Trends in Analytical Chemistry 103 (2018) 156–183

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

journal homepage: www.elsevier.com/locate/trac

# Miniaturized separation techniques as analytical methods to ensure quality and safety of dietary supplements

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ARTICLE INFO

*Article history:*
Available online 14 April 2018

*Keywords:*
Amino acid
Antioxidant
Capillary electrophoresis
Capillary electrochromatography
Contaminant
Dietary supplement
Food supplement
Micro/nano-liquid chromatography
Vitamin

ABSTRACT

Currently, dietary supplements are widely consumed over the world for health-related reasons. Even though, most of these supplements are beneficial for human health, they can also have side effects due to an excess of one of the supplement ingredients or to the presence of contaminants. It is then important to ensure their efficacy and safety. Recently, miniaturized separation techniques have emerged as popular analytical tools in several application fields. Rapid separations, low consumption of both samples and reagents, as well as high efficiency and reduction of production costs are some of the requirements of research laboratories and manufacturing companies. The aim of this review is to give an overview of the electromigration and miniaturized chromatographic methods for the analysis of dietary supplements. Applications for the determination of supplements related molecules including amino acids, peptides, selenium, vitamins, phenethylamines, nanomaterials, polyphenols, biomolecules, other components as contaminants and pharmaceutical drugs are described.



## 1. Introduction

A dietary supplement is defined as a source of nutrients that may otherwise not be consumed in sufficient quantities. U.S. authorities define dietary supplements as foods, while elsewhere they may be classified as drugs or other products. The consumption of dietary supplements has increasingly grown over the last decades, mainly pushed by marketing claims addressing their use to prevent diseases and enhance health [1,2]. A diet including an adequate variety of foods should provide all the nutrients needed for an overall health status. However, food alone may not supply adequate amounts of specific nutrients, especially when nutritional needs change due to diseases, aging, pregnancy, physical activities. Obviously, these products are not intended to prevent or treat any disease and can be dangerous in some circumstances. A large and growing literature has shown that ingredients in dietary supplements may sometimes cause unexpected side effects or hazardous intoxications, due to the presence of chemical contaminants, pesticides and mycotoxins. In addition, it has been reported that a wide number of marketed dietary supplements have been adulterated with pharmaceuticals, including new stimulants, novel anabolic steroids, unapproved anti-depressants, banned weight-loss medications [3].

Although dietary supplements were originally based on formulations containing minerals and vitamins, supplements and foods fortified with antioxidant molecules and other nutrients later appeared on the market. At the same time, dietary supplements have become commercially available not only in pharmacies and health stores but also in supermarkets and from vendors on Internet [4]. However, because supplements are not regulated as drugs and requirements are not consistent across countries, often very little or even no information concerning their safety, effectiveness, and quality (including ingredient information and quantities) is provided. First attempts to increase regulation of herbal products and other dietary supplements were made during the early 1990s by the U.S. Food and Drug Administration (FDA). Immediately after, a better definition of dietary supplements was given by the Dietary Supplement Health and Education Act (DSHEA), instituted in 1994. DSHEA started to coordinate scientific studies of dietary supplements in relation to health and to pay attention to regulation and evaluation of label claims. However, at the same time, DSHEA limited the capability of FDA to regulate dietary supplements in terms of rigorous scientific controls conducted to demonstrate their safety or efficacy. Conversely, the

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https://doi.org/10.1016/j.trac.2018.04.004
0165-9936/

