ISSN 1061-9348, Journal of Analytical Chemistry, 2017, Vol. 72, No. 8, pp. 823–836. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © D.R. Borisova, M.A. Statkus, G.I. Tsizin, Yu.A. Zolotov, 2017, published in Zhurnal Analiticheskoi Khimii, 2017, Vol. 72, No. 8, pp. 699–713.

REVIEWS

Subcritical Water: Use in Chemical Analysis

D. R. Borisova, M. A. Statkus, G. I. Tsizin*, and Yu. A. Zolotov

Department of Chemistry, Moscow State University, Moscow, 119992 Russia

**e-mail: tsisin@analyt.chem.msu.ru*

Received December 26, 2016; in final form, February 28, 2017

Abstract—The review shows prospects of the use of subcritical water instead of organic solvents and aqueous–organic mixtures at different stages of analysis. Subcritical water was applied to the extraction of target compounds from natural samples, such as soils, sand, and plant raw materials. The use of subcritical water expands possibilities of HPLC. The use of subcritical water as an eluent in HPLC is complicated by the possible destruction of the adsorbent and the decomposition of substances to be determined at elevated temperatures. Adsorbents based on zirconium and titanium oxides, some polymeric adsorbents, and porous graphitized carbon are stable in the medium of subcritical water. Subcritical water can be used at several stages of analysis, for example, for the extraction and subsequent chromatographic separation of analytes.

DOI: 10.1134/S1061934817080044

Organic solvents are well known to play an important role in chemical analysis. They are used for the preparation of reagent solutions, extraction of analytes from solid samples, extractions of analytes from liquid media, as constituents of mobile phases in the chromatographic separation of substances, etc. This very wide application of organic solvents is based their properties, differing from the properties of the most widespread solvent, water, first of all, their polarity. Thus, the vast majority of organic solvents possess lower polarity and weaker ability to the formation of hydrogen bonds compared to water. For this reason, organic solvents much better dissolve hydrophobic substances, first of all, organic, compared to water. Unfortunately, the majority of organic solvents are toxic; therefore, the search for ways to their replacement in different scenarios of chemical analysis seems expedient. One of such ways is the use of superheated liquid water under elevated pressure (so-called subcritical water). Works in this direction demonstrate rapid progress, a number of reviews on the use of subcritical water for the extraction of valuable components from herbs [1–4] and also as an eluent in HPLC [5–8] was published. As a rule, these articles are of very specific character. In this review, we tried to present a broader view on the use of subcritical water in the chemical analysis of different samples and discuss the advantages and disadvantages of corresponding solutions.

PROPERTIES OF SUBCRITICAL WATER

The idea to the use of water heated to 100–300°C under a pressure of 30–50 atm as an eluent for the separation of substances under HPLC conditions and also as a solvent (extractant) for the extraction of organic substances from solid samples was proposed and developed in a number of works published in the last 15–20 years. Temperature and pressure in this case are significantly lower than the critical parameters of water (t_{crit} = 374°C, P_{crit} = 218 atm [9], Fig. 1); therefore, water does not reach the conditions of the supercritical fluid and remains liquid. The conditions for obtaining subcritical water can be rather easily created using standard HPLC pumps and special, but rather simple devices for heating the mobile phase and the chromatography column (or extractor).

At elevated temperature and pressure, many physical and chemical properties of water (viscosity, dielectric permeability, etc.) significantly differ from those under normal conditions [9, 11]. For example, the dielectric permeability (ε) of water decreases from 80 to 35 with increasing temperature from 20 to 200°C [12]; for comparison, ε of acetonitrile at 20°C is equal to 39 (Fig. 2). Viscosity also gradually decreases with increasing temperature (Fig. 3). The concentration of protons and hydroxyl ions, i.e., the ion product of water, also changes, which is illustrated by Fig. 4.

In addition to significant changes in the physical and chemical properties of water at elevated temperatures, the generalized characteristics of water as an eluent for reversed-phase HPLC also change. Note that the "chromatographic" properties of water at 150–250°C are comparable with the properties of pure acetonitrile or methanol [9].

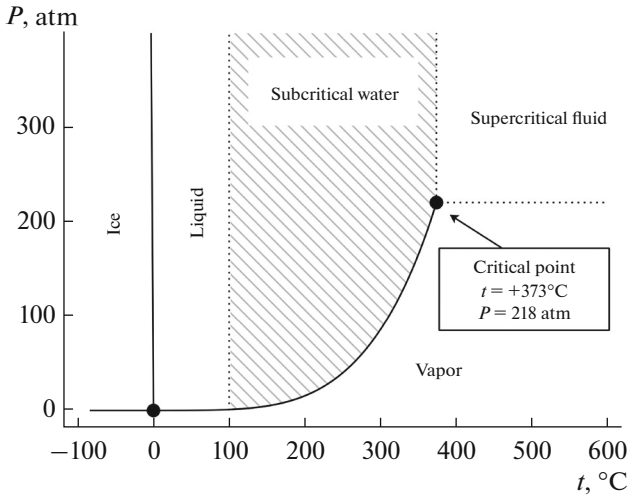

Fig. 1. Phase diagram of water [10].

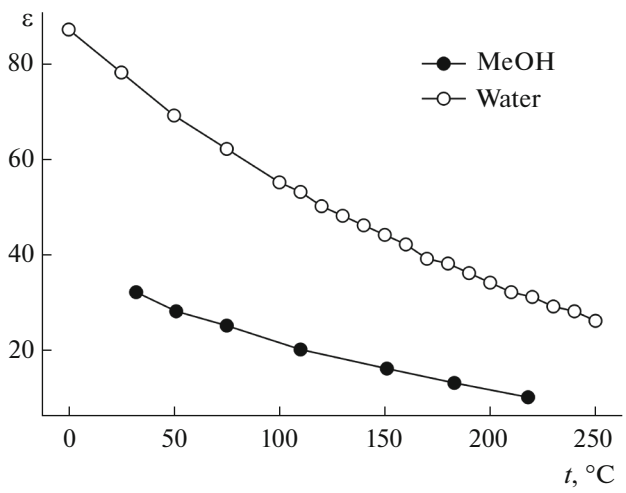

Fig. 2. Temperature dependence of the dielectric permeability of water [13, 14].

