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Comparison and applicability of Agilent EMR-Lipid and Captiva EMR-Lipid Sorbents in QuEChERS method for food analysis

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Abstract:

Agilent's innovative EMR-Lipid and Captiva EMR-Lipid sorbents efficiently replace the traditional QuEChERS d-SPE clean-up products in selective lipid removal from fatty matrices, thus improving instrumental analytical reproducibility, reliability, and long-term use. These products have dual functionality; a hydrophobic interaction between the sorbent with long aliphatic lipid chains of the matrices, which allows for complete lipid retention, and a size exclusion property that does not retain analytes, thus this maximizes, in principle, analyte recovery in any sample. As most of the analytes under study were polar or not highly nonpolar and had a relatively large size, the examination of small-sized nonpolar or less polar compounds is necessary to check for partial retention by the sorbents and if any, further precautions should be taken when using these sorbents. These queries are answered in our present communication concerning the analytes Trifluralin (logP: 5.27), Fipronil (logP: 4.0), and Clenbuterol (logP: 2.63).

Keywords: **Captiva EMR-Lipid, EMR-Lipid Sorbents, size exclusion and hydrophobic interaction with fatty materials, food analysis.**

Classification number: **2.2**

Introduction

The QuEChERS method has been widely adopted in sample preparation not only for pesticides but for other analytes as well. For fatty samples, Agilent replaced the traditional d-SPE products in the QuEChERS clean-up step with two new sorbents: the Enhanced Matrix Removal for lipids known as EMR-Lipid (2015) and the Captiva EMR-Lipid (2017). These nanosorbents have two similar functions; a hydrophobic interaction with long aliphatic chains allowing the selective removal of fatty materials from matrices and a size exclusion property preventing the retention of analytes [1, 2]. For optimum performance, the EMR-Lipid must be activated with water (3-5 ml of water per 1 g of sorbent) while the Captiva EMR-Lipid requires an organic extract containing 20% water by volume (Fig. 1).

The attractive pass-through for a Captiva EMR-Lipid cartridge version requires less manual work, which allows for easy and effective clean-up of the analyte without clogging, this is especially important in case of biological fluids. This feature constitutes a major advantage over the EMR-Lipid powder presentation. For example, the EMR-Lipid has been applied to the analysis of veterinary drugs in bovine liver (30 different drugs at concentrations of 2, 10, 50, 150, 250, and 750 ng/g with recoveries between 60-120%) [3], PAH in salmon (15 PAH at concentrations of 25, 100, and 500 ng/g with recoveries between 62-98%) [4], pesticides in avocado (23 pesticides at a concentration 50 ng/g with absolute recoveries without using deuterated internal standards between 60-110%, however it was below 50% with aldrin and DDT) [5]. EMR-Lipid was also used by our group in 2016 for the analysis of ethoxyquin in feedstuffs, where no matrix effect was detected and the recovery was almost quantitative [6]. Captiva EMR-

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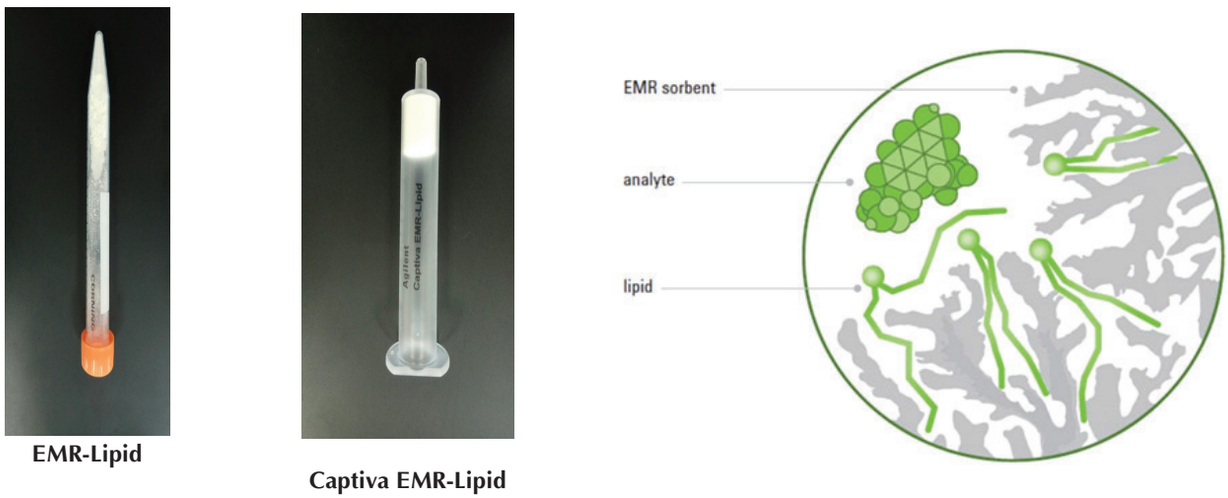


