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Stable fluorimetric detection of histamine using o-phthaldialdehyde derivatizing agent and surfactants in water-acetonitrile mixed solvent

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Highlights

- Fast and robust detection of histamine in food using fluorescence detection.
- Surfactants stabilize the derivative of histamine and o-phthaldialdehyde.
- The fluorescent complex is solubilized at the surface of surfactant micelles.

ABSTRACT

A new analytical method for the rapid detection of histamine (HA) in beverages using fluorescence detection has been devised. It is primarily based on the use of *o*-phthalaldehyde (OPA) as a derivatizing agent. This unstable complex has been efficiently stabilized by addition of surfactants. The physicochemical variables that influence the sensitivity of the method and the fluorescence properties of the complex species in surfactant solutions have been optimized. Different surfactants were checked: the anionic sodium dodecyl sulfate, the cationic hexadecyltrimethylammonium chloride and the nonionic tricoso(ethylene glycol)dodecyl ether C₁₂E₂₃. All surfactants stabilize the HA:OPA complex for long times. C₁₂E₂₃ provides excellent stability to the complex and higher fluorescence emission, allowing robust analysis conditions. Linear calibration curves allowing effective histamine determination and low limits of detection and quantification were established and the characteristics of the analysis method was validated. The correlation coefficient for histamine detection by fluorescence was 0.9978. The detection and quantification limits for histamine were 0.576 and 1.92 mg·L⁻¹, respectively.

Keywords: Histamine, *o*-Phthaldialdehyde, Surfactants, Fluorescence detection, Food analysis

1. Introduction

Biogenic amines are essential compounds in living systems that participate in a wide range of biological processes. They are present at significant concentrations in fermented foods such as cheese, fish and wine [1]. Histamine has sparked considerable interest due to its undesirable physiological effects in sensitive humans [2]. Histamine is the cause of most biogenic amine-related food poisoning. Particular attention has been paid to histamine in wines and beers [3,4] where this substance is usually present at low concentrations and can cause severe troubles to human health. For this reason, the development of an efficient method for the analysis of histamine in wine is a challenge that has been addressed in the present study.

Histamine can be analyzed using various biological, chromatographic, and spectroscopic methods. Fluorimetric methods have the highest sensitivity and selectivity [5]. However, direct detection by fluorescence is not possible because histamine lacks a fluorophore allowing strong enough fluorescence emission. This problem was alleviated by using derivatization reactions that convert histamine into a fluorescent derivative [6]. Many fluorescent reagents have early been proposed for the analysis of amine compounds. As instances, 2,3-naphthalenedialdehyde (NDA), 3-(2-furoyl)quinoline-2-carbaldehyde (FQCA), 3-benzoyl-2-quinoline-2-carbaldehyde (BQCA) and 3-(4-carboxybenzoyl)-2-quinoline carbaldehyde (CBQCA) [7] have been checked for the conversion of HA into a fluorescent derivative. The derivatization reactions of these reagents show slow kinetics (15 to 60 min at room temperature) that make their use quite tedious. The two most frequently used reagents for the derivatization of primary amines are *o*-phthaldialdehyde (OPA) known as the Roth's method [8] and fluorescamine (FLC) [9].

The OPA rapidly reacts with primary amines in the presence of a thiol (RSH such as 2-mercaptoethanol). The derivatization reaction is carried out at room temperature for 2 min in aqueous borate buffer (pH 9–11) to generate its fluorescent isoindole derivative [10] (Figure 1). Derivatization using FLC is also a fast reaction operating at room temperature [9] (Figure 2). However, the sensitivity of the method using the FLC is lower than that using the OPA [11]. In both cases, the fluorescent derivatives of HA are not stable [12,13], so that the fluorescence emission decays quite fast (within a few minutes) once the derivatizing reagents have been mixed with HA.

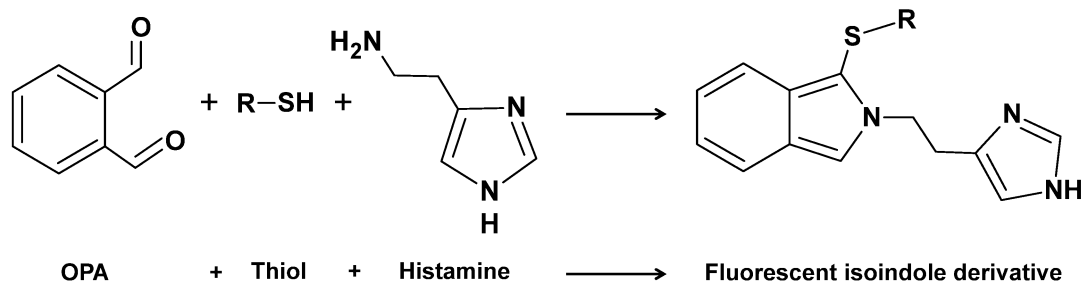


Figure 1. The reaction for the formation of the fluorescent OPA-HA derivative.

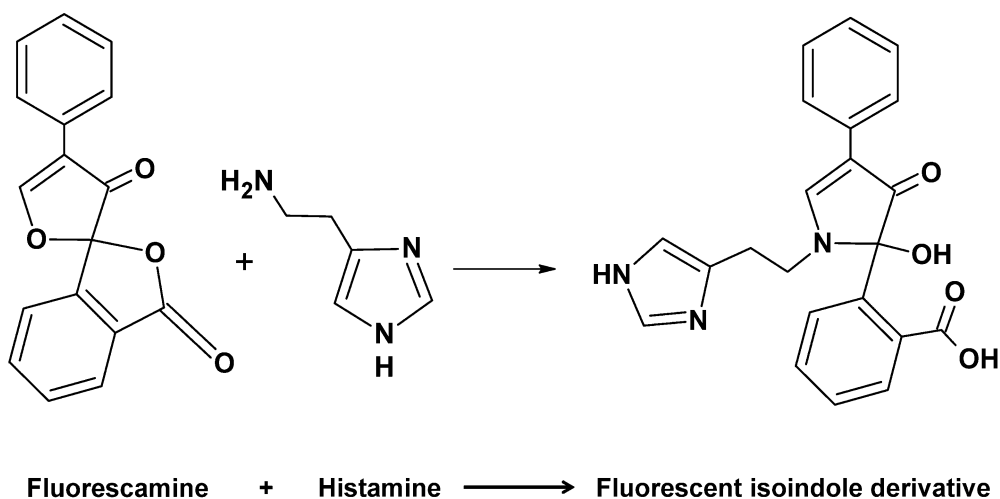


Figure 2. The reaction for the formation of the fluorescent FLC-HA derivative.

Considering to these documented drawbacks, an improved fluorimetric procedure for histamine determination using OPA as a labeling reagent and surfactants has been developed. It was inspired from a previous disclosure regarding FLC derivatives showing that the addition of surfactants increased the fluorescence emission of HA and stabilized the FLC-HA derivative in acetonitrile [14,15]. Surfactants have early been added in an empirical way to the Roth's reagent used in HPLC under post-column derivatization [16,17,18,19]. Any loss of fluorescence by degradation of the OPA-amine derivative is not dramatic when the derivatization is performed post-column of an HPLC because the same loss of fluorescence occurs for the calibration under the same flow rate condition. The degradation of the fluorescent adduct occurs during the short time required for flowing from the post-column injection to the fluorescence detector. The stabilization of the fluorescent adduct allows improving the detection limit. The determination of amines by direct measurement of fluorescence emission in a spectrofluorometer is more challenging because the time spent between the mixing of the amine sample with the Roth reagent and the fluorescence measurement should be the same for all calibration samples and the samples being analyzed. Stabilization of the fluorescent derivative is mandatory in that case.