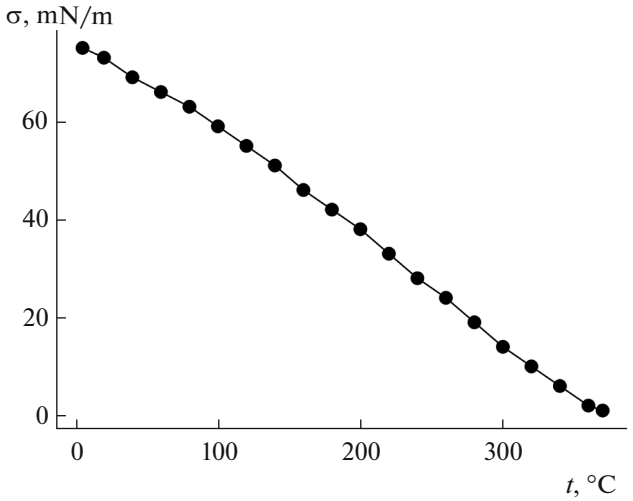

Fig. 3. Temperature dependence of the surface tension of water [15].

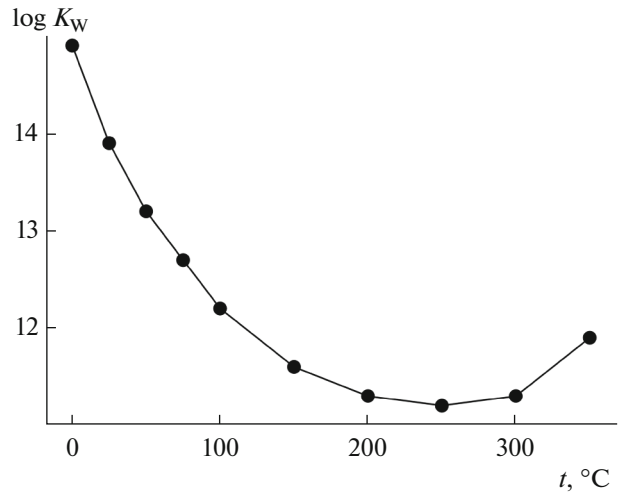

Fig. 4. Ion product of water at different temperatures [15].

EXTRACTION OF TARGET COMPONENTS FROM SOLID SAMPLES

An important task determining the priority development of many methods of chemical analysis is the determination of biologically active substances, including toxic ones, in environmental samples, foodstuffs, and plant raw materials. A similar task is the extraction of the required substances from natural samples for the preparation of medicines. A traditional approach to the extraction of analytes from solid samples both for analysis and drug production is extraction with organic solvents (methanol, ethanol, an acetonitrile, etc.). However, these solvents are not always convenient for the subsequent determination of analytes and, in the production of medicines, their residues can hardly be removed completely, thus creating hazard to human health. A good alternative is provided by extraction with supercritical carbon dioxide and also with subcritical water. Thus, subcritical water was applied to the extraction of polycyclic aromatic hydrocarbons (PAH), polychlorinated biphenyls (PCB), phenols, pesticides, and other toxic substances from sedimentary rocks, soils, and suspensions [16–19]. By regulating temperature affecting the polarity of subcritical water, analysts could extract not only nonpolar, but also polar components [1, 20, 21].

It is believed that the mechanism of extraction includes several consecutive stages [22]. At first stage, microcomponents diffuse from the center of sample particle to its surface, then they are transferred from the surface of sample matrix to the flow of extractant [16, 22–24]. The rate of extraction is limited by the

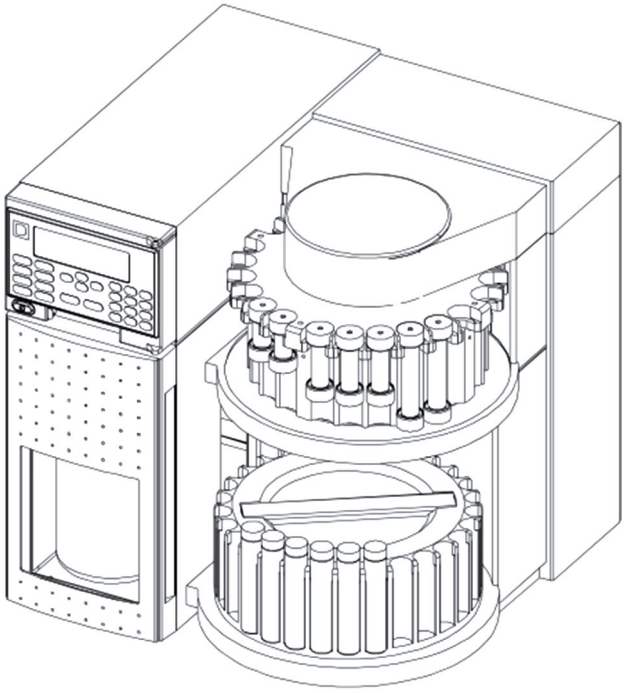

Fig. 5. Dionex ASE 200 installation.

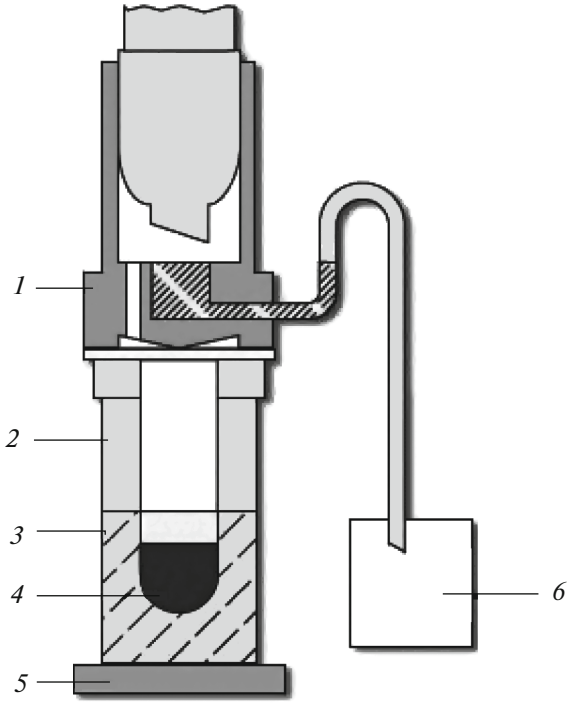

Fig. 6. Sectional view of Soxterm installation: (*1*) reflux condenser; (*2*) glass vessel for extraction; (*3*) solvent; (*4*) sample in a porous extraction cell; (*5*) heating element; (*6*) container for collecting solvent.

slowest of these stages. It was shown that the extraction of components from many natural samples is determined, first of all, by the desorption of microcomponents from the surface of the solid matrix [22, 23].

