



Review Article

Current sample preparation strategies for the chromatographic and mass spectrometric determination of furfural compounds

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ABSTRACT

Furfural compounds, formed during food storage and processing, are widely existed in food samples. Formation of furfural compounds may affect the safety and quality of foods. Thus, many countries and organizations have issued policies to limit the maximum content of furfural compounds. Therefore, it is necessary to develop analytical methods to monitor the concentration of furfural compounds in foods. However, the direct instrumental analysis of furfural compounds in foods is a continuous challenge, mainly because of complex samples and large amounts of co-existing interfering substances. Therefore, appropriate sample preparation methods, such as derivatization, liquid-liquid extraction, solid-phase extraction, solid-phase microextraction, and Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS), should be selected to remove the interferences and enrich target analytes before detection. The combination of effective sample preparation methods and appropriate instrument detection techniques is the key to determining the analysis efficiency and the result accuracy. To the best of our knowledge, there have been no review articles focused on sample preparation methods for the detection of furfural compounds in foods. Thus, this review aims to summarize the latest progress in sample preparation methods for furfural compound analysis in foods from 2012 to 2022. Their advantages and limitations are also discussed. The current review will help researchers choose suitable sample pretreatment and detection methods.

1. Introduction

Furfural compounds are heterocyclic compounds and mainly include: 5-hydroxymethylfurfural (HMF), furfural (F), 2-furylmethylcetone (FMC) and 5-methylfurfural (MF) [1]. It is reported that furfural compounds exist in high content in carbohydrate-rich foodstuffs, such as breads [2], fruit juices [3,4], honeys [5-7], coffees [8], wines [9], milks [10] and some other dairy products [11]. They are the products of Maillard reaction and mainly formed during food storage and processing, especially during heat processing. Some studies have revealed that their concentrations are closely related to the food processing and storage conditions, such as temperature and time of heating [12], pH [13,14], storage time [15], sugar type [16]. Therefore, furfural compounds can serve as indicators of the extent of the Maillard reaction [17], which is a hot issue in studying the effects of heat-processed on foods quality and safety. Although Maillard reaction provides delicious flavor and attractive color for foods, its products such as furfural compounds have negative effects on human health. Especially, HMF is

receiving a lot of attention than other furfural compounds because some studies have shown that HMF has cytotoxic, mutagenic effects, genotoxic and carcinogenic consequences [17-21]. Many countries and organizations such as the Codex Alimentarius of the World Health Organization and the European Union have set the regulations on maximum content standard for furfural compounds in foods [22]. Therefore, it is necessary to develop the quantitative analysis methods of furfural compounds in foods to achieve these limits, ensure food safety and quality, as well as to guide food processors to reduce the formation of furfural compounds in foods by optimizing food processing and storage conditions.

For the present, various analytical techniques have been developed to determine furfural compounds in food samples, including gas chromatography (GC) [23], high-performance liquid chromatography (HPLC) [24], mass spectrometry (MS) [25], electrochemical method [5] and spectrophotometric method [26]. Among these techniques, the chromatographic separation has the ability to separate interferences and analytes, and identify the analytes based on the retention times [27,28].

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The mass spectrometric techniques directly identify the analytes from the interferences based on their different mass-to-charge ratios [29]. Therefore, chromatographic and mass spectrometric techniques have become the most widely used detection techniques for the good detection selectivity/sensitivity and the ability of simultaneous detecting multiple components [30-32].

Despite the numerous characteristics of chromatographic and mass spectrometric techniques, the direct chromatographic and mass spectrometric analysis of furfural compounds in foods constitutes a challenging task. Considering the complex and diverse chemical properties of food samples and the low analytes content, practical problems still exist in the analysis of furfural compounds in food samples without sample preparation. The matrix interferences may prevent the furfural compounds of low abundance from successful detection and quantification [33,34]. The incompatibility between the complex food samples and the instrument detection may also exist. Complex samples can be homogenized, concentrated and enriched by pretreatment to improve the detection sensitivity and eliminate matrix interferences [35]. Therefore, employing suitable sample preparation prior to instrument detection is critical for unequivocal identification, confirmation, and quantification of furfural compounds.

At present, there are various sample preparation methods, often used in combination with chromatography and mass spectrometry (MS) [30,36-38], to achieve efficient sample preparation. These methods include liquid-liquid extraction (LLE), liquid-liquid microextraction (LLME), solid-phase extraction (SPE), solid-phase microextraction (SPME), Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS), and chemical derivatization. Different sample preparation methods have different application fields, advantages, and disadvantages. Recently, Martins *et al.* presented an overview of analytical methods for detecting HMF in food matrices [22]. However, to the best of our knowledge, there are no review articles focusing on sample preparations for the detection of furfural compounds in foods, which is a key process for the successful content determination. The aim of the present review is to introduce the recent developments in the sample preparation of the furfural compounds analysis in foods from 2012 to 2022 (Fig. 1).

2. Sample preparation techniques

Furfural compounds are usually present at low concentration in complex food sample matrices, with numerous co-existing interfering components, which renders the analytical task even more challenging. Suitable sample preparation methods can be applied prior to instrument detection. By effectively enriching the furfurals, removing the interferences, and transforming the furfurals into the desired morphology to strengthen the detection sensitivity and selectivity, the detection performance could be greatly improved.

2.1. Liquid-liquid extraction-based methods

LLE is a widely used technique of sample preparation in food analysis. Separation is achieved by partitioning the sample between two immiscible liquids or phases [39]. However, traditional LLE usually presents some drawbacks: high time and effort consumption, large required volumes of organic solvents, and poor performances in highly polar analytes. In order to overcome the drawbacks of traditional LLE, several microextraction techniques, such as LLME and DLLME, have become more popular, as they provide a series of advantages, including low costs, high efficiency, efficient recovery, and good enrichment factors [40-43]. Various analytical techniques (e.g., gas chromatography and high-performance liquid chromatography) are used in combination with DLLME or LLME for the detection of furfural compounds in food samples (Table S1). As a powerful analytical technique, the combination of DLLME and HPLC is frequently used, even today [44-46]. For instance, Madani-Tonekaboni *et al.* used DLLME coupled with HPLC to determine the contents of F and HMF in infant milk powder [36].

DLLME is a two-step procedure involving the extraction and dispersion of analytes as well as the separation of analytes by centrifugation. Extraction occurs in a ternary mixture of the extraction solvent, dispersive solvent and aqueous sample [47]. Manual shaking was used to promote the homogenization of the mixed solvent in the early stage. The emergence of very fine droplets provides extensive surface contact, which helps to enrich analytes in the extraction solvent. Finally, the dispersed phase can be separated by centrifugation [48]. As shown in Fig. 2, Altunay *et al.* successfully used magnetic ionic-liquid ultrasound-assisted dispersive liquid-liquid microextraction to determine the contents of HMF in honey samples [49]. Selecting suitable microextraction conditions based on the analytical objectives is critical for achieving a high extraction efficiency. These factors include the type and volume of the extraction solvent, the type and volume of the dispersive solvent, and extraction time [36,46,50].

