**Chromatographic methods and sample pretreatment techniques for aldehydes determination in biological, food, and environmental samples**

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## Abstract

Aldehydes are very reactive carbonyl compounds that are widespread naturally. Aldehydes can be produced in vivo by oxidative reactions and are able to disturb biological functions through binding and modifying biomolecules. Thus, it is necessary to determine their levels in biological samples to estimate their possible adverse effect on human health in addition to their consideration as a biomarker for oxidative stress-related diseases. Furthermore, aldehydes have been found in foodstuffs as by-products of food processing or deterioration and their amounts in food samples were used as an indicator of its quality. Aldehydes also are widely distributed in the environment sourced from the industrial and motor vehicular exhausts and human exposure to them could bring many adverse health effects. From these viewpoints, an effective analytical method for the determination of aldehydes should be essential in various fields including biological, clinical, environmental, and food sciences. Among analytical methodologies, chromatographic determination methods should be suitable tools for the simultaneous determination of wide variety of aldehydes. Derivatization reactions are frequently applied for aldehydes to improve their detection sensitivity as most of them do not possess detectable moiety. Also, derivatization can control their retention behavior on HPLC columns. Moreover, sample pretreatment procedures for aldehydes to modify their high volatility, reactivity, polarity, and inherent instability is vital for their pre-concentration and avoiding matrix effects. In this review, chromatographic determination methods for aldehydes are summarized mainly according to the recent reports with the analytical techniques including the effective extraction and chemical derivatization. Besides, the applications for the chromatographic determination of aldehydes are summarized and significant findings obtained by the application studies are described.

Keywords: aldehydes; chromatography; derivatization; sample pretreatment; biological fluids; food and environmental samples.

70 **1. Introduction**

71 Aldehydes are ubiquitous reactive carbonyl compounds that are widespread
72 naturally, while aldehydes can also be produced in vivo by oxidative reactions such as
73 oxidative stress-induced lipid peroxidation, carbohydrate autoxidation and enzyme-
74 catalyzed metabolic activation [1–4]. Oxidative stress derived from reactive oxygen
75 species (ROS) is known to be implicated in the pathogenesis of various diseases such
76 as diabetes, infertility, rheumatoid arthritis and cardiovascular diseases [5–8]. The
77 exposure to ROS causes a number of oxidative modifications of biological molecules
78 such as lipid peroxidation, enzyme deactivation, and oxidative DNA base damage. The
79 alteration of the structure and function of biological molecules resulting from these
80 oxidative modifications eventually cause pathological conditions [9–12]. It is known
81 that the oxidative modification of biological molecules generates various oxidative
82 byproducts through a process of iterative oxidation and cleavage reactions. Among
83 oxidative byproducts, aldehydes are the most commonly characterized ones. Numerous
84 aldehydes can be significantly formed through peroxidation process of polyunsaturated
85 fatty acids (PUFAs) in cellular membranes. Such PUFAs derived aldehydes include
86 alkanal, alkenal, hydroxyalkenal and dialdehydes. In addition to the lipid peroxidation
87 process, some aldehydes can be formed endogenously from Maillard reaction. The
88 autooxidation of carbohydrate including glucose and fructosyl-lysine generates glyoxal
89 (GO) [1–4]. Other than spontaneous endogenous formation, the treatment of anticancer
90 agents such as cyclophosphamide induces the production of acrolein (ACR) and
91 crotonaldehyde resulting from the metabolization by cytochrome P450 [13,14].

92 As similar to ROS, aldehydes are also regarded as toxic chemicals due to their
93 high reactivity towards biological molecules [15–18]. The chemical modification of
94 biological molecules by binding with aldehydes can disturb biological functions, and

95 finally induce many pathological conditions. Thus, it is necessary to determine
96 aldehydes levels in biological samples to estimate their possible adverse effect on
97 human health. Additionally, since aldehydes levels in the biological sample reflect the
98 oxidative degree of biological molecules, it can be considered as a biomarker for the
99 prediction and the early diagnosis of diseases related to oxidative stress [19–21].

100 As mentioned above, aldehydes are naturally ubiquitous compounds not only in
101 biological tissues. In actual, various aldehydes have been found in foodstuffs such as
102 wine, vegetable oil, and drinking water [22–24]. Aldehydes in foodstuffs can be
103 generated in many different ways. Firstly, aldehydes are formed as by-products in the
104 process of food maturing, deterioration, and or microbial fermentation. The Strecker
105 degradation of amino acids also leads to the formation of aldehydes [25].
106 Hydroxyalkenals are generated through the oxidation of PUFAs in food fats as like in
107 in-vivo tissue. The carbohydrate can be degraded to form some aldehydes such as
108 furfurals and α-oxoaldehydes [26,27]. Therefore, the amounts of aldehydes in food
109 samples was used as an indicator to evaluate the quality deterioration of food during
110 storage. In the case of drinking water, it was reported that sterilization treatment such
111 as chlorination and ozonation could induce the formation of aldehydes [24]. The
112 presence of aldehydes in food samples takes part in the pleasant flavor and attractive
113 color. However, much amount of aldehydes in food can cause hazardous events because
114 aldehydes are regarded as harmful chemicals.

115 In addition to biological and food samples, it is known that aldehydes are widely
116 distributed in the environment [3]. The major primary source of aldehydes in the
117 atmospheric environment is considered to be industrial and motor vehicular exhausts.
118 It is believed that aldehydes play a major role in the occurrence of photochemical smog
119 in the air [28]. Since the water-soluble compounds in the atmosphere can be washed

120 away to the surface water with rainfall, the presence of aldehydes is definite in the
121 rainwater and the surface water [29,30]. Also, aldehydes in the surface water can be
122 formed in aqueous phase by microbial or photochemical degradation of dissolved
123 organic chemicals [30]. On the other hand, in the room air, aldehydes are derived from
124 cooking fumes produced during high-temperature frying or cigarette smoke [31]. The
125 exposure to these aldehydes from the environment can bring adverse health effects on
126 human health owing to its acute and chronic toxicity.

127 From these viewpoints, an effective analytical method for the determination of
128 aldehydes should be essential in various fields including biological, clinical,
129 environmental, and food sciences. Among analytical methodologies, chromatographic
130 determination method should be a suitable tool for the simultaneous determination of a
131 wide variety of aldehydes. In this review, chromatographic determination methods for
132 aldehydes are summarized mainly according to the recent reports with the analytical
133 techniques including the effective extraction and chemical derivatization that can
134 improve the sensitivity and selectivity.

135

## 136 2. Chromatographic determination methods of aldehydes

### 137 2.1 High-performance liquid chromatography (HPLC)

138 HPLC is the most frequently used method for the determination of aldehydes.
139 There are various types of detection techniques coupled with HPLC analysis including
140 ultraviolet (UV), fluorescence (FL) and mass spectrometry (MS). In general, most
141 aldehydes do not possess detectable moiety for HPLC detectors such as chromophore.
142 Therefore, derivatization reactions are frequently applied before their detection in order
143 to improve the detection sensitivity. Other than the improvement of the sensitivity, the

144 derivatization techniques can increase the stability and can also control the retention
145 behavior of aldehydes on the HPLC column [32].
146
147 **2.1.1 HPLC-UV**
148 HPLC with UV detection method is the most conventional and simple
149 chromatographic method. Although aromatic aldehydes such as furfural can be
150 determined by HPLC-UV methods without derivatization [26], various derivatization
151 reactions have been adopted to determine aldehydes lacking chromophore moieties.
152 Hydrazine based derivatization reagents have been commonly used for the chemical
153 modification of aldehydes and carbonyl compounds. Among them, 2,4-
154 dinitrophenylhydrazine (DNPH) is the most popular derivatization reagent for the
155 HPLC-UV analysis of aldehydes [22,23,29,30,33–38]. The DNPH hydrazone
156 derivatives formed from the reaction of aldehydes with DNPH (Fig. 1a) can be detected
157 with their absorbance. Besides, 4-hydrazinobenzoic acid [39] and benzhydrazide [40]
158 were used for the derivatization of aldehydes instead of DNPH in order to improve the
159 water solubility of the reagent. In addition to HPLC, hydrazine based reagents could be
160 applied for the determination of aldehydes by micellar electrokinetic chromatography
161 with UV detection [39–41].
162
163 **2.1.2 HPLC-FL**
164 Although the HPLC-UV methods are widespread, the sensitivity of UV
165 detection is generally low and co-existing UV-absorbing compounds can often interfere
166 with the UV detection of the target analytes. Owing to low sensitivity and selectivity,
167 the application of HPLC-UV was difficult to determine trace amounts of aldehydes.
168 Since FL detection is generally more sensitive and selective than UV detection, various

169 derivatization reactions are employed for the conversion of non-fluorescent aldehydes
170 to strongly fluorescent derivative to develop a sensitive HPLC-FL method.
171 Fluorophores containing hydrazine group are representative reagents for the FL
172 derivatization of aldehydes. Until now, many types of fluorescent hydrazine reagents
173 were developed and used to determine aldehydes by HPLC-FL such as dansyl
174 hydrazine (DNSH) [42], 4-(*N,N*-dimethylaminosulfonyl)-7-fluoro-2,1,3-
175 benzoxadiazole (DBD-H) [43,44], 2-[2-(7*H*-dibenzo[*a,g*]carbazol-7-yl)-
176 ethoxy]ethylcarbonylhydrazine (DBCEEC) [45] and 1,3,5,7-tetramethyl-8-aminozide-
177 difluoroboradiaza-s-indacene (BODIPY-aminozide) [46] (Fig. 1b). However, there
178 have been reported several shortcomings for using hydrazine reagents for the
179 derivatization. In general, hydrazines are unstable flammable chemicals and it can cause
180 mucous membrane irritation. Therefore, alternative reagents of hydrazine-based
181 reagent have been developed to overcome these shortcomings (Fig. 2). 2,2'-Furil used
182 as a stable derivatization reagent to develop a sensitive fluorogenic determination
183 method for aliphatic aldehydes [47,48]. Aliphatic aldehydes were reacted with 2,2'-
184 furil in the presence of ammonium acetate to form highly fluorescent imidazole
185 derivatives. Recently, the imidazole-forming condensation reaction was applied
186 reversely and α-oxoaldehydes were derivatized with 4-carboxymethylbenzaldehyde
187 (CMBAL) /ammonium acetate as co-reagents producing also highly FL imidazole
188 derivatives that were determined by HPLC-FL [49]. As another type of stable reagent,
189 1-pyreneboronic acid (1-PyBA) was used for the derivatization of glyoxylic acid
190 (GOA) based on the Petasis reaction [50,51].

191 In addition, *o*-phenylenediamine (OPD) reagents such as 1,2-diamine-4,5-
192 dimethoxybenzene (DDB) and 4-methoxy-*o*-phenylenediamine (MPD) were used for
193 derivatization of ACR or α-oxoaldehydes [52–54]. Besides, 2-thiobarbituric acid

194 (TBA) was applied for the FL derivatization of dialdehyde such as malondialdehyde
195 (MDA) [55].
196
197 **2.1.3 LC-MS and LC-MS/MS**
198 LC-MS is a sensitive and selective chromatographic method which can provide
199 molecular weight information in addition to quantitative information. Even though the
200 instruments for MS are expensive, the application fields of LC-MS for the
201 determination of aldehydes have been wide-spreading owing to its excellent versatility.
202 Nowadays, LC with tandem mass spectrometry (LC-MS/MS) is becoming the
203 mainstream of LC-MS analysis because of the improved detection specificity of
204 multiple reaction monitoring (MRM) mode in MS/MS that can decrease interferences
205 and provides rapid analysis. Since the ionization efficiency of analyte greatly influences
206 the sensitivity of MS instruments, derivatization techniques have been frequently used
207 in LC-MS/MS to improve low ionization efficiency of aldehydes [56]. Derivatization
208 reagent for LC-MS usually possesses a highly chargeable ionizable functional group
209 (Fig. 3). Conventionally derivatization reagents designed for HPLC-UV and FL method
210 can be diverted to LC-MS because some of these reagents have highly ionizable moiety
211 [23,57,58]. When aldehydes are analyzed by LC-MS after the reaction with the
212 derivatization reagent, the appropriate ionization mode, either atmospheric pressure
213 chemical ionization (APCI) or electrospray ionization (ESI) in positive or negative ion
214 mode, should be selected in accordance with derivative to obtain higher ionization
215 efficiency [56]. DNPH, representative hydrazine-based reagent, has also been applied
216 to derivatize various aldehydes for LC-MS analysis. The ionization of DNPH
217 derivatized monoaldehydes such as 4-hydroxynonenal (HNE) was usually performed
218 using ESI(-), while the ionization of DNPH derivatized MDA was performed using