The mechanism of extraction under dynamic conditions is successfully described within the theory of frontal chromatography by the thermodynamic model, which includes two stages of mass transfer, the desorption of a microcomponent from the matrix surface and elution [25, 26]. Using examples of extraction of essential oils from chaber and PAH from soils, it was shown that the behavior of the microcomponent is determined, first of all, by its partition coefficient between the sample matrix and solvent [25].

Components were extracted under batch and dynamic modes. In the batch version, a constant volume of a solvent is used and, in the dynamic version, a flow of subcritical water is continuously passed through a column with a sample. For the batch version, one can use the commercial equipment, for example a Dionex ASE 200 installation (Fig. 5) [2, 3, 26, 27], which is intended for the extraction of organic compounds from different solid and semisolid samples. To maintain the solvent in the liquid state at elevated temperatures, the necessary pressure is created in the extraction cell. Analytes were also extracted at elevated temperatures using installations of the Soxtherm series (Fig. 6), which are intended for the determination of fat in food- and feedstuffs, pesticides and phenols in soils, and mineral oils or dyes in cloths.

Installations for the dynamic version were usually assembled independently from units of commercial chromatographic equipment [1, 20, 21]. Stainless steel capillaries and prepurified water were used to prevent corrosion. The heated elements, extraction cell and entrance capillary (to heat water to the working temperature, its length was usually 1.5 m and more) were placed in a heater (usually heaters are constituents of gas chromatographs). A pressure limiter was installed at the exit from the cell, outside the heater; it maintained water in the liquid state at temperatures above 100°C (Fig. 7). For the more efficient cooling of the extract, the exit capillary was placed in a vessel with cold water [17–19] or in another cooling device.

In batch extraction, an equilibrium the system sample–solvent is usually attained within the time of experiment. Therefore, recovery first of all depends on the partition coefficient of the microcomponent. In the dynamic mode, the continuous ingress of new portions of an extractant ensures a more rapid and complete extraction of analytes than in the batch mode because of the high concentration gradient. However, this version requires bigger volumes of solvent.

Recovery is affected by temperature, pressure, time of sample treatment, flow rate of subcritical water, and concentrations of possible additives modifying the extractant. As was shown on an example of the extraction of PAH from bottom sediments, the geom-

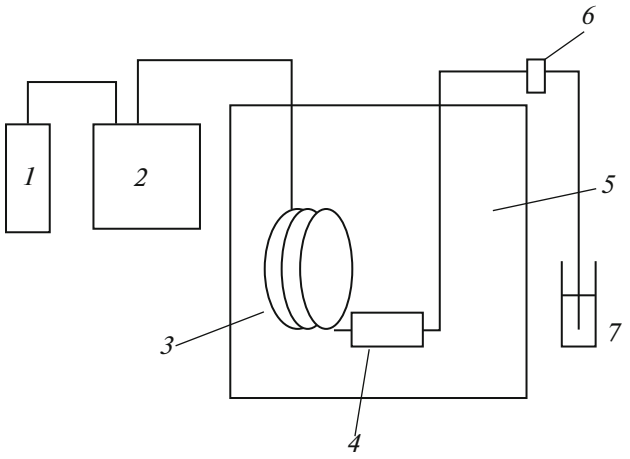

Fig. 7. Installation for extraction with subcritical water in the dynamic mode [1, 20, 21]: (*1*) flowing solvent degasser; (*2*) pump; (*3*) capillary for preliminary heating of solvent; (*4*) extraction cell; (*5*) heated thermostat; (*6*) backpressure regulating valve; (*7*) container for collecting extract.

etry of the extraction cell and the direction of the flow insignificantly affect recovery [28].

The temperature of subcritical water significantly affects the recovery of the microcomponents. As was already discussed, the dielectric permeability of water and, therefore, the solubility of the microcomponent and its partition coefficient depend on temperature. With increasing temperature, the diffusion rate of microcomponents [29] and, correspondingly, the rate of mass transfer also increase. Thus, it was shown that, on increasing temperature to 300°C, the solubility and recovery of PAH, phenolic compounds, and pesticides [4, 16, 18, 19, 30, 31] also increased. However, some compounds, for example, biologically active substances present in herbs, can be thermally unstable, oxidize, and decompose in the aggressive medium of subcritical water; therefore, it seems expedient extract then at rather low temperatures

Pressure. To keep subcritical water in the liquid state, pressure in the experiments was maintained in the range 10–80 atm [16, 31–34]. If pressure was sufficient for the prevention of water boiling, its further increase slightly affected the recovery of analytes. On the other hand, in comparison with extraction under atmospheric pressure, subcritical water under pressure penetrated into more distant regions of the sample matrix [29].

Duration of extraction in the batch version. Like temperature, the time within which the sample is treated by subcritical water, considerably affects the recovery of analytes. The duration of the experiment depends on the temperature of the extractant, nature of sample matrix, and the microcomponents to be extracted. It was shown that the time necessary for the quantitative extraction of analytes, such as eugenol and its derivatives, from plant raw materials can be reduced from 80 to 15 min by increasing temperature from 120 to 300°C [35]. It was found that the reduction of water temperature from 300 to 50°C led to the sharp reduction of the rate of extraction of the majority of PAH from soils, and some of them were not extracted under these conditions [16].

Flow rate of subcritical water. In extraction in the dynamic mode, an increase in the flow rate of the extractant often results in an increase in the recovery of microcomponents because of the maintenance of a high concentration gradient. Thus, the flow rate of subcritical water was chosen based on the specified duration of sample treatment and the desirable concentration of analytes in the extract [36]. It was shown that an increase in rate is expedient when extraction is limited by the solubility of the extracted substances, the diffusion of the extractant to the sample matrix, and the rate of analyze transfer to the matrix surface.

Organic additives to the extractant (modifiers). At the incomplete extraction of analytes, organic solvents, i.e., methanol, ethanol, and ethyl acetate, were added to water [3, 37]. Surfactants, sodium codicil sulfate and Triton X-100, were also used as modifiers [20]. It was shown that the introduction of such modifiers favors the formation of micelles, facilitating the extraction of PAH from plant raw materials [20]. For the efficient extraction of analytes, in this case one should optimize not only temperature and time of sample contact with subcritical water, but also the concentration of the surfactant. It was shown that an increase in the concentration of Triton X-100 above a certain value had no considerable effect on recovery [2, 20]. On the introduction of a surfactant, extraction can be performed at lower temperatures to reduce the probability of the thermal decomposition of analytes [2, 20]. The stability of analytes in the medium of subcritical water will be discussed below.

