carrier gas flow during the separation from the injector to the separation column. On the other hand it is possible to backflush the transfer line and the injector after switching the carrier gas flow to connector C1. Furthermore this enables the cutting of the solvent peak tail.

The carrier gas supply line to the injector and to the connector C1 are connected via a bypass to ensure that the connector C1 is purged with Helium during the sample injection phase prior to switching the carrier gas supply.

2.2.2. Headspace gas-chromatography

A Pal III autosampler (CTC Analytics AG, Zwingen, Switzerland) equipped with an agitator and a headspace tool was used to heat and shake the vials and to inject 1 mL of the sample headspace. Samples were shaken at 500 rpm (20 s shaking, 5 s break) at different temperatures and for different time intervals. The headspace syringe temperature was set to 150 °C.

Analysis were performed using a FF-TG-GC (HyperChrom, Strassen, Luxembourg) coupled with a BenchTOF-Select Time-of-Flight Mass Spectrometer from Markes International (Llantrisant, U.K.). The Rxi-624 Sil MS separation column (2.05 m column length, 0.1 mm internal diameter, 1.0 µm film thickness, Restek, Bellefonte, USA) was inserted into the resistively heated stainless steel capillary. A methyl deactivated fused silica capillary (0.1 mm internal diameter, Trajan Scientific, Ringwood, Australia) with a length of 15 cm was used to connect the separation column with the injector and a 25 cm long capillary to connect the mass spectrometer. Further the same fused silica capillary was used as a bypass of 47 cm length between the carrier gas supply lines to the injector and the connector C1.

The split/splitless injector was equipped with a Topaz 4 mm internal diameter straight inlet liner with wool (Restek, Bellefonte, USA). The split flow was adjusted to 60 mL/min and the septum purge to 10 mL/min. Injector and oven temperatures were set to 220 °C. Ion source and transfer line of the ToF-MS were heated to 300 °C, electron ionization occurred with an energy of 70 eV. Chromatograms are recorded with a measuring rate of 50 Hz.

Analysis were performed at constant pressure of 245 kPa (gauge) at the injector/connector C1 and 80 kPa (gauge) at connector C2 resulting in a column flow of 1.10 mL/min at 20 °C (Helium supply via injector) and 0.82 mL/min at 120 °C (Helium supply via C1). The temperature program was: from 20 °C to 30 °C with 30 °C/min, then with 66.5 °C/min to 71 °C and with 420 °C/min to 120 °C and held for 10 s. The total runtime of the temperature program is 74 s. To create a gradient, a fan setting of 80 % of the maximum fan power was selected. Due to the low temperatures of the temperature program, even at this setting only a relatively low

gradient of maximum 40 °C can be generated at the end of the temperature program (120 °C column temperature). Nevertheless, the use of the gradient leads to a reduction of the elution temperature by 25 °C compared to measurements without a gradient for m-Xylene.

2.2.3. Cryo trap

In cryofocusing, liquid carbon dioxide is sprayed through a M3 sapphire screw-in nozzle (0.15 mm i.d., Teschke, Duisburg, Germany) against a 1–2 cm long part of the resistively heated capillary near the inlet of the separation column (Fig. 1, F). Due to the pressure drop from 57 bar in the gas cylinder to atmospheric pressure, a phase transition occurs and a jet of cold carbon dioxide gas and solid carbon dioxide (dry ice) particles is created [15]. To reduce the temperature at the separation column as fast as possible to a range of –50 °C to –60 °C and to maintain it with minimum carbon dioxide consumption, carbon dioxide is released via a sequence of a long initial pulse (4 s) followed by ten short pulses (0.3 s). Between these pulses there is a break of 0.2 s. At a fixed time before sample injection, the autosampler transmits a signal, that starts an Arduino program and thus controls a valve for releasing the liquid carbon dioxide via a relay. Precise timing is crucial. Therefore, the capillary is pre-cooled prior to the sample injection. To achieve reproducible chromatograms, it is very important that the time interval between the start of cooling and the sample injection is kept exactly constant. In order to reduce the time interval deviations to a millisecond level, the autosampler operating software Chronos was modified in cooperation with Axel Semrau (Sprockhövel, Germany) and an updated PAL III Series II board was used with the PAL III hardware.

Dead volumes between the downstream orifice of the valve and the nozzle drill are filled with liquid carbon dioxide during spraying. After closing the valve, an evaporation of this liquid carbon dioxide leads to a further undesirable formation of cold gas and dry ice. For this reason a valve purchased by Asco Numatics (X949508791001F1, Ölbronn-Dürren, Germany) was modified by the in-house workshop in order to reduce this dead volume.

2.3. Preparation of standards

The analytes used in the measurements are divided into four groups: alkanes (n-Pentane, n-Hexane, Cyclohexane, n-Heptane), alcohols (Methanol, Ethanol, 2-Propanol, 1-Butanol), miscellaneous solvents (Acetone, DCM, MtBE, 2-Butanon, TCM, Benzene, Toluene and m-Xylene) and gases (Propane, iso-Butane, Butane, iso-Pentane). All stock solution were prepared fresh at the day of analysis with DMSO as the dilution solvent. According to experiments conducted by Urakami et al. DMSO showed the highest peak intensity ratios for almost all analytes analyzed in the current study in comparison to different dissolution solvents (e.g. N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), benzyl alcohol (BA), 1,3-dimethyl-2-imidazolidinone (DMI) or water) [13]. The only exception with poorer peak intensity ratios is the group of alcohols containing only 4 of 16 residual solvents analyzed in the current study. Further, a high boiling point is another important property of a dissolution solvent, since it must be well above the equilibration temperature [16]. This is necessary to allow a high desorption temperature. The boiling point of DMSO is comparatively high at 189 °C compared to DMF (153 °C), DMA (166 °C), DMI (105 °C) and water (100 °C). Solely BA has a higher boiling point of 204 °C [13,16]. Moreover, Urakami et al. found that especially DMF and DMA partially degrade at equilibration temperatures above 100 °C resulting in the formation of interfering artifacts [13].

For the pretest experiments a stock solution (S1) with a content of 100 ppm per alkane, 20,000 ppm per alcohol and 1,000 ppm

per miscellaneous solvent was prepared. To determine the limit of detection (LOD) and limit of quantitation (LOQ), a second independent stock solution (S2) was prepared from diluted individual standards of the respective solvents. The concentrations of the individual solvents contained in S2 are adjusted to the range of the detection limit and therefore different. The final concentration range of the diluted standards is shown in Table 3. A third stock solution (S3) containing 100 ppm per alkane, 4,000 ppm per alcohol and 200 ppm per miscellaneous solvent was prepared for linearity and repeatability experiments.

For the permanent gas sample experiments, a stock solution (S4) with the same concentrations as S3 was prepared, but no n-Pentane was added as it was already contained in the gas mix (see Section 2.1). Further an undiluted permanent gas standard (P1) was generated and subsequently diluted to P2. For P1, a 20 mL headspace vial with lid and septum was purged for 60 s with the gas mixture. For this purpose, two cannulas were pierced through the septum: One to the bottom of the vial to introduce the gas and the other one as an outlet only just below the septum. The cannulas were removed at the end of the purging process. To dilute the concentration of permanent gases, 2 mL of P1 were injected into a further empty headspace vial (P2).

2.4. Preliminary tests

To determine the ideal agitator temperature, samples were measured at a range of 50 °C to 110 °C in 10 °C steps at an equilibration time of 10 min. Subsequently further samples were analyzed with incubation times of 1 min, 2 min, 3 min, 4 min, 5 min, 6 min, 8 min and 10 min at an agitator temperature of 110 °C. Duplicate samples were prepared with a concentration of 10 ppm per alkane, 2,000 ppm per alcohol and 100 ppm per miscellaneous solvent.

2.5. Limits of detection and quantitation

The Limit of detection (LOD) corresponds to the smallest detectable analyte concentration with an error probability of 50 % [17,18]. The limit of quantitation (LOQ) is defined as the smallest quantifiable amount of analyte, that can be determined with an acceptable amount of precision [18]. Both, LOD and LOQ are identified using the calibration line method according to DIN 32645 [17].

LOD and LOQ were determined with an external standard calibration curve ($\alpha = 0.01$, $k = 3$) according to [17]. For this purpose ten concentration levels were analyzed in duplicate (concentration range is shown in Table 3). Before linear regression was performed, the data was checked for normal distribution using the Shapiro-Wilks test [18]. The linearity was then estimated by testing the goodness of fit according to Mandel [19].

2.6. Linearity and repeatability

Five calibration and ten repeatability samples were prepared from S3. The calibration standards with concentrations of 40 ppm, 80 ppm, 120 ppm, 160 ppm, 200 ppm (alcohols); 1 ppm, 2 ppm, 3 ppm, 4 ppm, 5 ppm (alkanes) and 2 ppm, 4 ppm, 6 ppm, 8 ppm, 10 ppm (miscellaneous solvents) were measured in duplicate for linearity tests. The linear regression line was determined according to the principle of ordinary least squares. For repeatability tests, further ten medium calibration standards were analyzed.

2.7. Permanent gas samples

For qualitative analysis of permanent gases in combination with residual solvents, samples with a concentration of 120 ppm per alcohol, 3 ppm per alkane (except n-Pentane) and 6 ppm per miscellaneous solvent were prepared. Using a 1.5 mL syringe with needle,

1 mL of the air-diluted gas mix (P2) was additionally injected into the sample vial. The sample was analyzed immediately. In order to show the effect of cryofocusing, the experiment was conducted twice, with and without cryofocusing.

2.8. Data acquisition

Autosampler and ToF-MS were controlled via Chronos and ProToToF respectively. The software ChromSpace (Markes International, Offenbach am Main, Germany) was used for background subtraction of the chromatograms via dynamic background compensation (DBC) and for automated analyte peak integration.

Microsoft Excel and LaborValidate - Labormethoden-Validierung Version 2.8 (LABC - Labortechnik Zillger KG, Hennef, Germany) were used for statistical calculations.

3. Results and discussion

3.1. Pretests

Peak intensities and thereby method sensitivity can be affected by many headspace-sampling parameters including equilibration time and temperature. Increased agitator temperatures promote the analyte partitioning in the sample headspace and increase equilibrium concentrations [13,16]. Thus, for all analytes response increased with increasing agitator temperature from 50 °C to 110 °C (Table S.2 in Supplements). For example, the peak area of 1-Butanol increased from 50 °C to 110 °C incubation temperature by factor 14. An approximately 5-fold increase in response was observed for Trichloromethane, Toluene and the other alkyl alcohols Methanol, Ethanol and 2-Propanol.

When selecting a suitable equilibration time, two factors must be weighed against each other: The time must be long enough for an equilibrium between the liquid sample and the vial headspace to be established. At the same time, long equilibration times lead to extended analysis times due to limited possibilities of parallel equilibration of several samples in the agitator. This in turn reduces the time saved by the extremely fast chromatography. A comparison of several peak intensity ratios for the respective equilibration times is shown for Pentane, 1-Butanol and m-Xylene in Fig. 2 in combination with temperatures measured in the vial headspace as well as in the liquid phase. For all analytes after 5 min 94 % or more of the respective normalized area (100 % refers to an equilibration time of 10 min) was reached (further details in Table S.2 in Supplements). After this time, stable temperatures have already been reached in the liquid phase (109.9 °C) and in the headspace of the vial (108.0 °C). Therefore it was determined that an equilibration temperature of 110 °C and an equilibration time of 5 min are optimal.

3.2. Cryofocusing

3.3. Theory of liquid CO₂ expansion

Opening the valve causes a sudden expansion of the liquid CO₂ from a pressure of 57.3 bar (at 20 °C) in the gas cylinder to atmospheric pressure. The pressure inside the gas cylinder remains constant due to permanent evaporation of liquid CO₂ during the release. A two-phase mixture consisting of solid dry ice particles and CO₂ gas is released from the nozzle [20].

The pressure drop is ideally a constant enthalpy process. When the CO₂ escapes through an orifice, the pressure drops while the enthalpy is constant. Thereby, the liquid CO₂ starts boiling and evaporates partially. At the same time, the drop in temperature causes the nucleation of liquid droplets and dry ice particles are formed at the liquid-gas and liquid-solid interface [15].

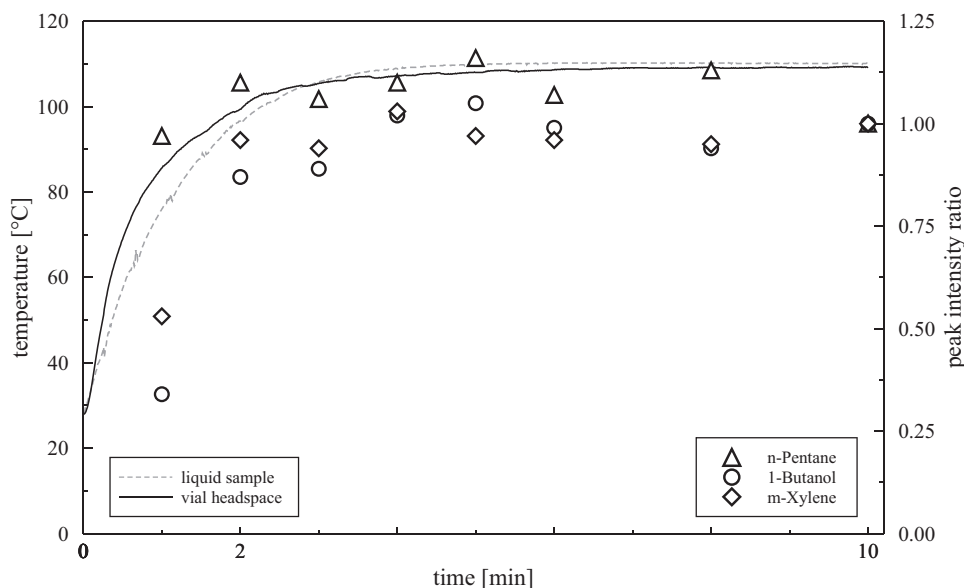


Fig. 2. Measured temperature increase in the liquid sample (dashed line) and in the vial headspace (solid line) as well as peak intensity ratios for selected analytes: Pentane (triangle), 1-Butanol (circle), m-Xylene (rhombus). In Table S.2 (supplements) data for all analytes are shown.

The occurrence of different spray patterns depends on nozzle dimensions, internal surface roughness, inlet fluid temperature, flow rate, properties of the used flow media, chamber pressure and bubble concentration at the nozzle exit [15,21].

3.3.1. Selection of suitable nozzles

In order to obtain steady CO₂ spraying conditions and reproducible temperature curves during cooling down different nozzle types were tested. First tests were conducted with self-made nozzles from fused silica transfer line pieces glued into a metal capillary tube. However, it has been shown that although low temperatures could be achieved with them, the spraying conditions were not reproducible at all as large fluctuations in the amount of dry ice released occurred. Possibly, the formation of gas bubbles in the nozzle has led to a reduction of the mass flow, as bubbles narrow the orifice opening or reduce the fluid density [22]. Further tests were conducted with sapphire nozzles (Teschke GmbH, WHD-Consulting.de) and different orifices obtained from Günther Frey GmbH and Co. Kg (Berlin, Germany). For all tested nozzles (self-made nozzles, sapphire nozzles and orifices), a reduced dry ice release could also be determined in the first measurement cycles. If further measurements were taken at short intervals, the conditions of the sapphire nozzles and the orifices were stable and reproducible temperature curves were recorded with a type K thermocouple inside the resistively heated stainless steel capillary (Fig. 3, used nozzle: 0.15 mm i.D. sapphire nozzle). Since liquid CO₂ also begins to boil in the gas cylinder during withdrawal [20], gas bubbles might ascend in the dip tube and accumulate in the CO₂ supply line before the valve, after long periods of standing.

Sapphire nozzles (Teschke) were selected to optimize cryogenic cooling for ease of handling. Nevertheless, further tests with the orifices (Günther Frey) are necessary, as they also provided very promising results.