219 ESI(+) [23,57,58]. This difference of proper use of ionization mode was attributed to
220 the difference of the structure of formed DNPH derivative in each case. Gosetti et al.
221 analyzed DNPH derivatized aldehydes using APCI(-) ionization in order to allow
222 simultaneous determination of DNPH derivatives and polycyclic aromatic
223 hydrocarbons [59]. On the other hand, the ionization of pentafluorophenylhydrazine
224 (PFPH) derivatized HNE was performed using ESI(+) [60]. As a shortcoming of DNPH,
225 it can also react with α-keto compounds not only with aldehydes. Eggink et al.
226 developed a novel reagent, 4-(2-(trimethylammonio)ethoxy)benzenaminium dibromide
227 (4-APC) for the selective derivatization of aldehydes [61,62]. The aniline moiety of 4-
228 APC was reacted with aldehydes at pH 5.7. Since 4-APC possess a permanent
229 positively charged trimethylammonium moiety, the 4-APC derivatized aldehydes can
230 be detected sensitively by ESI(+)-MS. Furthermore, Eggink et al. developed an
231 improved version of 4-APC, 4-(2-((4-bromophenethyl)dimethylammonio)ethoxy)-
232 benzenaminium dibromide (4-APEBA) [63]. 4-APEBA possess a bromophenethyl
233 group used for the detection of presence bromine in the derivatives with a characteristic
234 isotopic pattern of Br. Also, the higher molecular mass of 4-APEBA compared to 4-
235 APC provides a higher signal-to-noise ratio of formed derivatives. Similarly,
236 brominated benzylhydroxylamine, namely 1-((ammoniooxy)methyl)-2-bromobenzene
237 chloride (BBHA) was developed for the derivatization of 4-hydroxyhexenal (HHE) and
238 HNE [64]. The selective detection of the BBHA derivatized HHE and HNE could be
239 achieved via monitoring the characteristic isotopic patterns of bromine. As like 4-APC,
240 the reagent having a permanent positively charged moiety should be advantageous for
241 LC-MS analysis. From these aspects, (4-hydrazino-4-oxobutyl) [tris(2,4,6-
242 trimethoxyphenyl)phosphonium bromide (TMPP-PrG), Girard's reagent T and P
243 containing positively charged phosphonium, trimethylammonium, and pyridinium

244 moiety, respectively were used for the derivatization [65–67]. FL derivatization
245 reagents such as DNSH can also be used in a similar way to specially designed reagents
246 for LC-MS [68]. The dimethylamino group of fluorescent dansyl moiety could be easily
247 protonated under acidic conditions, and the positively charged derivatives could
248 generate a particular product ion targeted for MRM by collision-induced dissociation
249 (CID). 4-[2-(*N,N*-Dimethylamino)ethylaminosulfonyl]-7-*N*-methylhydrazino-2,1,3-
250 benzoxadiazole (DAABD-MHz) was synthesized as the fluorescent benzoxadiazole
251 agent modified for LC-MS/MS [69]. The formed DAABD derivative could be
252 effectively ionized by ESI(+), and the specific product ion at m/z 151 derived from
253 (*N,N*-dimethylamino)ethylaminosulfonyl group was formed by CID. Also, the thiol
254 primary amino acid, D-cysteine, could be used for the derivatization of aliphatic
255 aldehydes [70]. The produced thiazolidine derivative could be ionized and detected by
256 ESI(+)-MS/MS. Since the quinoxaline derivatives formed from the reaction between
257 OPD and α-oxoaldehydes can be ionized effectively using ESI(+) mode, OPD reagents
258 used for fluorogenic derivatization should also be useful for the LC-MS analysis of α-
259 oxoaldehydes [71,72]. Also, 1,3-cyclohexanedione (CHD) could convert low molecular
260 weight aldehydes to ionizable derivatives in the presence of ammonia [73,74]. In
261 addition, 9,10-phenanthrenequinone (PQ) produce highly ionizable imidazole
262 derivatives upon reaction with aldehydes in the presence of ammonium acetate. This
263 reaction was used for the development of very highly sensitive LC-MS/MS method for
264 aldehydes determination [75]. Although the LC-MS should be sophisticated methods,
265 the matrix effects caused by coexisting substances sometimes influence on the
266 ionization efficiency of the analytes. In order to solve this issue, isotope-coded
267 derivatization (ICD) has been adopted. For this purpose, the DNPH reagents substituted
268 with deuterium (D) or stable isotope nitrogen ($^{15}N$) were used for ICD in LC-MS/MS

269 analysis [76,77]. However, as mentioned previously, DNPH reagent has several
270 unavoidable shortcomings. Therefore, $D_3$-4-(1-methyl-1*H*-phenanthro[9,10-
271 *d*]imidazol-2-yl)phenylamine ($D_3$-MPIA) was designed and synthesized [78]. A pair of
272 non-isotope coded MPIA ($D_0$-MPIA) and $D_3$-MPIA were reacted with aldehydes and
273 were successively reduced to stable secondary amine derivatives by sodium
274 cyanoborohydride. Recently, commercially available $^{15}$N-ammonium acetate was
275 applied for the development of an ICD method for the determination of
276 hydroxyalkenals. The method is based on the condensation reaction between aldehyde,
277 $^{14}$N/$^{15}$N-ammonium acetate, and PQ to give light/heavy imidazole derivatives [79].
278

279 **2.2. Gas chromatography (GC)**

280 Gas chromatography (GC), especially when coupled with mass spectrometry
281 (GC-MS), is also widely used for the chromatographic analysis of aldehydes. In the
282 case of volatile aldehydes, direct GC analysis without derivatization could be
283 performed in the combination with headspace (HS) extraction [31,80,81]. However, a
284 large number of reported methods utilized derivatization to improve the stability,
285 volatility and ionization efficiency of aldehydes. As same as in the case of HPLC,
286 hydrazine-based reagents have been commonly used for the derivatization of aldehydes.
287 Although DNPH is actually used for the derivatization, it is reported that the volatility
288 and thermal stability of DNPH derivatives should not satisfy the required conditions
289 for GC analysis [2]. The volatility of PFPH derivatives is much higher than that of
290 DNPH derivatives, and the aromatic ring substituted by five fluorine atoms can be
291 detected sensitively by GC-MS with negative chemical ionization mode. Therefore,
292 PFPH was applied for the derivatization of aldehydes in GC-MS [82]. 2,4,6-
293 Trichlorophenylhydrazine (TCPH), an analog of halogenated phenylhydrazine, was

294 also used to form chlorinated hydrazine derivatives [83]. 2,2,2-Trifluoro-
295 ethylhydrazine (TFEH), a very volatile hydrazine, was applied for the derivatization of
296 aldehydes [84]. The derivatization with TFEH proceeded under mild conditions and the
297 highly volatile nature of TEEH derivatives could provide strong peak response. As the
298 alternative derivatization reagent for hydrazine reagent, hydroxylamine reagents are
299 also frequently used to form oxime derivatives after the reaction with aldehydes.
300 Among hydroxylamines, *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine (PFBHA) has
301 been preferably used for aldehydes derivatization [24,85–87]. In contrast to DNPH
302 derivatives, it was reported that PFBHA derivatives were thermolabile at high
303 temperatures. The formation of thiazolidine after the reaction of aldehydes with
304 cysteamine was used for derivatization in GC-MS analysis, however, the thiazolidine
305 derivative was moderately less volatile [88]. Even in the case of GC-MS, OPD reagents
306 were widely used for the derivatization of α-oxoaldehydes [89]. On the other hand,
307 TBA was not applied to GC analysis because of the low volatility of its derivatives [2].
308 Other than mass spectrometry, several detection modes such as electron capture
309 detection (ECD) and flame ionization detection (FID) could be used for the
310 determination of aldehydes after the reaction with derivatization reagents. Since GC-
311 ECD is suitable detection technique for the aromatic compounds that have electron-
312 withdrawing group, pentafluoro aldehydes derivatives formed from PFPH or PFBHA
313 could be detected with GC-ECD [90]. The pyrazine derivative formed from the reaction
314 of GO with 1,2-diamonopropane could be determined by GC-FID [91].
315
316
317

318 ## 3. Sample treatment techniques for aldehydes chromatographic analysis with
319 special emphasis on recent and successful techniques

320 The sample pretreatment procedures for aldehydes are vital for avoiding matrix
321 effect and also for pre-concentrating the target analytes as this can considerably
322 enhance the analytical performance parameters such as selectivity, sensitivity, accuracy,
323 and precision. Sometimes, aldehydes determination in simple matrices like beverages
324 and environmental water samples were carried out through direct derivatization without
325 any prior sample pretreatment [45,70,92]. Direct derivatization was also used by
326 Espinosa-Mansilla for determination of α-oxoaldehydes in urine samples followed by
327 filtration and direct injection into HPLC-FL system. They achieved very good recovery
328 ranged from 101-109% which could be attributed to the relatively low matrix effect of
329 urine on this derivatization reaction and on these analytes [93]. However, extraction of
330 aldehydes of different natures from complex matrices, such as blood, plasma, and food
331 samples, is a very difficult and challenging process due to their high volatility, reactivity,
332 polarity, and inherent instability. In the following sections, a survey of the sample
333 treatment techniques adopted for the extraction of aldehydes from different matrices is
334 presented.

335

336 ### 3.1. Protein precipitation (PPT)

337 Samples with complex matrices such as blood, plasma, urine, or tissue
338 homogenates contain a multifarious mixture of biogenic compounds that can easily
339 react with aldehydes which are themselves reactive in nature. This reaction will
340 negatively affect the recovery, and accuracy of the methods. PPT through the addition
341 of acids, organic solvent, or through centrifugation is carried out to overcome this
342 problem.

343 For the analysis of aliphatic aldehydes in biological matrices and tissue
344 homogenates, many methods adopted PPT followed by derivatization of the targeted
345 aldehydes. Some methods utilized organic solvents such as methanol [47,48,91,94–96]
346 and acetonitrile [46,49,97,98] and they all resulted in good recoveries (90-110 %).
347 Others used trichloroacetic acid for protein precipitation [55] but the efficiency of this
348 method was not confirmed by a recovery study. Other methods, especially those for
349 low molecular mass aldehydes (LMMAs), employed simultaneous derivatization and
350 protein precipitation [44,72] for plasma samples. These methods yielded acceptable
351 recoveries for the targeted aldehydes ranged from 80-127 %. Some methods employed
352 only centrifugation of the urine and plasma samples followed by direct derivatization
353 of the targeted aldehydes [61,63]. But it is difficult to assess the successfulness of this
354 technique since no recovery studies have been carried out.
355
356 **3.2. Liquid-liquid extraction (LLE)**
357 Despite having inherent demerits of using highly toxic volatile solvents, LLE is
358 still an affordable and efficient choice for extraction of aldehydes from complex
359 matrices. Tomono et al. developed an LLE method for the extraction of more than thirty
360 aldehydes of different nature from plasma using a mixture of methanol/chloroform (1:2,
361 v/v). After separation of the organic phase through centrifugation, this phase was
362 derivatized and injected in the chromatographic system. Despite the fact that this
363 method was applied for aldehydes of different nature; short and long-chain saturated
364 and unsaturated aldehydes and hydroxyl, epoxy, and oxoaldehydes, the recoveries of
365 this method were very convincing (70-112 %) [68]. On the other hand, for the extraction
366 of aldehydes from vegetable oils, LLE was adopted many times. HNE was extracted
367 efficiently using acetonitrile (recovery (89-108%)[60], while successive simultaneous

368 LLE with n-hexane and water was applied for extractions of furfurals (recovery 75-
369 108%) [99]. Also, Ma and Liu extracted highly reactive aldehydes including MDA,
370 HHE, and HNE after direct derivatization of oil samples with DNPH. They adopted a
371 relatively complicated extraction scheme that uses successive extraction with ethanol,
372 then dichloromethane, and finally with acetonitrile. In spite of its tediousness and time
373 consumption, this method resulted in excellent recoveries (96-104%) [35].