Fig. 1. EMR-Lipid, Captiva EMR-Lipid cartridges and schematic of the mechanism of action [1].

Lipid has also been applied to the analysis of mycotoxins in cheese [7]. For example, from parmesan and blue cheeses with mycotoxin concentrations of 1, 5, and 10 ng/g, the recoveries ranged between 70-112% for AFB1, AFB2, AFG1, AFG2, Mycophenolic acid, Ochratoxin A, Sterigmatocystin, and zearalenone. In many applications of these Agilent products, the highly selective removal of fatty materials from matrices was always emphasized while the role of the size exclusion property was mentioned much less. Indeed, careful examination has shown that these analytes were not highly nonpolar (logP<5.5) and had a relatively large size, therefore, they were not retained by the sorbents through either the hydrophobic interaction or by retention due to size effect.

In view of these experimental results and with the aim to detect a possible interaction between sorbent and analyte that may influence the recovery, we studied a selection of compounds with decreasing hydrophobicity in the following order: Trifluralin (logP=5.27), Fipronil (logP=4.0) and Clenbuterol (logP=2.63). Trifluralin, a pre-emergence dinitroaniline herbicide that is quite toxic to aquatic life, was banned in Vietnam in 2010 and in 2013 the Japanese revised their maximum residue level (MRL) standard to be 0.5 mg/kg in seafood products. This herbicide was analysed in Basa catfish by our group using gas chromatography-mass spectrometry (GC-MS) coupled with the QuEChERS method for sample preparation. In that work, no matrix effect was found and the recovery was nearly quantitative [8]. Fipronil, a highly toxic phenylpyrazole insecticide (EU MRL: 5 ppb) [9], was detected in 2017 in eggs in Belgium, the Netherlands, and later on in many other countries, thus causing a recall of millions of eggs from human consumption. Clenbuterol is not allowed to be used as a growth-promoter for pork in Vietnam (Codex MRL: 0.2 µg/kg and 0.6 µg/kg, respectively, for meat and liver). According to the Vietnamese circular No.01/2016/TT-BNNPTNT [10] dated February 15, 2016, a quick strip test for Clenbuterol detection in pig urine gives a positive screening result if the residue is above 3 µg/l.

To serve our purpose, we performed the analysis of Trifluralin spiked in blank shrimp, Fipronil in blank egg, and the direct analysis of Trifluralin and Clenbuterol standard solutions after treatment with these Agilent sorbents in sample preparation.

Both the pre-spiked and post-spiked samples for Trifluralin and Fipronil were analysed to estimate the matrix effect and to determine their recoveries by comparison with the corresponding standard solutions used to prepare them. For Clenbuterol and Trifluralin, the direct treatment of standard solutions with the sorbents would allow the prediction of their applicability to the quantitation of these analytes in various matrices. Both sorbent functions were examined in relation to the hydrophobicity and the bulkiness of these analytes.

Materials and methods

Chemicals

Standards: Trifluralin (99.5%, Dr. Ehrenstorfer), Fipronil (98.7%, Dr. Ehrenstorfer), Clenbuterol (99.34%, Dr. Ehrenstorfer), Trifluralin-d14 (100 mg/l in acetone, Dr. Ehrenstorfer).

