

Developing New Methods for Pesticides in Dietary Supplements

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New requirements for dietary supplements to be manufactured under current Good Manufacturing Practices (cGMP) regulations have created a need for methods to detect pesticides in these complex, largely botanical products. QuEChERS offers a simple, cost-effective approach that can reduce matrix interferences as well as variation among technicians. Here we demonstrate a procedure that incorporates a QuEChERS extraction, cartridge solid-phase extraction (cSPE) cleanup and gas chromatography-time-of-flight mass spectrometry (GC-TOFMS), resulting in good recoveries for a wide range of pesticide chemistries in dandelion root powder.

supplements are largely derived from botanical sources, they must be tested for pesticide contaminants in order to meet cGMP regulations. As a result of this requirement, labs are working to develop and validate methods, an endeavor which is complicated by the wide range of pesticides and matrices to be tested.

Labs can begin method development with the FDA Pesticide Analytical Manual (PAM), which includes procedures for plant materials. While PAM Method 303 is an appropriate starting point, it has several disadvantages, including high solvent consumption, manual procedures that contribute to analytical variation, and the inability to extract polar pesticides. As an alternative, we developed a QuEChERS-based method for analyzing pesticides in dietary supplements that has several advantages over PAM 303 (Table I). QuEChERS is an approach that was developed by developed by Anastassiades et al.² as a simple, rapid, effective, yet inexpensive way to extract pesticide residues from fruits and vegetables, followed by a novel dispersive SPE (dSPE) cleanup of the extract. We chose QuEChERS as an alternative to PAM 303 because of its speed, simplicity, and low solvent use, as well as its ability to produce good extraction efficiencies for relatively polar pesticides.²

Because of these benefits, this approach has become popular and expanded to include numerous other analytes and matrices and has found ap-

Introduction

Recently the U.S. Food and Drug Administration (FDA) announced that makers of dietary supplements (e.g., vitamins, herbal and botanical pills, etc.) will have to adhere to cGMPs, marking a major shift in regulatory oversight and testing for the industry. Previously, compliance was voluntary, but in 2003, due to public and industry concern, the FDA proposed requiring dietary supplement manufacturers to adhere to cGMP standards. The final rule was issued in June 2007 and is in full effect June 2010.¹ Basic GMPs require implementing comprehensive procedures to ensure product quality and safety. Since many dietary

	PAM 303 Method	QuEChERS + cSPE	Benefits of QuEChERS + cSPE
Solvent used (mL)	1,850	92	20x less solvent; cleaner, greener, & cost-effective
# of Solvents	4	3	
Salt and sorbent used (g)	35	6.6	5x less salt/sorbent
Glassware/lab equipment	<ul style="list-style-type: none"> • Separatory funnel (1L capacity) • Filter apparatus • Florisil column 	<ul style="list-style-type: none"> • Centrifuge • SPE manifold 	Fast, easy batch processing
Manual preparation	<ul style="list-style-type: none"> • Salt solution • Standards • Florisil column 	None—prepackaged salts and cSPE cartridge are ready to use	Highly reproducible; less manual prep means less human error

Table I: Decrease costs and increase reproducibility with a GMP-friendly QuEChERS approach to analyzing pesticides in dietary supplements.

plication outside of the food testing industry. Although originally used for pesticide residue analysis in fruits and vegetables with high water content, the QuEChERS approach has been adapted for residue analysis in grains, nuts, seeds, oils and animal muscle and tissue.³⁻¹¹

QuEChERS has also been used to investigate pesticide residues in vegetable-, fruit- and meat-based baby foods.¹⁷⁻²⁷

Within food testing, the QuEChERS approach has been used for testing residues other than pesticides including veterinary drug residues, mycotoxins and acrylamide in samples such as milk, liver and potato crisps.²⁸⁻³⁶ The benefits of QuEChERS sample preparation has attracted analysts outside of food testing and has crossed over into environmental, clinical and forensics testing. Environmental samples like soil, water and compost have used the QuEChERS approach to test for pesticides and other pollutants, like perfluorinated carboxylic acids and polyaromatic hydrocarbons.³⁷⁻⁴² Pharmaceutical residues in whole blood have been determined by applying the

dispersive solid phase extraction like that used in QuEChERS.⁴³ The QuEChERS approach, extraction and/or dispersive solid phase extraction, is growing into a general sample preparation technique that is expected to see widespread applicability in analytical chemistry.