374 We can conclude that LLE is a successful choice for extraction of aliphatic,
375 aromatic, and highly reactive aldehydes from biological and oil samples, however, it
376 possesses some drawback including the long extraction time and the environmental
377 hazards of using highly volatile solvents such as chloroform and hexane for this
378 extraction technique. To overcome these problems, salting-out assisted LLE (SALLE)
379 [100] and subzero-temperature LLE [101] were developed by Yoshida and coworkers.
380 In SALLE, lower chain alcohols or acetonitrile can be used for extraction of aqueous
381 samples through decreasing their solubility in water by adding a high concentration of
382 salt to the solvents mixtures to induce phase separation (Fig. 4). Our research group
383 used this technique for extraction of aliphatic aldehydes from human serum samples
384 with high efficiency (recovery>90 %), accuracy, and precision using acetonitrile as the
385 extraction solvent and NaCl as the phase separation inducer salt [75,79]. Also, Ojeda et
386 al. used the same technique and the same salt for the extraction of MPD-derivatized
387 aldehydes obtaining very good recoveries ranged from 92 to 103% [54]. Regarding
388 subzero-temperature LLE, acetonitrile is used as an extraction solvent where it could
389 be separated from aqueous samples through freezing at -20 °C. Under this condition,
390 the aqueous phase is converted to ice and acetonitrile still liquid and can be easily
391 separated (Fig. 4). Our research group used this technique for extraction of
392 benzaldehyde from plasma samples for evaluation of the activity of the aldehydes

393 producing enzyme, semicarbazide-sensitive amine oxidase. The obtained recovery was
394 excellent (94-98%) and it is considered the best among the reported extraction methods
395 for benzaldehyde from plasma samples [102]. This technique was also applied also for
396 the extraction of HNE but with a lower efficiency of 45% [43].
397

398 **3.3. Liquid-liquid microextraction (LLME)**

399 In the current decade, miniaturized pre-treatment techniques based on LLE were
400 evolved through substantially reducing the organic solvent amount, leading to the
401 development of the so-called LLME. These techniques are now very popular due to
402 their environmental greenness, low cost of the used solvents, and high analytes
403 enrichment capacity. Simultaneous derivatization-dispersive LLME method was
404 developed and applied by Xu et al. for the extraction of hexanal and heptanal from
405 plasma samples. They used acetonitrile, containing the derivatizing agent, as a
406 dispersive solvent and tetrachloromethane as extraction solvent. In addition, NaCl was
407 used to increase the ionic strength that results in decreasing the solubility of the analytes
408 in the aqueous samples and increasing its partitioning to the extractant. The
409 simultaneous derivatization and extraction were carried out within 3 minutes. The
410 enrichment factor was more than 60 and the recoveries were very good (94-110%) [103].
411 Pastor-Belda et al. combined SALLE followed by dispersive LLME for extraction of
412 α-oxoaldehydes from urine samples. They used the acetonitrile extract as dispersant
413 solvent and carbon tetrachloride as an extractant solvent. This combination resulted in
414 excellent extraction efficiency (recovery 95-107%) and high enrichment factor reached
415 140 [89].

416 Vortex-assisted LLME, a recently introduced microextraction technique, was
417 applied by Abu-Bakar et al. for extraction of furfurals from fruit samples. In this

418 technique, no need for a dispenser solvent as dispersion occurs through vortex agitation
419 causing a mild emulsification process. The formed fine droplets can extract the analytes
420 faster due to the smaller diffusion distance and the larger exposed surface area. They
421 decreased the solubility of furfurals in the aqueous extracts of food samples using
422 salting out by NaCl and they found that 1-hexanol is the best extractant for such analytes
423 yielding satisfactory recovery above 80% for all targeted furfurals [104].

424 Liu et al. have developed a single drop LLME for extraction and pre-
425 concentration of aldehydes from environmental water samples. They fixed a homemade
426 funnel at the tip of a syringe needle that enabled the use of 10 μL drop of ionic liquid
427 for direct immersion and extraction of aldehydes from the samples. Using this technique
428 they were able to achieve high enrichment factor of 150 with acceptable recoveries [30].
429

430 **3.4. Solid phase extraction (SPE) and Solid phase microextraction (SPME)**

431 One of the most popular techniques for samples pretreatment is SPE, in which,
432 cartridge columns are used as solid phase medium for extraction. These cartridges are
433 activated before sample loading, followed by washing, then elution of the analytes with
434 a suitable solvent. Aldehydes are very polar compounds that make them difficult to be
435 trapped in SPE cartridges. In a rare occasion, Hurtado-Sanchez et al. could extract
436 reactive α-oxoaldehydes without prior derivatization from urine samples using
437 ISOLUTE ENV+ SPE cartridges. This cartridge is a hyper crosslinked hydroxylated
438 polystyrene-divinylbenzene copolymer that has high surface area and mixed polarity
439 made it idyllic for extracting the highly polar aldehydes from large-volume water
440 samples such as urine with high efficiency and recovery ranged from 89 to 111% [52].

441 In fact, most of the reported methods carry out derivatization first, to decrease
442 polarity and to enhance the retention of aldehydes, followed by SPE. O'Brien-Coker et

443 al. extracted aldehydes from plasma samples after their derivatization with CHD using
444 $C_{18}$ cartridge [73] but no recovery study was conducted. Chevolleau et al. also used $C_{18}$
445 cartridges for the extraction of HHE and HNE form fecal water samples after their
446 derivatization with BBHA. Despite the complex nature of fecal water samples, the
447 obtained recoveries were fairly acceptable (67-91%) [64]. Zhang et al. extracted TBA-
448 derivatized α-oxoaldehydes from urine and water samples with HLB cartridge and
449 obtained a good recovery (>90%) [105]. HLB cartridges were also used by Prieto-
450 Blanco et al. for extraction and pre-concentration of DNPH derivatized carbonyl
451 compounds from environmental samples and acceptable recoveries were obtained (72-
452 109%) [33].

453 Recently, our research group introduced a new technique for aldehydes detection
454 and purification through their dual-labeling with a fluorophore and a purification tag
455 for the first time. We introduced taurine, as a purification tag, and 1-PyBA, the
456 fluorophore, to the carboxy aldehyde, GOA, using Petasis reaction. Labeling the
457 aldehyde with taurine resulted in a reaction product with a terminal sulfonic acid group
458 that could be selectively retained on an anion exchange sorbent, Bond Elut SAX,
459 permitting easy removal of the excess fluorescent 1-PyBA reagent and its fluorescent
460 decomposition products together with the interfering plasma endogenous components
461 (Fig. 5). This methods resulted in good recovery (87.0%) and allowed the quantification
462 with a simple and very rapid isocratic HPLC-FL method [51].

463 Fully online SPE coupled with LC-MS/MS system was developed by Gosetti et
464 al. [106]. It was then applied for the extraction of twelve aldehydes derivatized with
465 DNPH from cooked food samples homogenates [59]. Sample loading onto the cartridge
466 was carried out through autosampler. The cartridge was fitted into the loading position
467 of the 6-port switching valve. A Dual pump was equipped, where one pump was used

468 for sample loading onto the cartridge. While the analytes are retained on the SPE
469 column and the matrix is flushed to waste, the other pump was used for equilibrating
470 the analytical LC column by the mobile phase. In the injection step, the valve is
471 switched to the injection position in order to couple the SPE cartridge with the
472 analytical column, into which the targeted analytes are injected [106]. This automated
473 online SPE yielded satisfactory recovery ranged from 70.0 % to 120.0% for the targeted
474 aldehydes [59]. Eggink et al. used a similar system for on-line weak-cation exchange,
475 WCXE, SPE, and pre-concentration of the in-vial 4-APC derivatized aldehydes from
476 biological samples. The obtained recovery was satisfactory for all the targeted
477 aldehydes except for nonanal and decanal that have recoveries of 70 and 40%,
478 respectively [62]. Baños and Silva developed an automated SPE system for
479 simultaneous derivatization, extraction, and pre-concentration of aldehydes from urine
480 samples. The used SPE manifold consists of a peristaltic pump attached to two injection
481 valves and laboratory-made sorption column packed with of LiChrolut EN. One
482 injection valve was used for conditioning and impregnation of the cartridge with the
483 derivatizing agent, DNPH, and the other valve was used for introduction of the samples.
484 After simultaneous derivatization and extraction, elution was carried out to an
485 Eppendorf tube followed by injection into the analytical system. The obtained
486 recoveries were very good (92-100%) [57].

487 Lord et al, used a syringe pump, isocratic pump, gradient pump, and automated
488 switching system consists of two six-port valves for constructing online SPE
489 derivatization and extraction of MDA that is coupled to HPLC-FL analytical system.
490 The syringe pump loaded the derivatizing agent, DNSH, to a laboratory-made XAD
491 reactor cartridge prior to analysis. Meanwhile, the sample was introduced to the
492 cartridge through the isocratic pump. The simultaneous reaction and trapping were

493 completed within only 1 min. The gradient pump was then operated in reverse flow
494 mode in order to elute the products from the cartridge to the analytical column then
495 switched to the normal flow mode to perform separation of the sample on the analytical
496 column and the obtained recovery of MDA from mouse liver extract was very good
497 (106%) [107].

498 As we can notice, SPE systems are continuously developing starting from manual
499 ones to online SPE extraction, then automated simultaneous extraction and
500 derivatization, ending with online automated simultaneous extraction and
501 derivatization developed by Lord et al. [107].

502 Despite all these development in SPE, it cannot be considered as an
503 environmentally friendly extraction technique as it leads to discarding a plentiful
504 amount of organic solvents. Thus, Recently, SPME has been introduced for aldehydes
505 extraction from different matrices using a considerable less amount of solvent than SPE.
506 SPME depends on using a fiber coated with an extracting liquid (polymer) phase or a
507 solid (sorbent) phase. This fiber is introduced to the sample vials and stirring is carried
508 out to facilitate the transfer of the analytes from the sample matrix to the fiber. After
509 that, the SPME fiber is moved by a tweezer, then transferred to a microcentrifuge tube
510 containing a suitable organic solvent. Finally, desorption of the analytes from the fiber
511 to the organic solvent is assisted by ultrasonication [108]. Basheer et al. used $C_2$-
512 bounded silica impregnated with DNPH for simultaneous derivatization and extraction
513 of aldehydes from rainwater samples and obtained good recovery more than 85% [29].
514 Very recently, Xia et al. developed a novel efficient sorbent, mono-(6-
515 (diethylenetriamine)-6-deoxy)-beta-cyclodextrin-ploy(styrenedivinylbenzene-
516 methacrylic acid), impregnated also with DNPH for simultaneous derivatization and
517 extraction of aldehydes from food and cosmetics samples (Fig. 6). Despite the

518 complexity of the analyzed matrices, the obtained recovery was sufficient, ranging from
519 81-115 % [108].

520 SPME fiber is expensive and fragile, thus, a monolithic μ-SPE device was
521 developed by Xu et al. using a polypropylene frit with porous network structure as the
522 cast for the monolithic sorbent, poly(methacrylic acid-co-ethylene glycol
523 dimethacrylate). The monolith was synthesized within channels and macropores of the
524 frit. The polymer monolith frit was used for simultaneous DNPH derivatization and
525 extraction of aldehydes from biological samples with fairly sufficient recovery of 70-
526 89% [37]. Fernández-Molina and Silva developed a continuous-flow μ-SPE system for
527 the simultaneous derivatization and extraction of LMMAs in treated water samples
528 [41,109]. It is similar to the online SPE system developed before by Baños and Silva
529 [57], but they used a μ-SPE device packed with different types of sorbents. Telos™
530 ENV was the sorbent of choice resulting in the highest enrichment for aliphatic and
531 aromatic LMMAs [109]. Recently, Chen et al. could extract underivatized aldehydes
532 from urine samples using a fully automated in-tube SPME/LC-MS method. The used
533 online in-tube SPME extractor was poly(methacrylic acid-co-ethylene
534 glycoldimethacrylate) monolith providing a very good recovery ranging from 99.5-
535 116.8%. The eluate from the monolith was transferred automatically to the analytical
536 column through switching valves. After the LC separation of the aldehydes, they were
537 tee mixed with hydroxylamine hydrochloride (HAHC) to perform post-column
538 derivatization (PCD) followed by MS detection (Fig. 7) [110].

539

540

541 **3.5. Headspace and its related hyphenated extraction techniques**

542 Headspace (HS) extraction is the most used technique in case of GC analysis to
543 perform extraction and sampling simultaneously. It relies on transferring the analytes
544 from the matrix to the above vapor phase *via* heating, followed by removing analytes
545 from the HS with the carrier gas of the GC system. If only a fraction of this HS gas
546 phase was introduced automatically to the GC system, it is called static HS. It is well-
547 known that HS technique is very suitable for volatile compounds such as aldehydes.
548 Antón et al. utilized HS generation sampler for extraction of aldehydes from urine
549 samples, followed by their introduction to the GC system and finally aldehydes were
550 detected by MS without any prior derivatization. The obtained recoveries were between
551 86-120 % [80]. The same method was recently used by Wei et al. for extraction of
552 PFBHA derivatized $C_1$-$C_7$ alkanals from human blood with very good recovery ranged
553 from 92-106% [87].