In general, the dispersant solvent must be soluble in the extraction solvent and miscible with aqueous phases to form a cloudy solution, while the solubility of the extraction solvent in water has to be low [51]. In addition to a low solubility in water, a good extraction solvent has the following characteristics: it must have a density lower than that of water, it should have a melting point close to room temperature (10–30 °C) and it should have highly selective extraction characteristics for the analyte [52]. Because an appropriate dispersant solvent and extraction solvent are necessary to maintain a high efficiency, different types of solvents have been frequently tested during the development of extraction techniques to pursue optimal conditions. Shiri *et al.* developed a method combining DLLME and HPLC for rapid and efficient detection of HMF in fruit juice [52]. They studied the extraction efficiencies of 1-undecanol (density of 0.83 g/mL, melting point 19 °C), 1-decanol (density of 0.83 g/mL, melting point of 6.4 °C) and n-octanol (density of 0.824 g/mL, melting point of 16 °C) as the extraction solvents. The results indicated that 1-undecanol had the best extraction

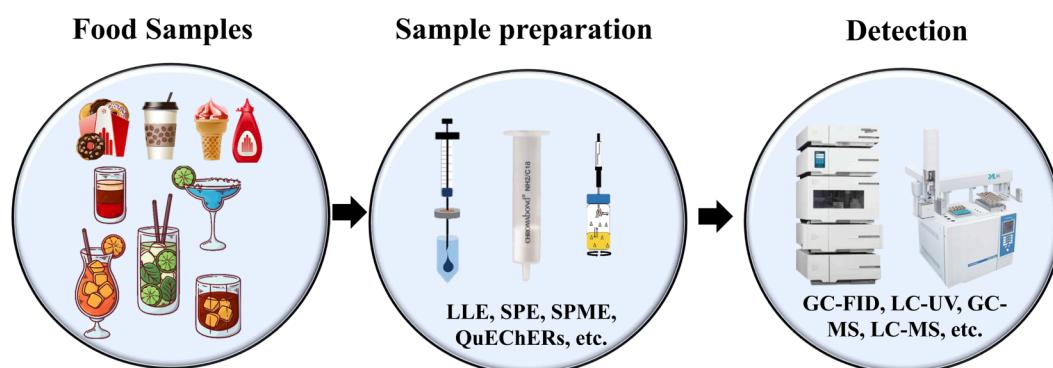


Fig. 1. A typical workflow for the determination of furfural compounds.

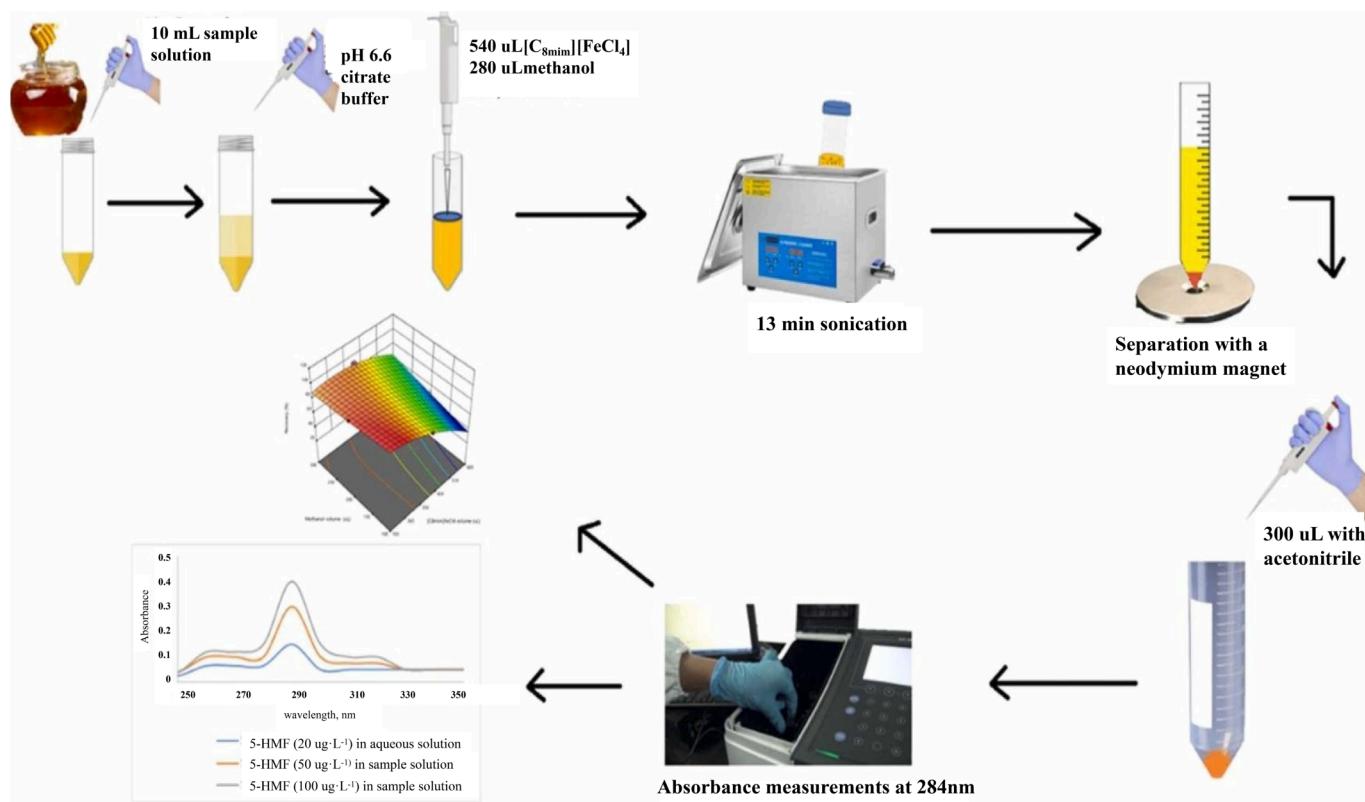


Fig. 2. Process of ultrasound-assisted dispersive liquid-liquid microextraction for the determination of HMF [49].

efficiency. For the choice of dispersant solvent, they found that methanol yielded a better extraction efficiency than acetonitrile. The optimal extraction conditions were 1-undecanol (40 μ L) as the extraction solvent, methanol (1.5 mL) as the dispersant solvent, and a pH of 4.0. The method demonstrated good linearity and had a high coefficient of determination ($R^2 > 0.99$). Moreover, the limit of detection (LOD) was 0.3 μ g/L and the relative standard deviation (RSD) for four replicates was 2.2%. Habibi *et al.* analyzed and optimized the extraction conditions of HMF by response surface methodology based on a Box-Behnken design [53]. The data of the Box-Behnken design showed that the best extraction conditions were 1-octanol (60 μ L) as the extraction solvent, ethanol (600 μ L) as the dispersant solvent, and a pH of 5.0.