The stabilization of OPA derivatives of various amines by surfactant micelles in aqueous medium [20] have shown an efficient stabilization of the OPA derivatives of hydrophobic amines that can solubilize inside the hydrophobic core of micelles. Conversely, hydrophilic amines could not be significantly stabilized. Therefore, these attempts aiming at the stabilization of the OPA-HA derivative by surfactant micelles in aqueous medium showed moderate fluorescence enhancements and weak stabilization of the OPA-HA derivative. This interesting study showed that the wavelength of fluorescence emission was corresponding to that in a solvent of medium polarity, suggesting that the stabilization was due to the solubilization of the OPA derivative in surfactant micelles [20]. As a whole, all these experimental results looked conflicting, probably because the experimental conditions were quite variable, especially the types and concentrations of surfactants and solvent media being either pure water or water-alcohol mixtures. On another hand, the stability of the OPA-HA derivative was much better in mixed water-acetonitrile solvent, so that it appeared interesting to combine the use of acetonitrile as a co-solvent and the addition of surfactant in the present study.

Several types of surfactants were investigated: the anionic sodium dodecyl sulfate (SDS), the cationic hexadecyltrimethylammonium chloride (cetyltrimethylammonium chloride, CTAC), and the nonionic tricoso(ethylene glycol)dodecyl ether ($C_{12}H_{25}(OCH_2CH_2)_{23}OH$, $C_{12}E_{23}$). The method applicability to wine samples was investigated after an efficient optimized method has been set and validated.

2. Experimental

2.1. Solvents and reagents

Histamine, *o*-phthaldialdehyde, 2-mercaptoethanol, fluorescamine, sodium hydroxide, hydrochloric acid, boric acid, sodium dodecyl sulfate, cetyltrimethylammonium chloride, tricoso(ethylene glycol)dodecyl ether (of commercial name Brij[®] 35 or Brij[®] L23), methanol and acetonitrile were all purchased from Sigma–Aldrich. Deionized water of 18 M Ω ·cm resistivity was supplied using a Millipore (Bedford, MA) water purification system.

A list of abbreviations of the products used in this work is presented in the [Table 1](#):

Table 1. List of abbreviations of the used products.

Product	Abbreviation
Histamine	HA
<i>o</i> -Phthaldialdehyde	OPA
Fluorescamine	FLC
Sodium dodecyl sulfate	SDS
Cetyltrimethylammonium chloride	CTAC
Tricosa(ethylene glycol)dodecyl ether	C ₁₂ E ₂₃

2.2. Methods

Fluorescence measurements were performed at room temperature using a Cary Eclipse Fluorescence spectrofluorometer controlled by the Cary WinFLR software. Sample holders were quartz fluorescence cuvettes of 1 cm optical path length. All analytical measurements were performed using the same parameters of the spectrofluorometer (Data mode: Fluorescence, Scan setup: Emission from 350 to 600 nm, Excitation wavelength: 340 nm, Excitation slit: 5 nm, Emission slit: 5 nm, PMT voltage: Medium).

Surface tension measurements were performed by the pendant drop method [21] using a Krüss DSA10 instrument. The density of the samples measured with a pycnometer was 0.933 g·cm⁻³. ¹H NMR spectra and DOSY experiments were performed on a Bruker AV500 spectrometer working at 500 MHz Larmor frequency. The chemical shifts of ¹H NMR spectra were measured with respect to internal tetramethylsilane reference (TMS). Dynamic light scattering (DLS) measurements were carried out using a NanoZS instrument from Malvern Panalytical. The viscosity of the Roth reaction medium at 293 K was measured with an Anton Paar MCR302 rheometer equipped with a cone-plate geometry in the shear strain rate range 0.1–100 s⁻¹. The flow behavior was Newtonian and the viscosity was 1.25 mPa·s. Dynamic light scattering measurements were carried out with a Malvern-Panalytical NanoZS instrument.

2.3. Procedures

2.3.1. Preparation of standard solutions

A HA stock solution (9 10⁻⁴ M) was prepared in deionized water; dilutions from this mother solution yielded the standard working solutions. The derivatization solutions were prepared using the method proposed by Uren and Karababa [22], using acetonitrile instead of methanol. 0.50 g of OPA and 40 μL of 2-mercaptoethanol were dissolved in 2 mL of methanol; the mixture was diluted to a volume of 10 mL with 0.04 M borate buffer (pH 9.5) [23,24]. The

same concentration as for OPA was used to prepare the standard solutions of FLC in the same borate buffer. All solutions were light-protected and stored at 4 °C.

Stock solutions of SDS (0.18 M), CTAC (0.18 M) or C₁₂E₂₃ (0.003–1 M) were prepared in 10 mL of acetonitrile. The solutions were degassed in an ultrasonic bath during preparation and before recording fluorescence spectra.

2.3.2. Samples preparation

The wine samples were purchased from a wine store. Each sample (100 mL) was degassed and filtered through a (0.45 µm) syringe filter before being mixed with 1,6-diaminohexane (0.5 mL). Finally, 5 mL of methanol was added to the sample (5 mL). The mixture was vortexed and sonicated for 10 min before being transferred to vials and stored at 4 °C before analysis [25].

2.3.3. Analytical measurements

The HA solution (0.5 mL) was added to the derivatization solution of OPA and mercaptoethanol (0.5 mL), and 0.5 mL of the surfactant solution was added. The mixture was vortexed for 10 s and introduced into the quartz cuvette for fluorescence measurement. The fluorescence emission spectrum was recorded by setting the excitation wavelength at the maximum absorbance of the OPA-HA fluorophore (340 nm). All fluorescence measurements were corrected for the solvent fluorescence ($IF = I(\text{measured}) - I(\text{solvent})$).

2.3.4. Validation of the method

The method was validated following the XPT 90-210 [26] and Eurachem/Citac guidelines [27]. The performance characteristics of the method were established by a single laboratory validation procedure governing analytical performance of the method and the interpretation of results. The following analytical parameters were assessed. A specificity assay was carried out to ensure the absence of interferences from other substances at the wavelength of histamine emission. The linearity of HA was investigated over a range of 0.7–13 mg·mL⁻¹. It was evaluated using 25 analyses of 25 different calibration-level preparations, and the slope and y-intercept of the calibration curve and the coefficient of determination (R^2) were calculated. The limit of detection (LOD) was defined as the lowest concentration at which the signal-to-noise (S/N) ratio was three, and the limit of quantification (LOQ) was defined as the concentration for which S/N ratio was ten [28].

3. Results and discussion

3.1. Choice of the complexing molecule

A preliminary study was carried out to select the appropriate derivatizing agent. To achieve the highest fluorescence intensity for the FLC-HA and OPA-HA complexes, the optimum excitation wavelength as a function of pH was determined. It has been demonstrated in the literature that the excitation and emission wavelengths differ depending on pH and that a basic pH (9.5) [29] allows for a higher fluorescent emission intensity. Maximum emission were at 456 nm and 487 nm for OPA and FLC respectively. Based on this, a comparative study showed that the fluorescence emission of OPA-HA was 15 times higher than FLC-HA (Figure 3), confirming that OPA was about an order of magnitude more sensitive than FLC using optimized fluorimetric detection [11]. The wavelength for maximum emission of the OPA-HA derivative in the mixed acetonitrile-water solvent (456 nm) was close to that reported in the original Roth's method operated in water (455 nm).

