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A new silylating reagent – dimethyl(3,3,3-trifluoropropyl)silyldiethylamine – for the derivatisation of non-steroidal anti-inflammatory drugs prior to gas chromatography–mass spectrometry analysis

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ABSTRACT

This paper discusses a new silylating reagent – dimethyl(3,3,3-trifluoropropyl)silyldiethylamine (DIMETRIS) – for the derivatisation of non-steroidal anti-inflammatory drugs (NSAIDs) prior to GC–MS analysis. DIMETRIS reacts with seven target compounds (diclofenac, ibuprofen, ketoprofen, naproxen, flurbiprofen and paracetamol, as well as salicylic acid, a degradation product of acetylsalicylic acid) at 30 °C for 30 min, producing mono-*O*-dimethyltrifluoropropylsilyl (mono-*O*-DMTFPS) derivatives. The mass spectra of these new derivatives are given and fully interpreted. The usefulness of mono-*O*-DMTFPS derivatives for the qualitative and quantitative analysis of NSAIDs using GC–MS is compared with that of trimethylsilyl and methyl analogues. Methyl derivatives are found to be less appropriate for this purpose because they yield the lowest detector responses during GC–MS measurements. Both silyl derivatives are more suitable for determining such NSAIDs, although the matrix effect with mono-*O*-DMTFPS derivatives is smaller. Finally, SPE-GC–MS(SIM) based on the derivatisation of NSAIDs by DIMETRIS is evaluated, validated and applied to the determination of these drugs in sea water (Baltic Sea) and wastewater samples collected in Poland. This work confirms that DIMETRIS is suitable for the trace analysis of NSAIDs in real samples and provides an interesting alternative to silylating and methylating reagents.

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are well-known drugs consumed in huge quantities. This is a large, heterogeneous group of anti-inflammatory drugs, analgesics and antipyretics, commonly known as painkillers, which act by inhibiting cyclo-oxygenase prostaglandin. These pharmaceuticals are among the most frequently detected drugs in environmental water samples [1–4]. The presence of NSAIDs in wastewater samples has been confirmed by many researchers (see Supplementary data, Table 1S, [5–14]) and this aspect continues to be of interest [15]. Concentrations of NSAIDs may be very high, up to 150 $\mu g\,L^{-1}$, in hospital wastewater [5]. Their partial removal in wastewater treatment plants means that their concentrations in effluent wastewaters are at the level of hundreds of $ng\,L^{-1}$ [16]. Despite dilution in rivers and other watercourses and the degradation processes during migration, NSAIDs are still recorded in both surface fresh waters and in sea waters (the final sink) (Table 1S, Supplementary data).

Although NSAIDs are detected in natural waters at low concentrations ($ng\,L^{-1}$–$\mu g\,L^{-1}$), their presence and pseudo-persistent character (continual entry into the environment) may lead to adverse effects in aquatic organisms. For example, prolonged exposure to diclofenac gives rise to its bioaccumulation and toxic effects in fish [17]. It was also found responsible for the catastrophic decline in the White-rumped Vulture (*Gyps bengalensis*) [18].

The methods for determining these pharmaceuticals in environmental samples usually employ separation techniques such as liquid chromatography coupled to mass spectrometry (LC–MS or LC–MS/MS) or gas chromatography coupled to mass-spectrometry (GC–MS or GC–MS/MS) (e.g. [1,6–8,19–21]). Despite the many advantages of LC–MS/MS, particularly the considerable simplification of sample preparation, this technique has some drawbacks, e.g. suppression/enhancement of ESI ionisation can occur, especially when highly complex matrices are analysed [22,23]. The second inter-laboratory exercise on NSAID analysis in environmental

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samples [24] demonstrated that with regard to sensitivity and measurement uncertainty, GC–MS was superior to LC–MS for the analysis of drugs in matrices of greater complexity. The lower cost of GC–MS analysis and the smaller amounts of solvent consumed also favour such an approach. Moreover, the widespread availability of the relevant instruments in laboratories means that GC–MS is an excellent tool for identifying and quantifying pharmaceuticals in environmental matrices and can be implemented much more quickly in routine analysis in environmental laboratories. However, because NSAIDs are polar compounds, these have first to be converted into suitable, volatile derivatives prior to GC–MS analysis.

Up to now, NSAIDs have usually been derivatised by silylation with *N-tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (MTBSTFA) [9,16,25–28], *N,O*-bis(trimethylsilyl) trifluoroacetamide (BSTFA) [26,29–31] or *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) [10,30,32,33], hexamethyldisilazane (HMDS) [34], acylation using pentafluorobenzyl bromide [35], and methylation by diazomethane, trimethylsilyldiazomethane (TMSD) [36–38] or methanol in sulphuric acid solution [39]. In addition, a few researchers have suggested converting NSAIDs into ion-pair complexes (carboxylate ion-pairs) with tetrabutylammonium hydrogen sulphate prior to GC analysis [40,41].

In our previous work, we proposed a new silylating reagent – dimethyl(3,3,3-trifluoropropyl)silyldiethylamine (DIMETRIS) – for the derivatisation of β-blockers and β-agonists [42] and oestrogenic compounds [43] prior to GC analysis. This agent possesses strong nucleophilic properties and reacts selectively with hydroxyl groups. The derivatisation reaction takes place in the absence of any catalyst. By introducing fluorine atoms into the structure of the derivatives, we were able to use GC-ECD to determine some of them.

