Modern Extraction Techniques

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Review Contents	

The central role of extraction during a chemical analysis compounds a critical review of developments in the field. Thousands of articles annually list "extraction" as a key word (about 2500 articles per year when searching only keywords for English chemistry journal articles). Consequently, narrowing the topic of this review is highly selective since about 10 000 articles survived the initial literature search. Hence, this review focuses on the most significant new developments and advances in the 2006–2009 calendar years, since the previous review (*1*). Articles focusing on applications were generally not considered in this review. The major trends in the field of extractions for chemical analysis appear to be the use of ionic liquids; development of electrically assisted extractions; alternative phases (including monoliths), quantitative methods, and geometries for sorptive extractions; approaches to membrane-based extractions; and single-drop and related low-volume microextraction approaches. This represents a change from the trend of developing enhanced methods based on the application of energetics, a field which has perhaps developed to some state of maturity. These new trends represent the bulk of this Review. In addition to development and fundamental research articles, key reviews are highlighted to draw the reader's attention to other state of the art discussions.

IONIC LIQUIDS

Ionic liquids are salts that are liquid at or near room temperature (generally defined as less than 100 °C) due to poor coordination of the ions. In many chemical processes, they are considered green solvents due to their negligible volatility, but emission of volatile organic carbon is not typically a concern in analytical laboratories. Additionally, the toxicity of some of these compounds renders them less completely "green" than often touted. These liquids exhibit a range of solvent properties, especially for the isolation of compounds from aqueous solution. Of greater importance is that these liquids tend to be highly viscous, limiting their use as a conventional solvent. Consequently, ionic liquids tend to be used in two different formats in analytical extracts, in the mode similar to conventional solvent-based

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extraction and as the stationary phase in sorptive extractions. Li et al. (*2*) reviewed the structures, solvent characteristics, extraction mechanisms, and applications of this class of solvents in analytical chemistry. They noted the selectivity and extraction efficiency of ionic liquid/aqueous two-phase systems. In nearly all of the reports of ionic liquids which follow, the liquid of choice was a 1-alkyl-3-methylimidazolium salt.

Due to a combination of the viscosity and the expense of ionic liquids, they tend to be used at the microscale for analytical extractions. For example, Gharehbaghi, Shemirani, and Baghdadi (*3*) demonstrated the recovery of aqueous mercury complexes from a dispersion of ionic liquid and acetone, followed by centrifugation of the ionic liquid droplets. This method appeared to be somewhat cumbersome and did not provide a low detection limit, but it did demonstrate a novel approach using dispersive liquid−liquid microextraction (DLLME). They also optimized a similar extraction by cooling the extraction system to induce droplet aggregation with greatly improved quantitative results (*4*). A similar report (*5*) of DLMME provided impressive quantitative results for the determination of pyrethroid pesticides when temperature control was applied to the system. Cruz-Vera et al. (*6*) avoided the time-consuming centrifugation step by performing DLLME with an ionic liquid solvent and the direct extraction of urinary nonsteroidal anti-inflammatory drugs in a syringe with good quantitative results. A three-phase organic/water/ionic liquid system combined with in situ complexation provided good selectivity to isolate Ni^{2+} preferentially over four other divalent ions (*7*). By combining an ionic liquid-impregnated hollow-fiber membrane in a three-phase extraction system, Basheer et al. (*8*) achieved a 210-fold enrichment of hydrocarbons extracted from aqueous solution in a system as convenient as traditional two-phase systems. The hollow-fiber approach was combined with extraction of the acceptor solution into a microsyringe for the liquid chromatographic (LC) determination of chlorophenols from aqueous solution, demonstrating the versatility of combining microextraction methods (*9*).

The viscosity of a water-immiscible ionic liquid renders it ideal for the headspace extraction of volatile compounds; however, the ionic liquid is far from an ideal injection solvent for subsequent gas chromatographic (GC) analysis. Zhao, Li, and Zeng (*10*) found that phenols could be desorbed from ionic liquid solution at 210 °C and the liquid withdrawn back into the syringe, while in another report (*11*) they placed a glass tube in the injection port to prevent the nonvolatile fluid from entering the column.