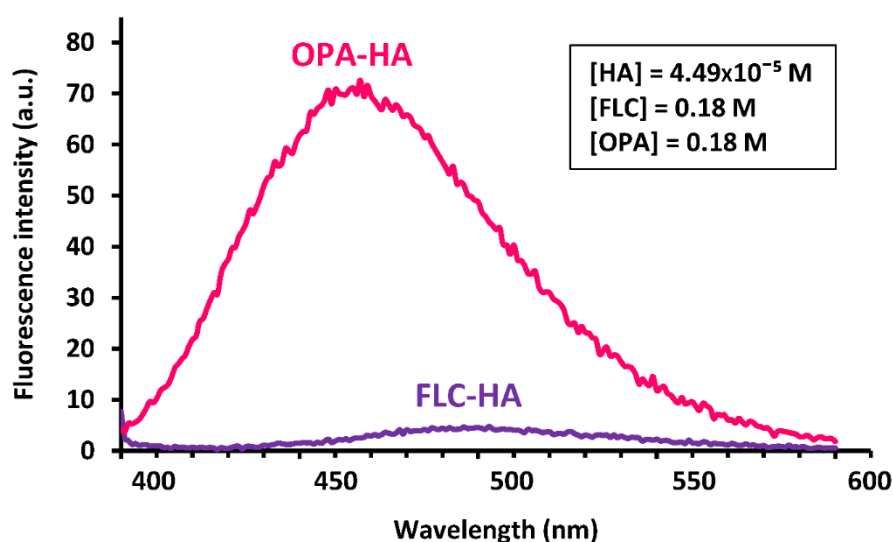


Figure 3. Emission spectra of the OPA-HA and FLC-HA derivatives at pH 9.5.

3.2. Effect of adding surfactants on the stability of the fluorescence signal

Accordingly, the chosen derivatization reagent for the detection of histamine was OPA, which, makes it possible to obtain a derivative detectable by fluorescence in a short time in the presence of a thiol and a basic medium. However, the OPA-HA derivative is chemically unstable [30]. In a kinetic experiment, the fluorescent signal of the OPA-HA derivative reached a maximum fluorescent emission intensity 2 min after mixing and thereafter decreases over time (Figure 4). Several report in the literature disclosed that surfactants stabilize the FLC-HA derivative. Hence, the stabilization of the OPA-HA derivative by surfactants was investigated through measurements of the fluorescence intensity of the OPA-HA derivative.

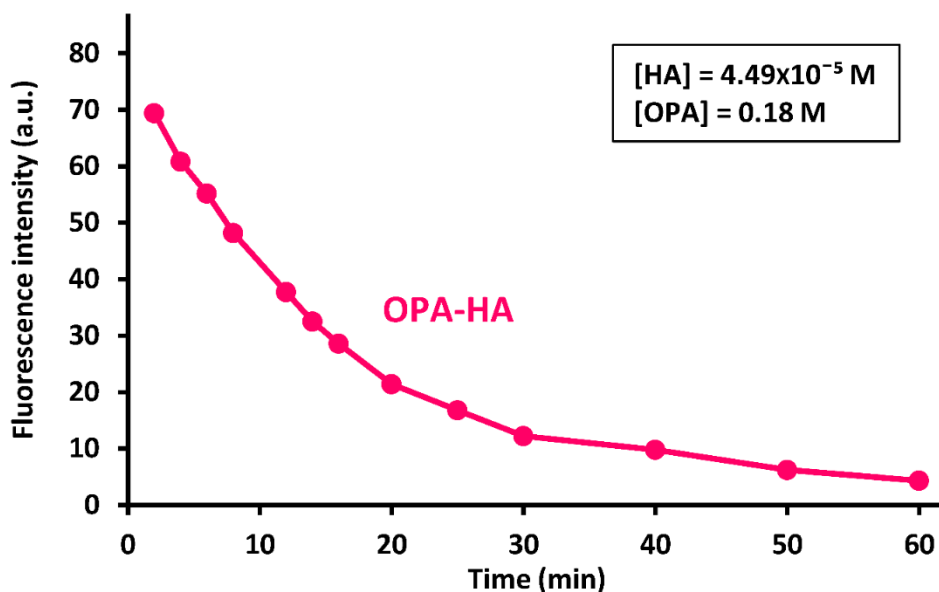


Figure 4. Decay of the fluorescence intensity of the OPA-HA derivative as a function of time in acetonitrile + borate buffer at pH 9.5.

Three different surfactants, SDS, CTAC and $C_{12}E_{23}$, were checked against their ability to stabilize the fluorescence signal of the derivative OPA-HA in acetonitrile. These surfactants were selected for covering the main classes of surfactants, namely anionic (SDS), cationic (CTAC) and nonionic ($C_{12}E_{23}$). The pK_a value of OPA-HA was expected close to that of 4-methylimidazole: $pK_a = 7.54$ in aqueous solution extrapolated to zero ionic strength [31]. The OPA-HA compound is essentially neutral at pH 9.5, only 1% being under its cationic form at such $pH = pK_a + 2$. Therefore, electrostatic interactions with ionic surfactants are not expected strong, and it is difficult to decide which surfactant would be optimum at stabilizing the OPA-HA fluorescent derivative. According to the literature survey, acetonitrile provides the condition for the best sensitivity compared to all protic and aprotic solvents investigated so far. The properties of the surfactants in the solvent medium containing a large fraction of acetonitrile are different of those known in water, making risky the *a priori* selection of a surfactant. A kinetic study in surfactant solutions of SDS, CTAC and $C_{12}E_{23}$ (0.18 M) in acetonitrile for 20 min at the same concentration as OPA was used to capture the variation of the fluorescence signal of OPA-HA. The addition of surfactants provided a very high stability of the fluorescence signal over time. The fluorescence intensity was stable in the presence of all surfactants. A slight decrease of fluorescence intensity was noticed for SDS. The fluorescence intensity was in the order $C_{12}E_{23} > CTAC > SDS$ (Figure 5). As a result, the $C_{12}E_{23}$ surfactant was chosen for the fluorimetric detection of histamine in the rest of the study.