Reagents: acetonitrile (≥99.9%, LCMS grade, J.T. Baker), isooctane (≥99.8% GC grade, Merck), acetic acid (≥98% ACS, J.T. Baker), anhydrous sodium acetate (≥99%, AR, Xilong), anhydrous magnesium sulfate (≥99%, AR, Xilong), anhydrous sodium chloride (≥99.5%, AR, Xilong), anhydrous sodium sulfate (≥99% ACS, Scharlau). All anhydrous reagents were re-dried at 110°C for 5 h before use.

Sorbents: EMR-Lipid (1 g in 15 ml tube, Part number 5982-1010, Agilent). Captiva EMR-Lipid (3 ml tube, 300 mg, Part Number 5190-1003 or 6 ml tube, 600 mg, Part number 5190-1004, Agilent).

Sample preparation and GC-MS/MS or LC-MS/MS operating conditions

The following Figs. 2-4 describe the sample preparation process and Tables 1-2 provide the equipment's operating conditions.

Extraction	EMR-Lipid Cleanup	Captiva EMR-Lipid Cleanup
Pre-spiked sample		
1 g of blank shrimp + 50 µl of 1 ppm T + 100 µl of 1 ppm T-d14, vortex, let stand for 1 hr ↓ Classical QuEChERS with 10 ml ACN (1% AcOH) + 1 ml H_2O + (2.4 g $MgSO_4$ + 0.6 g NaOAc) ↓ Vortex, centrifugate and collect the supernatant A	Supernatant A loaded into 15 ml EMR-Lipid tube preactivated with 3 ml H_2O ↓ Vortex, centrifugate , collect supernatant B + 1 ml isooctane + sufficient 4% NaCl solution, vortex and allow separation of the mixture into 2 layers ↓ Collect isooctane layer, filter through 0.22 µm nylon filter → solution ready for GC-MS/MS analysis	(A + 2.5 ml H_2O) loaded into a 6 ml Captiva EMR-Lipid cartridge and allowed flowing through the cartridge by gravity ↓ Subsequently wash with solution (1.6 ml ACN + 0.4 ml H_2O) ↓ Collect the entire solution + 1 ml isooctane+ sufficient 4 % NaCl solution and proceed as described in case of EMR-Lipid cleanup to get the isooctane solution ready for analysis
Post-spiked sample		
Repeat the extraction as above described but with only 1 g of blank shrimp (no standard solution) → Collect supernatant C	Treat C exactly the same way as above described for pre-spiked sample with EMR-Lipid until getting the isooctane layer ↓ Take 850 µl isooctane + 50 µl of 1 ppm T + 100 µl of 1 ppm T-d14, vortex, filter to get solution ready for GC-MS/MS analysis	Treat C exactly the same way as above described for pre-spiked sample with Captiva EMR-Lipid until getting the isooctane layer ↓ Take 850 µl isooctane + 50 µl of 1 ppm T + 100 µl of 1 ppm T-d14, vortex, filter to get solution ready for analysis
Standard solution		
Solution of 50 µl of 1 ppm T + 100 µl of 1 ppm T-d14 + 10 ml ACN	Treat the standard solution exactly as above described for A with EMR-Lipid cartridge preactivated with 3 ml H_2O to get the isooctane solution ready for analysis	Treat the standard solution + 2.5 ml H_2O exactly as above described for pre-spiked solution until getting the isooctane ready for analysis

Fig. 2. Sample preparation for Trifluralin (T).

Extraction	EMR-Lipid Cleanup	Captiva EMR-Lipid Cleanup
Pre-spiked sample		
5 g of homogenized egg + 1 ml of 10 ppb F, vortex, let stand for 1 hr ↓ Add 3 ml H_2O + ceramic homogenizer, vortex ↓ Add 10 ml ACN, vortex, add slowly 4 g $MgSO_4$ + 1 g NaCl, vortex, centrifugate, collect supernatant D	5 ml D loaded into 15 ml EMR-Lipid tube preactivated with 3 ml H_2O,vortex, centrifugate ↓ Collect supernatant, dry under N_2, ↓ Redissolve residue in 1 ml of MeOH:H_2O (1:1) + filter through 0.22 µm nylon syringe filter ↓ Solution ready for LC-MS/MS analysis	(5 ml D + 1.25 ml H_2O) loaded into the 6 ml Captiva EMR-Lipid cartridge and allowed flowing through the cartridge by gravity Subsequently wash with 1 ml ACN:H_2O (4:1) ↓ Collect supernatant, dry under N_2, 60°C ↓ Proceed as described in case of EMR-Lipid clean-up to get the solution ready for analysis
Post-spiked sample		
5 g of homogenized egg ↓ Proceed exactly as above described without standard ↓ Collect supernatant E	Treat E exactly as above described for pre-spiked sample with EMR-Lipid until drying the supernatant under N_2, 60°C ↓ Redissolve residue in 1 ml of 5 ppb fipronil standard solution + filter to get the solution ready for analysis	Treat E exactly as above described for pre-spiked sample with Captiva EMR-Lipid cartridge until drying the supernatant under N_2, 60°C ↓ Proceed as described in case of EMR-Lipid clean-up to get the solution ready for analysis