A handful of other studies investigated aspects of ionic liquid solvents for analytical extractions. Sieffert and Wipff (*12*) reported a molecular dynamics comparison of ionic liquids and chloroform for the extraction of calixarene-bound cesium. They found that

the ionic liquid systems took longer to equilibrate but exhibited greater intersolvent mixing. Extraction selectivity for yttrium over other lanthanides was made more favorable with the addition of an aqueous complexing agent to an ionic liquid system (*13*). Ionic liquid solutions were also used in a microwave-assisted extraction system for the isolation of plant-based natural products (*14*). It was proposed that the electron-rich aromatic π system of the ionic liquid facilitated the extraction. Related to the previously discussed dispersive extractions with ionic liquids, the addition of an ion-pairing reagent was added to a hydrophilic ionic liquid extraction system (*15*). A new, hydrophobic ionic liquid was formed containing the inorganic analytes and isolated by centrifugation. A fused-silica column filled with a mixed aqueous/ionic liquid mixture was the medium for the extraction and oil−microsolvent cluster formation, and analytes partitioned through the system in a chromatographic fashion (*16*).

Similar to their use in headspace analysis, the role of ionic liquids as a sorptive phase in the various solid-phase extraction approach appears to make the most sense. These approaches take advantage of both the solvating properties of the ionic liquids and their high viscosity. Polymeric ionic liquid coatings in solid-phase microextraction (SPME) were found to display exceptional film stability, high thermal stability, long lifetimes, and favorable extraction properties (*17*). Free radical polymerization was used to stabilize the ionic liquid coatings. Meanwhile, a light cross-linking with trifluoroacetic acid of a polymer-supported imidazolium salt provided a solid-phase extraction (SPE) media with the advantageous properties of ionic liquids and of solid supports (*18*). Finally, Shearrow et al. used two ionic liquids as the porogen in sol−gel reactions to form the extracting phase for capillary microextraction (*19*). The ionic liquid mixture was needed to overcome the slow reactions of the individually viscous liquids, and the resulting sol−gel provided a 28-fold improvement in extraction over analogous sol−gel coatings.

ELECTRICALLY ASSISTED EXTRACTIONS

Perhaps the most novel trend in extraction mechanisms during this review period is the application of electric potentials to facilitate extractions. While migration, the transport of ions in an applied potential, is the basis for the widely used electrophoretic family of separation methods, its use in bulk separation processes like extraction is minimal but intriguing. Since membrane-based separations operate due to some type of gradient across the membrane, the application of an electrical potential to create an enhancement of this gradient seems to be the most logical utilization of this approach to extraction. Gjeldstad et al. (*20*) were among the first to investigate this approach when they compared the extraction of basic analytes across a supported-liquid membrane (SLM) based on passive diffusion in a pH gradient and migration in an electrical field. Compared with mass transfer due to diffusion and convection, the improvement in extraction kinetics due to the applied potential was 6−17-fold. They also used the same approach for acidic drugs (*21*). The scale at which they worked was using a 300 μL donor solution, 30 μL acceptor solution, and 50 V applied field, whereas earlier they had applied a 300 V potential (*22*). These and related reports (*23*, *24*) provide the basis for interesting approaches to microscale extractions. Optimization studies (*25*, *26*) conclude that the volume and pH

of the acceptor and donor phases, organic solvent, and the applied voltage and duration are key factors for these extractions.

While migration in an electric field is a natural fit for membrane-based separations, there are several investigations into the application of such a potential in a bulk solvent system. When a potential was applied across two immiscible electrolyte solutions, a degree of selectivity was observed due to the rate of analyte migration in the applied field and, in some cases, a complexing agent was needed to facilitate effective extraction (*27*, *28*). When applied to semisolid and wet solid samples, this electrokinetic approach can avoid problems with sample drying (*29*). When applied to the leaching of lead from wet soils, the type of acid used to control pH could either enhance or suppress the extraction efficiency (*30*). Antioxidant activity was maintained when electrokinetically extracting natural products from plant materials and, as in all diffusion-based systems, particle size had a significant effect on the extraction recovery (*31*). Morales-Cid et al. (*32*) combined a voltage-assisted SPE with capillary electrophoresis-mass spectrometry and found enhanced reproducibility and sensitivity.