Table 1 presents examples of analyze extraction from different samples by subcritical water.

Temperature of 250°C is sufficient for the quantitative extraction of PAH from soils; its further increase does not lead to an increase in recovery [16, 17]. A method of the determination of the solubility of PAH and PCB in water at increased temperatures was developed in [17]. A cell with a weighed portion of sand, to which 10 wt % of PAH was added, was placed in the heater of a gas chromatograph adjusted to the necessary temperature. A flow of water was passed through the cell. The pressure in the system was necessary for the maintenance of water in the liquid state. After the attainment of an equilibrium, several fractions were selected, an internal standard was added, and the mixture was analyzed by gas chromatography with a flame ionization (FID) or a mass spectrometry (MS) detector. It was noted that, in using subcritical water, the limits of detection were tenfold lower in comparison with extraction in a Sox let apparatus [30].

Table 1. Examples of using subcritical water for the extraction of chemical compounds from solid samples

Samples	Extracted substances	Recovery, %	Reference
Soils and similar samples			
Soils	PAH	>90	[16]
		60–100	[25]
		–	[28]
		–	[30]
Bottom sediments	Herbicides	81–93	[19]
Sea sand	Phenols	>90	[31]
Samples of plant origin			
Scutellarie radix	Baikalein	–	[1]
Radix glycyrrhizae	Glycyrrhizin	–	[1]
Coptidis rhizhoma	Berberine	–	[1]
Radix Codonopsis	Unsaturated alcohols Tanshinone I and IIA	–	[20]
Salvia miltiorrhiza	Ginsenosides	–	[21]
American ginsene	Antioxidants	26–51	[2]
Spirulina platensis	Catechols	–	[26]
Tea leaves	Pesticides	–	[3]
Grape	Phenolic compounds	26–51	[4]
			[37]
Kava root	Lactones	–	[32]
Acorus tatarinowii	Essential oil components	–	[33]
Syzygium aromaticum	Eugenol and its analogs	–	[35]

A study of the dependence of the recovery of eugenol and its derivatives on the extractant volume at different temperatures showed that, in certain cases, an increase in temperature does not affect the position of the equilibrium, but only the rate of its attainment [35]. The dependence of the efficiency of extraction on the temperature of subcritical water and the duration of the process was also studied; it was shown that an increase in temperature, as the duration of sample treatment, caused an increase in efficiency.

The effect of the flow rate of subcritical water on the recovery of essential oils from plant raw materials was studied: it appeared that an increase in flow rate in the general case favored an increase in recovery [25, 36].

The addition of organic solvents to subcritical water not always leads to an increase in recovery; only the addition of a surfactant (Triton X-100 or sodium codicil sulfate) increases recovery three- to fourfold, as was shown on an example of extraction of gingenosides from ginseng [2, 20].

It was found that, in the extraction of herbicides from soil with subcritical water, the recovery of analytes was comparable to their recovery in extraction with organic solvents and aqueous–organic mixtures [1, 19]; extraction of tanshinone I and IIA with subcritical water appeared even more efficient [21]. Similar results were obtained in the extraction of lactones from kava roots [32]. It was shown that the extraction of essential oils from plants with subcritical water is more efficient than their water-stream distillation [33].

USE OF SUBCRITICAL WATER AS A MOBILE PHASE IN CHROMATOGRAPHY

Subcritical water was used as an alternative to aqueous–organic eluents based on acetonitrile and methanol in the separation of substances under the conditions of HPLC on reversed-phase adsorbents [5–7, 11, 38–46] (below this method of analysis is designated as SW-HPLC). The temperature of subcritical water affects the retention time of analytes and the efficiency and selectivity of their separation and determination. At an increase in temperature, the viscosity of the eluent is decreased; this allows work at higher flow rates, so that the duration of the experiment can be reduced. The possibility of regulating temperature and, correspondingly, the elution ability of subcritical water is undoubtedly promising for the expansion of the possibilities of HPLC.

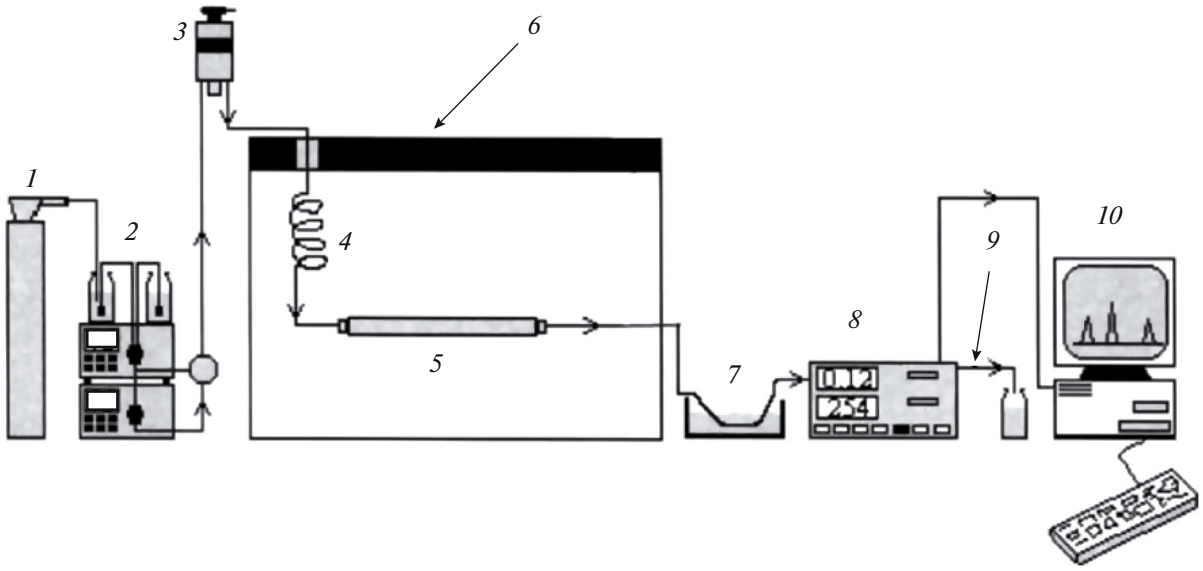

Fig. 8. Flow chart of equipment for HPLC separation using subcritical water [11]: (*1*) cylinder with nitrogen; (*2*) pump; (*3*) injector; (*4*) capillary for preliminary heating; (*5*) chromatography column; (*6*) thermostatically controlled heater; (*7*) capillary for cooling; (*8*) detector; (*9*) pressure limiter; (*10*) computer.