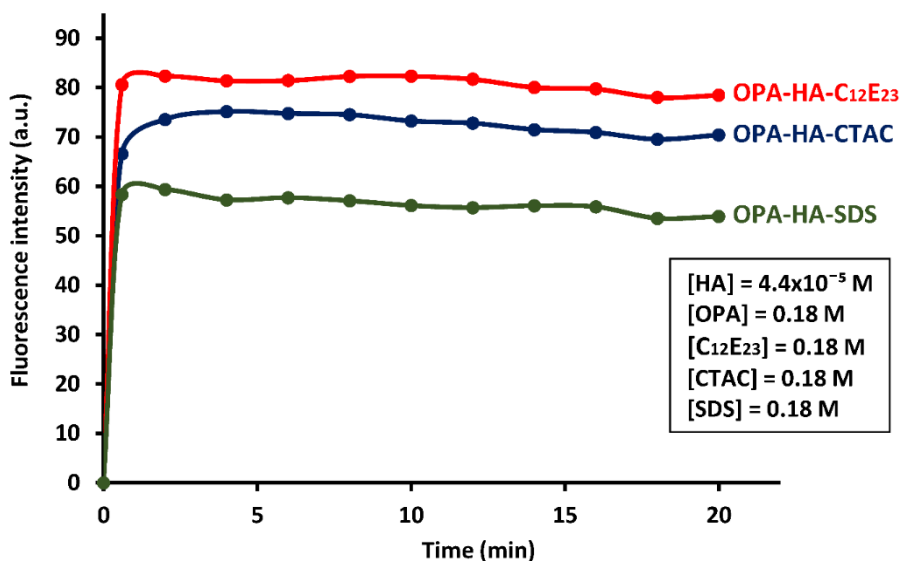


Figure 5. Fluorescence intensity of the OPA-HA derivative as a function of time upon addition of surfactant solutions of SDS, CTAC and $C_{12}E_{23}$ in acetonitrile + borate buffer at pH 9.5.

3.2.1. Optimization of the concentration of $C_{12}E_{23}$

While keeping the concentrations of HA and OPA constant in the reaction medium and varying the concentration of $C_{12}E_{23}$ (0.003–1 M), a significant change of the fluorescence intensity was observed, characterized by an increase of fluorescence intensity with increasing $C_{12}E_{23}$ concentration, until a plateau was reached. This effect is shown in Figure 6 for a delay of 6 min between the addition of HA into the reaction medium and the acquisition of the fluorescence intensity. The same trend was observed for all delay times. The main difference was the fluorescence intensity from surfactant free samples ($[C_{12}E_{23}] = 0$ M) at long times because the fluorescence intensity after very long delays have drastically decayed (Figure 4). The fluorescence intensity at the plateau reached above $[C_{12}E_{23}] = 0.03$ M was the same whatever the delay.

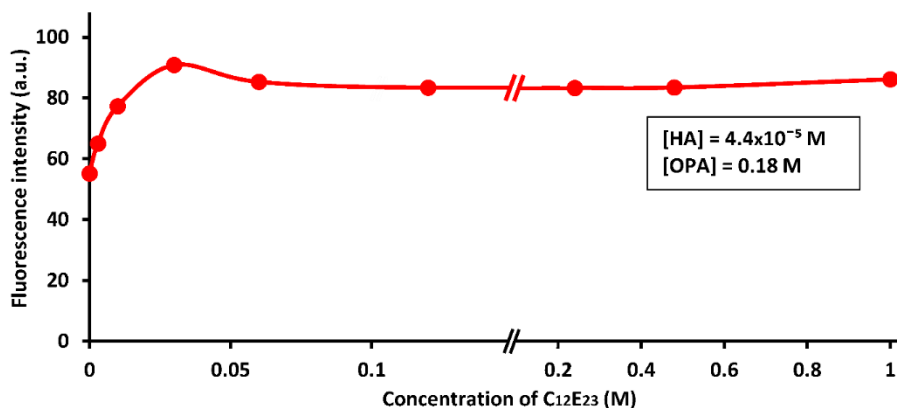


Figure 6. The effect of the $C_{12}E_{23}$ concentration on the fluorescence signal of the OPA-HA derivative 6 min after addition of HA.

The concentration of $C_{12}E_{23}$ yielding the highest fluorescence emission was 0.03 M. The fluorescence enhancement has been ascribed to the solubilization of the OPA-HA derivative inside micelles because the surfactant concentrations causing fluorescence enhancements of the FLC-HA derivative were larger than the critical micellar concentration (*CMC*) of aqueous solutions reported in the literature [14,15]. Indeed, the present $C_{12}E_{23}$ concentration was in large excess with respect to the *CMC* of $C_{12}E_{23}$ in water ($= 6 \cdot 10^{-5}$ M) [32,33]. The micellar self-assembly and the *CMC* of $C_{12}E_{23}$ might actually be different in the mixed organic-aqueous medium used for the analysis of HA. The lack of definite evidence for micelles being involved in fluorescence enhancement calls for a specific investigation of micelle formation and properties in the analysis medium.

3.2.2. Micelles of $C_{12}E_{23}$ in the analysis medium

Literature data on micelles in polar organic solvents and their mixtures with water shows that surfactant self-associate as looser assemblies than in water [32,34,35,36]. Indeed, the driving force that causes the formation of micelles is the hydrophobic interaction between alkyl chains. This interaction is operative in water, and it is weakened by the presence of organic solvents. The possible formation of micelles and their properties depend on the nature of the organic solvent [37,38]. In general, surfactants do not self-associate as micelles in the most common pure polar organic solvents (acetonitrile, DMSO), even protic ones (methanol, ethanol); only di-protic solvents (formamide, formic acid, glycerol) are cohesive enough (structure-forming) for allowing the formation of micelles [39,40,41]. Micelles may form in mixed organic-aqueous solvents, depending on their composition. The *CMC* is larger in such solvents than in water; and it dramatically increases upon addition of polar organic solvents into water [32,34,35,36]. Physicochemical investigation of the behavior of $C_{12}E_{23}$ in this complex medium (33% water + 33% acetonitrile + 27% borate buffer pH 9.5 + 7% methanol) has been done in order to infer whether this surfactant self-associates as micelles, and what are the properties of such micelles compared to the well-known behavior in pure water. Surface tension measurements were performed for the determination of the *CMC* of $C_{12}E_{23}$ in the analysis medium (Figure 7). The variation of the surface tension as a function of the $C_{12}E_{23}$ concentration had the same shape as in water. At low surfactant concentrations, increasing the surfactant concentration, slightly lowered the surface tension from that of surfactant-free mixed solvent ($38.1 \text{ mN}\cdot\text{m}^{-1}$); it decreased more steeply above a concentration of 0.3–0.5 mM, and reached a regime of linear decay with respect to the logarithm of the concentration; it finally reached a concentration assigned to the *CMC* above which the surface tension stayed constant ($34.6 \text{ mN}\cdot\text{m}^{-1}$). The

overall surface tension lowering was much less than in water because the surface tension of the surfactant-free mixed solvent was quite low. This behavior is characteristic of the self-association of the surfactant in micelles at concentrations above the *CMC*. The *CMC* was found to be $0.0035 \text{ mol}\cdot\text{L}^{-1}$ ($4.2 \text{ g}\cdot\text{L}^{-1}$), twenty times higher than that presently measured in pure water ($1.6 \cdot 10^{-4} \text{ mol}\cdot\text{L}^{-1}$, data not shown). Though the *CMC* in the reaction medium was higher than in water, the concentration used for the analysis of HA was still much higher than the *CMC*. These measurements confirmed the formation of $\text{C}_{12}\text{E}_{23}$ micelles in the analysis medium.