Based on preliminary studies, we knew that while the extraction part of QuEChERS would be successful, the dSPE cleanup step probably did not have the capacity to handle the matrix complexity of most dietary supplements. Thus, we compared dSPE to a cSPE cleanup and established a procedure that uses a QuEChERS extraction, cSPE cleanup, and GC-TOFMS for accurate determinations of 46 pesticides in dandelion root powder. This approach saves time and can reduce analyst variation by minimizing manual preparation with prepackaged extraction salts and snap-and-shoot standards. As shown in Figure 1, it also uses much less solvent, salt, and sorbent, making it a greener, more cost-effective method than PAM 303.

Procedure

Sample Wetting and Fortification

Fully processed dandelion root powder obtained from a dietary supplement manufacturer was used for this work. The powder was wetted and then fortified with 46 pesticides representing different chemical classes that have been previously reported in dietary supplements.⁴⁴ Typically, QuEChERS methods use 10-15 grams of material with high water content (>80%). Therefore, to prepare for a QuEChERS extraction with a dry commodity, it is critical to use a reduced amount of material and wet it with water prior to extraction. In this work, 1 g dietary supplement powder was combined with 9 mL water. After shaking to mix well, the wetted supplement was fortified with 200 µL of a 2 ng/µL pesticides spiking solution resulting in a 400-ng/g spike level, relative to the original commodity. Also, 100 µL QuEChERS Internal Standard Mix for GC/MS analysis was added. The sample was then allowed to soak for 2 hours prior to extraction.

QuEChERS Extraction

The EN 15662 QuEChERS method was used for sample extraction.⁴⁵ Ten mL acetonitrile was added to the wetted sample. After a 1-minute shake, Q-sep™ Q110 buffering extraction salts (4 g MgSO₄, 1 g NaCl, 1 g trisodium citrate dehydrate and 0.5 g disodium hydrogen citrate sesquihydrate) were added. Following another 1-minute shake, the sample was centrifuged for 5 minutes at 3,000 U/min. with a Q-sep™ 3000 centrifuge. Lastly, 5 µL of quality control standard anthracene was added to a 1 mL aliquot of extract to indicate fatal losses of planar compounds to Carbo-prep® 90 during cleanup.

Extract Cleanup

Two approaches were explored for extract cleanup: dSPE and cSPE. For dSPE, 1 mL extract was added to a Q210 dSPE tube containing 150 mg MgSO₄ and 25 mg PSA, shaken for 2 minutes, and then centrifuged for 5 minutes. The resulting final extract was then analyzed by GC-TOFMS.