**Abbreviations**

| | |
|---|---|
| Ar | aristolochic acid |
| AAs | amino acids |
| Ac-γ-CD | Acetyl-γ-CD |
| ACN | acetonitrile |
| Ado-Cbl | 5′-deoxyadenosyl-cobalamin |
| AFM | atomic-force microscopy |
| AgNPs | silver nanoparticles |
| Ala | alanine |
| AMP | adenosine 5′-monophosphate |
| AOT | dioctyl sulfosuccinate sodium salt |
| AQC | 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate |
| Arg | arginine |
| As(III) | arsenite |
| As(V) | arsenate |
| AsB | arsenobetaine |
| Asp | aspartic acid |
| AuNPs | gold nanoparticles |
| BGE | background electrolyte |
| BTEAC | benzyltriethylammonium chloride |
| $C^4D$ | contactless conductivity detector |
| CA | citric acid |
| CAPS | 3-(Cyclohexylamino)-1-propanesulfonic acid |
| CD | cyclodextrin |
| CE | capillary electrophoresis |
| CEC | capillary electrochromatography |
| CID | collision-induced dissociation |
| Cit | citrulline |
| cITP | capillary isotachophoresis |
| CLC | capillary liquid chromatography |
| CM-γ-CD | carboxymethyl-γ-CD |
| CMP | cytidine 5′-monophosphate |
| CN-Cbl | cyano-cobalamin |
| [(CN)2-cbn] | cobinamide dicyanide |
| CS | chondroitin sulfate |
| CSP | chiral stationary phase |
| CTAB | cetyltrimethylammonium bromide |
| CUF | centrifugal ultrafiltration |
| CZE | capillary zone electrophoresis |
| DMA | dimethylarsinic acid |
| DMAA | 1,3-Dimethylamylamine |
| DM-β-CD | Heptakis(2,6-di-*O*-methyl)-β-CD |
| DRC | dynamic reaction cell |
| DS | degree of substitution |
| ED | electrochemical detection |
| EKC | electrokinetic chromatography |
| EOF | electroosmotic flow |
| EP | ephedrine |
| ESI | electrospray ionization |
| ETAAS | electrothermal atomic absorption spectrometry |
| FEP | fluorinated ethylene propylene |
| FESI | field-enhanced sample injection |
| FITC | fluorescein isothiocyanate |
| FMOC | 9-fluorenyl-methylchlorformate |
| GA | glucosamine |
| GAG | glycosaminoglycan |
| GC | gas chromatography |
| GMP | guanosine 5′-monophosphate |
| HA | hyaluronic acid |
| HP-β-CD | (2-hydroxy)propyl-β-CD |
| HPLC | high performance liquid chromatography |
| HS-β-CD | highly sulfated-β-CD |
| 5-HPT | 5-hydroxytryptophan |
| I.D. | internal diameter |
| ICP-MS | inductively coupled plasma mass spectrometry |
| IFs | infant formulas |
| Ile | Isoleucine |
| IMP | inosine 5′-monophosphate |
| ITP | isotachophoresis |
| LA | lipoic acid |
| LC | liquid chromatography |
| LE | ligand-exchange |
| Leu | leucine |
| L-HP-Phe | L-N-(2-hydroxy-propyl)-phenylalanine |
| LIF | laser induced fluorescence |
| LOD | limit of detection |
| LOQ | limit of quantitation |
| LVSS | large volume sample stacking |
| Lys | lysine |
| MALDI-TOF | Matrix Assisted Laser Desorption Ionization Time-of-Flight |
| Me-Cbl | methyl-cobalamin |
| MEEKC | microemulsion electrokinetic chromatography |
| Me-EP | N-methylephedrine |
| MEKC | micellar electrokinetic chromatography |
| Me-Ψ-EP | methylpseudoephedrine |
| MMA | monomethylarsonic acid |
| MRM | multiple reaction monitoring |
| MS | mass spectrometry |
| nano-LC | nano liquid chromatography |
| NBD-Cl | 1-chloro-7-nitrobenzo-2-oxa-1,3-diazol |
| NDA | Naphthalene-2,3-dicarboxaldehyde |
| NMR | nuclear magnetic resonance |
| Nor-EP | norephedrine |
| Nor-Ψ-EP | Norpseudoephedrine |
| NPs | nanoparticles |
| OH-Cbl | hydroxo-cobalamin |
| OPA | *o*-phthalaldehyde |
| Orn | ornithine |
| PA-FESI | pressure-assisted field-enhanced sample injection |
| PEA | phenethylamine |
| PNP | programmed nebulizing gas pressure |
| Poly-L-SUCL | polysodium N-undecenoxycarbonyl-L-leucinate |
| PTFE | poly(tetrafluoroethylene) |
| S-α-CD | sulfated α-CD |
| S-β-CD | sulfated β-CD |
| S-γ-CD | sulfated γ-CD |
| SAM | S-adenosyl-L-methionine |
| SDC | sodium deoxycholate |
| SDS | sodium dodecyl sulfate |
| Se | selenium |
| Se(IV) | selenite |
| Se(VI) | selenate |
| $(SeCys)_2$ | selenocysteine |
| SEM | scanning electron microscopy |
| Se-MeSeCys | Se-methylselenocysteine |
| SeMet | selenomethionine |
| SIM | selected ion monitoring |
| SPE | solid phase extraction |
| Succ-γ-CD | succinyl-γ-CD |
| TDA+ | tetradecylammonium bromide |
| TEM | transmission electron microscopy |
| TM-β-CD | heptakis-(2,3,6-tri-O-methyl)-β-CD |
| TOF | time of flight |
| Tris | Tris(hydroxymethyl)aminomethane |