As centrifugation prolongs the sample preparation time, there has been growing interest in developing centrifuge-free mode to accelerate the extraction process. In the recent years, reports concerning the application of salt-induced demulsification DLLME for centrifuge-free mode have been proposed [54,55]. According to previous studies on the DLLME technique [36,56–58], the salt effect will affect the partition coefficients of hydrophobic compounds between the aqueous and organic phases. Consequently, the appropriate addition of salt may increase the extraction efficiency and facilitate automation. Abu-Bakar *et al.* found that the extraction efficiencies increased with increasing NaCl concentration from 0% (w/v) to 20% (w/v) and decreased with increasing NaCl concentration from 20% (w/v) to 25% (w/v) because of the increase of the solution viscosity [59]. The amount of MgSO₄ was also evaluated and optimized, which could promote phase separation and remove residual water. The highest enrichment factor was observed when MgSO₄ (1 g) and NaCl (0.5 g) were added [60]. In the study of Habibi *et al.*, 2 g of salt was found to be the optimal value for the DLLME based on the extraction efficiency [45]. More than 2 g of salt was insoluble in water, which could reduce the diffusion rate of HMF from the aqueous phase into the organic phase and the distribution rate in the organic phase. As a result, longer extraction times were required to reach equilibrium with high amounts of salt.

DLLME is mainly used for the pretreatment of liquid samples rather than solid samples. A combination of DLLME with other sample pretreatment method enables a limited ability to extract analyte in solid samples to be overcome and promotes the broad application of DLLME. Dispersive solid-phase extraction (d-SPE) is an effective solid sample extraction method, but it often results in a large number of co-extracted compounds in the extracted analytes. The combination of DLLME and d-SPE has the main advantages of a high efficiency and selectivity achieved in a short time during solid sample pretreatment. For this purpose, a combination of d-SPE and DLLME was developed for extraction of HMF in abalone products prior to HPLC coupled with triple-quadrupole MS analysis [46]. Three adsorbents were used to remove interfering substance in d-SPE treatment: octadecylsilane (200 mg), primary secondary amine (100 mg), and graphitized carbon black (10 mg). The optimal extraction conditions of DLLME were a dispersant solvent/extraction solvent volume ratio of 4:1, water/solvent volume ratio of 1:1, and extraction time of 5 min. The combination of the two methods could significantly improve the selectivity and sensitivity, with an R^2 of 0.999 and a limit of quantification (LOQ) of 0.3 μ g/L.

Furthermore, there are assisted energy fields, such as ultrasonic and vortex fields in LLME, which increase the efficiency of the dispersion step by mechanical shaking instead of manual shaking. Ultrasound-assisted liquid-liquid microextraction (UALLME) is different from DLLME. The sample will form micro-drops due to ultrasonic cavitation during sample processing, so a dispersion solvent is unnecessary. The UALLME method was used for detection of HMF in vinegar and soy sauce by Wu *et al.* [50], in which CHCl₃ was used as the extraction solvent. The optimization of extraction parameters, such as water volume (extraction volume), ultrasonic power density, and extraction time, improved the extraction efficiency. Research showed that the LOD and the LOQ were 0.03 and 0.10 mg/L, respectively. The recoveries of HMF obtained were in the range of 91.24%–109.39%.

Vortex-assisted liquid-liquid microextraction (VALLME) has an excellent extraction and separation efficiency, with the clear advantages

of a mild emulsification process, the short diffusion distance, and a large specific surface areas [61]. Abu-Bakar *et al.* developed an approach based on salting out-VALLME for the extraction of furfurals in 2014 [59]. Selecting appropriate organic solvents and salt additive achieved efficient extractions.

Due to the poor selectivity of DLLME in complex samples, an additional cleaning step is usually required. Moreover, using organic solvents is harmful to human health and leads to environmental pollution. There have been more efforts to find safer and greener extractants and dispersers. The applications of appropriate surfactants as dispersers in surfactant-assisted DLLME can overcome the shortcomings and break through its limitations. In addition, DLLME processes combined with other pretreatment methods, particularly field assisted extraction technologies, are being developed to improve the performance of DLLME and add the merit to this ecofriendly mode. It should be assumed that in the future, a connection of DLLME with some other extraction techniques (e.g., QuEChERS and d-SPE) will be research trends for analyzing solid samples.

2.2. Solid-phase extraction-based methods

Solid-phase extraction (SPE) has emerged as an alternative to LLE with the advantages of less solvent consumption, high selectivity and flexibility. The separation and enrichment of analyte are based on the relative retention abilities of the target compounds and interferents in sample matrix solution, elution solution and adsorbent. The recent SPE-based methods for furfurals detection are summarized in Table S2. As shown in Fig. 3, González-Gómez *et al.* applied functionalized mesostructured silica to SPE for the detection of HMF in insect-based foods [62]. Therefore, it is suitable for separating substances with different retention properties.

In general, small disposable plastic columns (filled with the sorbent) are often used in SPE procedures to remove interferents and concentrate analytes. As a consequence, it is necessary to select different adsorbents to ensure the adsorption capacity, selectivity and affinity. This selection critically depends on the characteristics of analyte and the sample matrix as well as the effective interactions established between the different functional groups of the analytes and the sorbents [63]. One of the critical factors that determines the success of the preconcentration is the choice of the sorbent material. However, researchers found that the commercially available sorbent materials are not sufficient to handle complex sample matrices. In this context, the synthesis of new advanced materials for the manufacture of more adsorbents is current trends to refine this method. In the past few years, various carbon-based materials have been applied as sorbents in SPE. In recent years, with the development of new advanced materials, silica dioxide or magnetic nanoparticles have been made into different types of adsorbents for the cleaning or preconcentration of furfurals in food [64]. Mesoporous silica presents the characteristics of large specific surface area, large pore volume, orderly structural arrangement, and high flexibility in functionalization. Its advanced physicochemical properties can increase the interaction or adsorption capability of the analyte with mesoporous silica to improve efficiency and selectivity [65].