554 HS is not used only directly for samples, but also for organic solvents extracts of
555 the samples. Zhang et al. used HS for pulling out the volatile aldehydes from the
556 methanol extract of the mainstream smoke gas phase obtained from a smoking machine.
557 HS introduced the aldehydes to the GC system and the recoveries ranged from 78.5%
558 to 115 % [31]. Serrano et al. used the static HS for simultaneous PFBHA derivatization
559 and extraction of LMMAs from drinking water [24] and a set of 15 aldehydes from
560 solid and liquid canned vegetables [85] and they obtained excellent recoveries in both
561 methods ranged from 89-99 % [24,85].

562 Hyphenated techniques that combine HS with microextraction techniques were
563 also applied for extraction and pre-concentration of aldehydes from different matrices.
564 An example of theses hyphenated techniques is HS single-drop microextraction (HS-
565 SDME). Li et al. used HS-SDME for extraction of PFBHA-derivatized aldehydes from
566 blood samples. After derivatization of the aldehydes, the formed oximes were HS

567 extracted and concentrated by a microdrop solvent. A hanging 2.0 μL 1-octanol was
568 introduced to the HS above the derivatized sample solution and extraction was aided
569 by stirring. The recovery was not less than 87 %. Also, due to the very low volume of
570 the extracting solvent, sub-nanomolar LOD could be obtained [86]. Fiamegos and
571 Stalikas developed in drop simultaneous derivatization and extraction of aldehydes
572 using a hanging drop of n-butanol containing TCPH. This method could extract
573 aldehydes from biological and oil samples with acceptable recoveries ranged from 87-
574 116% [83].

575 Another HS hyphenated extraction technique is the ultrasound-assisted HS-liquid
576 phase ME (HS-LPME). This technique involves the use of a polychloroprene rubber
577 (PCR) tube as a container to load extraction solvent to the HS (Fig. 8) [111]. Xu et al.
578 utilized HS-LPME for simultaneous derivatization and extraction of aldehydes from
579 human blood samples. Methyl cyanide, as extraction solvent containing DNPH, was
580 introduced to the HS using the PCR tube. The target aldehydes were HS extracted and
581 instantaneously derivatized in the droplet, followed by detection of the formed
582 hydrazones with HPLC-UV system. The obtained recovery was fairly acceptable
583 ranging from 75 to 101% [38].

584 HS-SPME is another hyphenated technique used for extraction and pre-
585 concentration of aldehydes. Olivero and Trujillo used HS-SPME for determination of
586 carbonyl compounds, including aldehydes, in wines. The used SPME fiber coated with
587 polyacrylate was introduced to the HS to extract underivatized carbonyl compounds.
588 The target analytes in this study are very different in their nature, thus the obtained
589 recoveries were very variable ranging from 30 to 190% which is considered a major
590 drawback [81]. Kim and Shin developed an automated HS-SPME method for extraction
591 of TFEH-derivatized aldehydes from water samples. Poly dimethyl siloxane

592 divinylbenzene was the sorbent of choice yielding the best extraction efficiencies. The
593 derivatization and adsorption were carried out simultaneously in the HS vial and aided
594 through continuous shaking. Then desorption occurred in the injection port and the
595 analytes are then passed onto the analytical column for analysis. No recovery study was
596 carried out to judge the performance of this method completely however excellent
597 sensitivity was obtained reaching sub-ppb detection levels [84].

598

599 **3.6. Gas-diffusion microextraction (GDME)**

600 An innovative extraction technique for volatile and semi-volatile compounds
601 called GDME was lately introduced by Goncalves and coworkers [34]. It depends on
602 using a novel extractor consists of a reduced dimensions Teflon tube that contains a
603 small microporous hydrophobic semipermeable membrane. The membrane avoids the
604 diffusion of the solvent but allows the mass transfer of volatile and semi-volatile
605 analytes. The extractor is immersed in the sample and the sample vial is closed around
606 the extractor (Fig. 9). Then, the derivatizing agent is dissolved in the extraction solvent
607 and both are placed inside the extractor device. Then the sample is thermostated and
608 constantly agitated in order to volatilize the targeted analytes, thus they can pass
609 through the semipermeable membrane to the extracting solvent. As the extracting
610 solvent contains the derivatizing agent, simultaneous extraction and derivatization are
611 achieved. As the extracted aldehydes are continuously drawn from the extracting
612 solvent through the derivatization process, a saturation of the extracting solvent will not
613 occur, providing significant enrichment and very high sensitivities. Goncalves and
614 coworkers successfully used GDME for determination of aldehydes in beer using
615 DNPH as the derivatizing agent [34]. Also, they used the same technique for the
616 determination of free and bound acetaldehyde in wine samples [112]. Lima et al.

617 adopted GDME for simultaneous extraction and derivatization of aldehydes from wine
618 using the new chromophore labeling reagent for aldehydes, 4-hydrazinobenzoic acid
619 [39]. According to Goncalves et al., the recoveries obtained from GDME were different
620 from different beer samples and slopes obtained from standard additions curves differ
621 according to the tested matrices, showing that this method is significantly influenced
622 by the sample matrix. This problem could be overcome using the standard addition
623 method [34].
624
625 **3.7. Miscellaneous extraction methods**
626 Steam distillation is a classical method of extraction, however, it is still in use.
627 Loi et al. used this method for the extraction of furfurals from crude palm oil samples
628 prior to its chromatographic analysis. The oil sample was placed into a round-bottomed
629 flask followed by the addition of distilled water. Then distillation of water was carried
630 out using a separation funnel containing distilled water to keep the level of water in the
631 flask constant and a condenser to bridge the flask to another distillate-receiving flask.
632 The distillation was completed within about one hour [26].
633 Neng et al. reported stir bar sorptive simultaneous derivatization and extraction
634 of α-oxoaldehydes adopting 2,3-diaminonaphthalene (DAN) as a derivatizing agent.
635 They used stir bars coated with polydimethylsiloxane, which was used for stirring water
636 samples with DAN for 18h. After that the stir bar was removed by a tweezer and
637 transferred into another vial containing methanol as the desorption solvent and stirred
638 for 15 min, followed by removing the stir bar and evaporation of methanol to a
639 minimum volume before injection into HPLC-DAD system. The obtained recovery was
640 very good (96%), however, the method includes multiple steps and lengthy
641 procedure [113].

642 Extraction of aldehydes using the reverse micelles technique was recently
643 reported [114]. Reverse micelles are formed by dispersing surfactants in a non-polar
644 organic phase containing a small amount of water. Under this condition, nanometer
645 inverted aggregates of surfactant molecules are formed and drawn together by hydrogen
646 bonding in the presence of minimal amounts of water to provide water-cores in the
647 organic solvent. After that, the water-soluble analytes are driven to the water core aided
648 by stirring. Then phase separation is achieved by centrifugation and the surfactant-rich
649 phase became viscous and settle at the bottom. Then the sediment phase is transferred
650 to another screw-capped centrifuge tube. Then, back extraction is carried out by mixing
651 the surfactant-rich phase with water and chloroform. After sonication and
652 centrifugation, two distinct layers are formed, the upper one is the surfactant-rich phase,
653 while the lower one is the organic solvent-rich phase containing the analytes. Then, the
654 lower phase is used for the analysis of aldehydes. Ramezani et al. recently used this
655 method for extraction of aldehydes from oil samples using Triton X-100 as the
656 surfactant. They used methanol as an organic modifier which leads to partial dissolution
657 of the micellar aggregates making the micelle–micelle interactions easier and leading
658 to the formation of larger surfactant aggregate. The obtained recoveries were more than
659 80 % for all target analytes [114].
660
661 **4. Analytical applications of aldehydes in biological, food and environmental**
662 **samples**
663 The applications for the chromatographic determination of aldehydes are
664 summarized in the following sections and the used sample pretreatment, analytical
665 method, and sensitivities are summarized in tables. Also, significant findings obtained
666 by the application study are described.

667 **4.1. Analysis of aldehydes in biological samples**

668 **4.1.1. Blood, plasma, and serum**

669 Majority of the published articles for the determination of aldehydes in biological
670 samples were devoted to the screening of plasma, serum, and blood specimens (Table
671 1). All these methods were dedicated to the determination of aliphatic aldehydes, α-
672 oxoaldehydes, or mixture of them as they could be used as diseases biomarkers.

673 Our research group developed HPLC-FL, LC-MS/MS and ICD LC-MS/MS
674 methods for determination of aliphatic aldehydes in serum [47,75,79] depending on
675 their reaction with α-diketo compound and ammonium acetate. The ICD LC-MS/MS
676 method has been applied for the determination and comparison of the concentration
677 levels of HHE and HNE in healthy humans and patients with diabetes, rheumatoid
678 arthritis, or cardiac disorders. The levels of both aldehydes were found to be elevated
679 in all these diseased conditions [79].

680 Since MDA is a very reactive dialdehyde that is frequently used as a good
681 biomarker for lipid peroxidation status, oxidative damage, and disease progression,
682 some recent reports are still developed and devoted to its analysis in plasma. For
683 example, the plasma level of MDA has been recently determined by HPLC-CL using
684 acidic potassium permanganate CL system [94] and by HPLC-DAD-FL and HPLC-
685 DAD-MS after derivatization with TBA [55].

686 Xu group has developed some analytical methods for determination of hexanal
687 and heptanal in blood [38,103] and serum [37]. Applications of these methods have
688 been extended to the determination of the two aldehydes as biomarkers for cancer [103]
689 or lung disease [37,38]. Hexanal and heptanal have been also derivatized with PFBHA
690 before their determination in the blood of healthy, diabetic, and lung cancer patients by
691 GC-MS. This study showed that the two aldehydes are biomarkers for lung cancer [86].

692 Twelve aldehydes ($C_1$-$C_{12}$ alkanals) have been also determined in serum from
693 healthy and hepatitis B humans. The contents of ($C_1$-$C_5$) aldehydes in the hepatitis B
694 patients' serum were two times greater than those of the healthy, while nonaldehyde
695 was detected in the patient serum but not in the healthy one [46]. Wei et al. determined
696 ($C_1$-$C_7$) alkanals in blood from bladder cancer patients and they found significantly
697 higher levels of ($C_1$-$C_3$) and ($C_5$-$C_7$) in patients' blood relative to normal subjects
698 suggesting their use as biomarkers for bladder cancer [87]. Additionally, Eggink and
699 colleagues proposed an LC-MS method for the preliminary assay of $C_5$-$C_{10}$ alkanals in
700 plasma samples [63]. While O'Brien-Coker et al. have determined alkanals, alkenals,
701 and hydroxyalkenals in *in vitro*-oxidized plasma [73]. Moreover, Fiamegos and Stalikas
702 developed a method for the determination of a set of carbonyl compounds including
703 alkanals, alkenals, heptadienal, and MDA in plasma from healthy volunteers [83].

704 As mentioned previously, the levels of α-oxoaldehydes in blood, plasma, and/or
705 serum are utilized as biomarkers for many diseases such as diabetic, rheumatic, cardiac
706 disorders, Alzheimer's disease, nephropathy, and macrovascular disease. Our research
707 group was also concerned with the determination of four α-oxoaldehydes; glucosone
708 (GS), 3-deoxyglucosone (DG), GO, and methylglyoxal (MGO), in the serum of healthy,
709 diabetic, rheumatic, and cardiac disorders patients using HPLC-FL. This study realized
710 that GS, DG, GO and MGO can be used as diabetes biomarkers while MGO only can
711 be used as a cardiac disorder indicator [49]. Moreover, the innovative strategy
712 developed by our group for in situ introduction of a purification tag and a fluorophore
713 has been successfully applied for the determination of GOA in serum as a biomarker of
714 diabetes [51].

715 Henning et al. proposed an approach for determination of a series of α-DC
716 including 4,5-dihydroxy-2-oxopentanal, 4-hydroxy-2-oxobutanal, GO, GOA, and

717 MGO via derivatization with the traditional derivatizing agent, OPD, followed by LC-
718 MS/MS. The application of the method included a comparison of the levels of these
719 compounds in plasma of healthy and hemodialysis patients which was found to be
720 considerably higher in the patients' samples [71]. Many studies have been also devoted
721 to the determination of GO and MGO in serum, plasma, or blood as biomarkers of
722 diabetes using the pre-column derivatization approach coupled with different detection
723 modes [72,91,95,96,98].