SORPTION-BASED METHODS

Meaningful advances in sorptive extractions have occurred in three broad areas during this review period, namely, sorptive-phase development, extraction device geometry, and calibration for quantitative methods. These extractions are generally classified into types. Conventional cartridge and disk approaches tend to be more exhaustive, so quantitative calibration is not needed and a wide variety of available phases allows isolation of analytes amenable to either GC or LC characterization. On the other hand, the formats which are equilibrium-based techniques require calibration for quantitative methods and typically, but not always, use phases more amenable for determination by GC.

We will begin this discussion by investigating phase development, including significant work with molecularly imprinted polymers. One review (*33*) explored new coatings developed in the 5 years immediately prior to this review, including different approaches for fiber production and use in alternative formats like in-tube extraction. Another (*34*) reviewed phases specifically for extracting polar compounds. These phases were found to be hydrophilic and possessed high surface area, and the morphology and chemistry of these phases were discussed. Gierak, Seredych, and Bartnicki (*35*) pyrolyzed methylene chloride, which they used with a specially prepared activated carbon as a carbon-fiber phase for SPME. Applied to petroleum compounds, these fibers exhibited high partition coefficients. Multiwalled carbon nanotubes were developed, not for microscale sorptive extractions but to expand the capacity of SPE approaches (*36*, *37*). Sae-Khow and Mitra (*38*) developed carbon nanotubes for use in the syringe-needle format of sorptive extraction. They showed that the packed fiber version was more effective than self-assembled nanotubes and that sorption followed a Freundlich isotherm. These phases were found to have enhanced capacity for the extraction of environmental waters and fruit juices. Pyrzynska (*39*) reviewed the use of carbon nanotubes in SPE discussing their sorption capacities, process parameters, and their interactions with organic compounds via hydrogen bonding, $\pi−\pi$ stacking, electrostatic forces, van der Waals forces, and hydrophobic interactions. A separate review (*40*) presented a variety of carbonaceous sorbent phases including

nanotubes and nanoparticles and the characteristics of each. A composite polydimethylsiloxane (PDMS) and β-cyclodextrin phase was prepared by the sol–gel technique and demonstrated enhanced selectivity toward polar compounds compared with PDMS-coated stir bars and greater capacity than fibers coated with the corresponding composite phase (41). Polyurethane foams were also developed as stir-bar coatings to expand the polarity range over the commercial PDMS phases (42, 43).

Other coatings moved beyond expanding the analyte polarity range of the extraction and looked into the kinetics of the process. For example, Mehdinla and Mousavi (44) developed and compared nano- and microstructured polyaniline coatings. Due to the larger surface area, the nanostructured coatings displayed higher extraction rates and shorter desorption times. Biocompatibility is important for in situ applications and Vuckovic et al. (45) developed a biocompatible binder for use with conventionally coated silica particles. They thoroughly evaluated the kinetics and characteristics of these coatings, which appear to have commercial interest.

One specialized type of sorptive phase is the class of molecularly imprinted polymers (MIP) used in molecular recognition separations. In these phases, a polymer is formed around a surrogate of the analyte(s) of interest resulting in a selective cavity when the model compound is removed. While MIPs have been available for quite some time, they traditionally have been custom-made and, consequently, somewhat expensive. Advances over the past decade or so have made the synthesis of MIPs more reproducible and more commonplace. Pichon and Haupt (46) reviewed the use of MIPs in affinity separations, including SPE, with special emphasis on chiral separations. Pichon (47) also appraised MIPs for SPE evaluating their synthesis and selectivity, while Tamayo, Turiel, and Martin-Esteban (48) provided an overview focusing on performance issues. Turiel et al. (49) showed that polymerization time and fiber thickness affected polymer morphology in MIPs used in SPME and solvent selection, time, and temperature influenced the binding and elution of the target analytes. Farrington and Regan (50) used a rational design approach to create an MIP specific for ibuprofen. They correlated nuclear magnetic resonance spectroscopy data with molecular modeling to predict performance over a variety of conditions. This approach addresses one of the prime difficulties with these phases, understanding the experimental parameters that impact performance. Toth et al. (51) took a more empirical approach toward gaining this understanding. The relationship between isotherms, binding site models, and selectivity were investigated, but it was concluded that the current state of the art is far from complete understanding of MIP performance. Sergeyeva et al. (52) formed semi-interpenetrating polymer networks to create porous free-standing MIP membranes. The membranes possessed high flux and greater capacity compared with MIP particles. A unique approach to extraction capacity and selectivity in the packed syringe-needle format was to electrochemically deposit an MIP over carbon nanotubes (53). An additional benefit of this approach is that the needle can be reused. A dual-phase system consisting of magnetic MIP beads in an aqueous system with small amounts of hexane showed a 9-fold improvement in efficiency compared with a purely aqueous system (54). The beads were suspended