The additional use of a metal mesh placed around the stainless steel capillary, in order to increase the dry ice enrichment during the spray phase, resulted in lower temperatures and a reduced CO₂ consumption. However, this slowed down the thawing by heating of the capillary as the dry ice particles were compressed and fixed at the capillary. Since a technically simple set-up was desired, the application of additional heating coils on the cold stainless steel

capillary parts were avoided to solve this problem. Therefore, the use of the mesh was discarded.

3.3.2. Optimization of the cryofocusing unit

During the optimization of cryofocusing, the following criteria were defined at the beginning:

1. technically simple set-up without modifications of the FF-TG-GC
2. lowest possible CO₂-consumption
3. fast release of frozen analytes by heating the stainless steel capillary (Fig. 1F) during the regular temperature program
4. high reproducibility of measurements with stable retention times (fluctuations below 1 s)

To ensure a technically simple set-up, valve and nozzle were aligned in front of the stainless steel capillary using a massive stand with a x-y-z linear translation stage for fine adjustment. This enabled the test setup to be modified very easily without major conversion work. Different distances as well as different spraying angles between nozzle and stainless steel capillary could be tested very easily. A distance of 3 - 4 mm and an angle of 90 ° were considered optimal. Unlike commercially available systems or previously published test set-ups that require a cryofocusing unit to be built into the GC [3,6,9,23,24], the FF-TG-GC does not require any modification.

A low CO₂ consumption could easily be realized by using sapphire nozzles with small nozzle diameters and the direct spraying on the resistively heated stainless steel capillary. For this purpose nozzle diameters of 0.08, 0.1, 0.125, 0.15, 0.2, 0.3 and 0.4 mm were tested. It was found that diameters between 0.08 mm and 0.125 mm lead to insufficient cooling. From a diameter of 0.15 mm to 0.4 mm sufficient low temperatures were reached. However, the dry ice/CO₂-gas mixture outlet velocity increased visibly with increasing nozzle diameters. Therefore less and less dry ice is accumulated at the stainless steel capillary, since it is solely blown away. That is why continuous spraying without pulses is necessary for larger diameters, which in turn contradicts the economical use of liquid CO₂. For the residual solvent experiments performed, a 0.15 mm nozzle was chosen.

Due to its low thermal mass, the cooled spot of the stainless steel capillary can be heated up very quickly without the use of

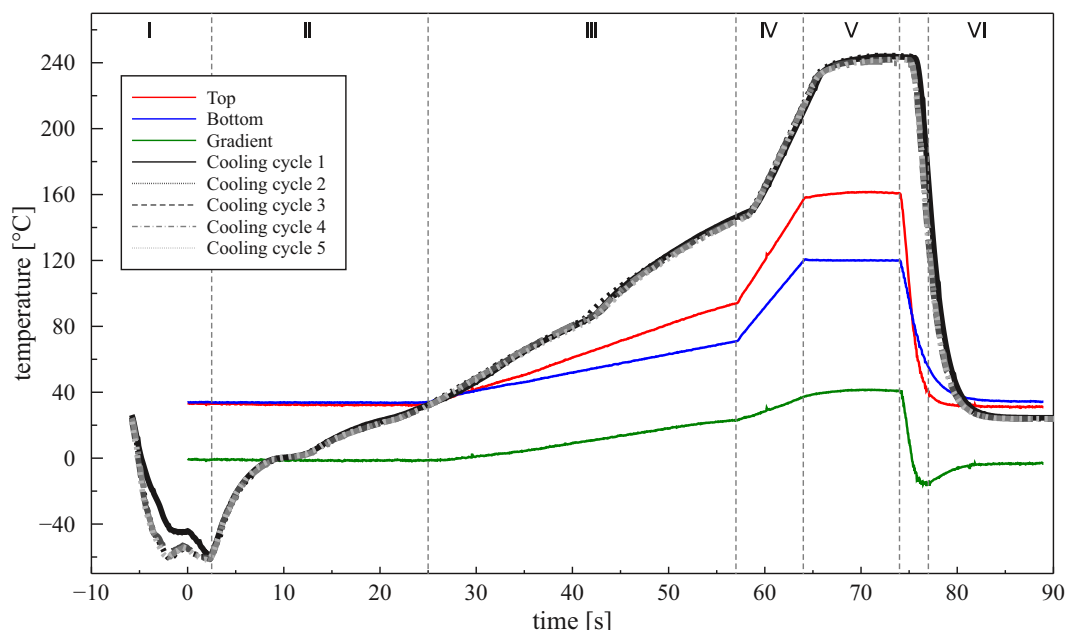


Fig. 3. Cooling cycle 1–5: Overlay of five temperature curves measured inside the resistively heated stainless steel capillary at the position of the cryospot (Fig. 1, F) with a 0.15 mm internal diameter sapphire nozzle (Teschke). Red line: Temperature measured at the upper IR-sensor (Fig. 1 G). Blue line: Temperature measured at the lower IR-sensor (Fig. 1 H). Green line: Calculated temperature gradient between the temperatures measured at the lower and upper IR-sensors. I - cryofocusing; II - first temperature ramp, III - second temperature ramp, IV - third temperature ramp, V - hold temperature, VI - fast cooling down. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

additional heating coils during the course of a regular temperature program. Thus for the application of cryofocusing, no modifications are needed at the FF-TG-GC and the cryofocusing set-up is kept very simple.

3.3.3. Improvement of chromatography

The temperature drop at the cryo spot leads to increased retention factors (k) and thus to reduced analyte mobilities μ (Eq. (1)). The analyte mobility is also called relative analyte migration rate R_f [4,25,26]. Further, it reduces the analyte velocity u_a , which can be calculated from μ and the carrier gas velocity u_c according to Eq. (2) [4].

$$\mu = \frac{1}{1+k} \quad (1)$$

$$u_a = \mu \cdot u_c \quad (2)$$

Retention factors are temperature dependent and change by a temperature change of 20 °C around about factor of two [4]. Thus, a temperature drop from 20 °C starting temperature to –60 °C resulting from cryofocusing, leads to an increase of an imaginary retention factor with a value of 1 to a value of 16. This results in a reduction of μ e.g. from 0.5 to approximately 0.06. In combination with a constant carrier gas velocity the analyte velocity is decreased by a factor of 8.3 and thus the analyte solute band transferred on the column via sample injection is narrowed [3].

3.3.4. Results of qualitative permanent gas and residual solvent experiments

Fig. 4 shows two chromatograms in overlay: one was recorded with and the other one without the use of cryofocusing. Further information on retention time, resolution and full width at half maximum (FWHM) are presented in Table 1.

The application of cryofocusing causes two effects visible in the chromatogram: First, retention times increase compared to the measurement without cryofocusing due to delayed analyte elution.

Second, FWHM decreases and resolution increases as analyte bandwidths decrease. Considering Table 1, it is evident that the effect of cryofocusing on the respective analytes varies in intensity. For both the most volatile compounds (Propane, iso-Butane, n-Butane) and the least volatile compounds (n-Heptane, 1-Butanol, Toluene and m-Xylene), the retention time is least affected. The temperature drop of –50 °C to –60 °C achieved during cryofocusing is not sufficient to focus the most volatile analytes. Nevertheless, the temperature reduction for all permanent gases is sufficient to improve the peak shape enough to reduce the FWHM and to improve the resolution. In contrast, the migration rate of the least volatile analytes is already reduced so much at the starting temperature of the measurement without focusing that the additional temperature reduction has only a marginal effect, even for FWHM and resolution. Apart from the permanent gases, cryofocusing leads to a considerable improvement (> 10 %) in FWHM for the analytes from Methanol to Methyl tert-butyl ether and in resolution even from Methanol to 2-Butanone.

3.4. Method validation

3.4.1. Selectivity

Selectivity describes the ability of a system to detect all relevant analytes side by side without mutual interference [18]. Pure solvent standards were measured individually to exclude the possibility of analyte coelutions (Table S.1 in Supplements). Further, all analytes were additionally identified by monitoring specific ions (Table S.1 in Supplements). The separation of all analytes from each other and from DMSO was performed in the experiments with cryofocusing at a resolution of 1.50 or higher (Table 1).

3.4.2. Linearity

Five calibration standards were analyzed to determine the calibration function. The linear regression line was received according to the principle of ordinary least squares. All coefficients of determination (R^2) had a value of 0.990 or higher with the ex-

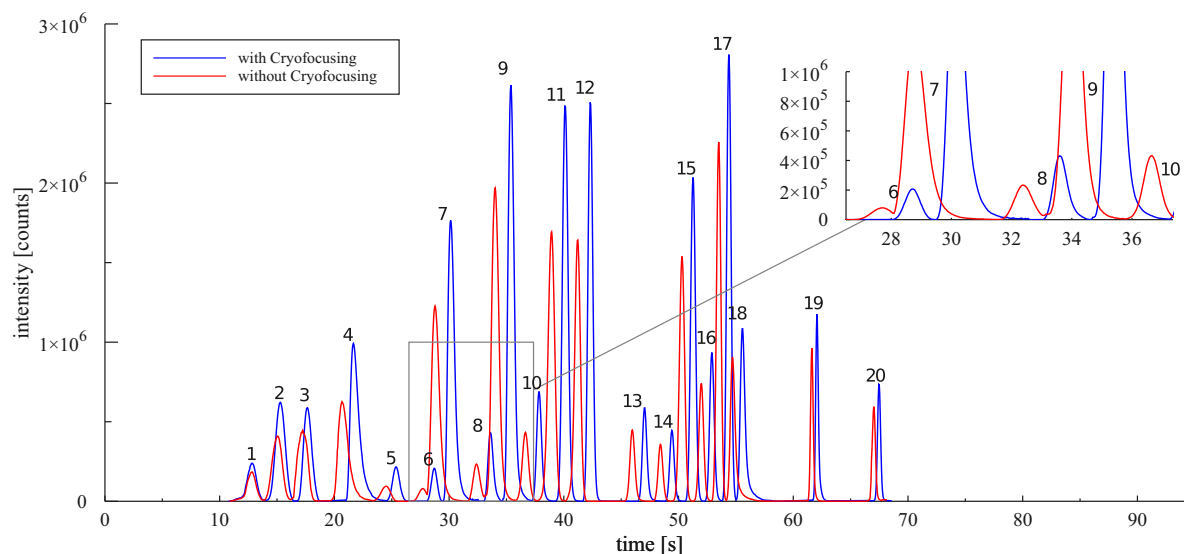


Fig. 4. Overlay of two chromatograms recorded with the application of liquid CO₂ for cryofocusing (blue line) and without cryofocusing (red line). The DMSO solvent peak is not shown in the chromatograms. 1 - Propane, 2 - 2-Methylpropane, 3 - n-Butane, 4 - Methanol, 5 - 2-Methylpentane, 6 - n-Pentane, 7 - Ethanol, 8 - Acetone, 9 - 2-Propanol, 10 - Dichloromethane, 11 - Methyl tert-butyl ether, 12 - n-Hexane, 13 - 2-Butanone, 14 - Trichloromethane, 15 - Cyclohexane, 16 - Benzene, 17 - n-Heptane, 18 - 1-Butanol, 19 - Toluene, 20 - m-Xylene. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Retention time, full width at half maximum (FWHM) and resolution (R) of permanent gas and residual solvent measurement with (On) and without cryofocusing (Off) and the relative change of the respective value in relation to the corresponding value without cryofocusing.

No.	Solvent	RT [s]		Δ[%]	FWHM [s]		Δ[%]	Resolution		Δ[%]
Cryofocusing →		On	Off		On	Off		On	Off	
1	Propane	12.8	12.8	0.1	0.97	0.94	3.8			
2	iso-Butane	15.3	15.1	1.2	0.97	1.04	−7.4	1.52	1.39	9.4
3	n-Butane	17.6	17.2	2.8	0.86	1.19	−35.2	1.50	1.07	39.2
4	Methanol	21.7	20.7	4.6	0.82	0.98	−17.0	2.82	1.93	46.2
5	iso-Pentane	25.4	24.5	3.4	0.71	0.93	−24.1	2.86	2.36	21.4
6	n-Pentane	28.7	27.7	3.6	0.58	0.78	−22.0	3.06	2.17	41.2
7	Ethanol	30.1	28.8	4.6	0.68	0.79	−12.1	1.35	0.83	61.6
8	Acetone	33.6	32.4	3.6	0.53	0.69	−17.0	3.36	2.86	17.5
9	2-Propanol	35.4	34.0	3.9	0.63	0.75	−12.7	1.81	1.33	36.0
10	DCM	37.8	36.7	3.1	0.49	0.63	−15.0	2.59	2.26	14.7
11	MtBE	40.1	39.0	3.0	0.57	0.66	−10.4	2.54	2.07	22.7
12	n-Hexane	42.3	41.2	2.7	0.48	0.56	−8.7	2.47	2.15	14.8
13	2-Butanone	47.0	46.0	2.3	0.45	0.49	−4.0	5.97	5.34	11.8
14	TCM	49.4	48.4	2.1	0.45	0.47	−2.2	3.12	3.02	3.4
15	Cyclohexane	51.3	50.3	1.9	0.49	0.52	−3.7	2.31	2.23	3.7
16	Benzene	52.9	52.0	1.8	0.46	0.47	−1.4	2.04	1.98	2.7
17	n-Heptane	54.4	53.5	1.7	0.44	0.45	−0.8	1.94	1.94	−0.2
18	1-Butanol	55.6	54.7	1.6	0.46	0.46	−0.3	1.54	1.55	−0.8
19	Toluene	62.1	61.6	0.7	0.26	0.27		10.57	11.14	
20	m-Xylene	67.5	67.0	0.7	0.31	0.31		11.08	11.04	

ception of Ethanol ($R^2 = 0.971$, Table 2). To obtain similar peak heights for each analyte, different analyte concentrations had to be analyzed.

3.4.3. Precision

To determine the method precision as a measure for the dispersion of the analysis results, ten mean standards of the calibration were prepared and measured on the same day. The relative standard deviations (RSD%) of the measurements range from 0.9 % to 4.6 % and are lower than 5 %. An acceptable precision is obtained for all analytes (Table 2).

3.4.4. Limits of detection and quantitation

As shown in Table 3 the LOD values range from 0.001 - 2.156 ppm and LOQ values from 0.002 - 7.075 ppm. Thereby it is apparent that LOD and LOQ values for alkyl-alcohols are at least two orders of magnitude above the respective alkane values. The

LOD and LOQ values for miscellaneous solvents are between the alkanes and alcohols. This is caused by intramolecular interactions: DMSO consists of two hydrophobic methyl groups and a highly polar sulfoxide group, which can act as a hydrogen bond acceptor with a hydrogen bond acceptor strength of 0.97 according to Table 4 [27,28]. Alcohols are the only solvents contained in the sample that have a hydrogen bond donor strength greater than 0.30 (Table 4). Therefore, hydrogen bonds are formed especially between the sulfoxyl group of DMSO and the hydroxy-group of the alcohols [29]. The values of the solvent/air distribution coefficient ($\log K_{(\text{solvent}/\text{air})}$, Table 4) behave similar to the LOD or LOQ values. The partition coefficients of the alcohols are higher than those of the alkanes. The alcohols are held more strongly in solution by the hydrogen bonds and evaporate less easily into the gas phase. The alkanes, on the other hand, do not have such attractive interactions with DMSO and can therefore transfer more easily into the gas phase.

Table 2

Analyte concentration range c and coefficient of determination (R^2) of the five-point calibration (prepared from S3) for linearity tests. Relative standard deviation (RSD) as the result of repeatability tests.

Solvent	c [ppm]	R^2	RSD [%]
Alcohols			
Methanol	40 - 120	0.9971	1.12
Ethanol	40 - 120	0.9712	1.35
2-Propanol	40 - 120	0.9987	1.33
1-Butanol	40 - 120	0.9979	4.58
Alkanes			
n-Pentane	1 - 5	1.0000	3.31
n-Hexane	1 - 5	0.9992	2.28
Cyclohexane	1 - 5	0.9987	1.91
n-Heptane	1 - 5	0.9919	1.64
Miscellaneous Solvents			
Acetone	2 - 6	0.9992	1.34
DCM	2 - 6	0.9991	1.77
MtBE	2 - 6	0.9977	2.08
2-Butanone	2 - 6	0.9995	1.45
TCM	2 - 6	0.9996	2.00
Benzene	2 - 6	0.9981	1.46
Toluene	2 - 6	0.9990	0.90
m-Xylene	2 - 6	0.9996	1.87

Table 3

Concentration range (c) of LOD and LOQ standards prepared from S2. LOD, LOQ and R^2 values computed according to the external standard calibration curve method.