Fig. 3. Sample preparation for Fipronil (F).

EMR-Lipid Cleanup	Captiva EMR-Lipid Cleanup
Add 30 µl of 100 µg/l clenbuterol standard to 10 ml of 1% AcOH solution in acetonitrile, vortex	
Load solution into a 15 ml EMR-Lipid cartridge, preactivated with 3 ml H_2O,vortex, centrifugate	- Mix with 2.5 ml H_2O - Load into the 6 ml Captiva EMR-Lipid column - Wash column by (1.6 ml ACN + 0.4 ml H_2O)
- Add 3 g anhydrous Na_2SO_4 vortex, centrifugate - Take the supernatant, evaporate by rotavaporization at 60°C under light vacuum - Redissolve in 1 ml of solution of [90% H_2O (0.1% HCOOH) + 10% ACN (0.1% HCOOH)], analyze on Shimadzu UPLC-MS/MS TQ 8050	

Fig. 4. Pre-treatment of Clenbuterol standard with Agilent sorbents.

Table 1. GC-MS TQ 8050 operating conditions for Trifluralin.

Equipment	GC 2010 Plus	MS TQ 8050
Shimadzu GC- MS/MS TQ 8050 equipped with Combi-Pal PTV	- Column: DB5 MS UI (30 m x 0.5 mm x 0.25 µm) - Injector temperature: 250°C - Mode: Splitless, Sampling time: 1 min - Flow rate: 1.5 ml/min - Temperature program: Rate (°C/min) / Final temperature (°C) / Hold time (min) - / 50 / 0 15 / 180 / 0 3 / 190 / 0 35 / 310 / 4	- Acquisition mode: EI - MRM - Emission current: 150 µA - Ion source temperature: 200°C - Transfer line temperature: 250°C - CID gas pressure: 180 kPa - MS Resolution: Q1 unit, Q3 unit - Detector: 1.11 kV - Precursor ion, *m/z*=306.00 - Quantifier ion *m/z*=264.00, CE: 9 ev - Qualifier ion: *m/z*=160.10, CE: 18 ev - Quantifier ion from precursor ion *m/z*=315.00 for Trifluralin-d14, *m/z*=267.10, CE: 9 ev

Table 2. Thermo scientific LC- tandem MS operating conditions for Fipronil and Clenbuterol.