in the organic layer which assisted in the focusing of the analyte for binding with the MIP.

A final type of sorptive phase significantly investigated during this period is the monolithic phase, including sol–gels. These phases have the advantage of large surface areas for sorption to occur. Altun et al. (55) prepared a methacrylate monolith inside a syringe and compared the phase with polymeric and silica-based sorbents. However, in this study, the polymeric phase displayed the best performance while the monolith had the lowest performance. In the coated stir bar format, Huang and Yuan (56) investigated polymerization parameters and thickness of the monolith layer and found good permeability with fast adsorption and desorption. The first germania-based sol–gel was prepared for capillary microextraction and GC (57). Three different ligands were explored, and the materials were able to withstand extreme pH values, high temperatures, and aggressive solvents. Finally, Liang and Chen (58) used emulsion photopolymerization to form monolithic microextraction tips. This approach created phases that did not require high pressures to draw sample through the pipet tip, and fast equilibria were obtained due to the high permeability and surface area.

A variety of different formats, or geometries, are springing up for sorptive-based extraction, usually of the equilibrium variety rather than exhaustive types. One of these alternative formats which have recent activity is the coated stir-bar technique. David and Sandra (59), credited with initial development of the method, reviewed the technique. In describing applications of stir-bar sorptive extraction (SBSE), they noted that the scope of the technique has moved from aqueous samples to headspace sampling and passive air sampling. An off-shoot of SBSE is a report using a rotating Teflon disk coated with PDMS (60). The reported disk had greater surface area and was rotated at a higher rate than commercial stir-bars, resulting in dramatically reduced adsorption and desorption times. Other SBSE developments focused on phase development and have been previously discussed. Much activity has also centered on syringe-needle or pipet-tip formats, using either fiber-packed needles as discussed or microextraction by packed sorbent (MEPS). Ogawa et al. (61) packed polymer-coated fibers longitudinally into a specially designed needle that they could subsequently transfer to GC injection modes. Abdel-Rehim (62) reviewed MEPS, which generally takes place in pipet tips rather than syringe needles, and noted that applications of particular advantage for this technique are in the clinical and forensic toxicology fields. Scintillation counting of radiolabeled analytes was used to investigate the factors controlling performance and carry-over in MEPS, necessary for optimization of the technique (63). Matrix solid-phase dispersion (MSPD) is a technique criticized as laborious but which can be quite flexible in performance with samples suited to the method, such as tissue samples. Kristenson, Ramos, and Brinkman (64) reviewed MSPD from the environmental analysis perspective. A miniaturized version of MSPD was coupled with in-tube SPME to extract and concentrate samples prior to analysis (65). The method was reported to be quite rapid and rugged. In addition to the in-tube version of SPME, capillary devices have been used in other variations as well, sometimes called capillary microextraction (CME). Similar to their work with fiber-packed needles reported earlier, the Toyohashi University of Technology group packed