Solvent	c [ppm]	LOD [ppm]	LOQ [ppm]	R^2
Alcohols				
Methanol	2.5 - 25	1.393	4.596	0.9979
Ethanol	1 - 10	0.345	1.137	0.9980
2-Propanol	1.5 - 15	0.455	1.512	0.9985
1-Butanol	3 - 30	2.156	7.074	0.9961
Alkanes				
n-Pentane	0.16 - 1.6	0.090	0.295	0.9985
n-Hexane	0.016 - 0.16	0.008	0.027	0.9981
Cyclohexane	0.002 - 0.02	0.001	0.002	0.9989
n-Heptane	0.0096 - 0.096	0.004	0.014	0.9985
Miscellaneous Solvents				
Acetone	0.16 - 1.6	0.065	0.213	0.9972
DCM	0.04 - 0.4	0.015	0.050	0.9982
MtBE	0.06 - 0.6	0.013	0.042	0.9996
2-Butanone	0.12 - 1.2	0.020	0.066	0.9997
TCM	0.16 - 1.6	0.029	0.096	0.9996
Benzene	0.08 - 0.8	0.022	0.074	0.9996
Toluene	0.08 - 0.8	0.020	0.067	0.9990
m-Xylene	0.12 - 1.2	0.054	0.180	0.9970

3.5. Time of analysis

The method developed in this study requires 74 s (respectively 1.23 min) for the temperature program and further 15 s (respectively 0.25 min) are necessary to cool the column down. Thus less than 90 s (1.5 min) are needed for the whole FF-TG-GC run. Due to the short sample equilibration time of 5 min, the first analysis is already finished after 6.5 min. Since several samples can be equilibrated in parallel, further samples can be measured directly after the first one resulting in a cycle time of 1.5 min. The main reason for the high measuring speed is the extremely short separation column of 2 m length and the small film thickness of 1 μ m [3]. Due to the new operating principle of the FF-TG-GC, a combination of a conventional temporal gradient with a spatial gradient, the separation is carried out at a high chromatographic efficiency despite the high analysis speed. The design of the FF-TG-GC with a low thermal mass heating system enables the extremely short cooling times of the column and thus contributes substantially to the achievement of fast results.

So far, the fastest residual solvent measurement was conducted by Chen et al. in 1998 [33]. Within 4.9 min, 40 solvents were

Table 4

Hydrogen bond donor strength (A), hydrogen bond acceptor strength (B) and solvent air distribution coefficient $\log K_{(\text{solvent/air})}$ [32].

	A	B	$\log K_{(\text{solvent/air})}$
Alcohols			
Methanol	0.43 ^a	0.47 ^a	3.52 ^d
Ethanol	0.37 ^b	0.48 ^b	3.54 ^d
2-Propanol	0.33 ^b	0.56 ^b	3.37 ^d
1-Butanol	0.37 ^b	0.48 ^b	4.35 ^d
Alkanes			
n-Pentane	0.00 ^b	0.00 ^b	1 ^d
n-Hexane	0.00 ^b	0.00 ^b	1.36 ^d
Cyclohexane	0.00 ^b	0.00 ^b	1.8 ^d
n-Heptane	0.00 ^b	0.00 ^b	1.73 ^d
Miscellaneous Solvents			
2-Propanone	0.04 ^b	0.49 ^b	2.86 ^d
DCM	0.10 ^a	0.05 ^a	2.97 ^d
MtBE	0.00 ^a	0.59 ^a	1.76 ^d
2-Butanone	0.00 ^a	0.51 ^a	3.08 ^d
TCM	0.15 ^a	0.02 ^a	3.31 ^d
Benzene	0.00 ^c	0.14 ^c	2.82 ^d
Toluene	0.00 ^b	0.14 ^b	3.21 ^d
m-Xylene	0.00 ^b	0.16 ^b	3.58 ^d
DMSO	0.00 ^a	0.97 ^a	-

^a Abraham et al. 2010 [30].

^b Abraham and Ibrahim 2006 [28].

^c Abraham et al. 2009 [31].

^d UZF-LSER database [32].

analyzed on a 10 m, 0.1 mm, 0.4 μ m DB-624 separation column at constant pressure. If a pressure program was used instead, the analysis time could be reduced to less than 1.5 min. The cooling time of the oven is not included in the indicated times. Rocheleau et al. [12] has published a 4 min (20 solvents) and for high-boiling point solvents a 3 min (3 solvents) fast EZ Flash GC method on a 10 m $\times$ 0.18 mm $\times$ 1 μ m RTX-624 column. With liquid injections less than 7 min are needed in total for the whole injection routine, analysis and cool-down time.

4. Conclusion

A fast method for the analysis of 18 residual solvents was developed and validated with the new FF-TG-GC. A hyper-fast separation in less than 90 s including a cool-down time of only 15 s, was shown. In combination with short equilibration times of 5 min high-throughput measurements are possible with a cycle time of 1.5 min. To the best of the authors knowledge this is the fastest GC-method including temperature program and the cooling down phase for the analysis of residual solvents.

For the improvement of the chromatographic separation, a new type of cryofocusing unit was developed. In contrast to conventional and commercially available cryotrap, the cooled column piece is considerably shorter and not several cm long. This has the advantage that on the one hand much less CO₂ is required for cooling and on the other hand less cold is introduced into the system, which subsequently does not have to be removed by a separate heating system for rapid release of the analytes. This simplifies the experimental setup enormously - no modifications to the FF-TG-GC are necessary for the use of the cryotrap. In addition, analysis time is saved by avoiding the time-consuming cooling process. With the new setup, liquid carbon dioxide was expanded through a 0.15 mm inner diameter sapphire nozzle and a mixture of dry-ice and cold carbon dioxide gas was used for cooling down a 1 - 2 cm long piece of the separation column to a temperature range of -50 to -60 °C. The temperature drop reduces the analyte velocity u_s and thereby narrows the analyte solute band after sample injection. Full width at half maximum and resolution are improved for almost all analyzed solvents and even for a selection of permanent

gases. A more detailed study on the effect of different nozzle types on the spraying conditions is needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Miriam D. Chopra: Conceptualization, Methodology, Software, Validation, Investigation, Writing - original draft, Writing - review & editing, Visualization. **Peter J. Müller:** Methodology, Software, Investigation, Writing - original draft, Writing - review & editing. **Jan Leppert:** Methodology, Validation, Investigation, Writing - original draft, Writing - review & editing. **Matthias Wüst:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition. **Peter Boeker:** Conceptualization, Writing - original draft, Writing - review & editing, Resources, Supervision, Project administration, Funding acquisition.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.chroma.2021.462179](https://doi.org/10.1016/j.chroma.2021.462179).

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Appendix B

Second Publication

**A fast thermal desorption unit for micro thermal desorption tubes, Part I:
Development of the system and proof of concept measurements with
hyper-fast gas chromatography**



Contents lists available at ScienceDirect

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A fast thermal desorption unit for micro thermal desorption tubes, Part I: Development of the system and proof of concept measurements with hyper-fast gas chromatography

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ABSTRACT

A system consisting of a thermal desorption unit (TDU) and micro thermal desorption tubes (μ TD-tubes, 1.4 mm I.D., 10 mg Tenax TA) for fast desorption of analytes was developed for the efficient combination of hyper fast gas chromatography with thermal desorption. The fast desorption is achieved by a significantly reduced thermal mass compared to conventional thermal desorption tubes. Therefore, extremely fast heating and cooling cycles are possible. Proof of concept measurements combining the new setup with a flow-field thermal gradient gas chromatograph (FF-TG-GC) and FID detection show good precision and linearity with $R^2 \geq 0.995$ in the analysis of an *n*-alkane mix (C_8 – C_{20}). Thermal desorption occurs within 12 s. The impact of reduced μ TD-tube dimensions on desorption time, full width at half maximum (FWHM), breakthrough volumes, tube flow rates ergo linear velocities, porosity and back pressure is discussed.

1. Introduction

Thermal desorption (TD) is a powerful and versatile sampling method for gas chromatography used for sample preparation and extraction. It allows a concentration enhancement of analytes by a factor of up to 10^6 . In addition to sampling from air sample containers or online manifolds, TD-tubes are often used and desorbed into an inert carrier gas stream against the direction of loading [1,2].

Conventional TD-tubes usually have inner diameters of several millimeters and contain 100–600 mg of adsorbent material, which ensures a high capacity for the analysis [1]. Large amounts of adsorbent and relatively thick tube walls come along with high thermal masses resulting in long desorption processes of typically 5–15 min for volatile organic compounds [3–5]. For analytes with high boiling points or low vapor pressures e.g. polycyclic aromatic hydrocarbons desorption times are considerably longer [6,7].

Due to the slow desorption of the primary sampling device and the associated broadening of analyte bands, a further concentration step with focusing traps is required prior to GC analysis. The desorbed analytes are refocused into a focusing trap at ambient or sub-ambient temperatures. Re-desorption takes place extremely fast with heating rates of up to 100 °C/s. This releases the analytes into a very small volume of carrier gas and thereby increasing the concentration enhancement factor and method sensitivity [1,8].

In order to fully utilize the potential of hyper-fast GC measurements in combination with thermal desorption, it is necessary to considerably reduce the desorption time by significantly reducing the thermal mass and amount of adsorbent. For this purpose, a new thermal desorption unit (TDU) and new micro thermal desorption tubes (μ TD-tubes) are developed. The μ TD-tubes contain only 10 mg Tenax TA and have an outer diameter of only 1.6 mm.

Analytical separation is conducted with a flow-field thermal gradient gas chromatograph (FF-TG-GC). The functional principle of this GC was first published in 2015 by Boeker and Leppert [9]. Differences compared to conventional GC systems as well as the construction of a FF-TG-GC are explained in Chopra et al. [10].

In order to reduce the desorption time and to avoid the refocusing step, there have already been several approaches with microtraps [11–14] and research regarding their characteristics in the past [15]. If the adsorbent quantity becomes too small, breakthrough can become a problem. However, it is not necessary to collect large quantities of sample in combination with the FF-TG-GC, as it works with thinner I.D. columns which have less sample loading capacity.

The objective of this study is the development of a low thermal mass TDU, that enables analytes to be desorbed very quickly. Proof-of-concept measurements were performed with an *n*-alkane mixture,

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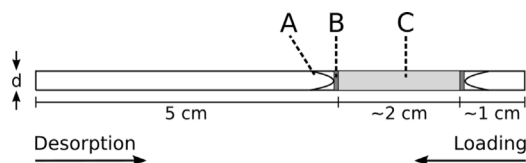


Fig. 1. Schematic drawing of the micro thermal desorption tube (μ TD-tube). Loading and desorption of analytes occur in opposite directions. A - spring wire, B - volumetric mesh disk; C - Tenax-bed (10 mg); d - 1.6 mm O.D. and 1.4 mm I.D.

including a calibration line, repeatability measurements, comparative tests of five different μ TD-tubes and breakthrough experiments. Further aspects such as linear velocity, porosity, back pressure and full width at half maximum (FWHM) were also discussed.

2. Material and method

2.1. Chemicals

The following solvents were applied: methanol (99.9% purity, Sigma-Aldrich, France), acetone (99.8% purity, Fisher Scientific, Loughborough, UK) and cyclohexane (ACS, Reag. Ph. Eur., VWR International, Fontenay-sous-Bois, France). Further *n*-alkanes from *n*-pentane to *n*-icosane were purchased from Sigma Aldrich (Steinheim, Germany) with a purity of at least $\geq 98\%$ with the exception of *n*-hexane (97%, VWR, Darmstadt, Germany) and *n*-heptadecane (99%, ThermoFisher, Kandel, Germany) (Table S.1, Supplemental material).

Helium (99.999 mol %) and nitrogen (99.999 mol %) were purchased by Air Liquide (Düsseldorf, Germany).

Tenax TA, 80/100 mesh was purchased from Sigma Aldrich (St. Louis, USA).

2.2. Instrumentation

2.2.1. Micro thermal desorption tubes (μ TD-tubes)

μ TD-tubes are made of stainless steel tubes with 1.6 mm O.D. and 1.4 mm I.D. (SWS Edelstahl GmbH & Co. KG, Emmingen-Liptingen, Germany). The tubes were cut into 8 cm long pieces and then deburred. Marking rings are engraved into the material to distinguish between the tubes. Subsequently, the tubes are cleaned with methanol and *n*-hexane, respectively, in an ultrasonic bath for 15 min. The μ TD-tubes are filled with 10 mg of 80/100 mesh Tenax TA.

Initially, some μ TD-tubes were also filled with Tenax TA 60/80 mesh. However, measurements of the pressure drop across the Tenax packaging have shown that the variations between the μ TD-tubes are greater with the coarser Tenax. For this reason, only μ TD-tubes with Tenax TA 80/100 mesh were used in the present study.

In order to hold the Tenax-bed in place, 1 cm long as 'U'-shaped spring wire pieces (0.4 mm diameter) and little disks (4 mm diameter) of a volumetric mesh (VG 230, GKD – Gebr. Kufferath AG, Düren, Germany) are placed in front of and behind the Tenax packaging (Fig. 1). The Tenax-bed is placed from 5 cm of the μ TD-tube towards the lower end (loading side). 10 mg Tenax TA have an approximate length of 2 cm. Freshly filled μ TD-tubes are then regenerated in a tube conditioner (TC-20, Markes International, Llantrisant, U.K.) under the following conditions: 2 h at 320 °C and 0.5 h at 335 °C with a nitrogen flow of 50–100 mL/min. Since the tube conditioner is designed for conventional TD-tubes with an outer diameter of 6 mm, it had to be previously modified for the μ TD-tubes by the institute's scientific workshop (Fig. S.1, Supplemental material).

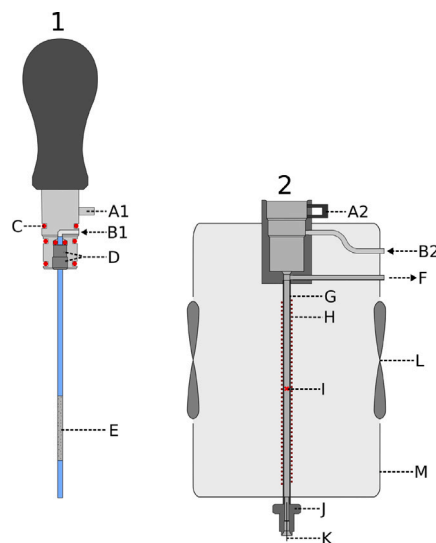


Fig. 2. Schematic drawing of the thermal desorption unit (TDU). 1 - handpiece; 2 - TDU base; A - bayonet lock; B - carrier gas supply (Helium); C - O-ring; D - sleeve and grub screw for holding the μ TD-tube; E - micro thermal desorption tube (μ TD-tube) with Tenax-bed; F - split; G - injector tube; H - heat winding; I - temperature control point; J - transfer line connection; K - transfer line; L - PC fans; M - polymer housing.

2.2.2. Thermal desorption unit (TDU)

The TDU (HyperChrom Deutschland GmbH, Alfter, Germany) consists of two parts, the handpiece (1, Fig. 2) and the TDU base (2, Fig. 2). The μ TD-tube (E) is inserted into the handpiece (1) and it is held by an O-ring as well as a sleeve and a grub screw (D). Via the bayonet lock (A1, A2) and further O-rings (C), the handpiece and the TDU base are connected gas-tight. Closing the bayonet lock automatically starts the measurement via a micro switch. Carrier gas is supplied through B1 and B2. F is the split outlet which can be optionally opened. A heating wire (H) is fixed at the injector tube (G), which is used to heat the TDU. The heating wire is electrically insulated with high-temperature insulating varnish. A thermocouple (I) for temperature control of the TDU is fixed at the center of the heat winding with a ceramic adhesive. To achieve the most even temperature distribution in the TDU, some sections of the stainless steel injector tube are additionally wrapped with aluminum foil. The heating is controlled by a microcontroller (Arduino Uno). A temperature profile along the injector tube (G) is given at different times after the start of heating to a set temperature of 250 °C in Fig. S.2 (Supplemental material). The TDU base is connected to the transfer line (K) by a modified 1/16" Swagelok connector (J). Both, the handpiece and the TDU base are placed into a 3D-printed polymer housing (M) in which two PC fans (L) are built-in for cooling. The use of plastic reduces the heat transfer from the permanently hot transfer line oven underneath (Fig. 3, B). The TDU base body, the tubings B2 and F as well as the components G and J (Fig. 2) are connected by laser welding.