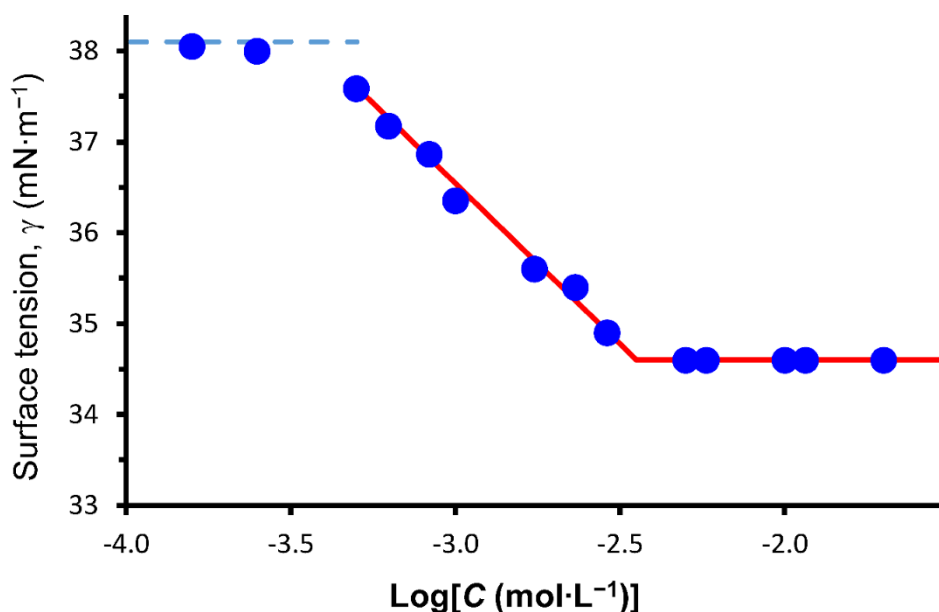


Figure 7. Surface tension as a function of $\text{C}_{12}\text{E}_{23}$ concentration in the medium used for HA analysis by fluorescence. The dashed line shows the surface tension of the pure solvent to which the experimental data asymptotically trends at vanishing surfactant concentrations.

The structure of micelles may be different in the reaction medium containing up to 40% of polar organic solvents. A first clue is the higher *CMC* in the reaction medium than in water. The area per surfactant molecule at the air-solvent interface showed the same trend. Thus, the Gibbs equation gives the surface excess (surface concentration, Γ) of surfactant as

$$\Gamma = -\frac{1}{RT} \frac{d\gamma}{d(\ln C)} \quad (1)$$

where R is the gas constant, T is the absolute temperature (293 K), γ is the surface tension and C is the surfactants concentration. This equation is valid in a pure solvent such as water; it has nevertheless also been used in the mixed solvent used as the reaction medium. The surface concentration of $\text{C}_{12}\text{E}_{23}$ at the *CMC* was $\Gamma = 2.9 \mu\text{mol}\cdot\text{m}^{-2}$ in water and $\Gamma = 0.63 \mu\text{mol}\cdot\text{m}^{-2}$ in the Roth reaction medium. The mean surface area per surfactant molecule ($1/N_{\text{Av}}\Gamma$ where N_{Av} is the Avogadro number) was 0.57 nm^2 and 2.64 nm^2 in water and in the Roth medium

respectively. Assuming that the lateral intermolecular interactions at the solution surface and at the surface of micelles are the same, the 4-fold larger area per molecule in the reaction medium means that micelles are looser assemblies of smaller size with a larger volume of the interfacial shell (sometimes called the "palisade layer") relative to that of the hydrophobic core.

The formation of micelles slows down the surfactants molecular motions, which causes a broadening of the surfactant ^1H NMR lines. The larger the micelles, the broader the NMR lines. Indeed, the ^1H NMR line of the terminal methyl and methylene groups of the dodecyl chain of $\text{C}_{12}\text{E}_{23}$ were quite broad in deuterated water solvent where large micelles formed, whereas they were narrow in deuterated acetonitrile solution where micelles probably did not form. The widths of ^1H NMR lines in the Roth reaction medium were intermediate between that in pure CD_3CN and D_2O (Figure 8), showing that aggregation as micelles did occur, but the association of $\text{C}_{12}\text{E}_{23}$ molecules was looser than in water: micelles were of smaller size and surfactant dynamics were faster.

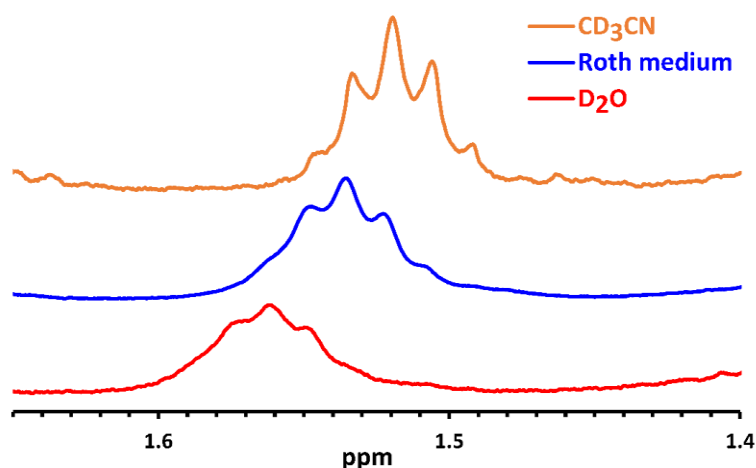


Figure 8. ^1H NMR spectra of the methylene in β position in the dodecyl chain of the $\text{C}_{12}\text{E}_{23}$ surfactant in $0.03 \text{ mol}\cdot\text{L}^{-1}$ solution in water, acetonitrile and Roth reaction medium.

The micelles size of $0.03 \text{ mol}\cdot\text{L}^{-1}$ solutions was inferred from measurements of the surfactant translational diffusion by the DOSY 2D NMR and DLS methods giving the surfactant diffusion coefficient (or diffusivity) D . The diameter of the diffusing species was calculated from D through the Stokes–Einstein relationship:

$$Diam = \frac{kT}{3\pi \eta D} \quad (2)$$

where k is the Boltzmann constant, T is the absolute temperature and η is the viscosity of the medium (Table 1). The diameter of the species involving the surfactant molecules was less than 2 nm in acetonitrile, which was of the order of the surfactant molecular size. This showed that the surfactant molecules did not self-associate in acetonitrile. The diameter of the micelles in

water was 10 nm, and that in the Roth medium was 4 nm. The smaller size of the C₁₂E₂₃ micelles in the Roth medium than in water is consistent with the conclusions of the surface tension measurements.

Table 1. Diffusion coefficient D at 293 K measured for 0.03 mol·L⁻¹ C₁₂E₂₃ solutions by DOSY and DLS, viscosity η , and species diameter in CD₃CN, D₂O and Roth reaction medium.

	D (m ² ·s ⁻¹) from DOSY	D (m ² ·s ⁻¹) from DLS	η (mPa·s)	$Diam$ (nm)
CD ₃ CN	6.6 10 ⁻¹⁰	–	0.345	1.9
D ₂ O	0.434 10 ⁻¹⁰	0.53 10 ⁻¹⁰	1.003	9.8
Roth medium	0.86 10 ⁻¹⁰	0.8 10 ⁻¹⁰	1.25	4.0

The solubilization of the OPA-HA derivative inside the C₁₂E₂₃ micelles was inferred by DOSY experiments of a solution C₁₂E₂₃ and OPA-HA in the Roth medium at concentrations typical of those used in fluorescence measurements: [C₁₂E₂₃] = 0.03 M, [OPA] = 0.03 M, [mercaptoethanol] = 0.03 M, [HA] = 0.01 M (Figure 9). The diffusion coefficients of the C₁₂E₂₃ molecules and OPA-HA derivative were equal ($D = 1.14 \cdot 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$), showing that these two molecules were involved in the same supramolecular assemblies, namely C₁₂E₂₃ micelles having the full content of OPA-HA solubilized inside. As a matter of reference, the diffusion coefficients of the free OPA-HA complex in the Roth medium was much higher: $D = 4.5 \cdot 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$. The diameter of the micelles loaded with OPA-HA calculated from the diffusion coefficient was 3.0 nm, larger than for the empty C₁₂E₂₃ micelles. The solubilization of the OPA-HA decreased the micellar size.