polymer-coated fibers into capillaries for extraction (*66*). They were able to couple the extraction capillaries online with chromatographic analysis. Hu (*67*) summarized the various packing materials in CME, as well as hyphenation of the technique with analytical instrumentation. Finally, a number of other approaches have been reported and, while interesting, have seen only limited use. Sisalli et al. (*68*) coated PDMS onto a sorbent tape for in vivo sampling of human skin. Another report coated a polyacrylate onto strips of glass-fiber fabric which were shaken with the aqueous sample and thermally desorbed for GC analysis (*69*). Ghiasvand, Hosseinzadeh, and Pawliszyn (*70*) used conventional SPME for headspace sampling but in such a way as to cool the SPME fiber while simultaneously heating the sample. This configuration improved the efficiency of analyte desorption from the sample and partitioning into the extraction fiber. Another highly specialized system was equipping a microfluidic cell lysis chip with an SPE unit for electrophoretic quantification of intracellular proteins (*71*). A space-resolved SPME method was developed to monitor heterogeneous samples by considering diffusion-based mass transfer and fiber dimension (*72*). To enhance the ruggedness of SPME, an acid-etched uncoated stainless-steel wire was used (*73*). Etching the wire enhanced the extraction recovery several hundred times over untreated steel wires. Finally, films, rather than rods, used for SPE in the 96-well plate format demonstrated more effective agitation and mass transfer, resulting in faster extraction rates and greater reproducibility (*74*).

Quantification in sorptive extractions, especially SPME, remains problematic in many laboratories and efforts are being taken to address this issue. Tena and Carrillo (*75*) performed multiple SPME steps to avoid matrix-effect errors by calculating the amount of analyte using peak areas from consecutive extractions. Meanwhile, Zhang et al. (*76*) developed a single-point kinetic calibration for in vivo dynamic monitoring based on preloading standards onto SPME fibers. They presented the theoretical foundation of the approach and demonstrated its application. Others (*77*) studied the modes for spiking standards onto the SPME fibers and found the optimal loading method varied with sample type.

MEMBRANE-BASED EXTRACTIONS

The use of membranes in analytical extractions has grown tremendously during the review period. Hylon and Mitra (*78*) reviewed these methods and noted that one particular advantage of this approach is that the sample and extraction phases can be brought into continuous contact without physical mixing. Functionalized carbon nanotubes have been employed in membrane extractions and act as solvents in transfer of solutes between the donor and acceptor phases (*79*). Hollow-fiber membranes were compared with nonporous and microporous membranes, and the underlying transport processes were investigated (*80*). Enrichment factors of 25−35 for volatile organic compounds were claimed for the hollow-fiber method. Hollow fibers were used to determine protein−drug binding (*81*), analyze pesticides in vegetables (*82*), and determine trace levels of chemical warfare agents (*83*). A solvent-bar microextraction system was developed where forward and backward extraction across an organic film immobilized in the pores of a polypropylene hollow fiber with both ends of the fiber sealed (*84*). Similar to the kinetic calibration approach in SPME, Ouyang and Pawliszyn (*85*) developed an analogous approach in hollow-fiber microextraction. They showed that sample volume and

sampling time do not affect the calibration method. Five hundred-fold enrichment was noted. Zirconia and titania hollow fibers were constructed, and it was found that the zirconia fibers performed better (*86*). Addition of surfactants into the organic acceptor phase was also shown to enhance extraction (*87*). The influence of temperature on diffusion, flux, and viscosity was explored in hollow fibers, and it was found that temperature effects were most pronounced when the mass transport was controlled by the donor or the membrane rather than the acceptor (*88*).

A novel approach combining membranes into an extracting syringe was directly coupled with a GC autosampler and compared favorably with more conventional techniques (*89*). Wang and Mitra (*90*) were able to protect the organic acceptor phase and enhance extraction yields by coating the membrane with a low permeability barrier film to provide diffusional resistance. Another novel membrane method combined electrochemistry to control the analyte redox state at the extraction membrane (*91*). MIPs have been used as the acceptor phase in a membrane system (*92*). Swelling and other MIP disturbances due to water were minimized in this approach. Xu and Lee devised a silica monolith for use in the solvent-bar approach (*93*). The silica monoliths were much more compatible with extreme conditions compared with polymeric hollow fibers. Chimuka et al. (*94*) found that temperature impacted membrane extractions in a flowing acceptor solution due to increased diffusion. On the other hand, Petersen et al. (*95*) applied an electric field to drive analytes into the acceptor phase and developed a theory for the kinetics of the extraction. The field of membrane separations, including analytical dialysis, was reviewed (*96*).