2.2.3. Flow-field thermal gradient GC (FF-TG-GC)

The FF-TG-GC (Fig. 3) setup is almost identical to the instrument described by Chopra et al. [10]. Instead of conventional GCs, an additively manufactured aluminum column fixture (Fig. 3, E) is now used, in which cooling channels are printed. The external water cooler (E200, Lauda, Lauda-Königshofen, Germany) stabilizes the measurement conditions and prevents a heating up of the column fixture (Fig. 3, E) due to heat radiation from the resistively heated capillary. Further, the water cooling allows a reduced cooling phase at the end of a measurement. The separation column temperature is set at the upper IR-sensor (Fig. 3, G). Unlike in Chopra et al. [10], the valve and sapphire nozzle for cryofocusing were not attached with an x-y-z linear translation stage, but can optionally be fixed directly to the GC housing via profile bars.

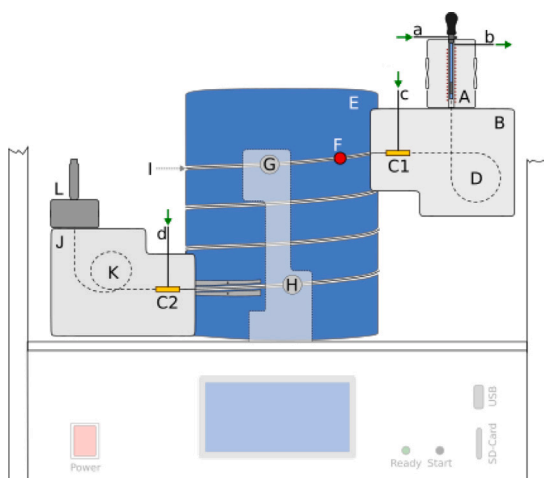


Fig. 3. Schematic drawing of the FF-TG-GC. A - TDU; B - transfer oven; C1/C2 - purged connectors; D - transfer line; E - column fixture; F - potential cryospot; G, H - upper and lower IR-sensor; I - resistively heated capillary; J - transfer oven; K - transfer line to the detector; L - FID

a - carrier gas supply of the TDU (phase I); b - split; c - carrier gas supply of the purged connector C1 (phase 0, II and III); d - carrier gas supply of the purged connector C2.

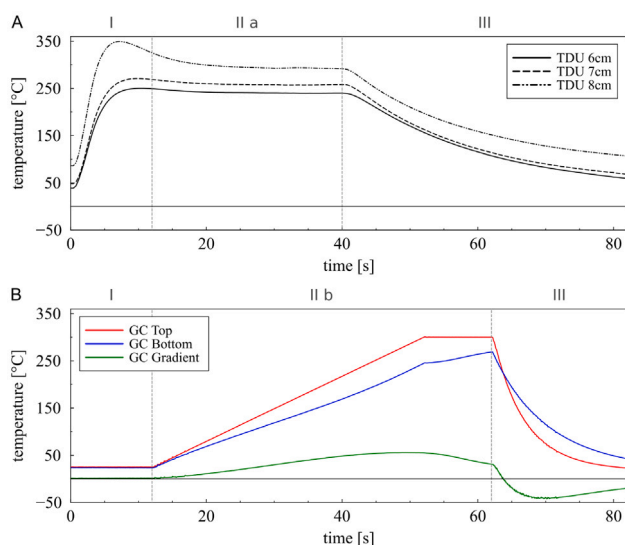


Fig. 4. Temperature program of the TDU (A) and the FF-TG-GC (B). The indicated positions refer to a depth measured from the top edge of the TDU base (Fig. 2, 2), thereby 6 cm corresponds to the upper and 8 cm to the lower end of the Tenax packaging in the μ TD-tube. The transfer oven (Fig. 3, B) had a temperature of 250 °C during temperature monitoring.

2.3. Functional principle

The major advantage of the new thermal desorption setup compared to conventional systems is the substantially reduced desorption time. The basic prerequisite for this is the reduction of the thermal mass of the TDU and the μ TD-tube to a minimum. Thus, extremely fast heating and cooling cycles are possible. Temperatures of 250 °C can be reached within 9 s at the TDU.

The analysis of a μ TD-tube can be divided into three phases (Fig. 4):

- 0 Inserting the μ TD-tube
- I Desorption
 - a μ TD-tube Conditioning
 - b Separation of analytes
- III Cool down

Before starting the analysis, the μ TD-tube is inserted into the TDU (phase 0) and the bayonet lock is closed. The TDU is open during the insertion process. To prevent oxygen from damaging the separation column, the carrier gas is supplied via the purged injector connector (Fig. 3, c) in standby mode. This ensures that only fresh carrier gas reaches the separation column and that the transfer line in C1 is backflushed. A reduced initial pressure in standby mode reduces the loss of helium, while the handpiece is removed.

Throughout the desorption phase (Fig. 4, phase I), the TDU is heated up according to a defined temperature program. Here, both controlled heating ramps and stepwise heating with holding phases at fixed temperatures are possible. During desorption, the carrier gas flows through the μ TD-tube contrary to the direction of analyte loading (Fig. 3, a) and transfers the analytes through the transfer line directly to the separation column. A low helium purge flow is introduced into the connector C1 via a bypass (Fig. 3, c). If the separation column was not looped through, a helium purge flow would also be introduced at C2 by a separate carrier gas line (Fig. 3, d) in order to avoid peak broadening due to non-purged dead volumes. At the end of this phase, the desorption of the analytes is complete.

In phase II, both the conditioning of the μ TD-tubes in the TDU and the gas chromatographic separation of the analytes during the temperature program take place (Fig. 4, II a and II b respectively). At the same time, the carrier gas supply of the system is switched from a to c (Fig. 3) and the split is opened (Fig. 3, b). This has the advantage that only clean carrier gas without impurities reaches the separation column. Moreover, the TDU is backflushed and low volatile impurities are now desorbed and blown out of the split. The settings of the gradient fan are selected in such a way that a temperature difference of 56 °C is reached, since the optimal gradient for a column of 4 m length is between 55 °C and 60 °C, depending on the compound class analyzed [16,17].

In phase III (Fig. 4) the TDU and GC are cooled down. It begins earlier with the TDU, as it cools down more slowly than the GC.

2.4. Determination of porosity

The pressure drop over the packed Tenax TA bed was measured over five different μ TD-tubes at nitrogen flows of 25, 50, 100 and 120 mL/min, which were adjusted with a mass flow controller (5850E Series, Brooks Instrument, Dresden, Germany). The pressure in front of and behind the μ TD-tube was measured with two absolute pressure sensors (Keller PAA-33X/ 10 bar and PAA-21 PHB/ 30 bar, Keller, Winterthur, Switzerland). Then the porosity ϵ was calculated according to Eq. S.1 and S.2 (Supplemental material) which is based on Eq. (1):

$$F = \frac{\pi}{2160} \cdot \frac{d^2 \cdot d_p^2}{L \cdot \eta} \cdot \frac{\epsilon^3}{(1 - \epsilon)^2} \cdot \frac{p_1^2 - p_0^2}{p_0} \quad (1)$$

with the flow rate F , d as the μ TD-tube inner diameter, the particle size d_p , the μ TD-tube length L , the viscosity η , the pressure at the μ TD-tube inlet p_1 and μ TD-tube outlet p_0 [18].

2.5. Preparation of standards

A mix standard of 16 *n*-alkanes from *n*-pentane to *n*-icosane with a target concentration of 0.2 mg/mL was prepared in methanol. The actual concentrations are listed in Table S.1 (Supplemental material).

2.6. Analytical method

2.6.1. Sampling

A direct liquid injection calibration gas generator (CGG) (HovaCAL digital 3435SP-VOC, IAS, Oberursel, Germany) was used to generate a sample gas stream with a constant analyte composition from the liquid stock solution. For this purpose, the stock solution was pumped into the CGG, evaporated there at a temperature of 120 °C and diluted with

compressed air. Detailed information on the CGG settings can be found in Table S.2 (Supplemental material).

A 50 mL original-Perfusor-syringe was equipped with a Discifix-3 three-way valve with connecting line (B Braun, Melsungen, Germany). For sampling, the connecting line was cut off 2 cm behind the Luer Lock connection and the μ TD-tube was pushed with the desorption side into the protruding piece of polymeric tubing. Then the loading side of the μ TD-tube was additionally connected to the calibration gas output a1 at the CGG via a Teflon ferrule. For loading the tube, the 3-way valve of the Luer Lock syringe was opened. The syringe is automatically filled with sample gas due to the overpressure in the CGG and the μ TD-tube is thus loaded at a sampling velocity of 120 mL/min. As soon as the desired sample volume was reached, the valve of the syringe was closed. To analyze sample volumes above 50 mL, the syringe was filled several times. The μ TD-tube was removed from CGG and syringe and it can then be analyzed in the GC. Only a few seconds lie between the end of loading and start of analysis.

A further developed test setup was used for the measurements to compare the μ TD-tubes with each other (Fig. S.3, Supplemental material). Firstly, a large split was installed at the CGG outlet a1 so that the sample could now be drawn at atmospheric pressure. Secondly, the Luer Lock syringe was drawn up with the aid of a stepper motor, allowing the sample to be taken at identical speeds. As soon as the target volume was reached at the syringe, the stepper motor was stopped. Then the μ TD-tube was removed and subsequently analyzed. The syringe was drawn up at a speed of 114 mL/min.

2.6.2. FF-TG-GC-FID analysis

All samples were analyzed with a flow-field thermal gradient gas chromatograph equipped with a TDU (HyperChrom Deutschland GmbH, Alfter, Germany) coupled to a FID (ThermoFischer Scientific, Waltham, USA) and an ultra low noise current meter developed by Wendt et al. [19] (Ackision, Hannover, Germany). The flows of air, helium and nitrogen (makeup gas) at the FID were as follows: 380, 35 and 35 mL/min respectively.

Within 9 s, the TDU is heated from 40 °C to 250 °C and held at that temperature for further 28 s. Subsequently, the TDU is cooled by ambient air. The split was closed during sample desorption.

The FF-TG-GC was fitted with a Rxi-5Sil MS separation column (4.25 m column length, 0.25 mm I.D., 0.25 μ m film thickness, Restek, Bellefonte, USA). The TDU and the separation column are connected via a 19 cm long piece of a methyl deactivated fused silica capillary (0.25 mm I.D., Restek, Bellefonte, USA). Instead of a transfer line to the FID, the separation column was looped through the purged detector connector. The transfer oven and purged connector temperatures (Fig. 3, B and J) are set to 250 °C.

Analytes were performed with the following separation column temperature program: 25 °C held for 12 s (duration of desorption), then with 412.5 °C/min to 300 °C and held for 10 s. The fan settings are selected in order to achieve a gradient of 56 °C during analyte separation (phase II b, Section 2.3). The pressure program at the TDU or purged injector connector (Fig. 3, a and c) was: from 110 kPa to 132 kPa in 2 s, held for 10 s, then in 40 s to 170 kPa and in 1 s to 180 kPa. 180 kPa are held for 9 s. During phase I (Section 2.3), the carrier gas is supplied via the TDU (Fig. 3, a) resulting in a flow of 1.87 mL/min through the μ TD-tube, then after 12 s the carrier gas supply is switched to the purged connector (Fig. 3, c). The flow through the column is approx. 2 mL/min for the duration of the analytical separation. After 53 s of the total runtime, the flow rate is increased to 2.46 mL/min in order to purge remaining impurities. The total runtime of desorption, separation, TDU as well as GC cool down is 82 s.

2.7. Proof of concept measurements

For linearity tests five different gas volumes (25, 50, 75, 100 and 125 mL) were sampled in duplicate and subsequently analyzed. The analyte quantities of the sampled gas volume is presented in Table 2 for all analytes. Sampling velocity was 120 mL/min. Outliers within the calibration line were determined using the Huber test. Linearity was evaluated by testing the goodness of fit according to Mandel.

To determine the method precision, a μ TD-tube was loaded five times with 50 mL of analyte gas respectively and analyzed immediately afterwards.

In addition, breakthrough experiments were carried out in which two tubes were loaded in series with a volume of 100 and 250 mL. The tubes were connected using a 1:1 connector. Due to the increased restriction caused by the simultaneous use of two tubes, the sampling rate was reduced to 74 mL/min.

In all measurements, the sample gas had a concentration of 0.5 ng/mL *n*-decane (leading substance). The samples were taken with a 50 mL Luer Lock syringe at overpressure.

2.8. Inter μ TD-tube repeatability

In order to compare the repeatability of different μ TD-tubes, measurements were carried out as a fivefold determination per individual μ TD-tube. The sample gas stream had a concentration of 1 ng/mL *n*-decane. Samples were taken at atmospheric pressure using the self-built electric sampling pump (Fig. S.3, Supplemental material). During sampling, the syringe was drawn up to a volume of 50 mL.

2.9. Data acquisition

FID data were collected with Meastool (Institute of Electrical Engineering and Measurement Technology, University of Hannover, Germany). Peaks were integrated using Origin 8. For statistical calculations, Microsoft Excel, IBM SPSS Statistics Version 29 and Labor Validate - Labormethoden-Validierung Version 2.8 (LABC - Labortechnik Zillger KG, Hennef, Germany) were used.

3. Results and discussion

3.1. Thermal desorption background

3.1.1. Optimization of μ TD-tube

In combination with a fast GC and thus short analysis times in the range of seconds to few minutes, a usual desorption period of 10 min is too time consuming and thus not efficient [3–5]. Therefore, our aim was the reduction of desorption time by significantly decreasing the thermal mass of the TDU as well as the TD-tube.

Conventional TD-tubes have an inner diameter of several millimeters (usually either 4 or 5 mm) and contain 100–600 mg of adsorbent material with a pack length of 6 cm depending on tube inner diameter, sorbent type and application [1]. This results in high masses of 10 g (metal) or 4.5 g (glass), depending on the TD-tube material. With 0.33 g the μ TD-tubes developed in this study are significantly lighter.

The μ TD-tubes have a wall thickness of only 0.1 mm but are nevertheless sufficiently insensitive to deformation and therefore stable enough for use. To ensure that the adsorbent packing heats up as quickly and evenly as possible, a small inner diameter of just 1.4 mm was chosen. The construction of μ TD-tubes is therefore more comparable to those of focusing traps, which have a diameter of $\sim$ 2 mm and only contain 10–50 mg of adsorbent [1,2].

Micro traps are another approach for accelerating thermal desorption and avoiding additional focusing steps [15,20]. Inner diameters are typically between 0.25–1.1 mm, thus they are considerably smaller than the μ TD-tubes used. Feng and Mitra [21] investigated the pulse time required for the complete desorption at three microtrap inner

diameters. Pulse times of 1.5 s at 0.53 mm I.D., 4 s at 1.1 mm I.D. and 5 s at 1.3 mm I.D. were required. Another approach of a cryogenic cooled microtrap with low thermal mass comes from Zhang et al. Here, a quartz tube (2 mm I.D.) filled with two different adsorbents is placed in a preconcentration device, which is cooled with cold CO₂ gas and rapidly heated by a heating wire during desorption. In contrast to the present study, the voltage was applied directly to the microtrap. Because the μ TD-tube is removed from the TDU for loading with analytes and then reinserted, a direct connection to a heating voltage is not feasible. For this reason, heat transfer takes place indirectly through heat radiation from the injector tube (Fig. 2, G). Although this process is slower, the analytes can still be desorbed very quickly within just 12 s.