In this study we decided: (1) to test DIMETRIS as a potential reagent for derivatising NSAIDs, (2) to interpret the mass spectra of the derivatives with regard to their usefulness for the qualitative analysis of NSAIDs, (3) to compare the usefulness of DIMETRIS for the quantitative analysis of NASIDs using GC–MS with that of the standard silylating (BSTFA + 1% TMCS (trimethylchlorosilane) and methylating (TMSD) reagents, (4) to evaluate and validate the SPE-GC–MS method based on the derivatisation of NSAIDs by DIMETRIS for their determination in aquatic environmental samples, and, finally, (5) to apply the suggested method to the analysis of selected drugs in wastewater and sea water (Baltic Sea) in Poland. It should be added that the literature describes just a few methods for determining NSAIDs in sea water because of the problems associated with ultra-trace level analysis [7].

Table 2S (Supplementary data) lists the chemical structures and selected physicochemical properties of the NSAIDs investigated in this study. Most of them are weak acids with pK_a near 4 (apart from paracetamol – pK_a 9.4). The increasing deprotonation of the carboxyl groups with increasing pH converts NSAID molecules into their hydrophilic forms [44,45]. The $\log K_{ow}$ values > 4 suggested that they are lipophilic compounds. However, this parameter was established for neutral forms of these drugs, whereas at environmental pH, $\log K_{ow}$ values are about 1. In water, acetylsalicylic acid is easily degraded to salicylic acid, so it is this compound rather than the native one that should be determined in environmental matrices [24].

2. Experimental

2.1. Chemicals

NSAID standards (>98% pure) – diclofenac sodium salt (DIC), flurbiprofen (FLU), ibuprofen (IBU), naproxen (NAP), ketoprofen (KET), paracetamol (PAR), salicylic acid (SALI, a degradation product of acetylsalicylic acid), as well as two internal standards (2-methylanthracene (IS1) and aminophenazone (IS2), not subjected to derivatisation) – were purchased from Sigma–Aldrich (Steinheim, Germany). TMSD (2.0 M solution in hexane) and a commercial mixture of BSTFA + 1% TMCS (hereafter BSTFA) and chloro-dimethyl(3,3,3-trifluoropropyl)silane (CDMTFPS) were also obtained from Sigma–Aldrich. All organic solvents (methanol, ethyl acetate, toluene, n-hexane and dichloromethane) and 37% hydrochloric acid (HCl) of analytical grade were supplied by Chempur (Piekary Śląskie, Poland).

2.2. Preparation of stock solutions

Stock solutions of the target compounds and aminophenazone ($1\,mg\,mL^{-1}$) were prepared in methanol, that of 2-methylanthracene ($1\,mg\,mL^{-1}$) in dichloromethane. All stock solutions were stored at −18 °C. Working standard solutions were prepared by diluting standard stock solutions in methanol; these were then stored at 4 °C. Working solutions of standards containing $10\,\mu g\,mL^{-1}$ of each target compound and IS1 were also prepared and used for testing the derivatisation procedures. Working calibration standard solutions (the concentration range of the analytes from 0.5 to $50\,\mu g\,mL^{-1}$) were prepared by diluting standard stock solutions containing each of the target compounds in the appropriate amounts in methanol and stored in the dark at <4 °C. To establish the standard calibration curves (see Section 3.4), 50 μL of the working calibration standard solutions and 50 μL of the IS1 solution ($10\,\mu g\,mL^{-1}$) were transferred to 2.0 mL reaction vials, evaporated to dryness under a gentle stream of nitrogen (at ambient temperature), and subjected to derivatisation and GC–MS analysis.

2.3. Derivatisation procedures

2.3.1. Synthesis of DIMETRIS

The synthesis of DIMETRIS was described in detail in our previous paper [39]. It involved the reaction of diethylamine (DEA) with chloro-dimethyl(3,3,3-trifluoropropyl)silane (CDMTFPS). This synthesis was repeated once a week in our laboratory. Briefly, a 2 mL mixture of hexane/acetone (1:1, v/v) and 300 μL DEA was transferred to a 4 mL reaction vial and stirred. Then 300 μL of CDMTFPS was added and the vial agitated for 5 min. Afterwards the mixture was centrifuged for 15 min (2500 rpm). The supernatant (pale yellow) was used as the derivatising reagent.

2.3.2. Derivatisation of NSAIDs by DIMETRIS, BSTFA and TMSD

Working standard solutions containing each target compound and IS1 (50 μL of $5\,\mu g\,mL^{-1}$ solution) and in one experiment also 50 μL IS2 (solution $5\,\mu g\,mL^{-1}$) (see Section 3.2) were transferred to 2.0 mL reaction vials and evaporated to dryness (at ambient temperature) under a gentle stream of nitrogen. The dry residues were derivatised under the conditions stated in Table 1. Each experiment was performed in three replicates. During the optimisation of derivatisation by DIMETRIS, the determinations were carried out using GC-FID; under optimal conditions by GC–MS (five injection replicates in both cases). The trimethylsilyl (TMS) and methyl esters of the target drugs were also analysed by GC–MS (Table 2).

The effectiveness of derivatisation was estimated from the relative response factor (RRF) values established for each derivative with respect to an internal standard that does not undergo chemical conversion (2-methylanthracene), exactly as in our previous study [38]. A higher RRF indicated the greater efficiency and better suitability of the tested method for the trace analysis of the target compounds. The RRFs were presented as the mean of five GC–MS

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