Figure 9. DOSY map for a solution of $C_{12}E_{23}$ $0.03 \text{ mol}\cdot\text{L}^{-1}$, OPA $0.03 \text{ mol}\cdot\text{L}^{-1}$, mercaptoethanol $0.03 \text{ mol}\cdot\text{L}^{-1}$ and HA $0.01 \text{ mol}\cdot\text{L}^{-1}$ in the Roth medium.

The solubilization site of the OPA-HA derivative inside $C_{12}E_{23}$ micelles was determined by ^1H NMR measurements of the shifts of the surfactant lines in the presence of the OPA-HA derivative. Indeed, the ^1H NMR lines of the surfactant are significantly shifted in the presence of aromatic solutes because of the magnetic field generated by the delocalized electrons of aromatic rings known as the "ring current" effect. The aromatic ring causes an upfield (negative) shift for protons located above and below the aromatic ring, and a downfield (positive) shift of protons located close to its edge. The largest shifts correspond to surfactant protons that are the closest to the aromatic rings. Therefore the shift of the surfactant ^1H NMR lines in the presence of a solubilized aromatic solute allows the localization of the solute inside the micelles [42,43,44]. The chemical shifts of the $C_{12}E_{23}$ lines in the presence and the absence of OPA-HA for solutions in the Roth medium were measured at the same concentrations as for the DOSY experiment (Table 2).

Table 2. ^1H NMR chemical shifts (ppm relative to TMS) of the $C_{12}E_{23}$ protons in the presence and the absence of OPA-HA.

	alkyl chain				polar part
	terminal CH_3	central CH_2	$\beta\text{-CH}_2$	$\alpha\text{-CH}_2$	PEG
$C_{12}E_{23}$ alone with	0.8759	1.2692	1.5340	3.44015	3.6375
OPA-HA difference	0.8734	1.2632	1.5283	3.4306	3.6379
	-0.0025	-0.0060	-0.0057	-0.0095	+0.0004

Such shifts of NMR lines induced by the presence of the OPA-HA derivative gave experimental evidence of the solubilization of OPA-HA in the C₁₂E₂₃ micelles. The largest shift was for the methylene in α position from the PEG polar part, which indicated its close proximity of the aromatic rings of OPA-HA. The shifts of the alkyl chain decreased from the CH₂ in α position to the terminal CH₃, for which the shift was very small. The isoindole aromatic ring causes an upfield (negative) shift for protons located above and below the aromatic ring, and a downfield (positive) shift of protons located close to its edge. The upfield shift of the lines of the alkyl chain indicated that the aromatic ring was inside the hydrophobic core of the micelles, close to its external surface. The shift of protons of the PEG polar part of C₁₂E₂₃ was not significant because most of the PEG of polymerization degree 23 was quite long for most of its protons were far away from the surface of the hydrophobic core where the OPA-HA molecules were solubilized. These results suggested a position of the OPA-HA with its isoindole hydrophobic aromatic ring located at the external surface of the hydrophobic core of micelles. The histamine part of the OPA-HA derivative may be located close to the PEG part because it is polar. There is no experimental indication of this claim however. The OPA-HA molecule has an amphiphilic structure with a hydrophobic part made of the isoindole ring and a polar part made of the histamine bound to it. Its amphiphilic nature with a short hydrophobic part manifests a co-surfactant or hydrotrope effect [45,46] causing a reduction of the micellar size from 4.0 nm to 3.0 nm. The position of the OPA derivative may be different in case of primary amines more hydrophobic than HA. A sketch of the solubilization site of OPA-HA in the C₁₂E₂₃ micelles is given in [Figure 10](#).

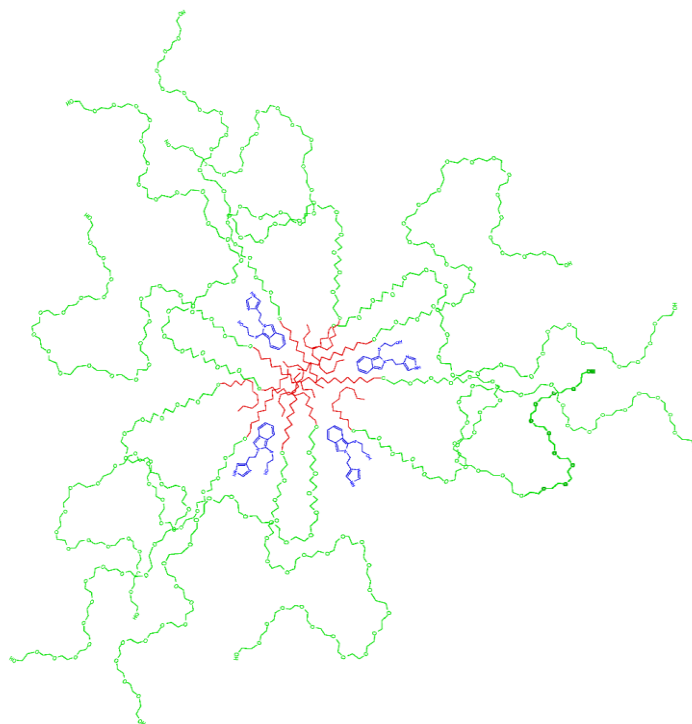


Figure 10. Sketch of the OPA-HA molecule solubilized in the $C_{12}E_{23}$ micelle. The dodecyl chains of $C_{12}E_{23}$ are colored in red, the PEG(23) polar parts of $C_{12}E_{23}$ are colored in green, and the OPA-HA derivatives are colored in blue.

The fluorescence emission increased with respect to the concentration of the $C_{12}E_{23}$ surfactant till a concentration of 0.03 M was reached (Figure 6). The fluorescence emission was constant above this latter concentration of surfactant. A slight but significant maximum of fluorescence emission occurred at a $C_{12}E_{23}$ concentration of 0.03 M for all delays between HA addition and fluorescence acquisition. This maximum concentration was 10 times higher than the *CMC* inferred by surface tension measurements in the same medium. These observations are discussed in the following and tentative explanations based on well-known phenomena are given. One matter of discussion is why the solubilization in micelles causes the fluorescence to increase. One another matter is the progressive rise of fluorescence emission between the *CMC* (0.0035 M) and $10 \times CMC$, followed by a plateau. Finally, the slight maximum at 0.03 M could not receive a definite explanation.