3.1.2. μ TD-tube handling

In contrast to conventional TD systems [22,23], in which the TD-tube is sealed into the gas flow with O-rings, the μ TD-tube is located entirely in the TDU. This means that external contamination of the μ TD-tube surface can get into the measuring system. For this reason, surface contamination, e.g. through skin or glove contact, must be avoided and the μ TD-tube must be handled with tweezers. External scratches that may occur during use are not a problem for contamination, as the μ TD-tube is baked out at the end of each analysis cycle and thus cleaned. If contamination adhering to the outside of the μ TD-tube is still a problem, it is possible to open the split and remove it during the measurement as carried out in part II of this publication (to follow).

3.1.3. Tube flow rate and breakthrough

Breakthrough occurs during the loading of a μ TD-tube when an analyte completely passes the sorbent bed and leaves the tube at the opposite end [1]. It is measured as breakthrough volume (BTV) in units of gas volume per unit adsorbent mass (L/g) [24]. Optimizing the desorption conditions by reducing the μ TD-tube dimensions results in an unavoidable reduction in adsorbent amount and therefore a decrease in breakthrough volumes [15]. For this reason, the safe sampling volume (SSV, Table S.3, Supplemental Material) which corresponds to 2/3 of the breakthrough volume should not be exceeded during sampling [8]. As soon as more than 5% of one or more analytes are found in the backup tube, a breakthrough has occurred [8].

Another factor that influences breakthrough volumes is the tube flow rate (F_c), which is calculated as follows:

$$F_c = 60 \cdot \pi \cdot r^2 \cdot u \cdot \epsilon \quad (2)$$

with the tube radius r , u as the linear velocity and the interparticle porosity ϵ which is given as 0.4 for typical sampling tubes [18,25]. The average porosity calculated for the TD-tubes used in this study (Section 2.4) is 0.51 ± 0.01 .

For 1/4-inch O.D. TD-tubes, flows of 10–200 mL/min with the optimum flow at 50 mL/min are recommended for sampling [8,26]. This corresponds to a linear velocity of 2.1–42.4 cm/s (Table 1). Due to the smaller inner diameter of the μ TD-tubes and taking into account the calculated interparticle porosity of 0.51, the linear velocity is ten times higher for the same flows. With conventional TD tubes, the maximum recommended flow rate of 200 mL/min results in a linear velocity of 42.4 cm/s. If samples are to be taken with a μ TD-tube at the same linear velocity, the flow rate must not exceed 20 mL/min.

Nevertheless, μ TD-tubes were loaded at higher flow rates in this study, since the influence of rapid sampling should be investigated. At 74 mL/min no breakthrough of *n*-octane to *n*-icosane was observed at sample volumes of 100 mL and 250 mL although the corresponding linear velocity of 157.1 cm/s was considerably higher than the recommended maximum sampling velocity for 1/4-inch O.D. tubes. The SSV was only exceeded for *n*-hexane at 250 mL and additionally for *n*-pentane at 100 mL sample volume Table S.3 (Supplemental material). Due to the clearly broadened peak and the coelution of methanol, *n*-pentane, *n*-hexane and *n*-heptane in the chromatogram of the first tube (Fig. 5, red line), it is not possible to determine which of these compounds break through into the second tube on the basis of the second chromatogram (Fig. 5, black line).

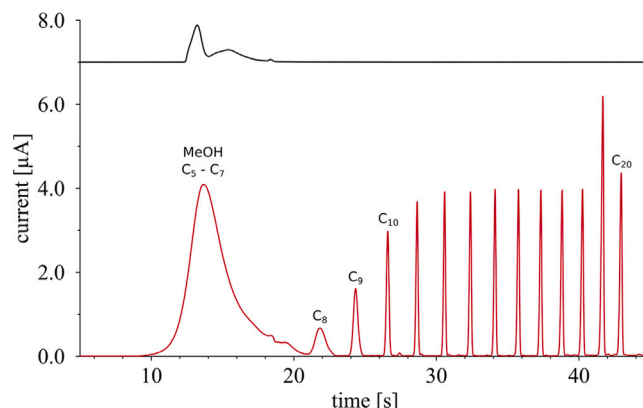


Fig. 5. Chromatograms of an alkane measurement, containing *n*-pentane to *n*-icosane in methanol. Two μ TD-tubes were connected in series during loading. They were loaded with 100 mL of analyte gas. The red line shows the chromatogram of the first, directly loaded μ TD-tube and the black line shows the chromatogram of the backup μ TD-tube. The black chromatogram has an offset of $7 \cdot 10^6$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.1.4. Back pressure

One disadvantage of reducing the internal diameter is the associated increase in pressure drop along the tube [20]. Many battery-operated air sampling pumps have a back pressure capacity of 45–80 mbar [25, 27,28]. This corresponds to sampling flows of 20 mL/min to 37 mL/min for μ TD-tubes. In Table 1 values of pressure drop for different flow rates are shown.

One way to reduce the pressure drop is to use Tenax TA 60/80 mesh instead of 80/100 mesh. However, it should be noted that the fluctuations observed with regard to the pressure drop are significantly greater when comparing several tubes.

3.2. Proof of concept measurements

3.2.1. Full width at half maximum

As shown in Table 2 the full width at half maximum (FWHM) as well as the relative standard deviation (RSD[%]) of FWHM decreases considerably from *n*-octane to *n*-undecane and remains relatively constant thereafter. Feng and Mitra [21] also observed a decrease in FWHM with increasing retention time for the following analytes: methanol, acetone, 1-propanol and 2-butanone. Analytes that elute later are refocused well at the upper end of the column during desorption and before the start of the temperature program. This effect decreases with decreasing retention time or, in this study, with decreasing volatility. Highly volatile analytes begin to migrate while desorption is still ongoing. This causes broad peaks and coelutions as can be seen for methanol, *n*-pentane, *n*-hexane and *n*-heptane in Fig. 5 (red line).

A possible solution for this problem is the use of smaller tube inner diameters, as the FWHM also decreases with decreasing inner diameter [21]. However, this causes an increase in pressure drop along the trap [20]. Another option for improving the resolution and reducing the FWHM is the use of cryofocusing [10].

3.2.2. Linearity and method precision

A five-point calibration was analyzed and the linear regression line was calculated according to the principle of ordinary least squares. All coefficients of determination (R^2) were higher than or equal to 0.995 (Table 2).

To determine the method precision, the 50 mL calibration standard was measured five times in a row. The relative standard deviation (RSD[%]) was between 0.4% and 3.5% (Table 2). Thus, a good precision was obtained for all analytes.

Table 1

Linear velocity u [cm/s] and pressure drop [mbar] at different sampling flow rates [mL/min] for the TD-tube inner diameters of 5 mm and 1.4 mm.

Flow rate [mL/min]	u [cm/s]		Pressure drop [mbar]
	5 mm ^a I.D.	1.4 mm ^b I.D.	1.4 mm I.D.
10	2.1	21.2 ± 0.5	22 ± 3
20	4.3	42.5 ± 1.1	46 ± 6
50	10.6	106.1 ± 2.7	110 ± 14
120	25.5	254.7 ± 6.4	263 ± 35
200	42.4	424.6 ± 10.6	439 ± 58

^a Interparticle porosity = 0.4 [18,25].

^b Interparticle porosity = 0.51 ± 0.01.

Table 2

Analyte quantity in ng that was contained in the sampled gas volume (25 mL to 125 mL) for linearity measurements. Coefficients of determination (R^2) calculated according to the five-point calibration curve. Mean value of full width at half maximum (FWHM) and respective relative standard deviation (RSD [%]) for all calibration measurements. Relative standard deviation as the result of repeatability tests with N=5.

Analyte	Linearity				Repeatability
	m [ng]	R^2	FWHM [s]	RSD [%]	RSD [%]
<i>n</i> -Octane	12.1–60.5	0.995	0.83	20.1	2.4
<i>n</i> -Nonane	12.6–63.1	0.997	0.37	15.6	1.9
<i>n</i> -Decane	12.6–62.8	0.997	0.20	5.4	1.7
<i>n</i> -Undecane	12.4–62.1	0.997	0.16	1.4	1.8
<i>n</i> -Dodecane	12.6–62.9	0.997	0.15	1.8	1.7
<i>n</i> -Tridecane	12.6–62.8	0.997	0.15	2.4	1.4
<i>n</i> -Tetradecane	12.7–63.4	0.997	0.15	2.3	0.8
<i>n</i> -Pentadecane	12.7–63.3	0.998	0.15	2.6	0.9
<i>n</i> -Hexadecane	12.6–63.2	0.998	0.16	2.2	0.6
<i>n</i> -Heptadecane	12.6–62.9	0.998	0.16	2.4	0.4
<i>n</i> -Octadecane	12.6–62.9	0.998	0.16	2.5	1.4
<i>n</i> -Nonadecane	20.5–102.3	0.997	0.17	5.6	2.3
<i>n</i> -Icosane	12.7–63.3	0.997	0.16	3.2	3.5

Table 3

Mean area of five replicate measurements per μ TD-tube and residual standard deviation of the four μ TD-tubes (B–E). The values in italics were identified as outliers (Nalimov test). Porosities of individual μ TD-tubes and RSD [%]. The porosity averaged over all μ TD-tubes is 0.51 ± 0.01.

	μ TD-tube					RSD [%]
	A	B	C	D	E	
Analytes	Area ($\cdot 10^8$)					
<i>n</i> -Octane	4.6	4.1	4.0	4.0	3.9	1.4
<i>n</i> -Nonane	5.0	4.6	4.6	4.5	4.5	1.5
<i>n</i> -Decane	5.2	4.7	4.8	4.7	4.6	1.3
<i>n</i> -Undecane	5.1	4.7	4.7	4.7	4.6	1.3
<i>n</i> -Dodecane	5.5	4.9	4.9	5.2	4.7	3.9
<i>n</i> -Tridecane	5.1	4.8	5.0	4.8	4.7	2.6
<i>n</i> -Tetradecane	5.1	4.9	5.0	4.8	4.7	1.9
<i>n</i> -Pentadecane	5.1	4.8	4.8	4.9	4.7	1.1
<i>n</i> -Hexadecane	5.2	4.8	4.7	4.9	4.7	1.8
<i>n</i> -Heptadecane	5.6	4.9	4.7	4.9	4.7	2.5
<i>n</i> -Octadecane	5.9	5.2	5.1	5.2	4.9	2.9
<i>n</i> -Nonadecane	10.6	9.3	9.6	8.7	8.5	5.6
<i>n</i> -Icosane	7.8	6.6	7.0	6.0	6.1	7.3
Porosity						
ϵ	0.52	0.51	0.49	0.51	0.50	2.6

3.2.3. Inter μ TD-tube repeatability

To evaluate the repeatability of various μ TD-tubes, five consecutive measurements were carried out per μ TD-tube. The mean values of the individual measurement repetitions per tube are shown in Table 3. They are very similar for μ TD-tube B–E, whereas the results for μ TD-tube A differ for most analytes. Values marked in italics were identified as outliers (Nalimov test). An examination of all non-averaged measured values using a one-way ANOVA confirmed these results. There is a significant difference between μ TD-tubes A–E ($F(4, 315) = 3.568$, $p = 0.07$), with μ TD-tube A differing from μ TD-tubes D ($p = 0.021$) and E ($p = 0.006$) according to the Tukey-HSD test. No significant difference was found between μ TD-tubes B–E ($F(3, 251) = 0.641$, $p = 0.589$) with a second one-way ANOVA.

Outliers were identified using the Nalimov test and removed from the data set. According to the David test, data was normally distributed for each μ TD-tube and there was homogeneity of variance (Levene's test, $p > 0.05$).

The small inner diameter of the μ TD-tube makes it difficult to fill it evenly with adsorbent. Irregularities such as cavities within the packaging can easily occur unnoticed. Pressure drop was measured across all tubes and porosities were calculated in order to evaluate differences between individual μ TD-tubes. The results of the porosity determination are shown in Table 3. However, it is not possible to explain the differences between the individual μ TD-tubes on the basis of these parameters. For this reason, it is recommended to characterize the tubes before use based on test measurements of a suitable analyte mixture and subsequent comparison of the areas.

4. Conclusion

The aim of this study was to optimize the desorption speed during thermal desorption in order to combine it efficiently with the fast measuring cycles of the FF-TG-GC. To this end, the thermal mass of both the TDU and the μ TD-tube was drastically reduced compared to conventional TD tubes and desorption systems. By controlling the TDU, fixed heating ramps and holding phases are possible.

The new μ TD-tubes have an inner diameter of 1.4 mm, a wall thickness of 0.1 mm and contain 10 mg Tenax TA. An alkane mixture from *n*-pentane to *n*-icosane could be desorbed in 12 s and separated by gas chromatography in a further 50 s. Including the cool down time of the system and the time required to insert a new μ TD-tube, this results in a cycle time of approx. 90–100 s.

n-Octane to *n*-icosane were baseline separated. Coelution and possibly breakthrough occurred under the tested conditions between methanol, *n*-pentane, *n*-hexane and *n*-heptane. One possible solution to this problem is to purge the solvent methanol from the tube with air and to use additional cryofocusing to refocus the analytes at the head of the separation column.

The impact of the new μ TD-tube dimensions on breakthrough, back pressure, porosity, linear velocity and FWHM was investigated and discussed. The optimized μ TD-tube design showed promise in achieving faster desorption times while maintaining analytical precision.

In an upcoming contribution (part II), a method for the thermodesorption of explosives and civil warfare agent (CWA) simulants will be developed and validated.

CRedit authorship contribution statement

Miriam D. Chopra: Writing – original draft, Methodology, Conceptualization. **Florian A. Menger:** Writing – review & editing, Software, Methodology, Data curation. **Benny Duong:** Software, Methodology, Data curation. **Matthias Wüst:** Writing – review & editing, Supervision, Project administration. **Peter Boeker:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Miriam Chopra reports financial support was provided by Federal Ministry of Defence Bonn. Peter Boeker reports a relationship with HyperChrom Deutschland GmbH that includes: board membership, employment, and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at <https://doi.org/10.1016/j.chroma.2024.465039>.

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Appendix C

Third Publication

**A fast thermal desorption unit for micro thermal desorption tubes, Part II:
Method development and validation for explosives and chemical warfare
agent simulants**



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A fast thermal desorption unit for micro thermal desorption tubes, Part II: Method development and validation for explosives and chemical warfare agent simulants

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ABSTRACT

A thermal desorption FF-TG-GC/MS method with a cycle time of just 164 s including cryofocusing, thermal desorption, analyte separation and system cool down was developed for the analysis of ten explosives and six chemical warfare agent (CWA) simulants. Sampling was carried out both in liquid and gaseous form using micro thermal desorption tubes (μ TD-tubes, 1.4 mm I.D., 10 mg Tenax TA). In addition to the desorption conditions, the effects of deactivated μ TD-tubes, the spatial temperature gradient along the separation column and additional cryofocusing to refocus the analytes were evaluated. Limits of detection between 0.17 and 9.18 ng/ μ L and R^2 values ≥ 0.983 for calibration curves (with the exception of PETN) were obtained. Relative standard deviations of mainly <15% were achieved for within day repeatability. The fluctuations in the peak areas were mostly below 20% with between-day repeatability measured across three days.

1. Introduction

The detection of explosives and chemical warfare agents (CWA) is of great importance for public safety, e.g. at national borders, in aviation or public transportation, critical infrastructure or at large events. In recent years, various terrorist assaults as well as the Novichok attacks on Segei and Yulia Skripal (2018) and Alexei Navalny (2020) [1] demonstrate the threat to the global civilian population. Particularly in a suspected case, rapid analysis is essential for deciding on further action and initiating potential measures. In addition to the actual analysis, sample collection and introduction into the analytical system are further time-critical steps.

The aim of this study was to develop a comprehensive method for fast analysis of ten explosives and six CWA simulants. Sample introduction was carried out via micro thermal desorption tubes (μ TD-tubes) and a corresponding thermal desorption unit (TDU) previously published in part I of this article [2]. Analysis were performed using a flow-field thermal gradient gas chromatograph (FF-TG-GC) with mass spectrometric detection (TOF-MS). Other common detection methods are e.g. ECD [3–5] or IMS [6–8]. This study continues previous projects on the thermal desorption of CWA simulants [9] and on explosives analysis using FF-TG-GC [10].