The use of subcritical water as an eluent instead of organic solvents is also expedient from the viewpoint of the reduction of toxicity.

Apparatus. A flow chart of an apparatus for separation by SW-HPLC is shown in Fig. 8 [11]. Chromatographic column *5* is placed in a thermostatically controlled heater *6*; the heater also contains capillary *4,* which connects column with injector *3*; this capillary is necessary for the preliminary heating of the eluent before its arrival at the column. Capillary *7*, which connects the column with the detector, serves for cooling the eluent, which prevents the damage of the detector because of its overheating. To prevent the vaporization of water in the column at 100–300°C, it is sufficient to maintain pressure of 30–50 bars in the system. As a rule, capillary *7* is also used as a pressure limiter, or additional pressure regulator *9* is installed after it. Note that, in most cases, chromatographic detectors are not intended for work at high pressures; therefore, it is expedient to install a pressure limiter before the detector. By now commercially available HPLC systems using subcritical water just appeared in the market; therefore, the authors of the majority of works considered in this review assembled similar systems independently from a conventional HPLC chromatograph, heaters (as a rule, for gas chromatographs), and a small set of additional elements, capillaries and serially produced pressure limiters.

New possibilities of detection. The use of subcritical water instead of aqueous–organic mixtures, traditionally used for separation in reversed-phase HPLC, allows the expansion of the range of detectors for liquid chromatography.

For example, the flame ionization detector, widely used in gas chromatography, produces signal on hitting almost any organic substance in the flame, which prevents its use in the separation of analytes with aqueous–organic eluents. In a number of works (for example, [39, 47, 48]), it was proposed to separate analytes (alcohols, carbohydrates, carboxylic and amino acids) using subcritical water and detection by FID: for this purpose, a flow of a mobile phase after the elution from an HPLC column was fed to the flame of the detector. Note that, in using FID, water must not be cooled before its arrival at the detector, as the range of working temperatures for FID is 200–400°C. In certain cases, FID is placed in the same thermostat as the HPLC column [47].

The working parameters of the detector must be optimized to achieve the maximum sensitivity of the determination and the long-term stable work of FID in combination with SW-HPLC. Thus, in the separation of alcohols, carbohydrates, carboxylic acids, and amino acids [39, 47–49], it was found that the optimum temperature of the detector depended on the flow rate of the mobile phase: at a higher flow rate of the eluent, the temperature of the injector required for efficient evaporation must be higher. In certain cases, such optimization allowed the researchers to lower limits of detection more than tenfold [49].

High-temperature HPLC is some cases cannot be directly combined with FID because of a difference in the optimum flow rates of the mobile phase at the stages of separation and detection. For example, it was shown that, in the analysis of alcohol mixtures using FID, the optimum flow rate of the solution at the detector was 20–50 μL/min, while the typical flow

rates of the eluent in using HPLC columns with an inner diameter of 2–4 mm were 200–1000 μL/min [47]. It seems necessary either to use capillary columns for separation at low flow rates of the mobile phase (as, e.g., authors of [47, 48]) or install a special flow splitter as an interface between the HPLC column and FID (see, for example [39]).

An original design of an interface between an HPLC column and a FID for the determination of easily volatile analytes was proposed in [50]. The eluent after cooling was fed to the interface chamber a rate of 30–1000 μL/min as separate drops with simultaneously feeding helium at a rate of 100–120 mL/min. Volatile analytes were partially transferred to the gas phase and moved to the detector flame with the helium flow. At such design of the interface, the analytical signal was formed only by volatile analytes, which increased the selectivity of the detection. In the determination of butanol, toluene, and other easily volatile compounds, the limits of detection were 1–10 μg/L and the linearity range of the calibration dependence covered six orders of magnitude, from 1 to 10^5 μg/L.

In using temperature gradient of the mobile phase (instead of gradient of composition in the classical version of HPLC), no significant drift of the FID baseline was observed in the work with silica C18 and polymeric and carbon adsorbents [6, 40]. However, in the separation of alcohols and aldehydes using temperature gradient, Inglese et al. observed a significant increase in the "noise" of the FID baseline in comparison with the isothermal mode [6]. To reduce the noise, it was proposed to maintain the temperature of the pressure limiter ("restrictor") at a constant level, irrespectively of the temperatures of the column and mobile phase. This was done using an additional thermostat.

The spectrophotometric detection of analytes, as a rule, requires the use of expensive high-purity organic solvents, which do not possess significant absorbance in the UV spectral region. The replacement of these solvents by subcritical water reduces the costs of analysis. Thus, a possibility of the spectrophotometric detection of aldehydes at wavelengths below 200 nm using subcritical water as an eluent was noted in [51]. In contrast to organic solvents, water does not possess significant absorbance at these wavelengths, which ensures an increase in the sensitivity of the determination. However, this advantage can hardly be realized in the analysis of real samples containing a great number of organic substances that absorb in this spectral region.

In the separation of ecdysteroids and barbiturates [41, 52], it was proposed to use NMR for detection in HPLC using deuterated subcritical water as an eluent. The combination HPLC–NMR was also used earlier; however, it required the use of large amounts of expensive deuterated organic solvents (methanol, acetonitrile, etc.) for the elimination of proton lines of the solvent from the NMR spectrum. Deuterated water is much cheaper, which allows the expansion of the possibilities of such method of analysis.

Paracetamol, caffeine, phenacetin in medicines [42], and also a number of biologically active substances in a ginger extract [46] were determined using an HPLC system with two detectors, NMR and MS, working simultaneously, which allowed a significant increase in the information content of the analysis. The application of subcritical water as an eluent opened a possibility of using such a combination of detectors.

It was noted that the replacement of aqueous–organic eluents by subcritical water reduces the drift of the baseline in the HPLC–MS determination of alkylbenzene, phenols, aryl alkyl ketones, carboxylic and amino acids, and hydrocarbons [53].