Analyte		Fipronil	Clenbuterol
Equipment		Thermo Scientific LC-MS/MS (Ultimate 3000 HPLC-TSQ Quantum Access Max)	Shimadzu UPLC-MS/MS TQ 8050
HPLC	Column	Agilent Poroshell C18 (100 x 2.1 mm, 2.7 µm)	Phenomenex Poroshell C18 (150 x 2.1 mm, 1.7 µm)
	Column T°	40°C	40°C
	Flow rate	0.3 ml/min	0.2 ml/min
	Injection volume	2 µl	5 µl
	Mobile phase	A: MeOH; B: H_2O	A: H_2O (0.1 % HCOOH) B: ACN (0.1 % HCOOH)
	Gradient program	Time (min) / A (%) / B (%) 0 - 3 / 60 - 70 / 40 - 30 3 - 6.6 / 70 / 30 6.6 - 6.7 / 70 - 98 / 30 - 2 6.7 - 10 / 98 / 2 10 - 10.1 / 98 - 60 / 2 - 40 10.1 - 16 / 60 / 40	Time (min) / A (%) / B (%) 0.01 - 1 / 90 / 10 1.01 - 2.5 / 90 - 65 / 10 - 35 2.51 - 8.5 / 65 / 35 8.51 - 9 / 65 - 90 / 35 - 10 9.01 - 14 / 90 / 10
MS	MS mode	ESI (-)	ESI (+)
	Parameters	- Spray voltage: 3.000 V - Vaporizer temperature: 300°C - Sheath gas pressure (N_2): 35 - Auxiliary gas pressure (N_2): 10 - Capillary temperature: 270°C - Collision gas (Ar): 1.5 m Torr - Q1, Q3 Peak resolution: 0.7u	- Interface voltage: 4000 V - Interface t°: 300°C - Nebulizing gas flow: 2 l/min - Heating gas flow: 12 l/min - DL temperature: 250°C - Heat block temperature: 350°C - Drying gas flow: 4 l/min
	Precursor ion	*m/z*=435	*m/z*=277
	Quantifier ion	*m/z*=330, CE: 17 ev	*m/z*=203, CE: 16 ev
	Qualifier ion	*m/z*=250, CE: 27 ev	*m/z*=259, CE: 10 ev

Results and discussions

Table 3 summarizes the analytical results obtained with Trifluralin, Fipronil, and Clenbuterol.

Table 3. Analytical results for Trifluralin, Fipronil, and Clenbuterol.

Agilent sorbents	Samples	Average Recovery H% (n=5)			
		Trifluralin		*Fipronil*	*Clenbuterol Std Solution*
		STD (50 µg/l)	ISTD (100 µg/l)	STD (5 µg/l)	STD (5 µg/l)
EMR-Lipid	Standard	51.81	51.24	-	63.27
	Pre-spiked sample	27.11	25.65	75.50	-
	Post-spiked sample	104.30	103.00	101.40	-
Captiva EMR-Lipid	Standard	65.99	63.75	-	44.67
	Pre-spiked sample	31.75	31.40	72.10	-
	Post-spiked sample	102.10	101.60	96.40	-

For Trifluralin, the analytical results indicated no matrix effect as in the original QuEChERS method of sample preparation [8]. However, they also showed that it would be unsuitable to use EMR-Lipid and Captiva EMR-Lipid in sample preparation for Trifluralin analysis because of quite low recoveries in pre-spiked samples; this was also shown in the direct treatment of a Trifluralin standard with the sorbents.

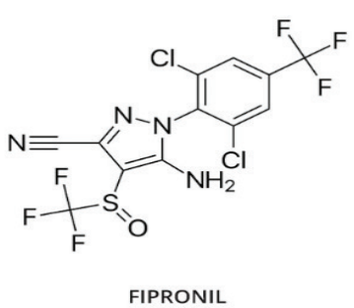
For Fipronil, the results indicated also no matrix effect and the recoveries for pre-spiked samples on treatment with both Agilent sorbents were acceptable in view of the complexity of the egg matrix.

For Clenbuterol, the quite low recovery of a standard solution after treatment with EMR-Lipid and Captiva EMR-Lipid sorbents indicated that they would not be appropriate for this analyte in any matrix.

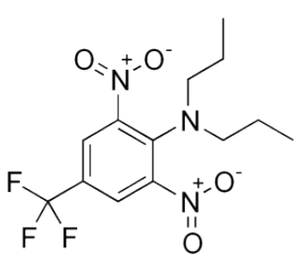
The analytical results showed therefore that Agilent sorbents could replace the well-known QuEChERS clean-up products for Fipronil [11]. However, for Trifluralin and Clenbuterol, both the Agilent EMR-Lipid and Captiva EMR-Lipid appeared not working properly. To our knowledge, no such information has been provided until now. Therefore, from our study and other previous works [3-5, 7] using these Agilent products for sample preparation, we propose an explanation of these effects that involve the analyte polarity, bulkiness, and the two functions of the sorbents.

Case of bulky and not highly nonpolar analytes

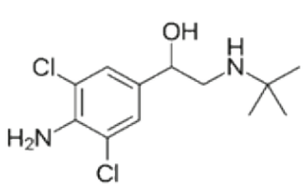
Almost all reported analytes that successfully used Agilent products were bulky and not highly hydrophobic (logP<5.5). Their bulkiness plays a somewhat more important role, which aids analytes from being retained by the sorbents because of the size exclusion property of the latter.