The analytes investigated have very heterogeneous chemical and physical properties and differ greatly in terms of vapor pressure, boiling point and decomposition temperature (Table 1), which has to be considered during method development. Structural formulas of the respective analytes are shown in Fig. 1. In addition to optimizing the desorption conditions, the effects of μ TD-tube deactivation, the spatial gradient and cryofocusing for analyte refocusing were investigated.

Due to the high toxicity of CWAs, suitable simulants that mimic the chemical and physical properties are necessary for method development [9]. Dimethyl methylphosphonate (DMMP), diethyl methylphosphonate (DEMP) and triethyl phosphate (TEP) were used as simulants for sarin, soman and tabun. Malathion and tributyl phosphate (TBP) are chosen as simulants for VX and tris(2-ethylhexyl) phosphate (TEHP) for the Novichoks.

2. Material and method

2.1. Chemicals

The workgroup of Prof. Klapötke on energetic materials (Department of Chemistry, Ludwig-Maximilians-University, Munich) provided

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Table 1

Abbreviation, name and retention time (t_R) in the chromatogram (Fig. 5) of the explosives and CWA simulants analyzed. Furthermore boiling point (T_{bp} , unless otherwise stated at 1013 hPa), decomposition temperature (T_{dec}) and vapor pressure (p_{sat} , at 25 °C) of the analytes are provided.

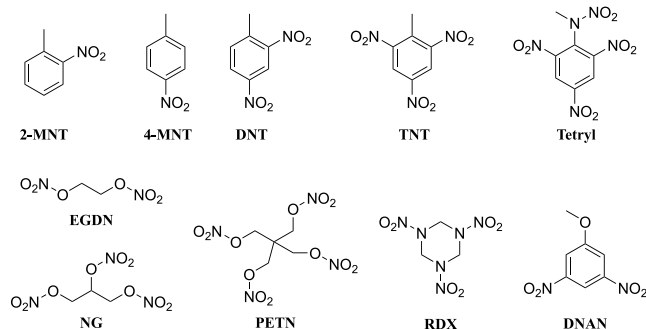
Analyte		t_R [s]	T_{bp} [°C]	T_{dec} [°C]	p_{sat} [hPa]
Explosives					
EGDN	ethylene glycol dinitrate	66.1	197.5 [11]	110 [12]	1.02E-01 [13]
2-MNT	2-nitrotoluene	72.6	222 [12]	232 [14]	1.91E-01 [13]
4-MNT	4-nitrotoluene	75.1	238 [12]	234 [14]	6.52E-02 [13]
PETN	pentaerythritol tetranitrate	76.6	–	157 [14]	1.54E-08 [13]
NG	nitroglycerin	79.6	245 [11]	167 [14]	6.41E-04 [13]
DNT	2,4-dinitrotoluene	85.4	–	>250 [12]	3.51E-04 [13]
TNT	2,4,6-trinitrotoluene	89.9	–	306 [14]	7.33E-06 [13]
DNAN	2,4-dinitroanisole	91.5	206 ^a [15]	–	3.40E-06 [16]
RDX	hexogen	94.2	–	208 [14]	3.49E-09 [13]
tetryl	N-methyl-N,2,4,6-tetranitroaniline	99.1	–	190 [14]	8.68E-09 [13]
CWA simulants					
DMMP	dimethyl methylphosphonate	58.9	181 [17]	–	1.11E+00 [17]
DEMP	diethyl methylphosphonate	65.3	192 [17]	–	5.59E-01 [17]
TEP	triethyl phosphate	70.5	215 [12]	–	4.0 E-01 [18]
TBP	tributyl phosphate	88.4	293 [12]	140 [12]	1E-03 [18]
malathion	[(Dimethoxyphosphinothioyl)thio]-butanedioic acid diethyl ester	96.4	156 ^b [15]	dec [15]	1.37E-03 [19]
TEHP	tris(2-ethylhexyl) phosphate	107.7	215 [11]	190–233 [20]	2.1E-07 [21]

dec: decomposition is observed at the stated boiling point.

^a At 12 mmHg.

^b At 0.7 mmHg.

Explosives



Chemical warfare agent simulants

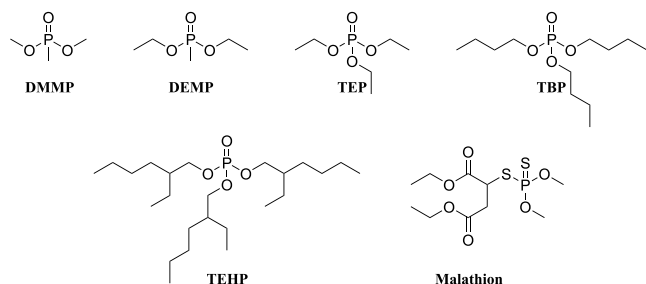


Fig. 1. Structural formulas of investigated analytes.

stock solutions in methanol or acetone, containing the following explosives: ethylene glycol dinitrate (EGDN), 2-nitrotoluene (2-MNT), 4-nitrotoluene (4-MNT), pentaerythritol tetranitrate (PETN), nitroglycerin (NG), 2,4-dinitrotoluene (DNT), 2,4,6-trinitrotoluene (TNT), 2,4-dinitroanisole (DNAN), hexogen (RDX) and N-methyl-N,2,4,6-tetranitroaniline (tetryl).

In addition, these chemical warfare agent (CWA) simulants were used: dimethyl methylphosphonate (DMMP, 97%, Aldrich Chemistry, St. Louis, USA), diethyl methylphosphonate (DEMP, 97%, Sigma-Aldrich, St. Louis, USA), triethyl phosphate (TEP, ≥ 99.8%, Sigma-Aldrich, St. Louis, USA), tributyl phosphate (TBP) and tris(2-ethylhexyl)

phosphate (TEHP, for synthesis, Merck, Darmstadt, Germany) and malathion (≥ 98.0%, Sigma-Aldrich, St. Louis, USA).

The following solvents were applied: methanol (99.9% purity, Sigma-Aldrich, France), acetone (99.8% purity, Fisher Scientific, Loughborough, UK) and cyclohexane (ACS. Reag. Ph. Eur., VWR International, Fontenay-sous-Bois, France).

Helium (99.999 mol%), nitrogen (99.999 mol%) and liquid carbon dioxide (99.7 vol%) were purchased from Air Liquide (Düsseldorf, Germany). The liquid carbon dioxide was taken from a gas cylinder with a dip tube. Tenax TA 80/100 mesh was purchased from Sigma Aldrich (St. Louis, USA).

2.2. Thermal desorption setup

For sampling and sample introduction into the FF-TG-GC low thermal mass micro thermal desorption tubes (μ TD-tubes) and a thermal desorption unit (TDU, HyperChrom Deutschland GmbH, Alfter, Germany) were used (Figs. 2 and 3). The construction and mode of operation are explained in part I of this publication [2].

Additional μ TD-tubes were fabricated from raw materials (tubing and volumetric mesh) that were deactivated with a SilcoNert coating by Silcotek (Bellefonte, USA) using the same procedure as described by Chopra et al. [2]. The volumetric mesh (VG 230, GKD - Gebr. Kuffenrath AG, Düren, Germany) is made of stainless steel and has a surface area of 236 dm²/m², which corresponds to a surface area of 118.63 mm² per 4 mm diameter disk. The inner surface of the μ TD-tube without filling is 3.5 cm². 10 mg Tenax TA 80/100 mesh have a surface area of 3500 cm² [22], which corresponds to an area ratio to the tube surface of 994.7.

2.3. Functional principle

The TDU can be heated up and cooled down very quickly due to its small thermal mass. In combination with the μ TD-tubes, a rapid desorption of the analytes is enabled.

The functional principle of the injector is described in detail in part I of the publication [2]. Only differences due to the different method are explained here.

The analysis of a μ TD-tube with an additional refocusing step by cryofocusing is divided into five phases (Fig. 4):

- 0 Inserting the μ TD-tube
- I Pre-cooling

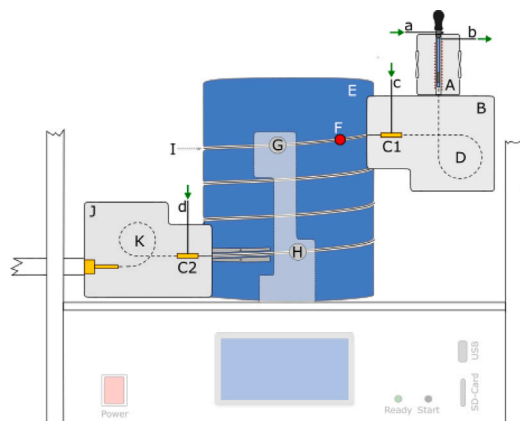


Fig. 2. Schematic drawing of the FF-TG-GC. A - TDU; B - transfer oven; C1/C2 - purged connectors; D - transfer line; E - column fixture; F - cryospot; G, H - upper and lower IR-sensor; I - resistively heated capillary; J - transfer oven; K - transfer line to the detector; a - carrier gas supply (phase I-III); b - split; c - carrier gas supply (phase III and IV). d - carrier gas supply for purged connector.

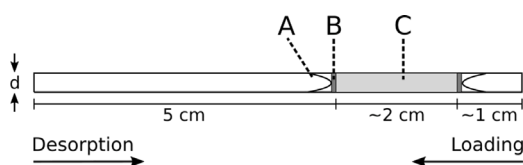


Fig. 3. Schematic drawing of the micro thermal desorption tube (μ TD-tube). Loading and desorption of analytes occur in opposite directions. A - spring wire, B - volumetric mesh disk; C - Tenax-bed (10 mg); d - 1.6 mm O.D. and 1.4 mm I.D.

II Desorption and analyte refocusing

III Separation of analytes/ TUD cool-down

IV GC cool down

Phases 0, II, III and IV are respectively equivalent to phases 0, I, II and III from Chopra et al. [2].

In phase I (Fig. 4, I), the cryospot is pre-cooled at the top of the separation column and temperatures of around -50°C are reached.

Then, in phase II (Fig. 4, II) the TDU is heated up and thermal desorption occurs in reverse sampling direction. High helium flows in combination with an open split are used to accelerate the desorption process. In order to avoid band broadening of the more volatile analytes, the cryospot is used for refocusing [23].

At the end of this phase, desorption is completed and the analytes are trapped at the cryospot. Furthermore, the μ TD-tube is conditioned and ready for reuse.

At the start of the GC temperature program (Fig. 4, phase III), the cryospot is re-heated by the resistively heated capillary. The analytes are released and separated. At the end of the FF-TG-GC temperature ramp the carrier gas supply is switched from the TDU to the purged connector C1 in order to backflush the transfer line and the injector to remove remaining impurities.

TDU and FF-TG-GC are cooled down in phase III and IV, respectively (Fig. 4).

2.4. Preparation of standards

Two groups of analytes are part of this study: CWA simulants (DMMP, DEMP, TEP, TBP, TEHP, malathion) and explosives (EGDN, 2-MNT, 4-MNT, PETN, NG, DNT, TNT, DNAN, RDX, tetryl). Individual CWA simulant standards with a concentration of 20 mg/mL were prepared in methanol. The single standards provided by the workgroup of Prof. Klapötke had a concentration of 20 mg/mL in methanol. Only PETN, RDX and tetryl were dissolved in acetone instead.

For a common stock solution (S1) of all CWA simulants and explosives, different target concentrations for the individual analytes were selected in order to achieve similar areas in the chromatogram. The respective concentrations are shown in Table S.1 (supplemental material). TNT was defined as the reference substance with a concentration of $100.3\text{ }\mu\text{g/mL}$ in S1. Therefore, the indicated concentrations refer to the TNT concentration of the respective dilution level. An intermediate dilution with 10 ng/mL TNT (S2) was prepared from S1.

2.5. Analytical method

2.5.1. Liquid sample application

For liquid sample application, the μ TD-tube is inserted with the desorption side into the polymeric connecting line of a 50 mL original-Perfusor-syringe with a Discifix-3 three-way valve (B Braun, Melsungen, Germany). $1\text{ }\mu\text{L}$ of the respective standard solution is injected from the loading side of the μ TD-tube onto the volumetric mesh disk (Fig. 3) using a $1\text{ }\mu\text{L}$ syringe (Hamilton, Whittier, USA). To remove the solvent and to transport the analytes to the Tenax TA bed, the μ TD-tube is subsequently flushed with 50 mL air by drawing up the syringe. The setup with stepper motor used in part I of the publication is used to pull up the syringe [2].

2.5.2. Adsorbent tube injector system

For sampling, an adsorbent tube injector system (ATIS, Supelco, Parsippany, USA) is applied. Nitrogen is used as a carrier gas for the analytes, maintaining a constant flow of 25 mL/min . Since the μ TD-tube is a considerable flow restriction, the nitrogen flow is controlled via a mass flow controller (5850E Series, Brooks, Dresden, Germany). The μ TD-tube is inserted into the ATIS by a teflon reducing ferrule. Via a $1\text{ }\mu\text{L}$ syringe (Hamilton, Whittier, USA), $1\text{ }\mu\text{L}$ of the standard solution is injected into the ATIS. The sample is evaporated at a temperature of 145°C and the loading time of the μ TD-tube is 4 min, resulting in a sample volume of 100 mL.

To determine the best conditions for loading the μ TD-tubes with the analytes investigated in this study, the following settings were previously tested on the ATIS: Nitrogen flows of 25, 50, 75 and 100 mL/min at temperatures of 117, 128, 142 and 147°C respectively. Further, the loading time was varied at a temperature of 145°C and a flow rate of 25 mL/min from 1 min to 5 min, with 1 min increments. To investigate analyte breakthrough when loading the μ TD-tube, additionally two μ TD-tubes were connected in series with the ATIS for different ATIS settings.

All analytes, except TEHP and EGDN, showed larger peak areas with higher ATIS temperatures. A temperature of 145°C was selected for the ATIS, since the equilibration time increases with increasing temperature. At the selected settings, breakthrough occurred only with TEHP ($<10\%$). For loading times of longer than 5 min or flows exceeding 25 mL/min , breakthrough also occurred with DMMP and DEMP and from a loading time of 7.5 min it was additionally observed with RDX and tetryl.

2.5.3. FF-TG-GC/MS analysis

A flow-field thermal gradient gas chromatograph equipped with the TDU and the cryofocusing setup (HyperChrom Deutschland GmbH, Alfter, Germany) coupled with a BenchTOF-Select Time-of-Flight Mass Spectrometer from Markes International (Llantrisant, U.K.) is used for analysis.

For rapid cooling of the cryospot, the liquid carbon dioxide is first released in an initial pulse of 4 s, followed by 70 cycles of 0.15 s spray duration and 0.35 s pause to keep the temperature at approx. -50°C . In total, this results in a cryofocusing duration of 39 s.

The temperature program of the TDU starts with a 4 s hold time of the initial temperature (44°C), because meanwhile the cryospot is cooled down (phase I). In addition, the oxygen that entered the system when the μ TD-tube was inserted is removed during this time.