724 α-Oxoaldehydes are also determined together with other reactive aliphatic
725 aldehydes in many reports. In our laboratory, we developed HPLC-FL [48] and HPLC-
726 CL [44] methods for their determination in sera of healthy, diabetic, and rheumatic
727 humans. It was found that GO, MGO, ACR, MDA, and HNE levels were elevated in
728 diabetic patients compared to the healthy subjects. On the other hand, only ACR, MDA,
729 and HNE levels were elevated in rheumatic patients compared to the healthy subjects
730 and there was no significant difference in GO and MGO levels among the two groups.
731 This aldehydes level patterns can be useful for understanding more and more about the
732 pathology of the studied two diseases. Recently, Tomono et al., successfully applied
733 LC/ESI-MS/MS for profiling and mapping of reactive carbonyl compounds, including
734 GO with another 30 aliphatic aldehydes, in mice plasma [68].

735 **4.1.2. Urine**

736 Determination of the levels of aldehydes in urine specimens has received also the
737 attention of many researchers as a biomarker for oxidative stress (Table 2). In this
738 context, Antón et al. developed a derivatization-free GC-MS method for $C_5$-$C_8$ alkanals
739 and benzaldehyde. This method was applied for the comparison of the concentrations
740 of these aldehydes in urine from smokers and non-smokers showing a non-significant
741 difference [80]. An automated PCD LC-MS/MS approach has been designed by Chen

742 et al. for the determination of hexanal and heptanal in urine as lung cancer biomarkers
743 [110].

744 There are many recent reports focused on the analysis α-oxoaldehydes
745 in urine samples as they are considered as a very important advanced
746 glycation end products biomarkers in this bio-specimen. Seven carbonyl
747 compounds including GO, MGO, GS, and DG were determined in urine
748 samples of healthy and diabetic humans by HPLC-FL [52]. As well, Many
749 methods were dedicated for analysis of GO and MGO only in urine samples
750 including HPLC-FL [54,93], GC-MS [89], and CE-AD [105]. The latter
751 method compared the levels of the two analytes in the urine of healthy
752 volunteers and urine from patients with nephrotic syndrome, diabetes,
753 hypertension, Parkinson and cancer showing significantly higher levels only
754 in case of diabetic and cancer patients. On the other hand the method of
755 Ojeda et al. [54] was applied to determine the levels of GO and MGO in
756 healthy volunteers (before and after alcohol intake), diabetic subjects, and
757 juvenile swimmers showing higher levels of GO in diabetic patients and
758 swimmers, while higher levels of MGO was observed in diabetic patients,
759 swimmers and healthy after alcohol intake. The GC–MS method was also
760 adopted for the determination of GO and MGO in the urine of healthy and
761 diabetic humans pointing to significantly higher levels of the two aldehydes
762 in diabetic subjects [89].

763 A wide range of oxidative stress-related aldehydes; including ($C_5$-$C_{10}$)
764 alkanals, *trans*-2-pentenal, cylcohexylcarboxaldehyde, and MDA, have been
765 determined simultaneously in urine by LC-MS/MS [61]. Also, a range of
766 LMMAs includes $C_2$-$C_6$ alkanals, ACR, and crotonaldehyde were determined

767 in urine matrix by GC-MS/MS [57]. In addition, Petasis reaction was utilized
768 by our laboratory for determination of GOA in human urine via HPLC-FL
769 [50].

770 It is noteworthy that, many of the methods mentioned before for analysis of
771 aldehydes in plasma or serum, were also successfully applied at the same time to urine
772 samples [37,63,83,94,95].

773 **4.1.3. Miscellaneous biological matrices**

774 In addition to blood derivatized matrices and urine samples, aldehydes were also
775 analyzed in some miscellaneous matrices including tissue homogenates and exhaled
776 breath condensates (Table 2). *N*-Propyl-4-hydrazino-1,8-naphthalimide has been used
777 as a sensitive derivatizing agent for HPLC-FL determination of a group of aliphatic
778 aldehydes ($C_3$-$C_{12}$) in mice liver and brain. This study revealed much higher levels of
779 nonanal and dodecanal than the other aldehydes in the liver, while the levels of
780 propanal, hexanal and nonanal were significantly higher than the other aldehydes in the
781 brain [97]. Williams et al. developed also LC-MS/MS method for determination of
782 aliphatic aldehydes ($C_3$-$C_{10}$) alkanals, ACR, and HNE after derivatization via Hantzsch
783 reaction. The method was applied to brain tissue from Alzheimer patients and control
784 subject of matched ages showing significantly higher levels of ACR and HNE in
785 Alzheimer patients [74]. MDA has been also determined in mice liver homogenate via
786 HPLC-FL [107].

787 Andreoli et al. developed LC-MS/MS method for the determination of various
788 aldehydes in exhaled breath condensate. The exhaled breath condensate is a biological
789 matrix that can be obtained via a non-invasive way for checking the pulmonary
790 condition. The study realized that the levels of MDA, ACR and n-hexanal are
791 particularly higher in case of smokers relative to non-smokers [58].

792

793 **4.2 Analysis of aldehydes in food samples**

794 The determination of aldehydes in food samples was usually performed to
795 monitor its quality and safety. Summary of the recently reported methods for the
796 determination of aldehydes in food samples is presented in table 3. Aldehydes in
797 vegetable oil have been determined by various chromatographic methods including
798 HPLC-UV [35], LC-MS/MS [23][60], and GC-FID [114]. During the extraction of
799 aldehydes from vegetable oil the antioxidative butylated hydroxytoluene was often
800 added into the sample in order to prevent the further oxidation of lipids. As common
801 findings of these studies, the concentration of aldehydes in vegetable oil was increased
802 according to the thermal oxidation. Therefore, these results revealed that aldehydes
803 contents in oil samples could be used as an index marker of lipid deterioration.

804 Aliphatic aldehydes, especially formaldehyde and acetaldehyde, were
805 extensively tested in alcoholic beverages [39,45,81]. It was found that the aldehydes
806 contents in red wines were higher than that in white wines [39,81]. Determination of
807 formaldehyde, furfural, and methylpropanal in beer samples has been also
808 accomplished by HPLC-UV and confirmed by LC–APCI–MS [34]. Abu-Bakar et al.
809 reported an HPLC-UV method for the determination of furfurals in fruit juice samples
810 based on the direct absorbance detection of furfurals after their extraction. They
811 reported that some apple and grape juice samples contained higher levels of 5-
812 hydroxymethylfurfural than the legal limit established by the International Federation
813 of Fruit Juice Producers. These results might be attributed either to storage under
814 unsuitable conditions, or long-time heating during the production process. [104].

815 Several determination methods of aldehydes in the drinking water have been
816 developed including GC-MS [24,84], and micellar electrokinetic chromatography [41].

817 Serrano et al. mentioned that the disinfection treatment of drinking water could induce
818 the formation of aldehydes in water [24]. Especially, they reported that the
819 concentrations of the aldehydes found in ozonated water were the highest compared to
820 those in water treated by chlorination or chloramination. Kim and Shin also reported
821 that commercial mineral water contained a much higher amount of aldehydes than
822 surface waters [84]. Also, it was reported that swimming pool water treated by
823 chlorination contained the same levels of aldehydes with drinking water treated by
824 ozonation [41].

825 Gosseti el al. determined 12 aldehydes in cooked food by LC-MS/MS and
826 investigated the influence of food matrices and cooking modes on the formation of
827 aldehydes [59]. For example, the amount of medium-chain aliphatic aldehydes such as
828 nonanal in the steak cooked in olive oil was much greater than those in the steak cooked
829 in butter. On the other hand, different food matrices did not contribute significantly to
830 the formation of aldehydes during the cooking process. A capillary micellar
831 electrokinetic chromatography with UV detection method was developed by Donegatti
832 et al. for the determination of $C_1$-$C_4$ aldehydes in yogurt and vinegar, and finally, only
833 acetaldehyde could be detected in both samples [40]. Determination of volatile
834 aldehydes in canned vegetables was carried out by GC-MS [85]. Fifteen aldehydes were
835 determined in the solid and the liquid phases of canned vegetables. It was noteworthy
836 that relatively harmful aldehydes such as formaldehyde and GO were mainly detected
837 in the liquid phases, namely, the non-edible portion of canned vegetables. α-
838 Oxoaldehydes including GO in various baby foods were determined by LC-MS [27].
839 Although the concentrations of α-oxoaldehydes were relatively low compared to DG,
840 they mentioned that food processing treatments could induce the formation of reactive
841 carbonyl species in high amounts.

### 4.3. Analysis of aldehydes in environmental samples

In general, the monitoring of aldehydes in environmental samples should be carried out to controlling the possible health risk of toxic aldehydes on human health. Recent reports for aldehydes determination in environmental samples were summarized in table 4. Various aldehydes including formaldehyde, benzaldehyde, and ACR in atmospheric particulates were determined by HPLC-UV and it was reported that concentrations of aldehydes in the rural site were slightly higher than those in the industrial site [33]. Rosenberger et al. determined 14 aldehydes in the cabin-air of a commercial aircraft. The concentrations of aldehydes in the air at taxi-takeoff-climb phases were higher than those at the total flight phases [115]. The concentration of 4 aldehydes in the gas phase of cigarette mainstream smoke was determined by GC-MS without any derivatization reaction. The concentration of aldehydes in the smoke of cigarettes sold in the United States was higher than that in the smoke of cigarettes sold in China.[31].

Short-chain aliphatic aldehydes in rainwater were determined by HPLC-UV. The order of abundance of aldehydes in rainwater was formaldehyde > acetaldehyde > propionaldehyde > valeraldehyde [29]. Liu et al. developed a determination method for aldehydes in environmental water samples. The developed method was applied to determine 7 aldehydes in river water, snow water, and seawater. As a result, aldehydes could not be detected in the river water, and while trace and a moderate amount of formaldehyde were detected in the snow water and the seawater, respectively [30]. Lin et al. reported a determination of aliphatic aldehydes in waters containing heavy metal ions. They mentioned that the photo illumination to Cu(II)/amino acid complex could induce the formation of aldehydes in the aqueous phase [36]. The determination of

867 aliphatic and aromatic aldehydes in swimming pool water sample was reported by
868 Serrano et al. The concentrations of aldehydes detected in the swimming pool water
869 were significantly higher than those in tap water and well water [116].
870

871 **5. Conclusions**

872 Herein, we summarized the various chromatographic techniques previously
873 reported for aldehydes determination in various matrices including HPLC analysis
874 coupled with UV, FL, and MS detection and GC methods. Effective derivatization
875 reactions that were applied for aldehydes to improve their detection sensitivity and
876 control their retention behavior on chromatographic columns were thoroughly
877 discussed. Since the extraction of aldehydes form complex matrices is a very difficult
878 and challenging process due to their high volatility, reactivity, polarity, and inherent
879 instability, different classical and recently reported sample pretreatment procedures of
880 aldehydes for their pre-concentration and overcoming matrix effect are summarized and
881 discussed in this review. Also, the fields in which the reported chromatographic
882 methods for aldehydes were applied and their obtained significant findings were
883 described and discussed. After going through the previously reported methods for
884 aldehydes, we can conclude that, in order to develop a successful integrative assay for
885 aldehydes, it is crucial to choose the appropriate derivatization and extraction technique
886 deepening on the characteristics of the target aldehydes and their objected matrices.
887

888 **References**

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1317 aldehydes in water, Anal. Chim. Acta. 784 (2013) 77–84.
1318