For cSPE cleanup,⁴⁶ 1 mL extract was processed with a 6 mL Resprep® Combo

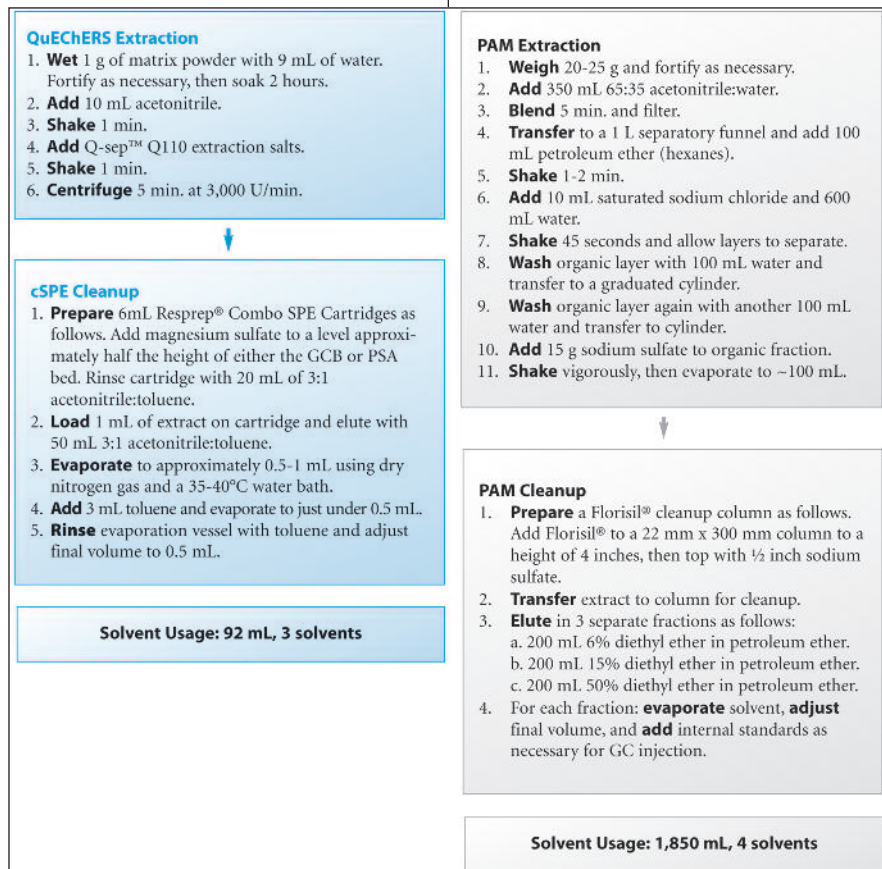


Figure 1: QuEChERS extraction and cSPE cleanup simplifies sample prep for pesticides in dietary supplements.

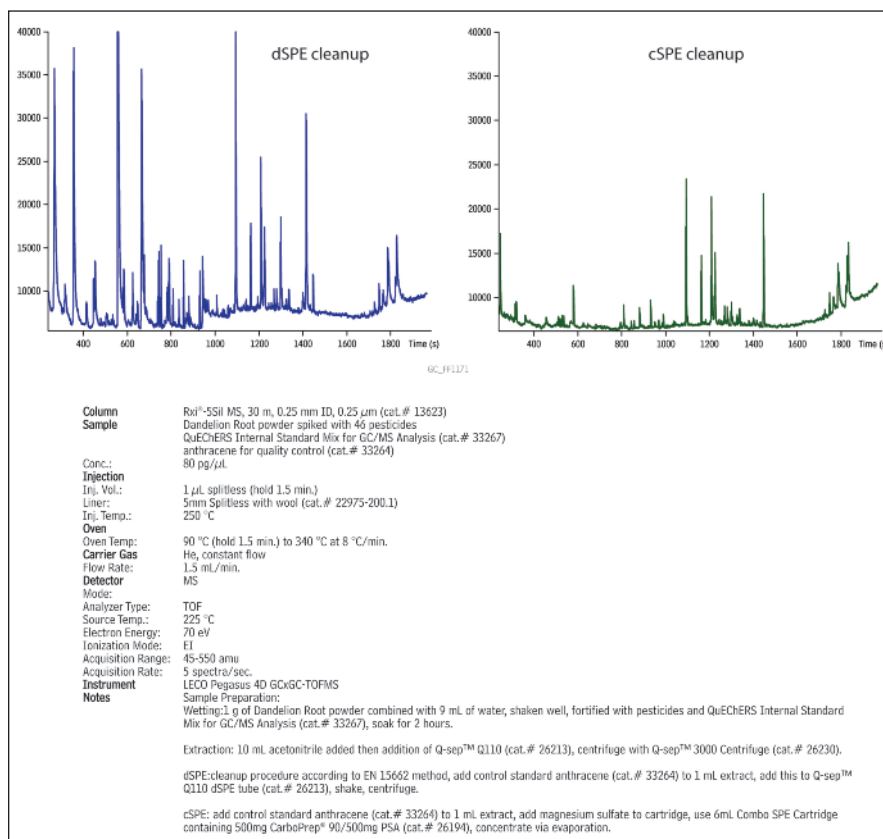


Figure 2: QuEChERS extracts of pesticides in dietary supplements benefit from cSPE cleanup, which minimizes matrix interferences by removing more sugars and fatty acids than dSPE (XIC m/z 60).