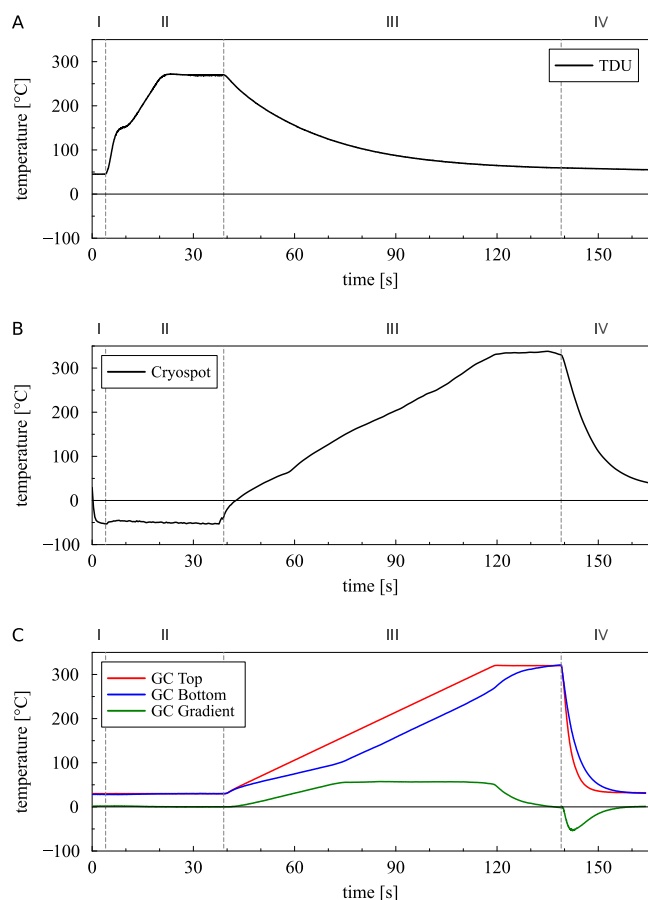


Fig. 4. Temperature program of the TDU (A) the Cryospot (B) and the FF-TG-GC (C).

Then the TDU temperature is increased from 44 °C to 150 °C in 3.5 s (30.3 °C/s), held for 1.5 s, then in 10 s to 270 °C (12 °C/s) and held for further 20 s (phase II). Subsequently, the TDU is cooled by ambient air (phase III). The sample is desorbed from the μ TD-tube at a flow rate of 15.9 mL/min and then transferred to the separation column at a flow rate of 0.87 mL/min.

The GC is fitted with a Rxi-5Sil MS separation column (4.0 m column length, 0.1 mm I.D., 0.1 μ m film thickness, Restek, Bellefonte, USA). TDU and separation column as well as separation column and TOF-MS are respectively connected via a 15 cm and 46 cm long methyl deactivated fused silica capillary (0.1 mm I.D., Restek, Bellefonte, USA). The transfer oven temperatures (Fig. 2, B and J) are set to 190 °C. The transfer line to the TOF-MS has a temperature of 225 °C and the ion source of 250 °C, electron ionization occurs with a voltage of 70 eV.

Analyses were performed with the following separation column temperature program: 30 °C held for 39 s (duration of cryospot pre-cooling and desorption), then with 217.5 °C/min to 320 °C and held for 20 s, with the column temperature set at the upper IR-sensor (Fig. 2, G). During separation, a temperature gradient of 14 °C/m (in total 56 °C) is reached along the separating column as quickly as possible. For a 4 m long column, the optimum gradient is between 55 and 60 °C [24,25].

The pressure program at the TDU or purged injector connector (Fig. 2, a and c) was: from 200 kPa to 380 kPa in 2 s, held for 37 s, then in 80 s to 570 kPa and in 5 s to 600 kPa, 600 kPa are held for 15 s. The carrier gas is supplied via the TDU (Fig. 2, a). After 119 s (in phase III, Fig. 4) the carrier gas supply is switched to the purged connector (Fig. 2, c). The pressure at the carrier gas supply line for the purged detector connector (Fig. 2, d) is constant at 230 kPa.

The analytes are separated at a carrier gas flow rate of 0.8–0.9 mL/min. The total runtime of cryofocusing, desorption, separation and GC cool down is 164 s.

2.6. Method development

2.6.1. Desorption conditions

The following temperature ramps were tested to determine the ideal desorption conditions: From 44 °C to 150 °C in 3.5 s, held for 1.5 s, in X s from 150 °C to 270 °C and held for 20 s, with X = 5, 10, 15, 20 and 25 s resulting in heating rates of 24, 12, 8, 6 and 4.8 °C/s. 1 μ L of the explosive mix S2 (containing 10 ng/mL TNT) was added to the μ TD-tube in liquid form. A triplicate determination was carried out.

2.6.2. μ TD-tube deactivation

To ascertain the influence of the SilcoNert coating on peak areas, comparative measurements were carried out as a tenfold determination using both a deactivated and a non-deactivated μ TD-tube. This experiment was conducted for both liquid and gaseous sample application via ATIS. In both cases the μ TD-tube was loaded with 1 μ L of the explosive mix S2 (10 ng/mL TNT).

2.6.3. Cryofocusing and spatial temperature gradient

To evaluate the effects of the spatial temperature gradient and cryofocusing, comparative measurements with and without gradient as well as with and without cryofocusing were carried out in triplicate, using liquid sample introduction (1 μ L explosive standard S2, 10 ng/mL TNT) and deactivated μ TD-tubes. In the case of measurements without a spatial temperature gradient, the heating rate of the GC was adjusted so that the elution time of TEHP is the same as for measurements with a gradient (retention time locked).

2.7. Method validation

The limits of detection and quantification (LOD and LOQ) were estimated according to the calibration line method from DIN 32645 [26]. For this purpose, the following calibration solutions were prepared from S2: 0.5 ng/mL to 5 ng/mL (increment 0.5) and additionally 6, 7, 8 and 9 ng/mL. A calibration line with 14 standards in the range of the detection limit was measured in triplicate.

To determine the linearity, measurements were conducted in triplicate at the following TNT concentration levels: 5, 10, 15, 20, 25, 30, 35, 45, 55, 65, 75, 85 and 95 ng/mL. The two lowest standards for linearity measurements were prepared from S2, all others from S1.

Repeatability experiments were carried out to determine both intra-day precision and inter-day precision across three different measurement days. Ten consecutive measurements with a concentration level of 10 ng/mL (TNT) were carried out per measurement day.

In all experiments, 1 μ L of the corresponding analyte solution was injected into the ATIS. The sample was applied to a deactivated μ TD-tube in gaseous form.

2.8. Data acquisition

TOF-MS was controlled with ProtoTOF (Markes International). For automated analyte peak integration and background subtraction of the chromatograms via dynamic background compensation (DBC) the software Xcalibur (Thermo Fisher) was used. For statistical calculations, Microsoft Excel, IBM SPSS Statistics version 29 and LaborValidate - Labormethoden-Validierung version 2.8 (LABC - Labortechnik Zillger KG, Hennef, Germany) were used.

Table 2

Influence of μ TD-tube deactivation: ratio of the averaged peak areas of the deactivated to the non-deactivated μ TD-tube (Area ratio [%]) and the relative standard deviations (RSD [%]) of the respective measurement series. The samples were applied to the μ TD-tube both in gaseous form via the ATIS and in liquid form using a syringe.

Area ratios in bold indicate a significant difference between the areas of a deactivated and a non-deactivated μ TD-tube, according to the Welch test ($p < 0.05$). A * marks measurement series for which the normal distribution according to Shapiro–Wilk test is not given ($p < 0.05$). Outliers were identified using the Nalimov test and removed from the data set beforehand. Detailed results of the Shapiro–Wilk test and the Welch test are shown in Table S.2 (supplemental material).

Analyte	Liquid injection		ATIS			
	Area ratio [%]	RSD [%]		Area ratio [%]	RSD [%]	
		Desact.	Not desact.		Desact.	Not desact.
Explosives						
EGDN	287	5.7	20.6	247	2.4	8.5
2-MNT	106	1.7	4.2	99	4.9	2.3
4-MNT	111	2.6	6.0	99	4.9	3.3
PETN	1634	9.3	37.5	629	26.4	26.7
NG	951	10.5	34.3	319	3.6	15.0
DNT	115	3.0	5.6	101	5.2	5.0
TNT	123	0.8	7.5	108	5.3	2.7
DNAN	130	2.3	8.7	110	6.9	6.3
RDX	220	9.4	16.5	174	23.9	27.1*
tetryl	174	12.5	31.4	144	14.1	26.2
CWA simulants						
DMMP	97	4.1*	5.0	102	6.2	5.3
DEMP	102	0.6	6.0	105	5.9	1.8
TEP	116	3.7	6.1	106	5.9	6.2
TBP	167	5.5	6.2	118	3.4	7.7
malathion	237	21.1	14.9	131	9.2	16.0
TEHP	541	12.1	24.3	127	22.1	21.1

3. Results and discussion

3.1. Method development

3.1.1. Desorption conditions

The evaporation and decomposition temperatures of the individual analytes differ greatly, with a temperature difference of 183 °C between the least volatile ($T_{bp, max.}$ (TBP)) and the most sensitive analyte ($T_{dec, min}$ (EGDN), Table 1). For this reason, it was not possible to determine a uniform desorption temperature for all analytes. The approach of running through different temperature stages during desorption has led to good results, but extremely long desorption times of 130 s (30 s at 170 °C, 50 s at 205 °C and 50 s at 240 °C). Therefore, a temperature ramp was selected for desorption. Only RDX showed an increase in peak area of approx. 30% with a reduction in the heating rate from 24 °C/s ($X = 5$ s) to 12 °C/s ($X = 10$ s). A consecutive reduction in the heating rate did not show any further improvement. For the other analytes, the peak area was not influenced considerably by different heating rates. Thus a heating rate of 12 °C/s ($X = 10$ s) was selected.

During method development split ratios of no split, 1:1, 1:10 and 1:20 have been tested. Finally, a split ratio of 1:20 was chosen, because analytes are transported out of the μ TD-tube more quickly and desorption is accelerated due to higher carrier gas flow rates (0.78 ml/min at no split, 3.84 ml/min (1:4), 8.41 ml/min (1:10) and 15.94 ml/min (1:20)). Faster removal of the analytes from the hot μ TD-tube is particularly advantageous for temperature-sensitive explosives and CWA simulants. Moreover, the signal to noise ratio increases with increasing split ratio.

3.1.2. μ TD-tube deactivation

To assess the influence of μ TD-tube deactivation on the peak area, ten replicate measurements were performed with liquid and gaseous sample application for both a deactivated and a non-deactivated μ TD-tube respectively. Results of the experiments are presented in Table 2. The chemically inert surface of the coating on the μ TD-tube surface and the volumetric mesh disk reduces the probability of chemical reactions and adsorption [27]. This effect is most pronounced with the thermolabile analytes PETN, NG and EGDN resulting in high area ratios

of 1634%, 951% and 287% (liquid) as well as 629%, 319% and 247% (ATIS).

According to the Welch test ($p > 0.05$) there is no significant effect of the deactivation coating on the peak area of DMMP and DEMP (liquid sample application) and 2-MNT, 4-MNT, DNT, DMMP and TEP (ATIS). This is also reflected in the corresponding area ratios of 100 ± 6 . One possible reason for this is their lower sensitivity to thermal decomposition (compare T_{dec} , Table 1) whereby the effect of the μ TD-tube coating on these analytes is reduced.

In general, area ratios for most analytes are smaller when samples are applied using ATIS. This effect is most pronounced with TEHP, as the area ratio is 4.3 times higher with liquid than with gaseous sample application.

For liquid sample application, the sample is injected with a syringe directly into the μ TD tube either on the tube inner wall or on the volumetric mesh. Because of the small inner diameter of the tube, exact positioning of the syringe is not possible. Due to the high boiling points, TEHP and the other analytes remain more on the inner μ TD-tube wall and the volumetric mesh disk (Fig. 3) and, in contrast to gaseous sampling via ATIS, are not or only partially transported into the Tenax TA packaging. Therefore, the deactivated surface has a much greater effect on desorption and thus peak areas with liquid sample application compared to gaseous sampling.

In addition to the peak area, deactivation also influences the relative standard deviation. The big difference in the surface areas of the μ TD-tube compared to the volumetric mesh, is a possible reason for the relatively high RSD [%] of the measurements with a non-deactivated μ TD-tube in liquid sampling (Table 2). The RSD [%] values for the explosives are significantly higher than the corresponding values determined with gaseous sampling (via ATIS). Presumably, the decomposition of the explosives on the mesh is significantly faster than on the tube wall due to the 33.7 times larger surface area. By using deactivation, the RSD [%] of the measurements with liquid sample application is reduced to a level comparable to or even better than the corresponding ATIS measurements. Only for nitroglycerine is the RSD [%] for the measurements with liquid sample application significantly higher than for gaseous sample application. RSD [%] are lower for liquid sample application compared to gaseous sample application and a

Table 3

Influence of the gradient: ratio of the averaged peak areas of measurements with and without a gradient (Area ratio [%]), as well as the respective relative standard deviations (RSD [%]) and elution temperatures (T_{elu}). The samples were applied to the μ TD-tube in liquid form using a syringe.

Area ratios in bold show a significant difference between the areas of measurements with and without a gradient, according to the Welch test ($p < 0.05$). A * marks measurement series for which the normal distribution, according to Shapiro Wilk test, is not given ($p < 0.05$). Detailed results of the Shapiro–Wilk test and the Welch test are shown in Table S.3 (supplemental material).

Analyte	Area ratio [%]	RSD [%]		T _{elu} [°C]	
		Gradient	No gradient	Gradient	No gradient
Explosives					
EGDN	116	2.7	6.0	86.7	122.6
2-MNT	101	3.7	4.0	98.8	141.3
4-MNT	104	3.3	4.3	105.9	148.7
PETN	154	3.6	17.1	111.0	153.3
NG	128	5.4	11.0	121.4	163.8
DNT	110	4.9	5.9	141.9	186.4
TNT	114	7.6	9.2	158.5	203.4
DNAN	116	8.4	11.1	164.5	209.6
RDX	263	8.5*	13.1	175.3	220.5
tetryl	162	11.1	29.7	191.1	237.4
CWA simulants					
DMMP	92	13.5	4.7	75.7	103.2
DEMP	96	11.6	7.7	85.3	120.6
TEP	90	9.0	5.6	93.9	135.1
TBP	105	7.6	7.4	152.7	197.4
malathion	102	6.6	13.1	181.2	226.8
TEHP	112	5.7	7.8	220.8	268.9

respective deactivated μ TD-tube, with the exception of malathion. The difference (Δ RSD [%]) is greatest for EGDN (14.9%), PETN (28.2%), NG (23.8%), tetryl (18.8%) and TEHP (12.2%). When samples are applied using ATIS, the standard deviations of the deactivated and non-deactivated μ TD-tube are comparable, with the exception of EGDN (6.1%), NG (11.4%), tetryl (12.1%) and malathion (6.8%).

The large non-deactivated surface area of the ATIS glass body and the increased temperature of 145 °C are additional factors affecting peak area, leading to analyte losses due to decomposition and adsorption even before the μ TD-tube is loaded.

3.1.3. Spatial temperature gradient

For all explosives besides 2-MNT and 4-MNT, an increase in the area ratio of at least 10% was observed for measurements with a gradient. This increase is most pronounced and statistically significant according to the Welch test ($p < 0.05$) for EGDN, PETN, NG, RDX and tetryl with respective area ratios of 116%, 154%, 128%, 263% and 162%. Furthermore, the standard deviations of these analytes for measurements with a gradient are on average 2.6 times lower than for measurements without a gradient (Table 3).

This is caused by the lowering of the elution temperature due to the spatial thermal gradient: with EGDN and RDX, the elution temperature is lowered below the decomposition temperature. Although the elution temperature for PETN and NG is already just below the decomposition temperature for measurements without a gradient (3.7 °C and 3.2 °C respectively), the further reduction in the elution temperature through the use of the gradient also leads to an increase in the peak area. For tetryl, both elution temperatures are above the decomposition temperature. As already reported by Leppert et al. [10], only the decomposition product N-methyl-2,4,6-trinitroaniline (TNA) can be detected in the mass spectra due to the complete degradation of tetryl. Nevertheless, the gentler conditions during the analytical separation with gradient lead to a significant increase in the peak areas, as it reduces the further decomposition of TNA. No improvement in peak area was observed for 2-MNT and 4-MNT since both elution temperatures are well below the decomposition temperature.

With the CWA simulants, the use of the gradient has no significant influence on the peak areas. For TBP, malathion and TEHP, the decomposition temperatures are well below the elution temperature both with and without a gradient.

On average, elution temperatures are reduced by 42.2 °C.