Table 1. Summary of the reported method for the determination of aldehydes in blood-derived samples

| Targeted aldehydes | Matrix/ Sample volume, µL) | Sample pretreatment | Reagent | Analytical method | LOD, nM | % Recovery | Ref. |
|---|---|---|---|---|---|---|---|
| $C_6$-$C_{10}$ alkanals | Serum/ 50 | PPT | 2,2`-Furil | HPLC-FL | 0.25-0.5 | 88-105 | [47] |
| $C_3$-$C_{10}$ alkanals | Serum/ 200 | SO-LLE | PQ+ ammonium acetate | LC-MS/MS | 0.004-0.1 | 93-111 | [75] |
| HHE and HNE | Serum/ 200 | SO-LLE | PQ+$^{14}$/$^{15}$N ammonium acetate | LC-MS/MS | 0.05-0.01 | 92-99 | [79] |
| MDA | Plasma/ 50, urine / 50 | PPT | $H^+$/$KMNO_4$ | HPLC-CL | 80 | 92-99 | [94] |
| MDA | Plasma/ 100 | PPT | TBA | HPLC-DAD, HPLC-FL, LC-MS | 250-2860 | N/A[a] | [55] |
| $C_6$,$C_7$ alkanals | Serum/ 500 | DLLME | DNPH | LC-MS/MS | 0.08-0.17 | 94-110 | [103] |
| $C_6$,$C_7$ alkanals | Serum/ 500 | HS-LPME | DNPH | HPLC-UV | 0.8 | 75-101 | [38] |
| $C_6$,$C_7$ alkanals | Serum/ 200 &Urine/ 200 | SPME | DNPH | HPLC-UV | 0.8 | 70-89 | [37] |
| $C_6$,$C_7$ alkanals | Blood/1000 | HS-SDME | PFBHA | GC-MS | 0.2-0.3 | 88-92 | [86] |
| $C_1$-$C_{12}$ alkanals | Serum/200 | PPT | BODIPY-aminozide | HPLC-FL | 0.4-0.7 | 94-110 | [46] |
| $C_1$-$C_7$ alkanals | Blood/1000 | HS | PFBHA | GC-MS | 2-7 | 92-106 | [87] |
| $C_6$-$C_{10}$, alkenals, HHE, HNE | Plasma/500 | SPE | CDH | LC-MS/MS | (10-100 Pg) | N/A[a] | [73] |
| $C_5$-$C_{10}$ alkanals, pentenal | Plasma/250 &Urine/140 | Centrifugat-ion | 4-APEBA | LC-MS/MS | N/A[a] | N/A[a] | [63] |
| $C_1$, $C_4$, $C_5$, $C_6$ alkanals, MDA, ACR, hexenal, crotonaldehyde, 2,4-heptadienal | Plasma, Urine, Oil/ 7000 | HS-SDME | TCPH | GC-MS | 12-321 | 87-116 | [83] |
| GS, DG, GO, MGO | Serum/ 25 | PPT | CMBAL + Ammonium acetate | HPLC-FL | 0.4-5 | 93-105 | [49] |
| GOA | Serum/ 50 | Purification tag + SPE | 1-PyBA + Taurine | HPLC-FL | 30 | 87 | [51] |
| 19 α-DCs | Plasma/ 500 | PPT | OPD | LC-MS/MS | 3-7 | 82-120 | [71] |
| DG, GO, MGO | Plasma/ 25 | PPT | OPD | LC-MS/MS | 5–100 | 72-126 | [72] |
| GO, MGO, DMGO | Serum/ 5000 | PPT + LLE | Stilbenediamine | CE-UV | 60–80 | N/A[a] | [96] |
| MGO, DMGO | Serum/ 5000 | PPT + LLE | 1,2-Diaminopropane | GC-FID | 555 | 97 | [91] |
| DG, GO, MGO | Plasma/ 500 | PPT + LLE | PFBOA + MSTFA | GC-MS | 79–433 | 67-90 | [98] |
| GO, MGO, DMGO | Serum/ 5000, urine/ 2000 | PPT + LLE | 5,6-Diamino-2,4-hydroxypyrimidine | GC-FID | 116–345 | 98-99 | [95] |
| GO, ACR, MDA, HNE | Serum/ 50 | PPT | 2,2'-Furil | HPLC-FL | 30-110 | 96-103 | [48] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MOG, ACR, crotonaldehdye, hexenal | Serum/100 | PPT | DBD-H | HPLC-CL | 4-7 | 87-104 | [44] |
| 31 aldehydes | Plasma/ 20 | LLE | DNSH | LC-MS/MS | 0.2-4 | 70-112 | [68] |

[a] N/A: Not available

Table 2. Summary of the reported method for determination of aldehydes in urine and other miscellaneous biological samples

| Targeted aldehydes | Matrix/ Sample volume, μL) | Sample pretreatment | Reagent | Analytical method | LOD, nM | % Recovery | Ref. |
|---|---|---|---|---|---|---|---|
| $C_5$-$C_8$ alkanals, Benzaldehyde | Urine/2500 | HS | none | GC-MS | 0.4-0.8 | 86-120 | [80] |
| $C_6$, $C_7$ alkanals | Urine/200 | SPME | HAHC | LC-PCD-MS | 9-15 | 100-117 | [110] |
| GS, DG, GO, MGO | Urine/ 300 | SPE | 6-Hydroxy-2,4,5-triaminepyrimidine | HPLC-FL | 0.8–27 | 89-111 | [52] |
| GO & MGO | Urine/ 1000 | Direct dilution | 2,3-Diamino-2,3-dimethylbutane | HPLC-FL | 91–93 | 102-109 | [93] |
| GO, MGO & DMGO | Urine/ 200 | SALLE | 4MPD | HPLC-FL | 3-8 | 92-103 | [54] |
| GO & MGO | Urine/ 2000 | Double SPE | TBA | CE-AD | 3-9 | 91-101 | [105] |
| GO & MGO | Urine/ 4000 | SALLE+DLLME | 2,3-Diaminonaphthalene | GC-MS | 1-2 | 86-112 | [89] |
| ($C_5$-$C_{10}$) alkanals, MDA, pentenal, cylcohexanal | Urine/250 | Centrifugation | 4-APC | LC-MS | 2-33 | N/A[a] | [61] |
| $C_2$-$C_6$ alkanals, ACR, and crotonaldehyde | Urine/10000 | Online SPE | DNPH | GC-MS/MS | 0.4-0.9 | 92-100 | [57] |
| GOA | Urine/50 | PPT | 1-PyBA + *N*-Methylbutylamine | HPLC-FL | 5 | N/A[a] | [50] |
| ($C_3$-$C_{12}$) alkanals | Liver and brain/300 mg | Homogeniza-tion + PPT | *N*-Propyl-hydrazino-1,8-naphthalimide | HPLC-FL | 0.3-1 | 95-109 | [97] |
| $C_3$-$C_{10}$ alkanals, ACR, HNE | Brain/ 100 mg | Homogeniza-tion + PPT | CHD | LC-MS/MS | 5-1500 pg | N/A[a] | [74] |
| MDA | Liver homo-genate/30 | Online SPE | DNSH | HPLC-FL | 0.3 | 106 | [107] |
| $C_6$,$C_7$,$C_9$ alkanals, MDA, alkenals | EBC/ 100 | none | DNPH | LC-MS/MS | 1 | N/A[a] | [58] |

[a] N/A: Not available

Table 3. Summary of the reported method for the determination of aldehydes in food samples

| Targeted aldehydes | Matrix/ Sample volume | Sample pretreatment | Reagent | Analytical method | LOD | % Recovery | Ref. |
|---|---|---|---|---|---|---|---|
| MDA, HHE, HNE | Vegetable oil/ 2 g | PPT | DNPH | HPLC-UV | 0.009-0.014 μg $mL^{-1}$ | 96-101 | [35] |
| MDA, HHE, HNE | Vegetable oil/ 2 g | PPT | DNPH | LC-MS/MS | 0.02-0.14 mg $kg^{-1}$ | 79-101 | [23] |
| HNE | Vegetable oil/ 3 mL | PPT | PFPH | LC-MS/MS | 3.4 ng $g^{-1}$ | 100-102 | [60] |
| $C_3$-$C_7$ alkanals | Vegetable oil/ 5 mL | Reverse micelles technique | none | GC-FID | 20.0-80.0 μg $L^{-1}$ | 80 | [114] |
| Alkanals, alkenals, benzaldehyde , furfural | Wine / 0.77 mL | HS-SPME | none | GC-MS | 2.0-8.0 μg $L^{-1}$ | 20-190 | [81] |
| $C_1$-$C_3$ alkanals, ACR, furfural benzaldehyde | Wine / 10 mL | GDME | 4-Hydrazinobenzoic acid | HPLC-UV | 0.005-0.21 mg $L^{-1}$ | N/A[a] | [39] |
| $C_1$-$C_{10}$ alkanals | Alcoholic beverage/ 20-30 μL | none | DBCEEC | HPLC-FL | 0.20-1.78 nmol $L^{-1}$ | 99-104 | [45] |
| Acetoardehyde, furfural and methylpropanal | Beer / 10 mL | GDME | DNPH | HPLC-UV | 1.5-12 μg $L^{-1}$ | N/A[a] | [34] |
| Furfurals | Fruits juice / 5 mL | Salting out-vortex assisted LLME | none | HPLC-UV | 0.28-3.5 μg $L^{-1}$ | 82-105 | [104] |
| $C_1$-$C_5$ alkanals, GO, MGO, benzaldehyde | Drinking water /10 mL | HS | PHBHA | GC-MS | 0.002-0.08 μg $L^{-1}$ | 97-99 | [24] |
| $C_1$-$C_{10}$ alkanals | Drinking water /4.0 mL | HS-SPME | TEFH | GC-MS | 0.0001-0.0005 mg $L^{-1}$ | N/A[a] | [84] |
| $C_1$-$C_{10}$ alkanals, benzaldehyde | Drinking water /100 mL | SPME | DNPH | MEKC-UV | 65-775 ng $L^{-1}$ | N/A[a] | [41] |
| $C_1$-$C_{10}$ alkanals, ACR, benzaldehyde | Cooked meat/10 g | Homogenizati-on + on-line SPE | DNPH | LC-MS/MS | 0.002-0.272 μg $kg^{-1}$ | 71-100 | [59] |
| $C_1$-$C_3$, $C_5$ alkanals | Yoghurt/ 0.5 mL | Filtration | Benzhydrazide | MEKC-UV | 0.40-0.53 mg $L^{-1}$ | 80-125 | [40] |
| $C_1$-$C_9$ alkanals, GO, MGO, benzaldehyde | Canned vegetable/ 2 g | HS | PFBHA | GC-MS | 0.02-0.1 μg $kg^{-1}$ | 89-99 | [85] |
| GO, MGO, DMGO | Baby food / 1 g | PPT | OPD | LC-MS | 2.9-27.1 μg $kg^{-1}$ | 88.9-110 | [27] |

[a] N/A: Not available

Table 4. Summary of the reported method for the determination of aldehydes in environmental samples

| Targeted aldehydes | Matrix/ Sample volume | Sample pretreatment | Reagent | Analytical method | LOD | % Recovery | Ref. |
|---|---|---|---|---|---|---|---|
| $C_1$-$C_{10}$ alkanals, ACR, benzaldehyde | Atmospheric particulates on quartz fiber filter | Ultrasonic extraction | DNPH | HPLC-UV | 2.5-10.1 ng $mL^{-1}$ | 86-110 | [33] |
| $C_1$-$C_6$ alkanals, ACR, benzaldehyde | Cabin air | SPE | DNPH | HPLC-UV | 8-20 ng | 98-103 | [115] |
| $C_2$, $C_6$ alkanals, ACR, crotonaldehyde | Cigarette smoke | HS | none | GC-MS | 0.014-0.12 μg $cigarette^{-1}$ | 79-115 | [31] |
| $C_1$-$C_5$ alkanals | Rainwater / 5 mL | μSPE | DNPH | HPLC-UV | 0.027-0.15 μg $L^{-1}$ | 85-107 | [29] |
| $C_1$-$C_5$ alkanals, ACR, crotonaldehyde | Environmental water / 10 mL | Single drop LLME | DNPH | HPLC-UV | 0.04-2.03 ng $mL^{-1}$ | 84-107 | [30] |
| $C_1$-$C_9$ alkanals | Environmental water / 0.5 mL | none | DNPH | HPLC-UV | 7-121 nM | 93-115 | [36] |
| $C_1$-$C_5$ alkanals, GO, MGO, benzaldehyde | Swimming pool water/ 9 mL | LLE | PFBHA | GC-MS | 0.7-80 ng $L^{-1}$ | 96-99 | [116] |