SPE Cartridge, which is designed for pesticide residue cleanup and contains 500 mg CarboPrep® 90 and 500 mg primary secondary amine (PSA). To prepare the SPE cartridge, magnesium sulfate was first added to a level approximately one-quarter height of the total bed; then the cartridge was rinsed with 20 mL of 3:1 acetonitrile: toluene, which was discarded. For cleanup, 1 mL of extract was loaded onto the prepared cartridge and then eluted with 50 mL 3:1 acetonitrile: toluene. The eluent was then evaporated and solvent exchanged using dry nitrogen gas and a 35-40 °C water bath. Evaporation was allowed to proceed until approximately 0.5-1 mL eluent was left, at which point about 3 mL of toluene was added. The mixture was evaporated to just under 0.5 mL, and then the evaporation vessel was rinsed with toluene to bring the sample to a final volume of 0.5 mL. The resulting final extract was then analyzed by GC-TOFMS.

Standards

Matrix-matched standards were prepared at 80 pg/µL, as 80 pg/µL is the ex-

pected final concentration in extract of the 400 ng/g matrix spikes (assuming 100% recoveries). Matrix-matched standards were prepared by adding standard solution to the final extract (post-cleanup) from a control sample. Actual recoveries were calculated by comparing peak areas for fortified samples that were extracted and cleaned, to areas of a matrix-matched standard, using the internal standard quantification method.

GC-TOFMS

A LECO Pegasus III GC-TOFMS instrument was used and all data were processed with LECO ChromaTOF™ software. Gas chromatography was performed using an Rxi®-5Sil MS column (30 m × 0.25 mm × 0.25 µm). Instrument conditions are shown in Figure 1. Temperature and flow settings yielded an analysis time of 32.75 minutes.

Results

One aspect of this investigation was to compare the applicability of two sample cleanup methods, dSPE and cSPE for QuEChERS extracts of pesticides in

dietary supplements. While dSPE has the advantage of improved speed and less solvent usage, it does not have the sorbent capacity to adequately clean up these samples (Figure 2). Since cSPE uses more sorbent, it is a better choice for dietary supplements (and other complex samples, e.g., spices, essential oils) as it can remove more matrix components, such as fatty acids, sugars, and pigments. QuEChERS methods developed for dietary supplements of botanical origin can benefit from the extra sorbent capacity of cSPE, which reduces GC inlet/column contamination and chromatographic interference from complex botanical matrices.

Even with effective extraction and cleanup techniques, dietary supplements can be challenging to analyze due to their complexity. Coelutions are common and pesticide residues can be overwhelmed by abundant matrix compounds not only qualitatively, but also by interfering with quantification masses. Figure 3 plots the total ion chromatogram (TIC) and extracted ion m/z 312 corresponding to the quantitation mass for carfentrazone ethyl. It is clear that target pesticide signals can be obscured in the TIC. LECO ChromaTOF™ software was able to identify target pesticides by comparison with reference spectra using automatic peak find and spectral deconvolution algorithms, along with calibration and quantification. TOFMS makes this powerful data processing possible with very fast acquisition rates and unbiased mass spectra, and by having pg level sensitivity in full-mass range mode, which allows the potential for finding non-target pesticides. An alternate GC/MS approach for targeted pesticides in dietary supplements would be to use selected ion monitoring with a typical quadrupole mass spectrometer.