Fipronil



Trifluralin

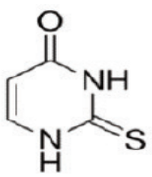


Clenbuterol

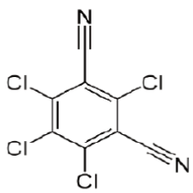
However, for a few nonpolar compounds (logP>6) such as permethrin (logP=6.1), aldrin (logP=6.50), and DDT (logP=6.91), their low recoveries (permethrin=63%, aldrin and DDT<50%) would probably be caused by the hydrophobicity of the sorbent EMR-Lipid, which partially retained the analytes through a nonpolar interaction during the clean-up step [5].

Case of small-sized compounds

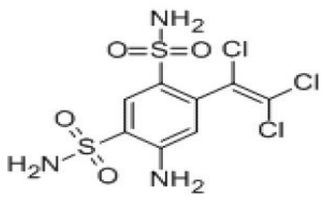
There are a few small-sized compounds that could benefit from Agilent sorbents during sample preparation due to their strong polar character (i.e. the veterinary drug 2-thiouracil in bovine liver with logP=-0.28) or the presence of polar substituents around the nucleus (i.e. the veterinary drug clorsulon in bovine liver with logP=1.25 and the pesticide chlorothalonil in avocado with logP=2.94).



2-Thiouracil



Chlorothalonil



Clorsulon

Our case studies

In our case, Agilent sorbents may be used for Fipronil residue analysis (logP=4.0) because of its somewhat bulky structure with two rings and the presence of polar substituents on the pyrazole ring. Likewise, our previous work on the analysis of ethoxyquin (logP=4.01) in feedstuffs with EMR-Lipid (which had been made available since 2016), gave good analyte recoveries of 95.95-99.33% at concentrations ranging between 6-15 mg/kg of ethoxyquin [6]. This was probably due to the bulkiness of the analyte with two fused rings and the presence of the polar quinoline ring. At this point, we would like to note that in 2013 our study showed that the traditional QuEChERS method of sample preparation worked well in the analysis of ethoxyquin in shrimp (recovery better than 95%) [12].

For Trifluralin (logP=5.27), the hydrophobic character, the relatively small size of the analyte with only one ring structure, and the presence of two hydrophobic propyl groups would favour its partial attraction and retention by the sorbents. In 2010, however, we showed that the traditional QuEChERS clean-up worked well in the analysis of this analyte in Basa fish (no matrix effect and recoveries >91% for all samples) [8]. For Clenbuterol (logP=2.64), its insufficient polar character and less bulky structure would justify its partial retention through interaction of its nonpolar part with the Agilent sorbents.

Furthermore, results also showed that in the case of Trifluralin in shrimp, the low recoveries with a pre-spiked standard solution originated mainly from the incomplete recovery on the direct treatment of Trifluralin standard with the sorbents. Therefore, the direct treatment of an analyte standard with EMR-Lipid and Captiva EMR-Lipid would provide a simple way to quickly predict the applicability of these sorbents to the analyte in sample preparation. This was the case of Clenbuterol for example, showing that the use of these sorbents in sample preparation might not be appropriate.

Conclusion

Agilent EMR-Lipid and Captiva EMR-Lipid were applied to the analysis of Trifluralin in shrimp, Fipronil in eggs and Clenbuterol standard for the purpose to find any possible interaction of the sorbents with the analytes. In fact, we found that only Fipronil worked well. An explanation was proposed to understand any difference in comportment of the sorbents toward various analytes. In general, Agilent sorbents may be successfully used for polar analytes, bulky analytes and even small-sized analytes with polar substituents surrounding the nucleus. Agilent sorbents may not be correctly applied to highly nonpolar compounds or small-sized analytes bearing hydrophobic substituents. A quick way to evaluate the applicability of the sorbents for

an analyte is to perform the analysis by direct loading of a standard solution of the analyte into the sorbents.

The authors declare that there is no conflict of interest regarding the publication of this article.

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