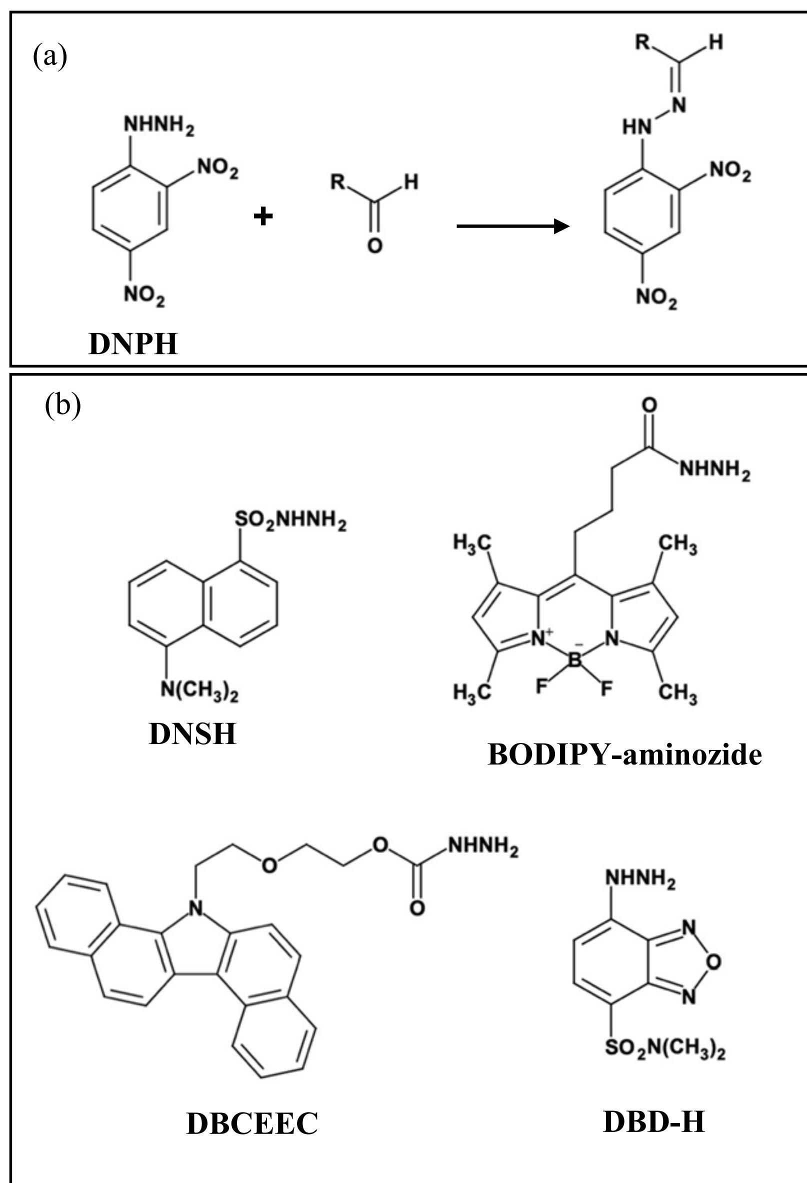


Fig. 1. Hydrazine reagents for the derivatization of aldehydes where a) the derivatization reaction between DNPH and aldehydes and b) the structure of aldehydes fluorescence labelling hydrazine reagents

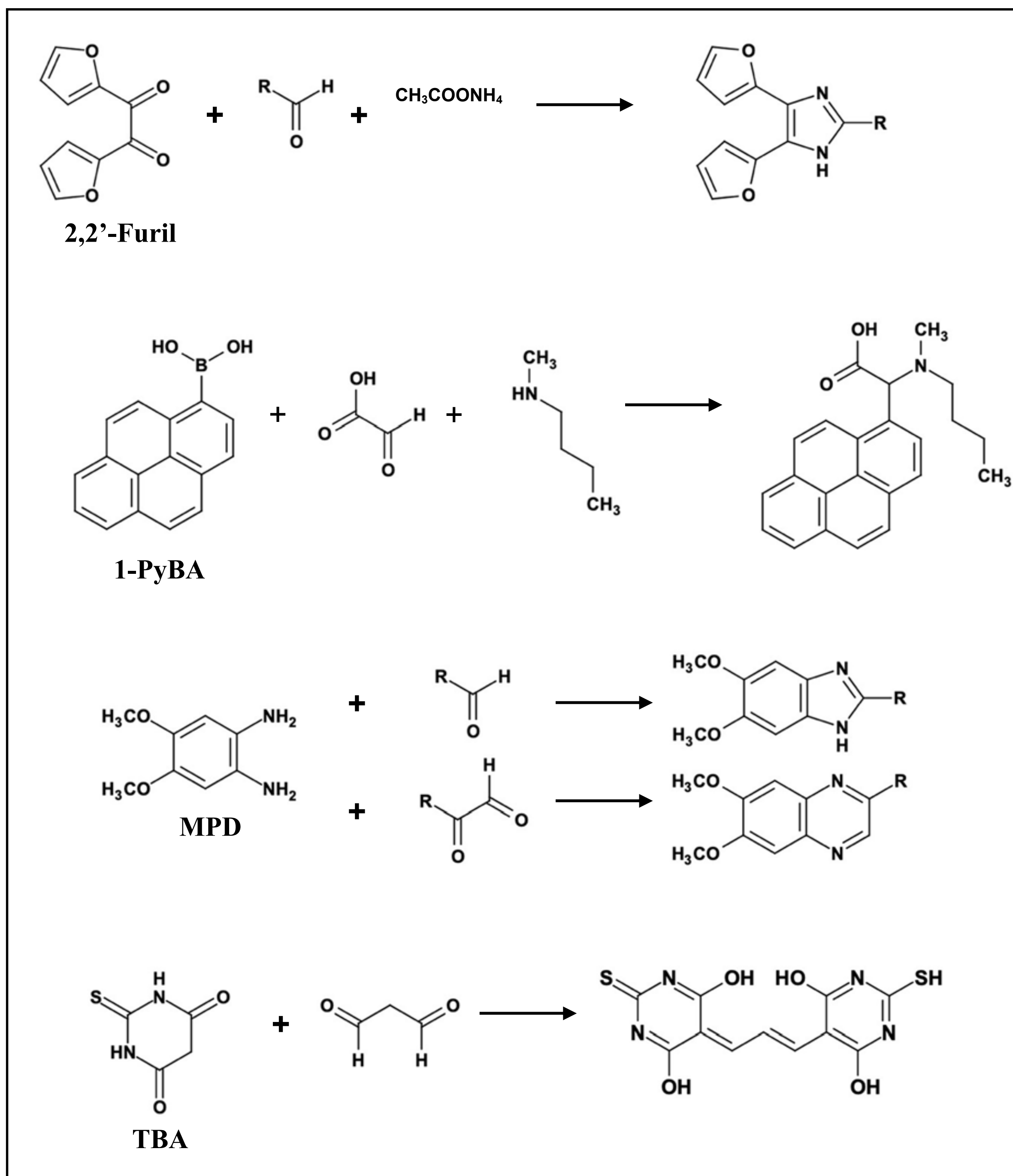


Fig. 2. Fluorescence derivatization reagents other than hydrazines, and the formed derivatives after their reaction with aldehydes.

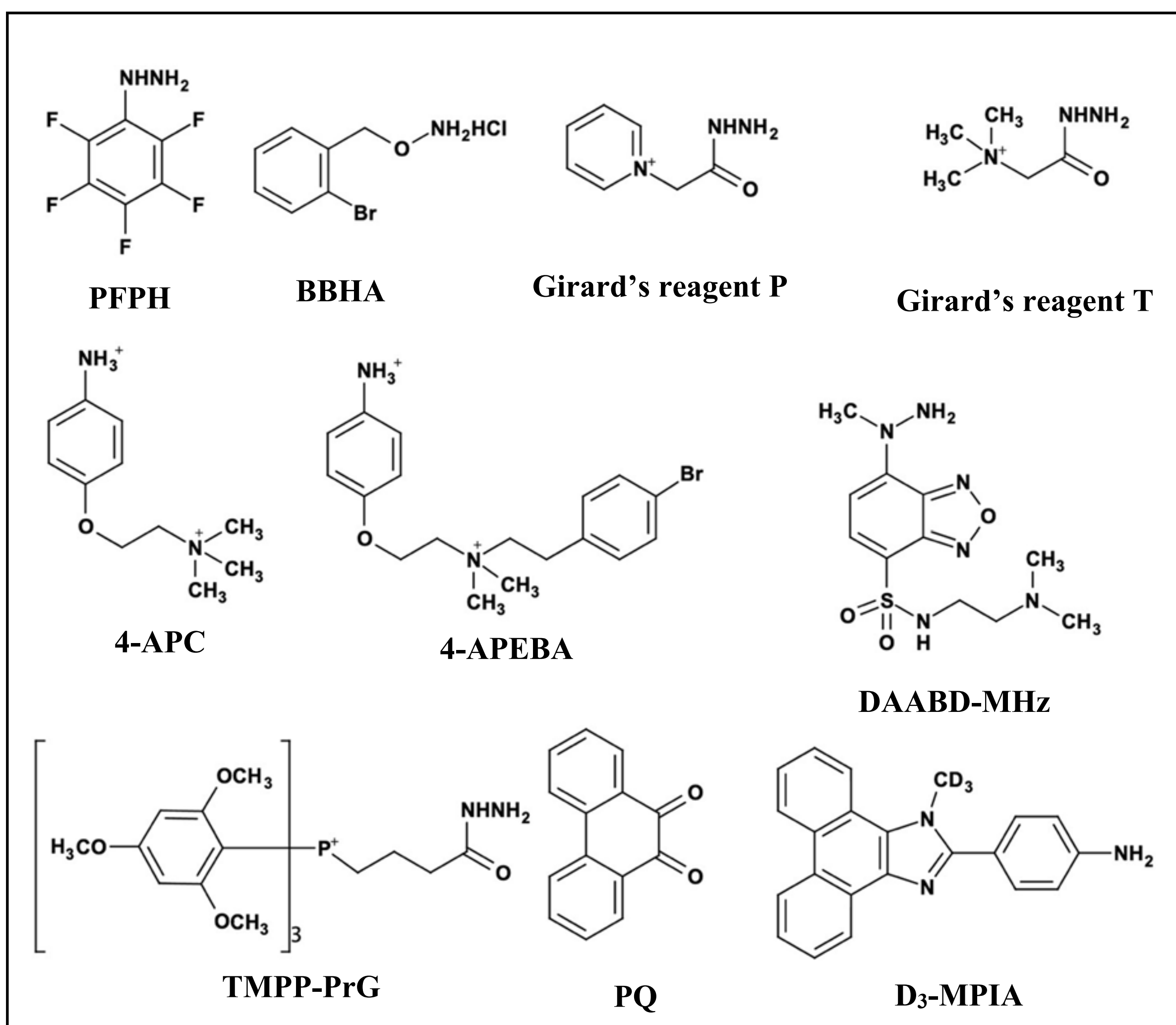


Fig. 3. Derivatization reagents for the LC-MS analysis of aldehydes

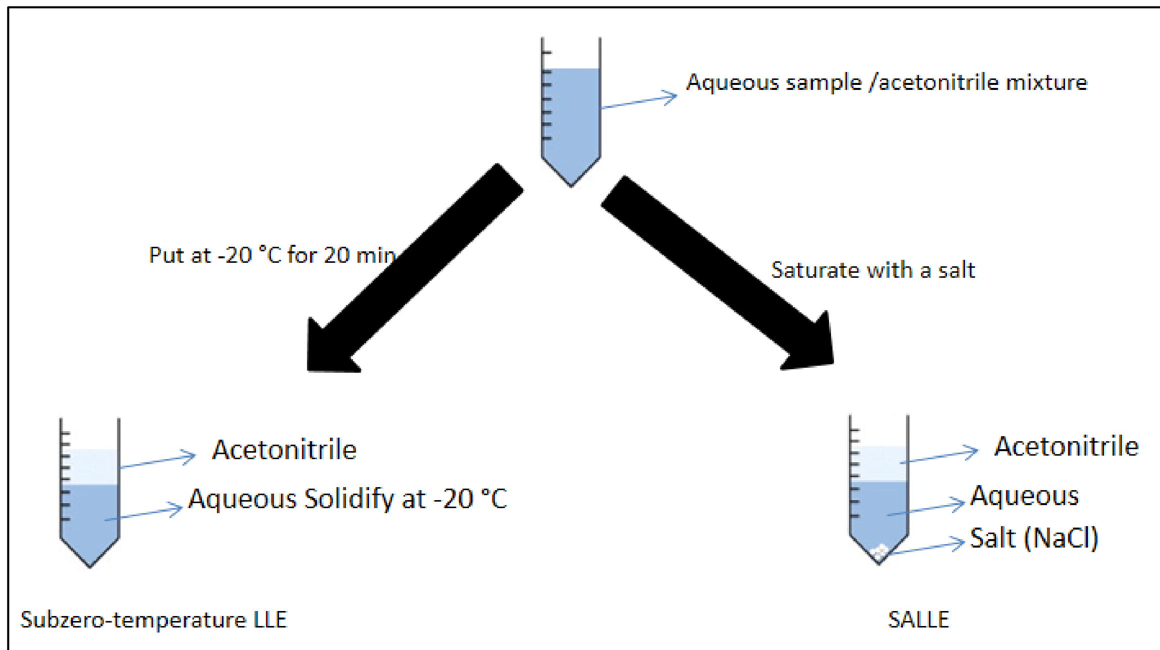


Fig. 4. Representative diagram for subzero-temperature LLE and SALLLE.