- The fluorescence emission increased as a function of the surfactant concentration between the *CMC* and 0.03 M. Two phenomena are causing this effect. The first obvious one is the fast degradation of the free form of the fluorescent OPA-HA derivative that manifests in the absence of surfactant ($[C_{12}E_{23}] = 0$ M in Figure 6) or when a part of the OPA-HA derivative is not solubilized inside the micelles. The second phenomenon is the fluorescence enhancement of

the OPA-HA derivative solubilized inside micelles. Evidence of its effect is given by the fluorescence enhancement observed at high surfactant concentrations. Thus, the fluorescence intensity was 87 a.u. in the presence of high concentrations of C₁₂E₂₃ (Figure 6) against ~75 a.u. in a surfactant-free medium and no degradation of OPA-HA inferred by extrapolation of the time dependence of the kinetics of fluorescence decay to time zero in Figure 4. The fluorescence enhancement by solubilization inside micelles is weak but significant. Solubilization inside micelles increases the fluorescence emission because the surfactant molecules are tightly packed in micelles, the surfactant molecules are compacted by a lateral pressure coming from the packing constraints for filling the hydrophobic core of the micelles [47]. This causes a slow-down of the molecular motions of both the surfactant molecules and the solubilized molecules [48,49,50]; a present experimental evidence of this phenomenon is given by the broadening of NMR lines of the surfactants in micelles compared to the free molecules (Figure 8). In other words, the viscosity (“apparent microviscosity”) increases inside the micelles [51]. The consequence is a slower non-radiative decay of the excited state of the fluorescent dye and therefore a stronger fluorescence emission by radiative decay [52,53,54]. This effect was presently weak compared to measurement reported in aqueous micellar media [52,53,54] because the C₁₂E₂₃ micelles in the acetonitrile-rich reaction medium are looser aggregates of surfactant molecules than in pure water, as inferred from the measurements of CMC and micelle size presented above in this paper.

- The fluorescence emission did not increase to its maximum at low concentrations of surfactant because the concentration of micelles was low compared to that of OPA (0.18 M). The solubilization power of micelles is known to be limited [55], so that a high enough concentration of micellized surfactant is required to solubilize the full OPA and OPA-HA derivative. The increase of fluorescence is related to the increase of the solubilized fraction of OPA-HA. Such full solubilization was reached for the surfactant concentration of 0.03 M. The solubilizing power of the C₁₂E₂₃ micelles for OPA is therefore 0.18/0.03 = 6, which is quite a high value compared to aqueous micellar solutions [56]. The fluorescence emission no longer varies once the full OPA-HA (and OPA) is solubilized inside micelles.

- We do not have a simple (and unique) explanation for the maximum fluorescence emission at 0.03 M. We believe that several phenomena act in opposite directions for a maximum is occurring. An in-depth discussion would therefore be too speculative to be convincing.

3.2.3. Kinetic study of stability

A kinetic study of the fluorescence intensity in the surfactant solution of $C_{12}E_{23}$ (0.03 M) in the reaction medium was performed for 4 h, showing the very high fluorescence stability (Figure 11), and demonstrating the excellent stability of the OPA-HA fluorophore when compared to the surfactant-free reference (Figure 4). Therefore, addition of $C_{12}E_{23}$ into the reaction medium is well-suited for the analysis of histamine by fluorescence.

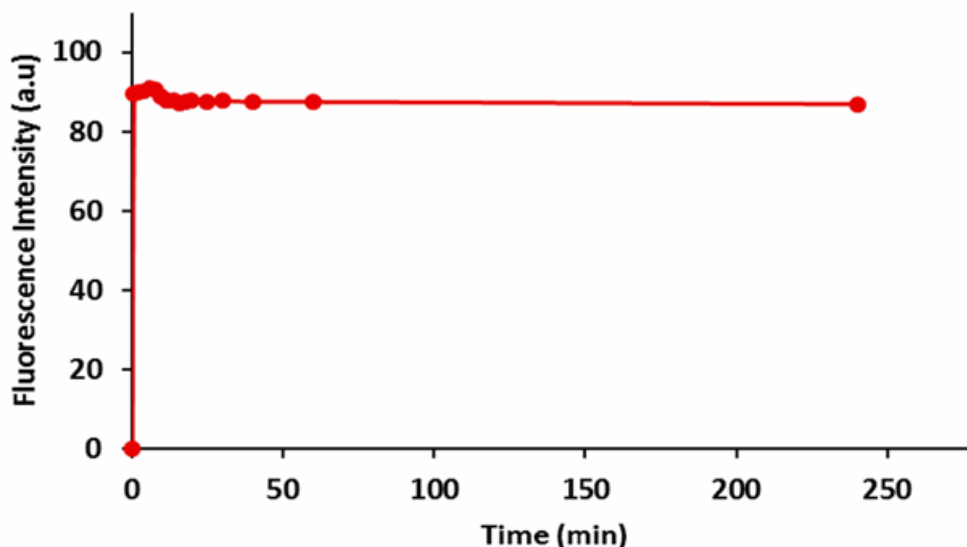


Figure 11. Kinetic study of the fluorescence emission of the OPA-HA derivative in $C_{12}E_{23}$ solution of in the reaction medium at pH 9.5.

3.3. Validation of the method

The characteristics of the present analytical procedure were investigated, namely the linearity, the specificity, the limits of detection (LOD) and quantification (LOQ), the repeatability and the reproducibility [57,58]. The methodology of the AFNOR NF V 03-110 standard [59] for intra-laboratory validation of methods for food analysis was applied.

3.3.1. Linearity, LOD and LOQ

The analytical performance of the method was assessed through calibration curves for the fluorescent derivative in the optimized medium under optimal analytical conditions. A set of five replications of a five-points calibration curve collected in the concentration range 0.7–13 $\text{mg}\cdot\text{L}^{-1}$ over five days was used to assess the linearity.

Firstly, a Cochran test did not disclose any outlier data point. Linear regression yielded $y = 12.988x + 15.534$ (Figure 12) with a good correlation coefficient ($R^2 = 0.9979$). The linear

model was validated using a Fisher F -test for 1% risk ($\alpha = 0.01$). The sum of squared residuals is the sum of two contributions coming from deviations of experimental data from the predictions of the linear model and non-linearity of the calibration curves. The F value related to the validity of the linear model was $F_{\text{LOF}} = 5.2$. It was larger than the critical value, $F(p-2, p(n-1), 1-\alpha) = F(3, 20, 0.99) = 4.94$, showing the validity of the linear model. The F value for the significance for the coefficients of the linear regression was 2175, larger than the critical $F(1, p(n-1), 1-\alpha) = F(1, 20, 0.99) = 8.10$, showing the significance of coefficients values. As whole, the Fisher F -test validated the calibration and its linearity.

The LOD and LOQ were 0.58 and $1.9 \text{ mg}\cdot\text{L}^{-1}$, respectively. These values were lower than the several safety limits given in the various national regulations and directives [60,61]. A general safety threshold of $10 \text{ mg}\cdot\text{L}^{-1}$ has been devised from a compilation of all of them. Such LOD and LOQ are far lower than the range required for usual analyses in food. However, they are higher than the lowest reported LOQ for HPLC methods using post-column derivatization with OPA [62]. The presently reported direct fluorescence measurements are simpler and faster, and they may be enough in many practical cases. The main benefit is the excellent stability of the fluorescence intensity.