Possibility of using temperature gradients instead of gradients of composition of the mobile phase. Among the advantages of subcritical water in comparison with organic solvents is a possibility of the variation of mobile phase properties directly in the course of elution by changing the temperatures of water and the column, an approach alternative to gradient elution in liquid chromatography. It was found that an increase in water temperature by 4°C is equivalent to an increase in the concentration of the organic component by 1% in an aqueous–alcoholic or an aqueous–acetonitrile mixture [54, 55]. This version of gradient elution, in which only the temperature of the system is changed, is technically simpler than the creation of a gradient of the composition of the mobile phase, because only a device for temperature regulation is required for separation in this case [56].

In the temperature gradient mode, substances whose peaks were not resolved in elution at a constant temperature were successfully separated [40, 42, 46, 47, 57]. SW-HPLC in the temperature programming mode was used for the separation of alcohols [40], biologically active substances [42], and herbicides [57]. For example, the separation of components of a ginger extract was attained in the temperature gradient mode in the range from 50 to 130°C [46].

The separation of carboxylic acids, alcohols, and heterocyclic compounds on a chromatographic adsorbent BEH C18 was studied using subcritical water as an eluent in the temperature programming mode [56]. The temperature of the eluent was changed in the range 60–180°C using two methods. In the first method, the flow rate of the eluent remained constant and in the second one, constantly increased rate with increasing temperature for the maintenance of a constant pressure in the system. It was found that the complete separation of a mixture of substances was attained only under isobaric conditions; in this case, flow rate in the analysis could be increased almost fourfold, from 0.3 to 1.1 mL/min.

Table 2. Viscosity of HPLC eluents

Mobile phases	Temperature, °C	Viscosity, cP
Methanol	25	0.56
Acetonitrile	25	0.35
Water	30	1
	100	0.3
	200	0.15

Reduction of the time of analysis and increase in the efficiency of chromatographic separation at elevated temperatures. The use of subcritical water instead of aqueous–organic mixtures, traditionally used for separation in reversed-phase HPLC, in some cases, ensures the improvement of the characteristics of separation. Thus, at elevated temperature, the retention times of analytes usually decreased, which allowed the reduction of the separation time. A decrease in the viscosity and surface tension of water at elevated temperatures also improved the kinetic efficiency of the system. Below we consider these two factors in more detail.

The effect of temperature on the retention factor is generally described by the function of free energy variation in an interaction between the dissolved substance and the stationary phase (Vant Hoff's equation):

$$\log k = -\frac{\Delta H_0}{2.3RT} + \frac{\Delta S_0}{2.3R} + \log \Phi,$$

where ΔH_0 and ΔS_0 are enthalpy and entropy of the system, T is absolute temperature, R is universal gas constant, and Φ is phase coefficient of the system.

The linearity of the dependence of log$k$ on $1/T$ in the temperature range from 25 to 180°C was checked experimentally [11, 58, 59] in the separation of a number of test substances, such as alkylbenzene, on different stationary phases using aqueous–organic eluents. It was found that, for the majority of the studied systems, the Vant Hoff dependence remained linear in the whole range of the studied temperatures, but, on zirconium dioxide coated with polybutadiene, the plot of the dependence of log$k$ vs. $1/T$ exhibited a kink, which can point to a partial change in the retention mechanism. However, the general trend to a decrease in retention factors remained the same and the duration of chromatographic separation in this case could be reduced by increasing the temperature of the mobile phase.

The efficiency of chromatographic separation is usually described within the concept of theoretical plates. The height of a theoretical plate can be calculated by the Van Deemter equation:

$$H = A + B/v + Cv,$$

where A is eddy diffusion coefficient (determined by the geometry of stationary phase particles), B is longitudinal diffusion coefficient, C is coefficient of resistance to mass transfer, and v is linear flow velocity. The coefficient C is associated with difficulties of mass exchange in the column and determines the behavior of the Van Deemter curve at high flow rates of the mobile phase. To decrease the coefficient C and improve the separation, one should reduce the viscosity of the mobile phase [11]. Data on the viscosity of mobile phases used in the reversed-phase HPLC were presented in [11] (Table 2). It can be seen that subcritical water with an increase in temperature becomes less viscous in comparison with organic solvents, which leads to an increase in the rate of diffusion in the system solution–solute. This results in the improvement of mass transfer and, correspondingly, in a decrease in coefficient C in the Van-Deemter equation; the minimum in the curve is shifted towards higher linear flow velocities. Therefore, one can increase the linear flow rate of the eluent without a loss in the efficiency of separation [5, 60]. For example, an increase in the temperature of the mobile phase to 150°C allowed an increase in the flow rate of the mobile phase to 15 mL/min and the reduction of the duration of the HPLC separation of a mixture of five alkylphenols from 20 min to 20 s [5].

It was shown that use of temperature gradient at constant compositions of the eluent instead of classical gradient elution reduced the time of analysis without the deterioration of separation [56].

RESTRICTIONS AND TECHNICAL PROBLEMS ASSOCIATED WITH THE USE OF SUBCRITICAL WATER AS A SOLVENT

The work with subcritical water is associated with a number of difficulties due to the impact of high temperatures on the equipment, analytes, and adsorbent used for the extraction or separation of components. These difficulties restrict the range of substances that can be extracted and separated using subcritical water and also the range of adsorbents used in SW-HPLC.

Stability of separated substances using subcritical water as a mobile phase. As subcritical water is relatively recently used in chemical analysis, data on the stability of various substances in this aggressive media are relatively scanty and constantly replenished.

Thus, the stability of alkylbenzene, caffeine, anisole, and methyl benzoate was studied in chromatographic separation using subcritical water [61]. It was noted that the oxidation of the separated substances can lead to the formation of split "double peaks" in the chromatogram. The degree of peak distortion is proportional to the residence time of substances in the column (in the zone of elevated temperature) and reaction rate. However, if the rate of

reaction is rather high and a substance is completely converted into a reaction product within a short time (small in comparison with the total residence time in the chromatography column), the chromatogram must contain one undistorted peak. The stability of a number of substances (alkylbenzene and substituted aromatic amines used as medicines) at elevated temperatures was experimentally studied in [61]: the zone containing a substance was injected into a column heated to 100–190°C. The adsorbent was zirconium dioxide coated with polybutadiene. It was found that, of the whole range of model substances, only norpseudoephedrine underwent chemical transformation in the column at elevated temperatures; with an increase in temperature, the distortion of the peak shape in the chromatogram was observed; however, even taking into account this distortion, no significant deterioration of the sensitivity and reproducibility of the determination was noted. The fivefold reduction of the residence time of the separated substances in the heated zone led to the restoration of the peak shape of norpseudoephedrine.