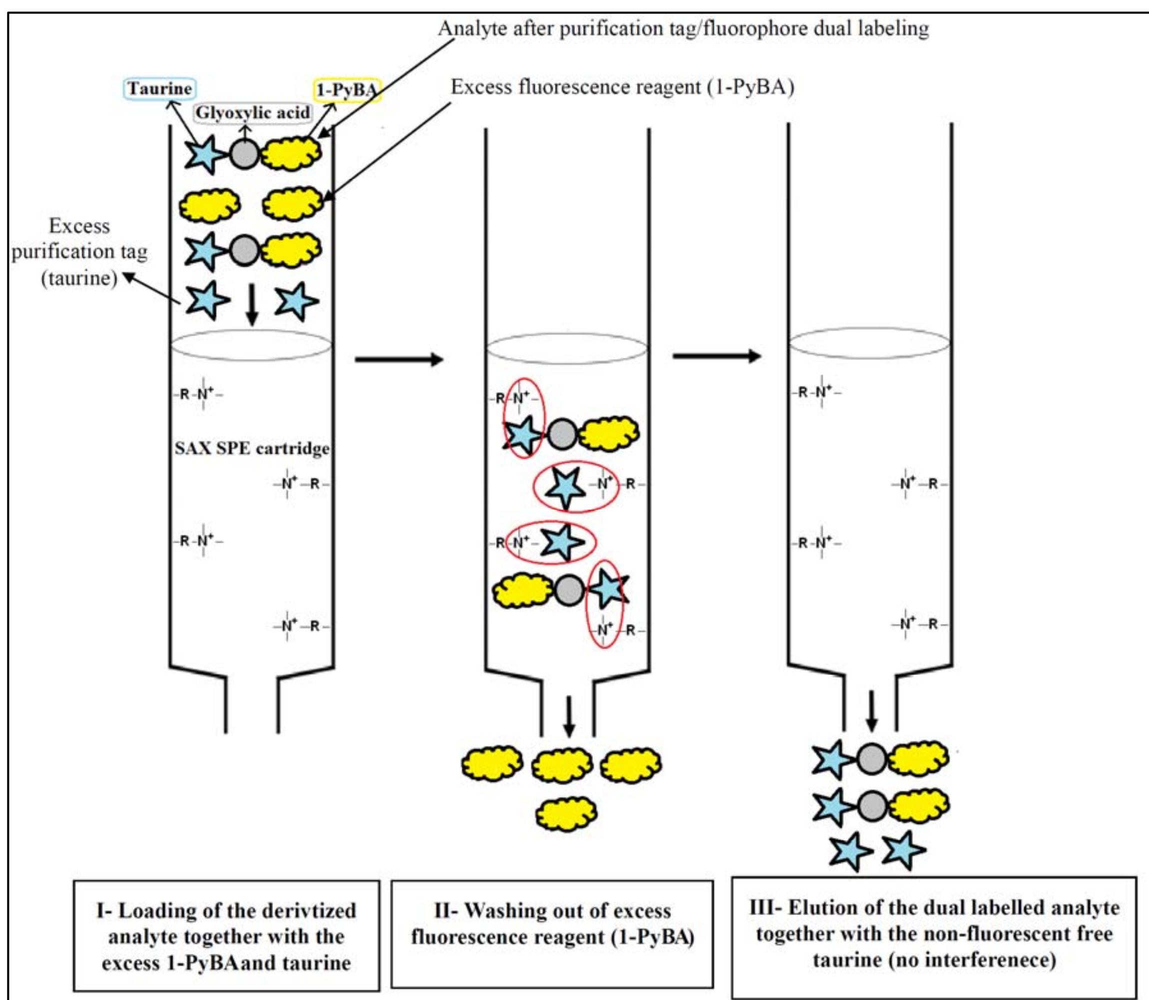


Fig. 5. Separation of the derivatized analyte from excess fluorescence reagent by solid-phase extraction after purification tag/fluorophore dual labeling. Reprinted with permission from Ref. [51] © Elsevier.

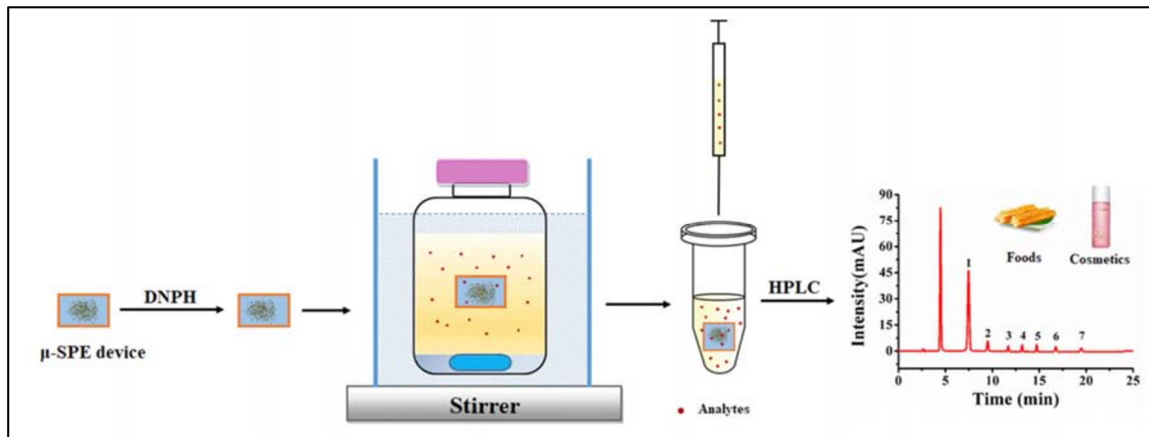


Fig. 6. Schematic diagram of membrane protected μ-SPE-D-HPLC method. Reprinted with permission from Ref. [108] © Elsevier.

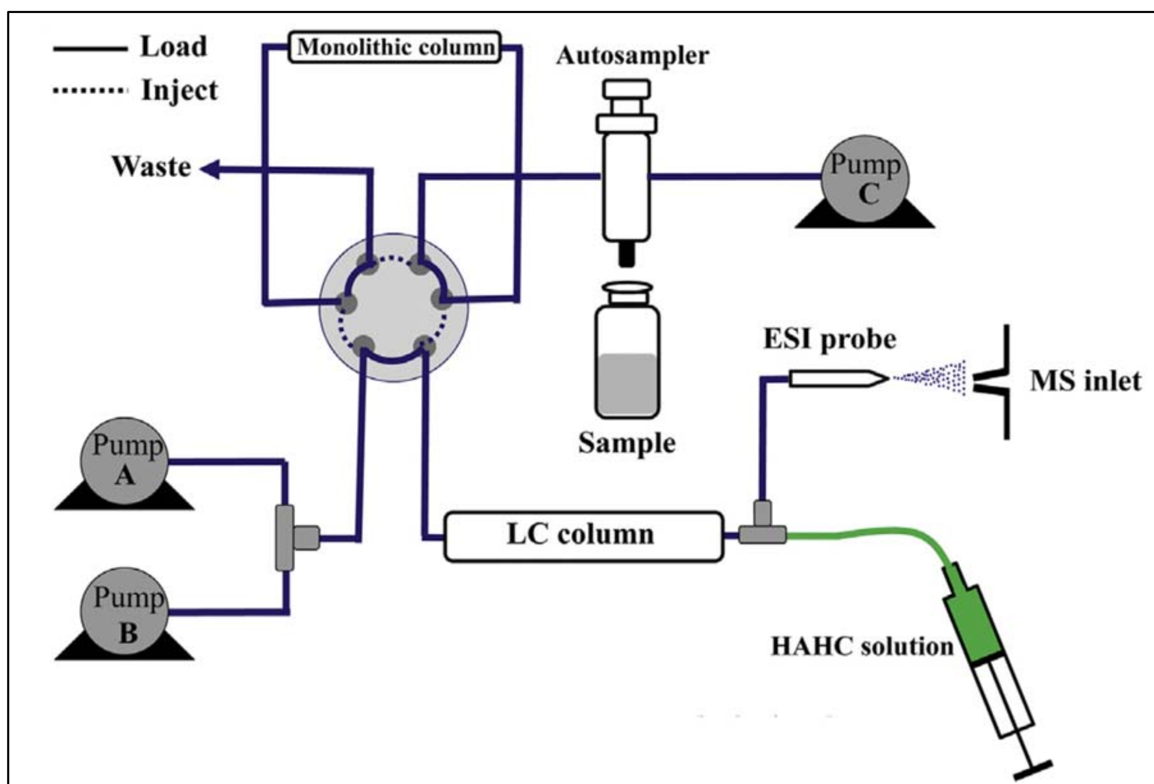


Fig. 7. The scheme for the fully automated in-tube SPME/LC-PCD-MS analysis of aldehydes. Reprinted with permission from Ref. [110] © Elsevier.

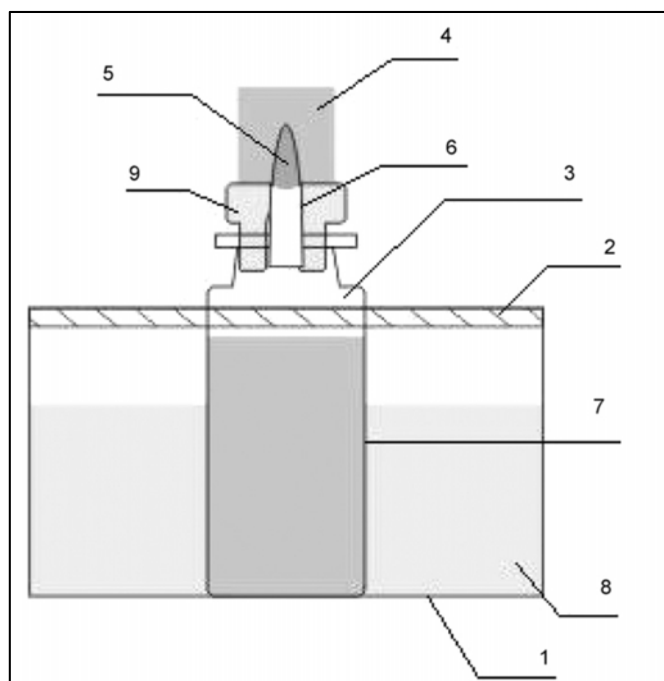


Fig. 8. The schematic diagram of HS-LPME apparatus. (1) Ultrasonicator; (2) adiabatic baffle; (3) headspace phase; (4) ice bag; (5) extractant; (6) PCR tube; (7) sample vial; (8) water bath; (9) rubber cover. Reprinted with permission from Ref. [111] © Elsevier.

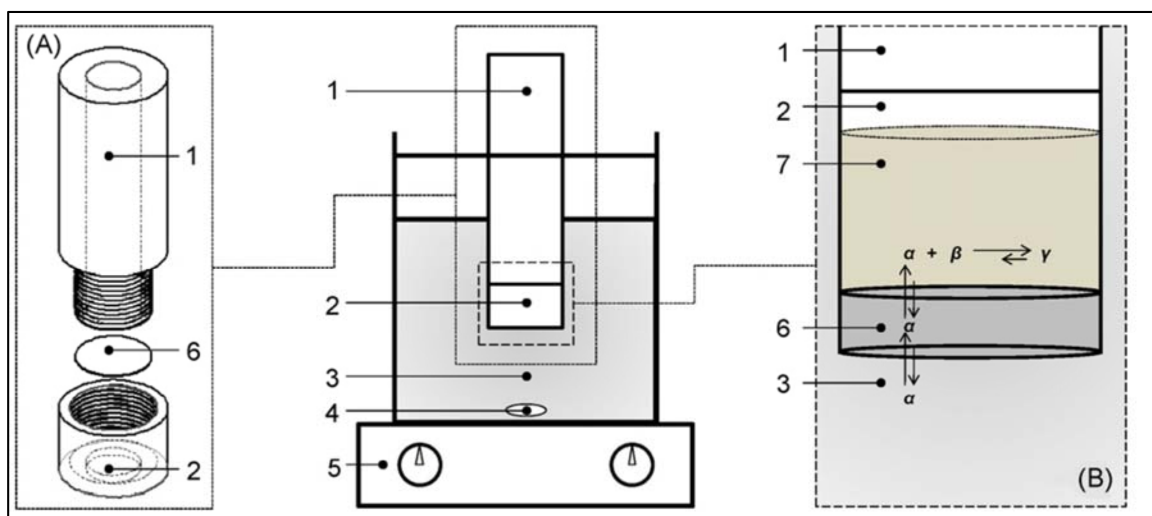


Fig. 9. A scheme of GDME. (A) Exploded computer-aided design view of the extractor, (B) schematic detail of the chemical equilibria; 1–extractor's superior piece, 2–extractor's lower piece, 3–sample solution, 4–magnetic stir bar, 5–heating element with magnetic stirring, 6–membrane, 7–acceptor solution; α– analyte, β–derivatizing agent, γ–derivate. Reprinted with permission from Ref. [34] © Elsevier.