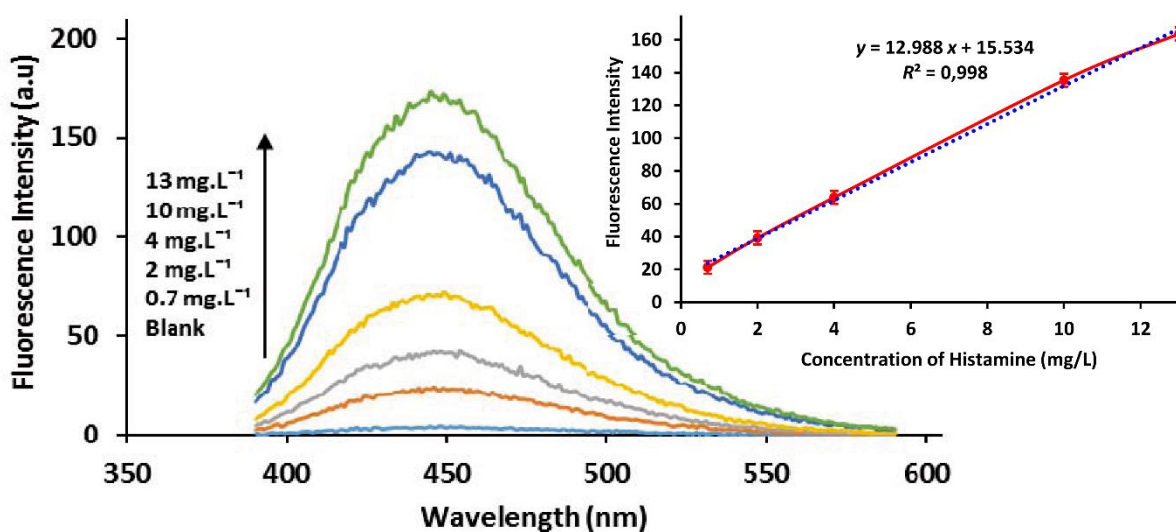


Figure 12. Fluorescence emission spectra of the OPA-HA derivative as a function of histamine concentration. Right side: Calibration curve of histamine from the fluorescence emission at 456 nm (red) and result of linear regression (dashed blue line).

3.3.2. Specificity

Specificity is an evaluation of the analysis in the presence of impurities, interfering molecules and/or matrix, among other things [63]. The method of standard additions was applied through measurements of the concentration of varied amounts of histamine ranging from 0.7 to $1 \text{ mg}\cdot\text{L}^{-1}$

into several wine matrices. For all samples, excellent histamine recoveries (%*R* = 75–99%) were obtained (Table 3). The distribution of the experimental recovery data was satisfactorily linear, with a coefficient of determination $R^2 = 0.883$. The present method yielded clean spectra, free of interfering peaks, confirming that it is suitable for the determination of HA in complex matrices such as wine samples.

Table 3. Experimental data for the determination of the specificity.

Sample	Concentration (mg·L ⁻¹)		Measured concentration (mg·L ⁻¹)		%R
	before addition	added	after addition	added	
1	6.48	1.00	7.33	0.85	85
2	6.63	1.00	7.61	0.98	98
3	7.20	1.00	8.11	0.91	91
4	6.53	1.00	7.47	0.93	93
5	7.51	1.00	8.47	0.96	96
6	6.40	0.70	7.08	0.68	98
7	6.56	0.70	7.21	0.65	92
8	6.43	0.70	6.96	0.53	75
9	6.72	0.70	7.37	0.65	93
10	6.64	0.70	7.33	0.69	99

3.3.3. Repeatability

Ten repeated measurements were investigated using the same sample (white wine) to evaluate the method robustness, under similar operational conditions (same analyst, same equipment, same laboratory), and within a short period. The findings are presented in Table 4 together with the mean (\bar{X}), the variance (CV_r) and the standard deviation of repeatability (S_r).

Table 4. Experimental repeatability data and statistical results of repeatability.

Measurement number	Measured concentration (mg·L ⁻¹)
1	1.20
2	1.12
3	1.25
4	1.17
5	1.25
6	1.13
7	1.25
8	1.40
9	1.40
10	1.28
Number of repetitions	10
\bar{X} (mg·L ⁻¹)	1.24
S_r	0.0997
CV_r	7.86%

The standard deviation of repeatability was $S_r = 0.10$. The fidelity in terms of repeatability is considered acceptable based on these experimental results and their statistical processing.

3.3.4. Reproducibility

The internal reproducibility describes the fidelity of the method from day to day.

A reproducibility study of four measurements was performed on a sample of white wine laced with 2 ppm of HA at four different days to mimic an inter-laboratory assessment of variability. The experimental data and the statistical results for the evaluation of internal reproducibility are shown in Table 5. Based on these measurements and their statistical analysis, the fidelity in terms of internal reproducibility is low enough for a reliable comparison of histamine contamination with respect to the limits of a regulation.

Table 5. Experimental data and statistics of internal reproducibility.

Run number	Date (y-m-d)	4 repetitions			
		Concentration (mg L ⁻¹)			
1	2022-03-23	2.0	2.1	2.0	1.8
2	2022-03-25	1.8	2.0	1.9	2.0
3	2022-03-28	2.1	2.2	2.0	1.8
4	2022-04-05	1.8	1.5	1.6	1.7
Statistics					
Intra-level variance S_r^2				0.016	
Inter-level variance S_L^2				0.022	
Internal reproducibility variance S_R^2				0.038	
S_r				0.13	
S_R				0.19	
Reproducibility coefficient of variation CV_R (%)				10.2	

3.4. Histamine determination in wine samples

The histamine concentration in 18 white wines purchased from a wine store have been measured. Table 6 summarizes the results that show the detection of trace amounts of HA in 7 wine samples. The HA concentrations in the 11 remainders were below the detection limit. The contamination levels in the 7 positive samples were 0.51, 0.77, 1.01, 1.47, 2.33, 3.31 mg·L⁻¹. These histamine contents in contaminated samples either did not exceed or were close to the range of the various limits of national food regulations (between 3.5 and 10 mg·L⁻¹ [60]).

Table 6. Histamine concentration ($\text{mg}\cdot\text{L}^{-1}$) measured in white wines.

Wine samples	Histamine content ($\text{mg}\cdot\text{L}^{-1}$)
Sample 1	Not detectable
Sample 2	Not detectable
Sample 3	Not detectable
Sample 4	2.33
Sample 5	Not detectable
Sample 6	Not detectable
Sample 7	Not detectable
Sample 8	Not detectable
Sample 9	0.77
Sample 10	Not detectable
Sample 11	3.31
Sample 12	Not detectable
Sample 13	0.51
Sample 14	1.01
Sample 15	Not detectable
Sample 16	Not detectable
Sample 17	3.70
Sample 18	1.47

4. Conclusion

The presence of surfactants efficiently stabilizes the OPA-HA complex and enhances the fluorescence signal. This allows accurate determination of histamine by recording a simple fluorescence spectrum using a classical spectrofluorometer without having to pay careful attention to the delay between mixing the reagents with the sample containing histamine and the fluorescence measurement. The stabilization of the fluorescent complex comes from its solubilization inside the surfactant micelles. The solubilization site of the OPA-HA complex is in the polar surface region of the micelles. Such addition of surfactant at a concentration above its *CMC* in the reaction medium improves the sensitivity, stability, and simplicity of the fluorimetric method for determining histamine in wine samples. The method has been validated against the linearity, specificity, repeatability and reproducibility by analysis of repeated experiments using statistics. The findings suggest that the method is suitable for quality control of wine, and possibly other beverages and foods.

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