

Hybrid QuEChERS–micro-scale solid-phase extraction for LC-MS/MS determination of chloramphenicol in milk and muscle

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Abstract

Introduction: The determination of chloramphenicol (CAP) in milk and food-animal muscle is analytically challenging because of matrix complexity and matrix effects in LC-MS/MS analysis. **Material and Methods:** A hybrid sample-preparation method combining QuEChERS extraction with micro-scale solid-phase extraction (MSPE) using C18P-PVDF microspin filters was developed for the determination of CAP in these matrices. The method was validated in accordance with European Commission Implementing Regulation (EU) 2021/808. Matrix effects and the influence of membrane type (PVDF, nylon or PTFE) were evaluated. **Results:** The method demonstrated satisfactory analytical performance, with apparent recoveries ranging from 97.5% to 101.8%, repeatability below 10% and detection capability (CC_β) established at 0.12 µg kg⁻¹ for both matrices. Matrix-effect values ranged from 91.8% to 111.2% for milk and from 89.1% to 112.3% for muscle. The best clean-up performance was given by PVDF membranes, which contributed to a stable analytical response during MSPE clean-up. **Conclusion:** The proposed hybrid method provides effective clean-up and satisfactory control of analytical interferences without extensive additional clean-up procedures, making it suitable for routine determination of CAP in milk and muscle matrices.

Keywords: chloramphenicol, analytical method validation, veterinary drug residues, food safety, matrix effects, QuEChERS-MSPE.

Introduction

Chloramphenicol (CAP) is a broad-spectrum antibiotic prohibited in food-producing animals in the European Union because of its adverse effects, including aplastic anaemia, and because of public health concerns associated with food contamination (9). Its use is strictly controlled within the European regulatory framework governing residues of pharmacologically active substances in food of animal origin (1, 2). For regulatory enforcement, reliable determination of CAP in animal-derived foods, including milk and muscle, is required. This requires highly sensitive analytical methods capable of detecting trace-level residues in complex biological samples (5, 8), in accordance with current EU requirements for analytical performance and result interpretation (2).

However, accurate quantification remains challenging because of matrix effects in LC-MS/MS analysis (7, 8). Milk and muscle differ significantly in composition and represent substantially different physicochemical environments, providing a useful model for the evaluation of matrix-dependent analytical performance. Milk is a lipid–protein emulsion, whereas muscle contains high levels of membrane-derived phospholipids and proteins, which may interfere with electrospray ionisation and affect analytical performance (7, 11). Reliable quantification is best ensured by minimising matrix effects with optimised sample preparation. Traditional SPE-based sample preparation procedures provide effective clean-up and good selectivity, but are often associated with increased preparation time and procedural complexity. In contrast, quick, easy, cheap, effective, rugged and

safe (QuEChERS) approaches offer simplicity and high throughput, although often with insufficient removal of co-extracted matrix components (5, 13). In particular, residual phospholipids, proteins and other endogenous components may contribute to ion suppression or enhancement during electrospray ionisation, thereby reducing quantitative reliability in trace-level LC-MS/MS analysis (3, 7).

The initial analytical approaches for CAP determination in milk were based on conventional GC-MS and LC-MS methodologies (12). Recently, hybrid extraction strategies combining QuEChERS with additional clean-up approaches, including dispersive SPE, membrane-assisted clean-up and micro-scale SPE techniques, have been proposed to improve extract cleanliness and reduce analytical interferences (8). Despite these developments, the applicability of hybrid QuEChERS-MSPE approaches across different biological matrices has not been systematically evaluated, particularly in simplified workflows without defatting or enzymatic hydrolysis (4). The present study addresses this gap by developing and validating a hybrid QuEChERS-MSPE method for CAP determination in milk and muscle matrices, reducing matrix effects while maintaining simplified sample preparation by avoiding defatting.

Material and Methods

Reagents and materials. Chloramphenicol and an isotopically labelled internal standard (CAP-D5) were purchased from Dr. Ehrenstorfer (LGC Labor GmbH, Augsburg, Germany). Stock standard solutions were prepared in methanol at a concentration of 1 mg mL^{-1} and stored below -18°C for up to 12 months. Working standard solutions and internal standard solutions ($0.1 \text{ } \mu\text{g mL}^{-1}$ and $0.01 \text{ } \mu\text{g mL}^{-1}$, respectively) were also prepared in methanol and stored at $2\text{--}8^\circ\text{C}$ for a maximum of 6 months. LC-MS-grade acetonitrile and methanol were obtained from J. T. Baker (Avantor Performance Materials Poland S.A., Gliwice, Poland), whereas isopropanol was supplied by VWR Chemicals (Avantor Performance Materials Poland S.A., Gliwice, Poland). Acetic acid was purchased from Honeywell (Charlotte, NC, USA). Microspin filters containing C18P sorbent combined with polyvinylidene fluoride (PVDF), nylon or polytetrafluoroethylene (PTFE) membranes were supplied by Chromservis (Jakobiho, Prague, Czech Republic). Ultrapure water was produced using a Milli-Q purification system (Merck Millipore, Burlington, MA, USA).