SINGLE-DROP EXTRACTION

The simplicity of the single-drop extraction approach is gaining increasing acceptance. The solvent use in this approach is negligible, and the entire extract can be directly injected into a chromatographic system. Xu, Basheer, and Lee (*97*) reviewed the status and limitations of the technique and postulated on the future. In addition to liquid−liquid extraction, the approach can also be used in the headspace mode (*98*). In certain circumstances, a mixed-solvent droplet is necessary for suitable quantitation (*99*). While the traditional method of performing single-drop extraction involves a solvent drop suspended from the tip of a syringe, others have added miniscule amounts of immiscible solvent to the liquid sample system and removed the extracting solvent following stirring. This approach was enhanced by cooling the system and removing the extracting solvent as a frozen droplet (*100*, *101*). Enrichment factors of 500−1500 were reported. Another variation of the single-drop method used coacervates comprising surfactant aggregates of aqueous and reverse micelles and vesicles (*102*). The intermolecular forces between the surfactant headgroups led to the formation of supramolecular aggregates in the needle tip. Another form of single-drop extraction took place in a microfluidics channel (*103*). Hydrophilic and hydrophobic surface patterning also aided in phase contact and analyte mass transfer in microchannels (*104*). In addition to the expected parameters, channel dimensions and droplet spacing influenced the extraction efficiency. Dispersion of the solvent drop is sometimes favored to increase extraction yields (*105*). While in other cases, the droplet was allowed to form a thin film on the sample solution surface and the extraction vial was rotated to

facilitate phase contact (*106*). In either approach, once the extracting drop is withdrawn into the syringe, analyte derivatization is possible (*107*).

OTHER EXTRACTION ENHANCEMENTS

A myriad of other approaches to enhancing extractions have been developed and explored during this review period. One of these is hot water. In the 150−250 °C range, water takes on a polarity similar to organic solvents, as well as increased diffusion and lower viscosity. However, most analysts are reluctant to work at these temperatures; solvent concentration (i.e., water evaporation) is more difficult with water than with organic solvents, and material issues all leave the use of hot water extractions unexplored in all but a few laboratories. The use of this approach has been reviewed (*108*, *109*). Chienthavorn et al. (*110*) used a phase-transfer catalyst to derivatize phenoxy acids during hot water extractions. For the recovery of flavinoids, the hot water method extracted less material than the Soxhlet extraction but was performed in 35 min rather that 48 h (*111*). Additives, such as organic cosolvents or surfactants, were shown to improve extraction efficiency and precision (*112*). Diana used a boron sorption index and hot water extractions to determine boron availabilities in soils (*113*).

A variety of other alternative solvents, aside from ionic liquids, sorptive phases, and hot water, are utilized in analytical extractions. Solvent mixtures in enhanced techniques such as pressurized solvent extraction (PSE) can find selective results, and Jeannotte et al. (*114*) evaluated a number of mixed solvents for discrimination of extractable lipids. Derivatization agents compatible with solvents for microextractions can add another aspect to the analysis (*115*). Integration of detection systems, derivatization reactions, and applications were discussed. Amphiphile-based supramolecular solvents are water-immiscible liquids of nano- and microscale aggregates dispersed in a continuous aqueous phase and are used to isolate trace contaminants from liquid samples (*116*). The reversed micelles that are formed provide the extraction medium.

Sonic probes are finding a slight resurgence in analytical utilization. In addition to the input of sonic energy, the localized heating can possibly yield favorable extraction results. Villar et al. (*117*) found that optimized conditions were cost-effective compared with other extraction techniques; mixed solvents can also be beneficial in ultrasonic extractions (*118*). One particular advantage of the ultrasound method compared with other enhanced extraction methods is the elimination of the time required for solvent cool down (*119*).

Other extraction enhancements during this review period include a biphasic recognition chiral extraction system using an organic solvent and a hydrophilic cyclodextrin derivative (*120*), surfactant-coated carbon nanotubes as pseudophases (*121*), use of microwaves during steam distillation (*122*), rotating-coiled columns containing solid samples through which extraction solvent is passed (*123*), and surfactant derivatization following cloud point extraction (*124*).

CONCLUSION

Extraction methods are receiving increasing attention now and in the future. Sorptive extractions will continue to be developed,

though the number of useable formats will settle to those with key advantages. Ionic liquids and related "green" solvents will see increased use in analytical extraction. Parallel extraction systems will increase sample throughput. It is anticipated that these will be the primary developments in the near future.

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