González *et al.* separated the samples by solid-liquid extraction (SLE), followed by preliminary purification with SPE [65]. They tested three types of functionalized mesostructured silica with a large pore (SBA-15-LP), including SBA-15-LP combined with aminopropyl-groups, SBA-15-LP associated with octyl-groups and SBA-15-LP bifunctionalized with both ligands, SBA-15-LP combined with aminopropyl-groups was selected as the SPE sorbent because a high recovery (nearly 100%) was achieved. Similarly, for the simultaneous detection of furfural compounds, González-Gómez *et al.* employed an SPE-based sensitive

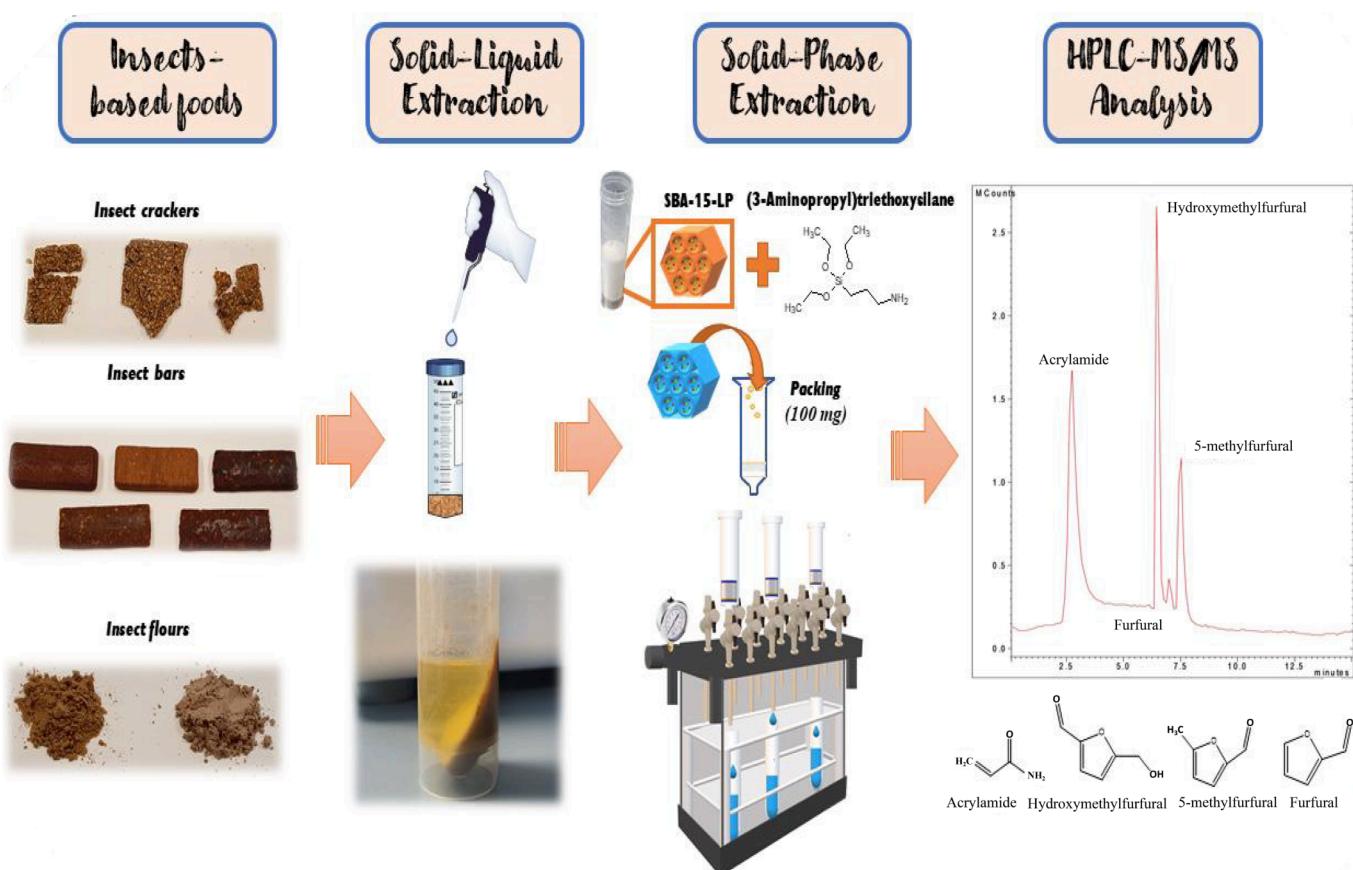


Fig. 3. Process of solid-phase extraction coupled with solid-liquid extraction for the determination of furfural compounds [62].

and reliable method, using SBA-15-LP associated with aminopropyl groups as the adsorbent followed by SLE. The SLE procedure was first carried out with cold water acidified with hydrochloric acid, and subsequently, the adsorption properties of different amounts adsorbents for the analytes were tested. With the increase in the sorbent quantity, better recoveries were attained. The results showed that good recovery (70–113%) was found using 100 mg of material, while satisfactory linearity and accuracy, as well as low quantification limits, were obtained. There has been a recent development termed “magnetic-SPE” based on magnetic nanoparticles/composites for the preconcentration of HMF in baby food and dry milk powder. Unlike non-magnetic nanocomposites, magnetic porous carbons (MPCs) were separated by magnetic separation, thereby omitting the filtration and centrifugation steps, resulting in a more efficient and convenient process [67]. The LODs and linearity for the studied furfurals were obtained in the range of 1.0–2.0 µg/kg and 3.0–500 µg/kg, respectively.

Furthermore, a suitable elution solvent plays an important role in increasing the clean-up efficiency. In general, non-polar organic solvents such as carbon tetrachloride are used to elute the target components adsorbed by the normal phase adsorbent, while polar organic solvents such as methanol are used to elute analytes adsorbed by the reverse phase adsorbent. As furfural compounds are easily dissolved in polar organic solvents, methanol can be used as the eluent. Sadiki *et al.* found that a higher recovery was obtained for the target analytes by methanol elution than by acetonitrile and ethyl acetate [68]. They also measured the effect of methanol eluents with different contents of 0%, 10% and 20% when formic acid content was 2%. It was observed that by choosing 10% methanol as washing solution (5 mL) and eluent (5 mL), the result was the best. Moreover, selecting methanol as the eluent for the preconcentration of F and HMF in baby food and dry milk powder yielded the best performance of a variety of eluents (methanol, ethanol, acetonitrile, acetone, 2-propanol and ethyl acetate) [66].

The achievements of SPE are due to its merits, such as high efficiency, good selectivity, lower consumption of organic solvents, and environmental friendliness. However, some aspects still need further improvement. It is clear that the selectivity of the adsorbent is not high enough for trace concentrations of furfural compounds and the complex matrices in food samples. Moreover, a large number of impurities may cause a blockage of the flow path of the solid phase extraction column, resulting in instrument failure. Furthermore, to avoid cross contamination of samples, commercial SPE are commonly disposable, which results in a high-test cost.

2.3. Solid-phase microextraction

Solid-phase microextraction (SPME) is a solvent-free sample pretreatment technology that integrates sample collection, preconcentration of analytes, purification, and sample introduction in a single step [69]. In recent years, as the modified form of SPE, SPME has come to be regarded as a greener sorbent-based sample preparation method and has been applied, coupled with chromatography and a variety of detection methods, to the analysis of furfural compounds in food [70,71]. The recent SPME-based methods for furfurals detection are summarized in Table S2. The SPME process involves several steps. Fused silica fibers are used with an adsorbent or absorbent polymer as the matrix support to partition analytes from sample matrix into an immobilized stationary phase. After achieving equilibrium, the extracted analytes are desorbed from the fiber of SPME in a GC injector without organic solvents or by liquid chromatography (LC) with an organic mobile phase [72]. Compared with solvent-based and time-consuming conventional techniques, SPME offers high efficiency and selectivity, a small sample volume, simple operation, and minimum matrix interference [72,73]. In particular, it overcomes the shortcomings of a low recovery and easy blockage of the adsorbent channels in SPE. Therefore, SPME can be used to replace some traditional methods.