Subcritical water was used for the extraction of amines and PAH from soils under batch conditions, after which the substances were isolated from the cooled water extract by solid-phase microextraction and determined by gas chromatography [62]. It appeared that some of the separated substances decomposed during extraction (60 min, 250°C). Under the described conditions, only deuterated anthracene (internal standard) and an urea derivative decomposed with the formation of methylamine, which led to the incorrect determination of methylamine. Undeuterated PAH proved to be stable in the medium of subcritical water.

Pesticides carbofuran, carbosulfan, and imidacloprid were extracted from dust samples with subcritical water (30 min, 250°C) under dynamic conditions [63]. The recovery of carbofuran was 115%, and the extraction carbosulfan failed. It was supposed that, carbosulfan in the course of extraction decomposed to carbofuran, so that the recovery of the last substance was overestimated. Esters were extracted from soil with subcritical water at 100–150°C [64]. It was noted that, under these conditions, ethers hydrolyzed and were then determined as acids; recovery was 80%.

Subcritical water was also used for the chromatographic separation of steroids, oncology drugs, and antibiotics on a column with ZirChrom-PDB [12]. In the separation of a mixture of steroids (estriol, androstenedione, estrone, and dehydroepiandrosterone), the temperature of subcritical water was varied from 120 to 185°C, and no decomposition of substances was observed. However, in the separation of a mixture of medicines, amoxycillin, cytarabine, chloramphenicol, and etoposide, the decomposition of an amoxycillin was observed just at 40°C.

The stability of substances is affected not only by the temperature of subcritical water, but also by the composition of the stationary phase [65]. Thalidomide was determined on an adsorbent consisting of a styrene–divinylbenzene copolymer in one case and zirconium oxide coated with a carbon film in the other case; the temperature of subcritical water was changed in the range 60–180°C. In using the organopolymer adsorbent with increasing temperature to 180°C, the asymmetry of the peak decreased at an insignificant decrease in its area. The application of the adsorbent based on zirconium oxide led to opposite effects: at an increase in temperature, the area of the peak decreased, which points to the decomposition of thalidomide; decomposition was complete at 180°C.

Stability of adsorbents (stationary phases in HPLC) to the action of subcritical water. In review [66] devoted to the stability of stationary phases for HPLC at elevated temperatures, it was noted that adsorbents based on silica under such conditions are unstable: the degradation of their properties was observed already on passing subcritical water in an amount of 300–500 of the column volume. The maximum temperature of the eluent in this case did not exceed 120°C. An increased stability of XTerra silica (Waters) to the action of subcritical water in comparison to similar silicas of other brands and producers was noted; however, the maximum recommended temperature for these adsorbents was also low and reached 130°C [46].

The stability of two silicas XTerra and XBridge (Waters) with attached phenyl groups at elevated temperatures was studied in [7]. The efficiency of the separation of a mixture of test compounds on an XTerra column is significantly deteriorated after several days of using subcritical water at 200°C as a mobile phase; significant degradation of an XBridge column under the same conditions was not observed. The stability of "hybrid" (with ethylene bridges between silicon atoms) silicas Gemini C18 and Gemini NX (Phenomenex) was compared in [67]. The properties of Gemini C18 degraded much quicker than those of Gemini NX.

Columns with adsorbents based on zirconium dioxide modified by various organic compounds are more stable at elevated temperatures [66]. For example, ZrO_2 coated with polybutadiene is stable at 200°C on passing subcritical water in an amount of 1300 column volumes. The adsorbent based on zirconium dioxide was successfully used in a number of works as a stationary phase in the chromatographic separation of substances in the medium of subcritical water at temperatures up to 200°C [5, 68]. Zirconium dioxide with a polybutadiene coating is more hydrophobic in comparison with silica-based analogs. From this viewpoint, adsorbents based on modified zirconium dioxide offer big advantage over adsorbents based on silicon dioxide, as they ensure the achievement of an efficient separation of substances at lower temperatures

Table 3. Adsorbents and temperature ranges used in HPLC with subcritical water as a mobile phase

Adsorbent type	Trade mark, producer	Temperature range, °C	Reference
Porous graphitized carbon	Hypercarb, Thermo Scientific	180–225	[76]
Styrene–divinylbenzene copolymer	PLRP-S, Polymer Laboratories	140–205	[76]
	PRP-1, Hamilton	100–150	[75]
	The same	100–200	[75]
Styrene–vinylpyrrolidone copolymer	Oasis, Waters	165–210	[76]
Surface-modified zirconium dioxide	Zir-Chrom PDB, ZirChrom Separations	100–130	[76]
	The same	50–130	[46]
	Zir-Chrom CARB, ZirChrom Separations	180–220	[76]
	ZirChrom-PS, ZirChrom Separation	100	[75]
Silica with attached alkyl phase	XTerra RP18, Waters	20–160	[76]
	C18 BDS, Hypersil	20–160	[76]
	Zorbax RX-C8, DuPont	100	[75]
	Nucleosil C18 AB, Keystone Scientific	100	[75]
	Hypersil BDS C18, Keystone Scientific	100	[75]
	Xterra C18, Waters	50–130	[46]
	Chromatorex C-18, Fuji Silysia	80–140	[80]
	Zorbax RX-C-18, MAC-MAD Analytical	60–140	[80]
	XTerra C8 XTerra C18, Waters	160	[41]

and lower concentrations of the organic solvent, which is particularly important in using subcritical water as a mobile phase [69–71]. More hydrophobic adsorbents based on zirconium oxide, for example, coated with carbon (ZirChrom-Carb) and bearing attached C18 groups (ZirChrom-Diamond Bond) are also known. ZirChrom-Carb demonstrated exclusive stability at temperatures up to 225°C and at considerable variation of pH of the mobile phase [72].