Overall, the combination of QuEChERS extraction, cSPE cleanup, and GC-TOFMS used in this method produced good recoveries for most compounds tested (Table II). Although early eluting compounds trended toward lower recoveries, most analytes, including more polar compounds, showed excellent recoveries. The potential for good recoveries of polar pesticides is a major

Compound	RT (sec.)	Recovery (%)	Class	Type
1,2,3,5-Tetrachlorobenzene	418.0	46	Organochlorine	Chemical intermediate
Pentachlorobenzene	587.0	51	Organochlorine	Metabolite
Tetrachloronitrobenzene	648.8	72	Organochlorine	Fungicide
2,3,5,6-Tetrachloroaniline	678.0	64	Organochlorine	Fungicide
alpha-BHC	739.4	69	Organochlorine	Insecticide
Hexachlorobenzene	744.4	56	Organochlorine	Impurity
Pentachloroanisole	754.6	62	Organochlorine	Metabolite
beta-BHC	780.5	88	Organochlorine	Insecticide
Pentachloronitrobenzene	784.2	62	Organochlorine	Fungicide
Pentachlorobenzonitrile	790.0	70	Organochlorine	Impurity
gamma-BHC	791.2	85	Organochlorine	Insecticide
Diazinon	816.6	71	Organophosphorus	Insecticide
Chlorothalonil	819.2	100	Organochlorine	Fungicide
delta-BHC	836.4	85	Organochlorine	Insecticide
Pentachloroaniline	857.6	75	Organochlorine	Metabolite
Pentachlorothioanisole	931.2	66	Organochlorine	Metabolite
PCB 52	932.0	-	Organochlorine	Internal standard
Chlorpyrifos	952.6	92	Organophosphorus	Insecticide
Dacthal	958.8	83	Organochlorine	Herbicide
Parathion	963.2	91	Organophosphorus	Insecticide
Heptachlor epoxide	1008.4	93	Organochlorine	Metabolite
Procymidone	1027.4	100	Organonitrogen	Fungicide
Endosulfan I	1059.8	70	Organochlorine	Insecticide
4,4'-DDE	1094.6	90	Organochlorine	Metabolite
Dieldrin	1097.8	91	Organochlorine	Insecticide
Myclobutanil	1100.6	100	Organonitrogen	Fungicide
Endosulfan II	1141.6	110	Organochlorine	Insecticide
Oxadixyl	1149.4	100	Organonitrogen	Fungicide
4,4'-DDD	1152.2	98	Organochlorine	Insecticide, Breakdown product
2,4'-DDT	1155.0	94	Organochlorine	Insecticide
Carfentrazone ethyl	1188.0	110	Organonitrogen	Herbicide
Endosulfan sulfate	1194.8	105	Organochlorine	Metabolite
Fenhexamid	1202.4	94	Organonitrogen	Fungicide
4,4'-DDT	1203.8	96	Organochlorine	Insecticide
Piperonyl butoxide	1237.6	93	Other	Insecticide synergist
Iprodione	1261.0	110	Organochlorine	Fungicide
Cypermethrin 1	1466.8	130	Pyrethroid	Insecticide
Cypermethrin 2	1474.8	86	Pyrethroid	Insecticide
Cypermethrin 3	1478.6	75	Pyrethroid	Insecticide
Cypermethrin 4	1481.8	100	Pyrethroid	Insecticide
Pyraclostrobin	1538.0	92	Organonitrogen	Fungicide
Fluvalinate 1	1541.4	100	Pyrethroid	Insecticide
Fluvalinate 2	1546.8	94	Pyrethroid	Insecticide
Difenoconazole 1	1562.0	99	Triazole	Fungicide
Difenoconazole 2	1566.6	81	Triazole	Fungicide
Azoxystrobin	1596.0	93	Organonitrogen	Fungicide

Table II: This QuEChERS-based method provides good recoveries for a variety of pesticides found in dietary supplements.

advantage to QuEChERS methods; this difference is due to the use polar acetonitrile as the extraction solvent, rather than petroleum ether (hexanes), which is used in PAM 303. The lower recoveries here of early eluting compounds may be due to evaporative loss during concentration steps, due to their higher volatility. Additionally, in the case of planar compounds, reduced recoveries may be due to interaction with the CarboPrep®

90 sorbent used to remove pigments and other matrix compounds, although the planar quality control standard, anthracene, did not show drastic losses during cSPE. Overall, the chromatography and recovery results seen for a broad range of pesticides in dandelion root demonstrate the utility of the QuEChERS approach for dietary supplement testing.