Direct-immersion solid-phase microextraction (DI-SPME), headspace

solid-phase microextraction (HS-SPME), and diaphragm-protected solid-phase microextraction are the common types of SPME methods. Their distinctions are the way in which the stationary phase coating lies in contact with the sample matrix. Nevertheless, the analysis of furfural compounds in food constitutes a challenging task because of complex environmental matrixes containing macromolecular interfering substances in food samples. DI-SPME suffers from significant limitations. In particular, when quartz fibers coated with the extraction stationary phase is directly inserted into the sample matrix, the interfering substances are easily adsorbed on the fused silica fibers, resulting in relatively short persistence lives of the SPME fibers and the analytical GC column. Unlike DI-SPME, the fibers of the headspace method are not in contact with the liquid phase, which can reduce the risk of contamination, prolong the lifetime of the coating, and reduce the cost of pre-treatment. As shown in Fig. 4, Piñeiro-García *et al.* determined the content of furfural through HS-SPME using reduced graphene oxide coatings [74]. Furthermore, diaphragm-protected solid-phase microextraction needs the longest time to reach equilibrium, which is often used to analyze dirty samples or as a substitute when both direct extraction and headspace extraction cannot be used. In this sense, HS-SPME has been one of the most popular sample pretreatment techniques. The applicability of HS-SPME coupled with ion mobility spectrometry was successfully examined by the detection of F and HMF in baby formula by Kamalabadi *et al.* [69]. Analysis was carried out using dodecylbenzenesulfonate-doped polypyrrole fibers, which were more affordable and accessible than the carboxen/divinylbenzene/polysimethylsiloxane (CAR/DVB/PDMS) fibers. A noteworthy increase in the extraction efficiency occurred with the following optimal conditions: pH of 7.0, NaCl concentration of 2 mol/L; extraction time of 30 min, and extraction temperature of 50 °C.

In SPME process, several significant factors (the type of fiber, extraction temperature, pH, weight of sample, stirring speed, extraction time, and salt addition) affecting the extraction efficiency have continued to attract the attention of various researchers [30,69,75,76]. The extraction process of SPME depends on the partition coefficient of analytes between the coating and samples. Therefore, selecting appropriate materials of fibers is the core of this technology. The initially developed commercial fibers include polidimetilsiloxano (PDMS) fibers and polyacrilato (PA) fibers, which are coated on the surface of fused silica fibers to form fiber heads. The restricted choice of commercial coatings limits the further development of the sample preparation methods and cannot deal with complex environmental matrices in food samples. In this sense, a variety of commercial coating fibers have been continuously developed, such as the poly(dimethylsiloxane)/divinylbenzene (PDMS/DVB) fibers, CAR/DVB/PDMS fibers, and carboxen/polysimethylsiloxane (CAR/PDMS) fibers. The synthesis of these new materials as sorbents in microextraction procedures enables the development of higher sample throughput and more environmental friendly techniques [73]. Using PDMS/DVB fibers, Tsai *et al.* carried out SPME with on-fiber derivatization of furfural in food samples at 80 °C for 20 min with continuous magnetic stirring at 1100 rpm and the addition of 40% NaCl [77]. Then, GC/MS was used for the analysis of derivatives formed on the fibers. Similar to the SPME method described above, PDMS/DVB fibers were used for the extraction of furfural from port wines [78], beer [79,80], roasted plantains [81], and honey [71].

Moreover, CAR/DVB/PDMS fibers are widely used. For example, Condurso *et al.* optimized the HS-SPME conditions for the furfural analysis in baby food [75]. They tested the properties of CAR/PDMS fibers and CAR/DVB/PDMS fibers, and the CAR/DVB/PDMS fibers showed the best performances. The analytes were extracted at 35 °C for 15 min and thermally desorbed from the fibers by a hot splitless GC injection port at 260 °C for 3 min. Satisfactory precision and recoveries were obtained. Then, the LODs and LOQs were in the ranges of 0.018–0.035 ng/g and 0.060–0.117 ng/g, respectively. A report concerning the selection of four different fibers (PDMS, PDMS/DVB, DVB/CAR/PDMS and PA) was also presented by Figueroa *et al.* [82]. Research