Sample preparation. The study included bovine milk and poultry, porcine and bovine

muscle samples. After homogenisation of muscle samples, a 2 g portion of milk or homogenised muscle was transferred into a centrifuge tube and spiked with the internal standard (CAP-D5). Extraction was performed using 10 mL of acetonitrile with the addition of 0.5 g of sodium chloride, followed by vortex mixing and centrifugation ($2,930 \times g$, 10 min, 6°C) using a QuEChERS-based procedure. An aliquot of the supernatant (8 mL) was collected and evaporated to dryness under a gentle stream of nitrogen at $45 \pm 5^\circ\text{C}$. The residue was reconstituted in 0.35 mL of 30% methanol prior to MSPE clean-up. The solvent composition was selected to ensure adequate analyte solubility while retaining sufficient chloramphenicol on the C18 sorbent during the clean-up procedure.

MSPE clean-up procedure. The C18P-PVDF microspin filter was preconditioned with 0.7 mL of 30% methanol followed by 0.2 mL of ultrapure water. The reconstituted extract was then transferred to the filter. Following sample loading, the filter was centrifuged at $1,430 \times g$ for 3 min at room temperature. Elution was carried out using 0.2 mL of 70% methanol under identical conditions. The solvent composition was selected based on preliminary experiments to balance analyte retention on the C18P sorbent and efficient elution while minimising co-extracted matrix components.

LC-MS/MS. Chromatographic separation was performed on a phenyl-hexyl column ($50 \times 2.1 \text{ mm}$, $5 \text{ } \mu\text{m}$) with a corresponding guard column ($3.0 \times 4.6 \text{ mm}$, $2.1 \text{ } \mu\text{m}$) (Phenomenex, Torrance, CA, USA). A gradient elution was applied using 0.1% acetic acid in water (A) and methanol (B): 20% B up to 4.0 min, increased to 80% at 4.0 min and held until 4.20 min, then returned to 20% at 4.30 min and maintained until 7.0 min. The total chromatographic run time was 7 min. The column temperature was 40°C and the flow rate was 0.4 mL min^{-1} . Detection was carried out by LC-MS/MS in multiple reaction monitoring (MRM) mode using negative electrospray ionisation (ESI[−]). The monitored transitions were m/z 321.1 $\rightarrow$ 152.0, 257.0 and 193.9 for CAP, and m/z 326.06 $\rightarrow$ 156.9 for CAP-D5. The source parameters were as follows: spray voltage $-4,000 \text{ V}$, source temperature 450°C , curtain gas 40 psi, and ion source gases 1 and 2 at 50 psi. The declustering potential and entrance potential were set at -40 eV and -10 eV , respectively. Collision energies were -24 eV (CAP-152 and IS), -16 eV (CAP-257) and -17 eV (CAP-194).

Validation. The method was validated in accordance with Commission Implementing Regulation (EU) 2021/808 (2). The evaluated parameters included selectivity, linearity, apparent recovery, repeatability (RSDr), within-

laboratory reproducibility (RSDwR), decision limit (CC α), matrix effects, robustness and measurement uncertainty.

Identification criteria were also evaluated according to Commission Implementing Regulation (EU) 2021/808 (2). The relative retention time of chloramphenicol to that of the internal standard was required to remain within $\pm 1\%$, and at least one ion ratio was monitored and accepted within $\pm 40\%$ relative deviation from matrix-matched standards at comparable concentration levels. Selectivity was verified using 10 blank milk samples obtained from different individual animals and 10 blank muscle samples originating from different animals and different species, with no interfering peaks observed at the retention time of CAP (Figs 1 and 2). Linearity was assessed using six-level matrix-matched calibration curves in the range of 0.10–2.0 $\mu\text{g kg}^{-1}$ with 1/x weighted linear regression. Precision and recovery were evaluated at three fortification levels (0.10, 0.15 and 0.30 $\mu\text{g kg}^{-1}$) using seven replicates per level. Repeatability was assessed within a single analytical run, whereas within-laboratory reproducibility was evaluated in three independent analytical runs performed on different days by different operators. Robustness was assessed by introducing small variations in selected MSPE parameters, including membrane type, solvent composition, elution volume, reconstitution volume and mixing time (Table 3). The PVDF, nylon and PTFE membranes were compared during preliminary qualitative optimisation by assessing extract flow behaviour, elution performance and overall analytical reproducibility during MSPE clean-up. The membranes made of PVDF demonstrated the most stable analytical performance and were selected for further validation experiments. Matrix effects were evaluated by comparing the responses of matrix-matched standards with those of solvent-based standards. Measurement uncertainty was estimated at 0.15 $\mu\text{g kg}^{-1}$ using a coverage factor of $k = 2$.

Results

The developed hybrid QuEChERS–MSPE procedure demonstrated satisfactory analytical performance for the determination of CAP in both milk and muscle matrices. The validation results obtained are summarised in Table 1.