Adsorbents based on titanium dioxide coated with various polymers, for example polyethylene, were also used for the separation of substances under the conditions of high-temperature HPLC. As zirconium dioxide, titanium dioxide was also modified by carbon particles, and the adsorbent with a carbon coating was much more hydrophobic than its analog with a polymer layer. In using subcritical water without additives of organic solvents as a mobile phase, columns based on titanium dioxide coated with polyethylene demonstrated higher stability. However, the application aqueous–organic mixtures at high temperatures as eluents led to the decomposition of the polymer layer and the deterioration of column properties. Thus, a considerable decrease in retention factors of *p*-cresol, nitrobenzene, and ethylbenzene was noted after the use of an eluent based on a mixture of water with tetrahydrofuran [73].

Adsorbents based on styrene–divinylbenzene copolymers and their analogs exhibit rather high stability to the action of subcritical water at 100–200°C. An essential drawback of such adsorbents is their insufficient mechanical stability under the specified conditions. At the variation of the temperature of the mobile phase, granules of these adsorbents change their volume, which prevents their use in gradient elution with subcritical water [38, 39, 66, 74]. The long-term stability of an adsorbent based on a copolymer of styrene with divinylbenzene (PRP-1, Hamilton) was studied using subcritical water as a mobile phase [38]. Water was continuously passed through the column at a rate of 0.2 mL/min at 100–150°C within 144 h (6 days). After each 24 h, a solution of phenol and *p*-cresol was injected into a chromatograph and retention parameters were compared; the change in retention times within the experiment was no more than 1%. Long-term stabilities of various adsorbents (silicas with an attached alkyl phase, zirconium dioxide coated with polystyrene, styrene–divinylbenzene copolymer) were compared in using subcritical water as a mobile phase for the HPLC separation of a model mixture of substances [75]. It was shown that the adsorbent based on styrene and divinylbenzene was the most stable; no degradation of the adsorbent was observed even after passing 3 L of the mobile phase at 150°C.

Adsorbents based on styrene and vinylpyrrolidone copolymers (for example, Oasis, Waters) also possess high stability to subcritical water. For example, an Oasis adsorbent was used at 160–210°C [76]. It was found that the Oasis adsorbent underwent mechanical rupture under the effect of high pressures necessary for the desorption subcritical water [77].

Table 4. Procedures for the HPLC separation of substances including the use of subcritical water as an eluent

Test sample	Analytes	Stationary phase		Separation conditions	Detector*	Reference
		type	trade mark			
River water	Phenols	Super cross-linked polymer	PS-DVB	150°C	SP, 220 nm	[38]
Plant extracts	Steroids	Silica	C18 XTerra	160°C	H^1 NMR, SP, MS	[41]
	Vaniline, dihydroferulic acid, zingerone	The same	XTerra RP C18	50–130°C, temperature programming	NMR	[46]
Foodstuffs	Alcohols	Super cross-linked polystyrene	PRP-1	120–150°C, temperature programming	FID	[40]
Model solutions	Alkylphenones	Modified zirconium dioxide	ZrO_2-PS	150°C	SP, 254 nm	[5]
	Carboxylic acid	Super cross-linked polystyrene	PRP-1	160°C	FID	[39]
	Alcohols	The same	PRP-1	125°C	FID	[6]
	Medicinal preparations	"	PS-DVB	80–150°C, temperature programming	H^1 NMR, MS	[42]
	Vitamins	"	PLRP-S	200°C	H^1 NMR, MS, FL	[44]
	Phenols, acetophenones	Silica	XTerra MS C18, XBridge	100°C, 200°C	SP, 230 nm	[7]
	Steroids	The same	XTerra MS C18	130°C	SP, 230 nm	[43]
	Antioxidants	"	Kromasil C18	30–100°C, temperature programming	SP, 280 nm	[45]

* Detectors: SP is spectrophotometric, NMR is NMR spectrometric, FL is fluorimetric.

The stability of adsorbents based on porous graphitized carbon (PGC) was noted in [59]. The retention mechanism on this adsorbent strongly differs from the mechanism known for silica-based adsorbents [78, 79]; therefore, efficiency and selectivity in using these adsorbents are also different. PGC proved to be efficient in the separation of structurally similar compounds, for example, stereoisomers [11, 47, 72].

More detailed data on temperature ranges of stability of various stationary phases for HPLC are presented in Table 3.

As the SW-HPLC method was proposed only recently, the majority of works were devoted to the study of the potentials and restrictions of the method; however, a number of articles aimed at fulfilling applied tasks by means SW-HPLC were also published. For example, SW-HPLC was used to determine biologically active substances in plant extracts [41, 46], phenols in waters [38], and alcohols in foodstuffs [40]. More detailed information on the use of SW-HPLC is provided in Table 4.

COMBINED METHODS USING SUBCRITICAL WATER

Subcritical water can be used not only at individual stages of chemical analysis, extraction or separation, but also for the implementation of the whole cycle. Thus, methods of soil analysis including the following stages were proposed [57, 81–83]: extraction of analytes with subcritical water; extraction of analytes from the extract after its cooling on a column with a reversed-phase adsorbent; desorption of analytes from the adsorbent with subcritical water; and analysis of the concentrate obtained by SW-HPLC. The whole cycle of analysis, including, extraction, adsorption, desorption, and SW-HPLC determination was performed in an automatic on-line mode without using organic solvents; subcritical water was used instead of them [57, 81, 83]. Biologically active substances [81, 84], herbicides [57], and PCB [83] were extracted; temperatures of extraction, desorption, and SW-HPLC separation were 120–170, 165–200, and 75–250°C, respectively.

A similar scheme was proposed for the determination of aniline and phenols in sand and flavonoids in orange skin; however, after the termination of the adsorption step, the column with the adsorbent was manually disconnected from the system and connected to an SW-HPLC chromatograph for carrying out desorption (at 130°C) and separation (at 80°C) [82].

Methods of sorption–SW-HPLC determination of some phenols and mono- and disubstituted phthalates were proposed in [85, 86]. Analytes were extracted on a Hypercarb carbon adsorbent and desorbed with subcritical water; the concentrate zone was extracted with a dosing loop; analytes were focused in an entrance section of an HPLC column with octadecylsilica, separated, and determined in the isocratic mode with spectrophotometric detection. It was shown that the efficiency of analyte desorption with subcritical water at 175–200°C in using a Hypercarb adsorbent is comparable with the efficiency of desorption with acetonitrile at room temperature; and peaks in the chromatogram obtained after preconcentration from 10 mL of a solution were 1.5- to two times narrower than those in the direct HPLC analysis of 20 μL of solution.

ACKNOWLEDGMENTS

This work was supported by the Russian Science Foundation, grant no. 14-23-00012.

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Translated by E. Rykova