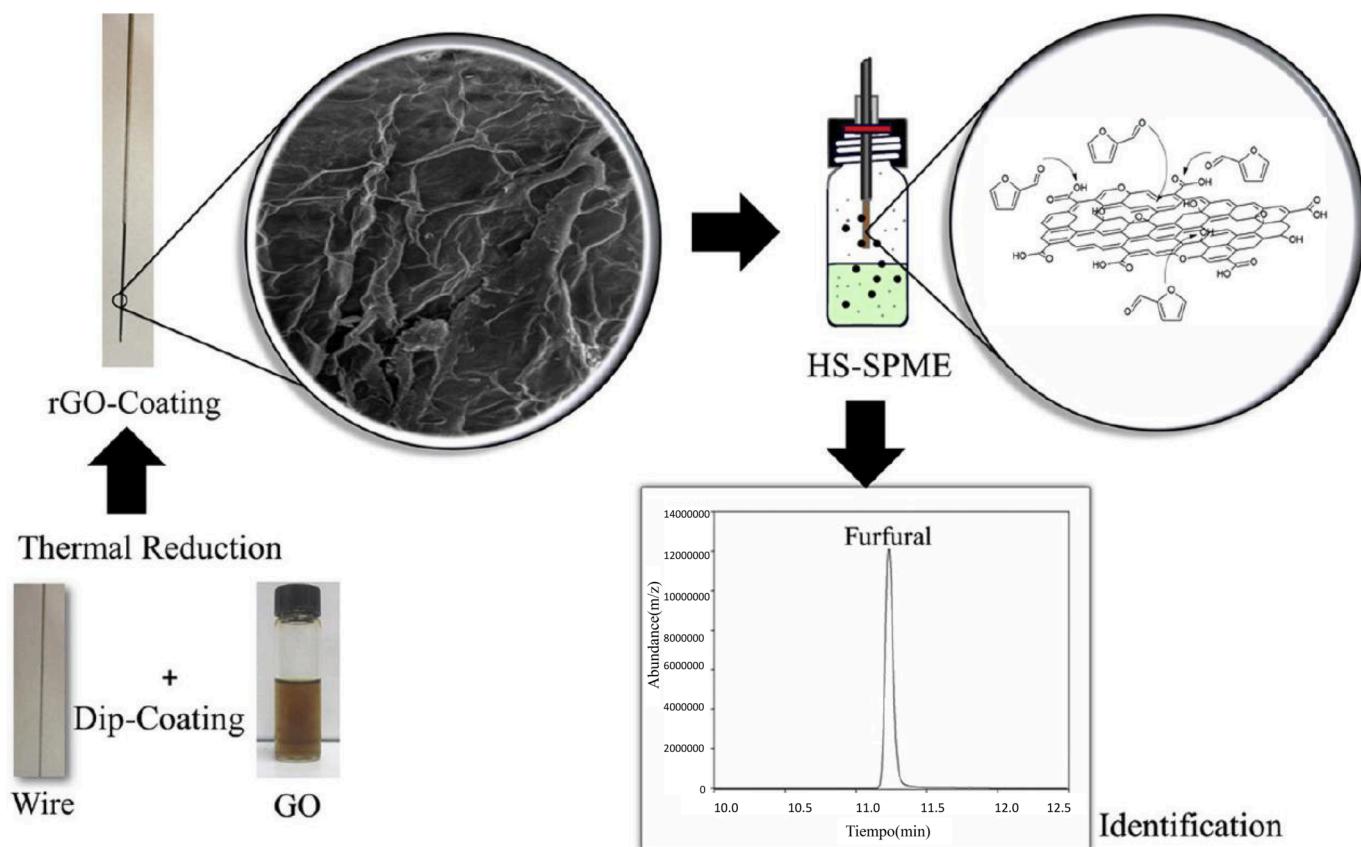


Fig. 4. Process for determination of furfural by solid phase microextraction with reduced graphene oxide coating [74].

showed that with the increase in the number of fibers, more compounds could be extracted. Among the fibers analyzed, CAR/DVB/PDMS fibers performed the best because they could extract 44 kinds of the most representative aroma extracts. In addition to fused silica fibers, nano-material fibers have been widely used in food analysis because of their large surface areas and the improvement of fiber extraction capacity and extraction amount based on the conductive compounds [69,83].

As crucial parameters that determine success of sample preparation, the extraction temperature and extraction time also need to be evaluated and optimized [2,69,75–80,84]. The increase in the extraction temperature promotes the diffusion of analytes to the top space, which has a great effect on the extraction efficiency [85]. Since SPME is a dynamic equilibrium process between the sample and the headspace and between the headspace and the fibers, the equilibrium time determines the maximum amount of analyte that can be extracted from the fibers [76]. For the extraction of furfural in preserved dried fruits and roasted nuts, Batool *et al.* successfully confirmed that the extraction temperature and extraction time were of great importance in extracting analytes [76]. The optimal conditions of HS-SPME were 50/30 µm CAR/DVB/PDMS fibers, 20% NaCl (w/v), and 25-min extraction at 50 °C.

The addition of NaCl [69,75–77] and pH [69] are significant for the extraction. The salt effect can change the distribution of analytes between the sample matrix and the adsorbent by affecting the solubility of analytes in water samples, which affects the extraction efficiency of the target compounds [75]. In addition, the sample flow rate [83] and stirring speed [76,84] are also crucial parameters for the optimization of SPME. However, the loading sample volume appeared not to have much impact on the SPME [83].

Though SPME methods have played an important role in the sample preparation, they have some negative aspects: the fragility and high costs of fibers, inconsistency of the fibers, low sorption capacities, restricted selectivities of commercially stationary phases and fibers, and

relatively strict extraction conditions [86]. The development and synthesis of new materials (e.g., magnetic materials and nanomaterials) have proved their great potential as sorbents, which could offer new opportunities for improving SPME. Moreover, current trends in SPME involve enhancing the extraction performance by coupling with assistive technologies [87]. However, further research is still desirable for the efficient analysis of samples of different properties by SPME.

2.4. QuEChERS

In 2003, the QuEChERS method was first proposed by Anastassiades and co-workers for the detection of pesticide residues [88]. QuEChERS is gaining in popularity, as it provides good recovery and reproducibility as well as accurate results using an internal standard in the high-throughput analysis of furfural compounds in food (Table S3). It is also in accordance with the Green Analytical Chemistry requirements due to its low consumption of solvents and time as well as low generation of waste and toxic compounds [89]. The choices of the types and quantities of salts and extraction solvents in salting-out extraction for the first step of the QuEChERS method are made on the basis of the nature of analytes, followed by a d-SPE procedure to eliminate the remaining matrix interference [90]. As shown in Fig. 5, Huang *et al.* successfully used QuEChERS followed by a d-SPE procedure using enhanced matrix removal lipid (EMR-Lipid) as the d-SPE sorbent to determine the HMF contents in heat-processed foods [91].

QuEChERS provides a better alternative to the traditional methods. Wu *et al.* compared the performances of three different pretreatment methods (LLE, SPE and QuEChERS) based on the analysis results of milk samples [92]. The data showed that the recoveries of the first two methods were not ideal, while the QuEChERS method had a high recovery and repeatability. In recent years, QuEChERS has been routinely used with a variety of technologies to detect harmful substance residues