Conclusion

Demonstrated here is a QuEChERS approach that helps accomplish the pesticide testing now required for dietary supplements. The basic methodology presented here for dandelion root can be modified for other analytes and matrices and illustrates the advantages of the QuEChERS approach for labs developing cGMP methods. Analytical benefits include reduced interferences and good

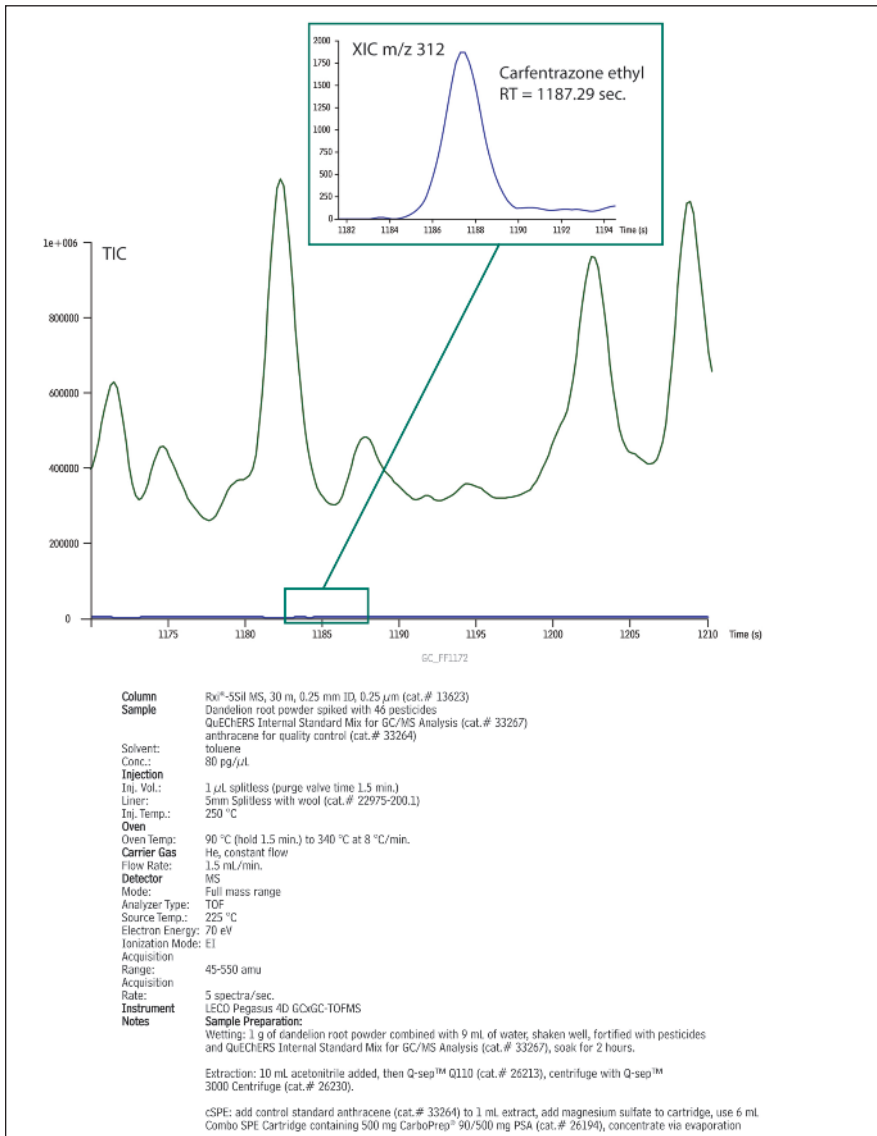


Figure 3: Using TOFMS allows definitive identification and quantification, even when matrix components coelute with target analytes. (Inset: carfentrazone ethyl S/N = 105; extracted ion chromatogram, m/z 312.)

recoveries, even of polar compounds. Other benefits include an overall savings of both materials and prep time compared to the PAM 303 method, and better expected reproducibility due to the straight-forward procedure with fewer manual preparations.

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