3.1.4. Cryofocusing

The use of cryofocusing results in a reduction of FWHM by 39% and 8% for the first eluting components DMMP and DEMF respectively (Table S.4, supplemental material). For all other analytes, it leads to a broadening of the signals, whereby the signals of NG (181.7%), TBP (253.5%) and RDX (209.1%) are broadened the most. The reason for this is the very slow thawing of the cryospot. A temperature rise from –50 °C to 35 °C takes approx. 10 s (8.5 °C/s). However, very fast heating rates (up to 100 °C/s) are required to release the analytes as a sharp band [28]. One way to speed up the reheating process is to apply an additional heating voltage to the cryospot. It is also possible to set a higher temperature at the cryospot by extending the pause between the spray pulses or using a Peltier element. However, it must then be verified whether temperatures of –10 °C to –20 °C, for example, are sufficient to focus DMMP.

DMMP and DEMF are very easily desorbed by Tenax TA but are not completely retarded at a column starting temperature of 35 °C. Without cryofocusing, the peaks are broadened over the duration of the desorption phase. In the course of method development, the cryofocusing settings were optimized. Long desorption phases of 130 s were used at this time. Without cryofocusing, only an extremely broadened peak could be integrated for DEMF and no signal was detected for DMMP. By improving the measurement conditions, the desorption duration could be reduced and thus the use of cryofocusing is no longer absolutely necessary.

3.2. Method validation

3.2.1. Selectivity

To check the selectivity of the measurement system, individual standards of all analytes were determined. In addition to differentiation by retention time, the analytes were also identified using specific ion ratios (Supplemental material, Table S.1). Even in a TIC chromatogram (Fig. 5), the analytes are baseline-separated with the exception of DEMF and EGDN. Peak tailing occurs in the signals of DMMP, DEMF, TEP, TBP, RDX and malathion due to a mismatch between column and analytes

3.2.2. Limit of detection and quantification

Limit of detection (LOD) and limit of quantification (LOQ) were calculated using the calibration line method [26]. Due to the differing concentrations in the standard mix and the strongly varying physico-chemical properties, 5–7 suitable concentration levels were selected for each analyte from the calibration line. The highest calibrator was less than ten times the LOD.

The LODs determined for the explosives range from 0.17 ng/ μ L (2-MNT) to 9.18 ng/ μ L (tetryl) and for the CWA simulants from 0.36 ng/ μ L (TBP) to 6.72 ng/ μ L (TEHP) (Table 4), whereby they correlate approximately with the vapor pressure (Table 1). Another factor influencing the LOD is the sensitivity to thermal decomposition. Decomposition of thermolabile analytes such as EGDN, NG, PETN and tetryl leads to higher LODs compared to values estimated solely on the basis of vapor pressure.

Leppert et al. [10] conducted explosive measurements with liquid injection via FF-TG-GC/MS instead of thermal desorption. The LODs determined in their study, under measurement conditions comparable to those in the present study, are displayed in Table 4 as $m_{LOD, literature}$. The differences in the m_{LOD} s can be attributed, among others factors, to the heat load while thermal desorption. During the TDU temperature program, decomposition temperatures of EGDN (110 °C), PETN

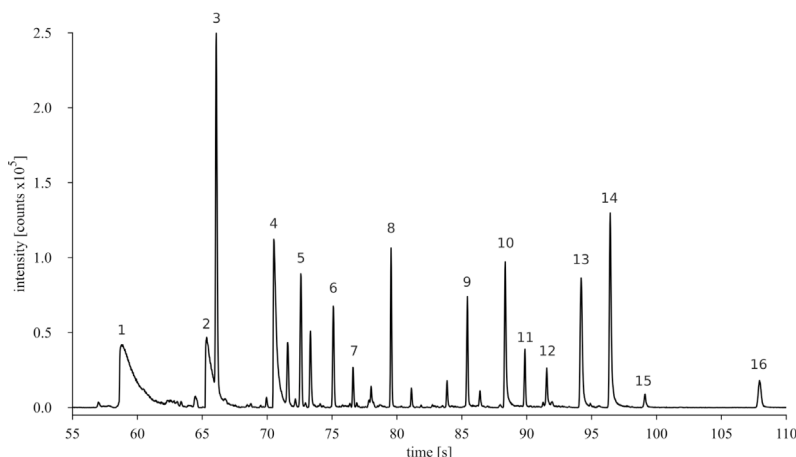


Fig. 5. TIC chromatogram of an explosive and CWA simulant mixture. The chromatogram was recorded using a spatial temperature gradient but without cryofocusing. The concentration in ng/mL of the respective analyte is given in brackets after the abbreviation 1 - DMMP (9.7); 2 - DEMP (9.7); 3 - EGDN (8.0); 4 - TEP (5.0); 5 - 2-MNT (4.0); 6 - 4-MNT (4.0); 7 - PETN (40.6); 8 - NG (10.1); 9 - DNT (8.0); 10 - TBP (5.0); 11 - TNT (10.0); 12 - DNAN (10.0); 13 - RDX (40.1); 14 - malathion (15.0); 15 - tetryl (40.3); 16 - TEHP (10.0).

Table 4

Concentration range c [ng/mL] and coefficients of determination (R^2) of the calibration line used to determine the LOD and LOQ. The calculated LOD and LOQ values are given as concentrations [ng/μL]. For comparability with literature values ($m_{LOD, literature}$ [pg]), the analyte mass on the separation column [pg] was calculated at the respective LOD. These results are given as m_{LOD} . To facilitate comparability, Table S.5 (supplemental material) compares the method used in this study with the methods of Leppert et al. (2018) [10] and Leppert et al. (2012) [9].

Analyte	c [ng/mL]	R^2	LOD [ng/μL]	LOQ [ng/μL]	m_{LOD} [pg]	$m_{LOD, literature}$ [pg]
Explosives						
EGDN	2.8 – 6.4	0.980	1.05	1.96	63.6	3.6
2-MNT	0.2 – 1.0	0.993	0.17	0.41	8.1	1.4
4-MNT	0.2 – 1.2	0.988	0.19	0.46	9.1	2.6
PETN	16.2 – 36.6	0.981	6.00	11.22	295.4	7.6
NG	3.0 – 7.1	0.974	1.31	2.25	64.6	3.5
DNT	0.4 – 2.8	0.980	0.47	1.15	22.7	4.5
TNT	0.5 – 3.0	0.979	0.63	1.50	30.1	25.7
DNAN	3.0 – 7.0	0.953	1.76	2.93	86.6	–
RDX	12.0 – 24.0	0.939	8.89	20.29	438.9	17.2
tetryl	16.1 – 36.3	0.955	9.18	15.23	461.4	61.8
CWA simulants						
DMMP	0.5 – 2.9	0.982	0.56	1.33	27.1	142.5
DEMP	0.5 – 2.9	0.987	0.47	1.14	22.5	105.0
TEP	0.25 – 1.5	0.963	0.42	1.13	20.1	40.0
TBP	0.25 – 1.5	0.973	0.36	0.89	17.3	–
malathion	0.75 – 4.5	0.961	1.30	3.59	62.6	145
TEHP	4.0 – 9.0	0.709	6.72	49.55	330.8	–

(157°C) and NG (167°C) are quickly exceeded. This results in the largest losses for these analytes and detection limits that are two orders of magnitude (factor 17.6–38.8) higher than the m_{LODs} calculated by Leppert et al. [10]. The m_{LODs} of 2-MNT, 4-MNT, DNT and tetryl, however, are one order of magnitude (factor 3.5–7.5) higher as they are not so sensitive to thermal decomposition (T_{dec} between 190°C and 250°C). Despite having a decomposition temperature of 208°C, the factor for RDX is 25.5. For TNT, m_{LOD} is in the same order of magnitude (factor 1.1) since its decomposition temperature is well above the maximum desorption temperature of the TDU (270°C).

The detection limits (m_{LOD}) of the CWA simulants DMMP, DEMP, TEP and malathion are an order of magnitude (factor 0.19–0.5) below the values determined with TD-GC/MS by Leppert et al. [9]. The sensitivity of the new setup is therefore significantly improved compared to a conventional TD-GC/MS system. Further tests with a lower stock solution concentration and longer loading times on the ATIS are necessary to assess whether the tested experimental setup can be used to achieve values below the protective action criteria (PAC) of the U.S. Department of Energy (DOE) [29]. The possibility of analyte breakthroughs must be taken into account during these experiments.

A comparison with other literature values is not provided at this point, as the comparability is not given due to widely differing methods or the use of other analytes.

3.2.3. Linearity

Linearity was evaluated by testing the goodness of fit according to Mandel and a linear regression line was calculated according to the principle of ordinary least squares. Outliers within the measurement repetitions of each concentration level, as well as in the calibration line were identified using the Nalimov and Huber tests, respectively, and removed from the data set.

For the majority of analytes, the coefficients of determination were higher than 0.990 (Table 5). Exceptions to this were EGDN (0.987), 4-MNT (0.988), PETN (0.972), DEMP (0.983) and TEHP (0.986).

3.2.4. Repeatability

To determine the precision within a day, the relative standard deviation of the respective analyte is considered. For almost all analytes RSD [%] is below 15% (Table 5). Exceptions include PETN, with an RSD of 16.4% on day B and RDX, with RSDs of 60.9% on day A and 17.2% on day B.

Table 5

Analyte concentration range (*c*), number of calibration points (*N*) and coefficient of determination (R^2) as results of linearity experiments. Three measurement series (A, B and C) were recorded to assess repeatability. Areas normalized to the mean value of the three measurement series (Area ratio [%]) are used to assess the between-day comparability and relative standard deviations (RSD [%]) for intra-day comparability.

Analyte	Linearity			Repeatability					
	c [ng/μL]	N	R ²	Area ratio [%]			RSD [%]		
				A	B	C	A	B	C
Explosives									
EGDN	8.0 – 52.1	9	0.987	101.1	107.7	91.2	4.9	6.0	5.9
2-MNT	2.0 – 30.2	11	0.993	103.7	107.1	89.2	4.8	4.4	3.3
4-MNT	2.0 – 26.0	10	0.988	103.9	106.5	89.6	3.8	5.9	5.0
PETN	20.3 – 304.7	11	0.972	141.6	87.4	71.0	5.3	16.4	9.6
NG	5.0 – 95.7	13	0.987	121.4	97.3	81.3	4.8	10.0	7.6
DNT	4.0 – 68.3	12	0.992	103.8	106.9	89.3	5.1	8.4	5.7
TNT	5.0 – 95.2	12	0.998	100.3	105.7	93.9	4.4	7.7	5.2
DNAN	5.0 – 75.1	10	0.996	99.9	111.3	88.8	10.1	8.0	6.7
RDX	20.0 – 380.8	12	0.987	33.5	134.3	132.2	60.9	17.2	11.5
tetryl	20.2 – 342.6	11	0.995	114.3	99.5	86.2	9.0	10.1	6.7
CWA simulants									
DMMP	4.9 – 34.0	7	0.995	101.1	104.8	94.1	7.8	7.7	13.9
DEMP	4.9 – 63.1	10	0.983	100.3	108.3	91.4	7.3	5.5	7.5
TEP	2.5 – 47.4	11	0.998	100.3	109.0	90.7	4.6	6.7	8.1
TBP	2.5 – 17.5	7	0.991	93.3	111.6	95.1	9.5	6.5	6.3
malathion	7.5 – 142.5	13	0.991	116.4	97.4	86.2	4.3	9.7	7.6
TEHP	5.0 – 95.0	12	0.986	160.9	71.8	67.3	2.7	12.1	10.7

The mean values of each measurement series (A, B, and C) were normalized to the overall mean across the three series for comparison. The between-day precision is then assessed for each analyte by calculating the maximum difference between the three normalized mean values (largest minus smallest value). The corresponding differences are mostly below 20%. Deviations up to 30% are observed for DNAN (22.4%) and tetryl (28.1%). Extreme day-to-day fluctuations were found at PETN (70.6%), NG (40.0%) RDX (100.8%) and TEHP (93.6%). These results are consistent with those of the previous tests. The analysis using thermal desorption FF-TG-GC/MS is the most challenging for the analytes PETN, NG, RDX, tetryl and TEHP due to thermal decomposition or surface adsorption.

4. Conclusion

The development and validation of a comprehensive thermal desorption FF-TG-GC method for the explosives EGDN, 2-MNT, 4-MNT, PETN, NG, DNT, TNT, DNAN, RDX and tetryl as well as the chemical warfare agent (CWA) simulants DMMP, DEMF, TEP, TBP malathion and TEHP was the aim of this study. It is shown that a small amount of only 10 mg Tenax is enough for the adsorption of a sufficient amount of analyte for the analysis. Thus, long desorption times due to TD-tubes with high thermal masses are not necessary. Very fast measurements can be performed with a cycle time of 164 s including 4 s for pre-cooling the cryospot and only 35 s for thermal desorption.

Due to low decomposition temperatures, low vapor pressures or adsorption on surfaces, EGDN, PETN, NG, RDX, tetryl, malathion and TEHP are particularly challenging to analyze using thermal desorption. The application of deactivated μ TD-tubes and the spatial temperature gradient, which lowers the elution temperature by an average of 42.2 °C, greatly improves the sensitivity of the method, especially for these analytes. Due to the slow heating of the cryospot, only the FWHM of the first two peaks, DMMP and DEMF, are reduced. To avoid broadening of the remaining signals, further optimization of the refocusing setup is necessary.

Low LODs between 0.17 ng/μL and 9.18 ng/μL and coefficients of determination of ≥ 0.983 in linearity tests (exception PETN) were obtained. Relative standard deviations of <15% were achieved for all analytes except PETN and RDX in within-day repeatability tests. Between three different measurement days, the deviations mostly remain below 20%. Deviations up to 30% are observed for DNAN and Tetryl. However, huge deviations are observed for PETN, NG, RDX and TEHP.

CRediT authorship contribution statement

Miriam D. Chopra: Writing – original draft, Validation, Methodology, Conceptualization. **Benny Duong:** Validation, Software, Methodology, Data curation. **Florian A. Menger:** Software, Methodology, Data curation. **Thomas M. Klapötke:** Writing – review & editing, Resources. **Matthias Wüst:** Writing – review & editing, Supervision, Project administration. **Peter Boeker:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Miriam Chopra reports financial support was provided by Federal Ministry of Defence Bonn. Peter Boeker reports a relationship with HyperChrom Deutschland GmbH that includes: board membership, employment, and equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at <https://doi.org/10.1016/j.chroma.2024.465537>.

Data availability

Data will be made available on request.

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Appendix F

List of abbreviations

2-MNT	2-nitrotoluene
4-MNT	4-nitrotoluene
AChE	acetylcholinesterase enzyme
BTV	breakthrough volume [L/g]
CWA	chemical warfare agent
DCM	dichloromethane
DDNP	diazodinitrophenol
DEMP	diethyl methylphosphonate
DMMP	dimethyl methylphosphonate
DNAN	2,4-dinitroanisole
DNT	2,4-dinitrotoluene
EI	electron ionization
EGDN	ethylene glycol dinitrate
FF-TG-GC	flow field thermal gradient gas chromatograph
FID	flame ionization detector
FWHM	full width at half maximum
GMP	good manufacturing practice
GC	gas chromatography
ICH	International Council for Harmonisation
I.D.	inner diameter
LOD	Limit of detection

LOQ	Limit of quantification
MS	mass spectrometer
MtBE	methyl tert-butyl ether
NG	nitroglycerin
O.D.	outer diameter
PETN	pentaerythritol tetranitrate
RDX	hexogen
RS	residual solvent
SSV	safe sampling volume
TBP	dibutylphosphate
TCM	trichloromethane
TEHP	tris(2-ethylhexyl) phosphate
TEP	triethyl phosphate
TD	thermal desorption
TDU	thermal desorption unit
Tetryl	N-methyl-N,2,4,6-tetranitroaniline
TNT	2,4,6-trinitrotoluene
ToF-MS	time of flight mass spectrometer
VOC	volatile organic compounds
μTD-tube	micro thermal desorption tube

Appendix G

List of symbols

d	μ TD-tube inner diameter
d_p	particle size
F_c	flow rate
L	μ TD-tube length
p_i	pressure at the μ TD-tube inlet
p_o	pressure at the μ TD-tube outlet
r	radius
R_s	resolution
u	linear velocity
t_R	retention time [s]
w_b	peak width at baseline level
w_a	weight of adsorbent within a TD-tube
ϵ	interparticle porosity
η	viscosity