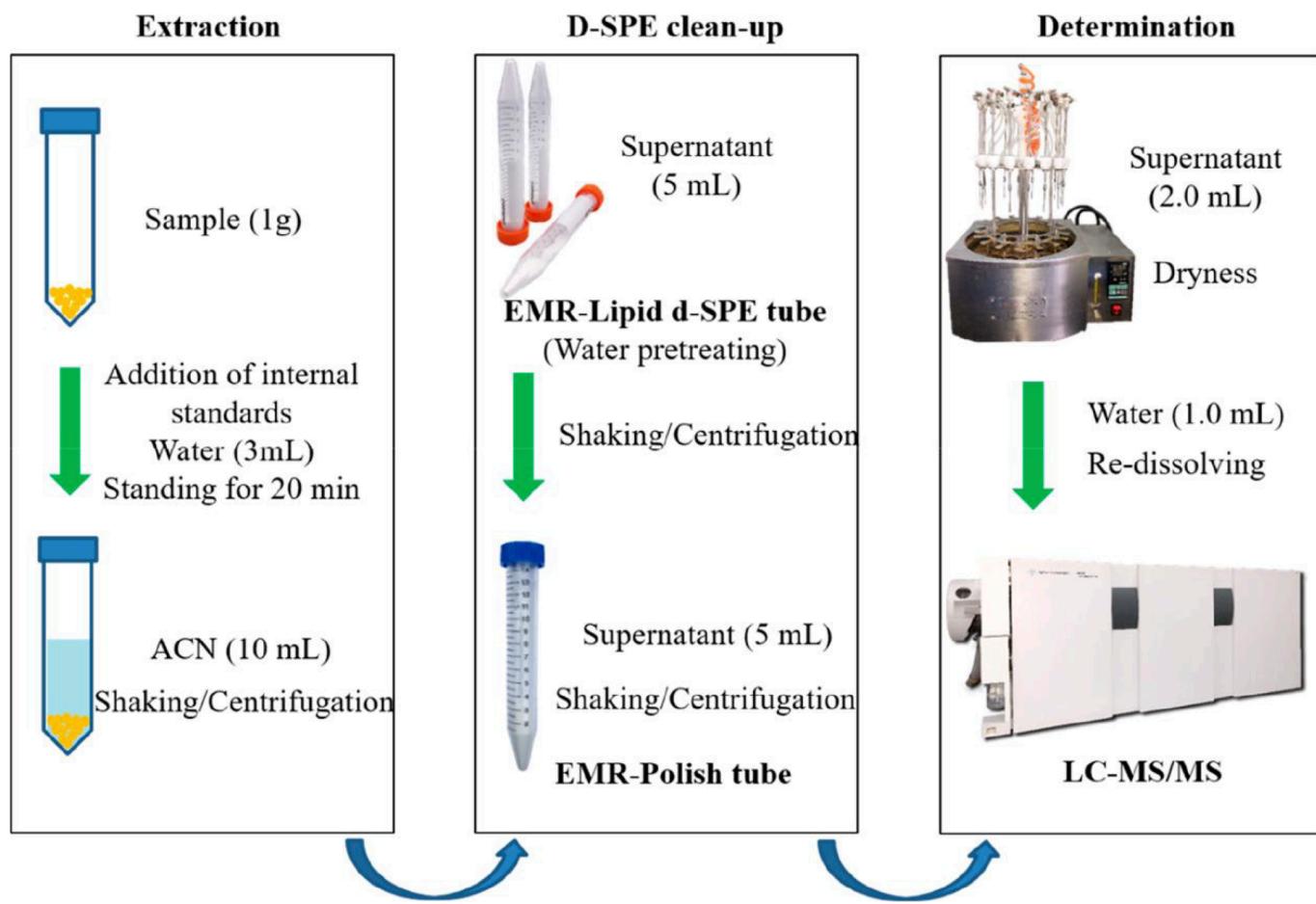


Fig. 5. Process for determination of HMF by QuEChERS [91].

in food. For instance, Tomasini *et al.* combined QuEChERS with HPLC-MS for the detection of HMF [93]. In the study by Wu *et al.*, QuEChERS was applied for the simultaneous analysis of seven furfural compounds in milk powder using GC coupled with triple quadrupole MS [92]. Kasiotis *et al.* combined QuEChERS with HPLC coupled with a diode array detector to detect HMF in honey [94].

Many microextraction technologies have been developed subsequently, such as SPME and UALLME, which meet the requirements of having high efficiencies, low costs, user-friendliness and environment protection capabilities. Nevertheless, many microextraction technologies are not suitable for the detection of solid samples [60]. In contrast to conventional clean-up methods, this combined method provides the advantages of both strategies, which can improve the selectivity and sensitivity of QuEChERS and microextraction technologies. Feng *et al.* used a pretreatment method of the modified QuEChERS method combined with DLLME, which was employed after the d-SPE procedure to detect trace level of HMF in rice matrices [60]. The best results were obtained when 10 g of sample was extracted using 10 mL of acetonitrile (ACN), 1 g of MgSO₄, 0.5 g of NaCl, and a mixture of 50 mg of PSA and 60 mg of C18 that was rapidly shaken for 1 min and centrifuged at 8000 rpm for 5 min. After the d-SPE procedure, DLLME was carried out using a mixture of CHCl₃ (as the extraction solvent), 2.5 mL of ultrapure water and 2 mL of ACN (as the dispersant solvent). Then, the mixture was centrifuged at 8000 rpm for 5 min and the organic phase (lower layer) was concentrated and volatilized with a mild N₂ stream. Lastly, the sample (re-dissolved with ultrapure water) was injected into the UPLC-ESI-MS/MS system. Under the optimized conditions, the highest enrichment factor was obtained. In addition, it had excellent repeatability, linearity, accuracy and recovery.

To reduce interference of co-extracted compounds, the most suitable approach is to use an appropriate extraction solvent, which can affect the output, quality and process economy of the extraction products in QuEChERS. Hence, different types of solvents with specific functional characteristics (e.g., selectivity, extraction/partitioning capacity, and the compatibility with the target compound) [89] were frequently tested during development of QuEChERS to pursue the optimal conditions. For example, in the analysis of furfural substances in milk powder, all the recoveries of ACN, ethyl acetate, and acetone were good. Nevertheless, ACN extraction could greatly reduce interference [95], while co-extracted of ethyl acetate or acetone contained more matrix components, such as some lipophilic components in milk products [96]. Most of these approaches used ACN extraction as the most suitable extraction solvent in QuEChERS due to its high sensitivity and good recovery [97,98], which resulted in fewer co-extracted components and enabled rapid separation of the target analytes from the water phase by salting out [95]. Four different extraction solvents (acetone, ethyl acetate, ACN, and dichloromethane) were tested to extract four bitter compounds (e.g., HMF, MF, F) from caramel-colored beverages. ACN was selected because it co-extracted fewer interfering compounds and yielded satisfactory recovery [99]. It is worth noting that the pH of the solution also has a certain influence on the state of the analytes [60]. Shen *et al.* conducted experiments to compare the effects of ACN and acidified ACN with different concentrations of acetic acid (0.05% and 0.5%, (v/v)) on the extraction efficiency for detecting potential and free furfural compounds [95]. The obtained results indicated that the recovery of pure ACN was less than 80%, while acidified ACN yielded better recovery (81.1–108.9%). Nevertheless, the concentrations of acetic acid appeared not to yield significant differences of the recovery in their work.

Turkmen compared the effects of pure ACN and ACN with 1% acetic acid on the recovery and RSD [16]. The results showed that both the recovery and RSD of ACN with 1% acetic were better than those of pure ACN. The QuEChERS for HMF in fruit-based baby foods provided LOD and LOQ levels of 1.54 ng/spot and 4.67 ng/spot, respectively.

However, the sensitivity of the initial single-phase extraction in QuEChERS is usually insufficient for detecting these furfural substances at trace levels. Consequently, the choices of the types and concentrations of salts play a central role, because they can affect the recovery values of analytes, especially polar compounds, by inducing phase separation. Different types of salts including NaCl, MgCl₂, NaNO₃, Na₂SO₄, and MgSO₄ were evaluated. Generally, the combination of NaCl and MgSO₄ is the most commonly used method, which can reduce the amount of water phase required and adjust the polarities of solvents [15,96]. It was reported that good repeatability, linearity, and sensitivity were obtained by using ACN (10 mL) as the extraction solvent, NaCl (3 g) and sodium acetate anhydrous (1 g) as the salting-out agents, and MgSO₄ (3 g) as the drying agent by Shi *et al.* [100]. Shen *et al.* investigated the differences of the extraction efficiencies for six combinations of drying agents and salting-out agents [95]. By using the combination of 1.2 g NaSO₄ + 1.2 g NaCl + 0.3 g NaAc, the recovery values (96.5–107.0%) for furfural compounds in the process of infant formula production were slightly higher than those of the other five combinations. Similar to this QuEChERS method above, the effects of four improved methods using various salt pockets were tested in an analysis of furfural substances in caramel-colored beverages. Satisfactory recoveries (70.1–101.5%) of four bitter compounds (e.g., HMF, MF, F) were obtained with the combination of 4 g anhydrous MgSO₄ + 1 g anhydrous sodium acetate.

In the QuEChERS method, because ACN is immiscible in nonpolar solvents, it fails to achieve good performances in the extraction of lipophilic components. For this reason, a d-SPE cleaning step with PSA as the adsorbent is usually in order to eliminate the majority of the remaining matrix interference after the ACN extraction [15,91]. The separation principle in QuEChERS is mainly for the interaction between the adsorbent and impurities in the matrix. As for the clean-up stage by d-SPE, mixtures of crude extract and the adsorbent are used to purify or concentrate the target analyte and accelerate the chemical reaction. Shi *et al.* used ACN as the extraction solvent for the detection of furfurals in milk [100]. Both adsorbents (C18 and PSA) were selected to achieve satisfactory recovery in d-SPE. Recently, a product called EMR-Lipid had been proposed, which can selectively remove lipids without losing the target substance [101,102]. For example, Huang *et al.* applied EMR-Lipid to d-SPE for the detection of HMF in heat-processed foods [91]. In the recovery study using each cleanup method (n-hexane, d-SPE with primary secondary amine, d-SPE with EMR-Lipid, and not using the cleanup step) for QuEChERS extracts, d-SPE with EMR-Lipid had the most significant ability to reduce the matrix interference of co-extraction compounds and achieved the best extraction efficiency.

Currently, the optimized QuEChERS method is often used with a variety of analyzers. Due to the matrix interference, an additional cleaning step, such as the addition of d-SPE and DLLME, is needed. Moreover, although rapid progress has been made to automate QuEChERS, this progress is still far from being fully automatic. As the method has the main advantages of being simple, economical, and efficient as well as providing satisfactory repeatability and accuracy, it has a broad prospects in the pretreatment of furfural compounds.

2.5. Derivatization technology

If the separation and detection of the analyte are inconvenient, the target compound in the sample can be quantitatively transformed into another compound that is easy to be detected by derivatization technology [103]. Then, the quantitative and qualitative analyses of the target compound can be achieved through the analysis of the latter. There are many kinds of derivatization reagents including: silylation, acylation, alkylation, fluorescent derivatization, ultraviolet

derivatization reagents. Generally, the following elements are characteristics of a good derivatization reagents: the derivatization reagents should be abundant and stable, the derivatization reaction must be able to be completed entirely in a short time, and the derivatives must be easily separated. It is crucial to select an appropriate derivatization reagent to deal with the analytical challenge of achieving precise and efficient quantitative analysis of the sample. The application of HPLC for detection of HMF after forming derivatives using o-(2,3,4,5,6-Pentafluorobenzyl) hydroxylamine was reported by Pappalardo *et al.* [104]. Compared with conventional methods, the new method used a stable anisole internal standard for the quantification of target analytes, thus improving the repeatability and efficiency and diminishing the risk of an unstable internal standard.

Fluorescent derivatization reagents are commonly used to improve the hydrophobicity and spectral responses of analytes in experiments [38]. An established approach based on fluorescent derivatization using 4-hydroxylaminopropyl-7-methoxylcoumarin (HAMC) as a fluorescent reagent was developed for the pretreatment of HMF prior to HPLC with fluorescence detection analysis [38]. With 0.2 mM HAMC (20 µL) and 0.2 mM aniline (10 µL) as the derivatization reagent and catalyst, respectively, derivatization was carried out at room temperature for 30 min at a pH of 3.5. This method offered advantages of producing no isomeric products, yielding high fluorescence intensities, and allowing efficient labelling at room temperature. The results provided high recoveries (89.7–106.7%) and low LODs at the sub-nM level (0.08–0.1 nM).

Very recently, a method of derivatization after labeling HMF with stable isotopes has been proposed for the extraction of HMF in drinks by Wang *et al.* [29]. Selecting 3-nitrophenylhydrazine (3-NPH) and ¹³C₆-3-Nitrophenylhydrazine hydrochloride as pared labelling reagents could avoid the ionization suppression and potential mass spectrometer contaminations as much as possible, because 3-NPH has neutral properties and does not ionize in the mass spectrometer. In this work, 100% ACN and 0.5 mg/mL 3-NPH were used to obtain good derivatization and the ionization efficiencies. In addition, 3.5% acetic acid was used as the catalyst. They carried out bath derivatization with a multi-well thermostatic oscillator for 10 min at 35 °C. The optimal analytical results showed satisfactory reproducibility, and the LOQ of the studied HMF ranged from 0.050 to 5.0 µg/mL. The intraday variability and interday variability were less than 4.89% and 5.42%, respectively.

In addition to the methods above, Marsol-Vall *et al.* introduced an online derivatization method called injection-port derivatization using N-Methyl-N-(trimethylsilyl)trifluoroacetamide as the derivatization reagent [105]. The method offered a simple and efficient approach for sample processing, overcoming the weaknesses of off-line procedures such as the contamination of the samples and interference of water during the analysis. Under the optimal conditions, the LOD and LOQ for the studied HMF ranged from 0.7 to 1.6 µg/kg and 2 to 5 µg/kg, respectively.

3. Conclusions and future perspectives

The detection of furfural compounds in food matrices has become a necessity for food safety. Since the contents of furfural compounds in the food matrix are small and there are a large number of interfering substances, it is indispensable to clean and enrich the samples before detection in order to obtain reliable quantitative and qualitative results. The current review presented an overview of recently reported sample preparations for the detection of furfural compounds in food samples. The LLME, SPME, QuEChERS, and derivatization extraction approaches are the most widely used. The development of new materials and their integration in microextraction techniques have resulted in simple, economical, efficient methods for the analysis of furfural compounds in foods. The optimal combination of various sample preparation methods and more automatic methods will become the development goals of future pretreatment methods in the years to come. Furthermore, mainly

for economic reasons, the challenge of modern pretreatment methods is to design methods that are less time consuming, less solvent consuming and more cost-effective through their miniaturization. This review will help researchers choose suitable sample preparation methods and detection techniques based on their different needs.

CRediT authorship contribution statement

Yu-Mei Gan: Writing – original draft. **Kai-Xuan Li:** Writing – original draft. **Nan Zhang:** Writing – review & editing. **Xia Xu:** Writing – review & editing. **Di Chen:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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