Overall, the method provided satisfactory repeatability, within-laboratory reproducibility and apparent recovery across all tested fortification levels. Expanded uncertainty ranged from 0.021 to 0.035 $\mu\text{g kg}^{-1}$ for milk and from 0.028 to 0.042 $\mu\text{g kg}^{-1}$ for muscle. Decision limits and

detection capabilities fulfilled current regulatory requirements for chloramphenicol determination. The optimisation study included evaluation of different membrane materials used during the MSPE clean-up procedure (Table 2). Among the tested materials, PVDF membranes performed best, with the most reproducible extract flow and elution behaviour and no apparent analyte loss. In contrast, nylon membranes showed inconsistent flow and partial analyte retention, whereas PTFE membranes exhibited reduced elution efficiency and unstable behaviour during centrifugation. These observations indicated reduced robustness and greater variability in analytical response when alternative membrane materials were used. Consequently, PVDF membranes were selected for further validation studies.

The membrane comparison presented in Table 2 was performed as a preliminary qualitative optimisation step intended to assess extract flow behaviour and overall analytical reproducibility during MSPE clean-up.

The robustness of the proposed MSPE clean-up procedure was additionally assessed by evaluating selected analytical parameters (Table 3). Variations in loading-solvent composition, elution-solvent composition, elution volume, reconstitution volume and mixing time did not significantly affect analytical performance within the tested ranges. Only minor effects on analytical response were observed for changes in elution-solvent composition. Overall, the obtained results confirmed satisfactory robustness of the proposed workflow and demonstrated that the analytical performance remained reproducible under minor procedural variations.

The method's selectivity is shown in Figs 1 and 2. The chromatograms show good selectivity with no interfering peaks observed at the retention time of CAP. The summary of analytical performance confirms that the developed method provides reproducible results across both tested matrices. Satisfactory analytical performance was obtained for both milk and muscle matrices, indicating that the proposed workflow is applicable to matrices with substantially different physicochemical properties.

The distribution of matrix effect values for milk and muscle samples is presented in Fig. 3. The observed matrix effect values ranged from 91.8% to 111.2% for milk and from 89.1% to 112.3% for muscle samples. The mean matrix effect values were approximately 100.2% (SD = 6.6%) for milk and 102.5% (SD = 8.5%) for muscle. Although slight signal suppression and enhancement were observed, all values remained within ranges generally considered acceptable for quantitative LC-MS/MS analysis. The slightly broader distribution observed for muscle samples was

likely associated with the higher content of endogenous phospholipids and other co-extracted components known to affect electrospray ionisation efficiency. Comparable distributions of matrix effect values were obtained for both

matrices despite their different physicochemical composition, indicating effective control of matrix-related interferences and reproducible analytical performance of the proposed workflow.

Table 1. Validation results for chloramphenicol determination in milk and muscle matrices

Parameter	Matrix	0.10 $\mu\text{g kg}^{-1}$	0.15 $\mu\text{g kg}^{-1}$	0.30 $\mu\text{g kg}^{-1}$
RSDr (%)*	Milk	7.5	6.8	5.6
RSDwR (%)*	Milk	8.9	8.1	6.7
Apparent recovery (%)	Milk	99.2	97.5	101.8
Expanded uncertainty ($\mu\text{g kg}^{-1}$, $k = 2$)	Milk	0.021	0.027	0.035
CC α ($\mu\text{g kg}^{-1}$)*	Milk	0.10	-	-
CC β ($\mu\text{g kg}^{-1}$)*	Milk	0.12	-	-
RSDr (%)*	Muscle	8.2	7.4	6.1
RSDwR (%)*	Muscle	9.8	8.7	7.2
Apparent recovery (%)	Muscle	97.8	98.5	101.2
Expanded uncertainty ($\mu\text{g kg}^{-1}$, $k = 2$)	Muscle	0.028	0.035	0.042
CC α ($\mu\text{g kg}^{-1}$)*	Muscle	0.10	-	-
CC β ($\mu\text{g kg}^{-1}$)*	Muscle	0.12	-	-

*RSDr – repeatability relative standard deviation; RSDwR – within-laboratory reproducibility relative standard deviation; CC α – decision limit; CC β – detection capability; $k = 2$ – coverage factor used for estimation of expanded measurement uncertainty

Table 2. Effect of membrane type on micro-scale solid-phase extraction clean-up performance

Membrane	Qualitative observations	Impact on method performance
PVDF	Stable flow, reproducible elution, no apparent analyte loss	Consistent analytical response and good reproducibility
Nylon	Inconsistent flow and partial analyte retention	Increased variability and reduced reproducibility
PTFE	Poor elution efficiency and unstable behaviour during centrifugation	Reduced robustness and potential analyte loss

PVDF – polyvinylidene fluoride; PTFE – polytetrafluoroethylene

Table 3. Robustness evaluation of selected micro-scale solid-phase extraction parameters

Parameter	Tested range	Effect on analytical performance
Loading solvent (MeOH %)	25–35%	No significant effect observed
Elution solvent (MeOH %)	60–70%	Minor effect on analytical response
Elution volume	0.18–0.22 mL	No significant effect on quantification
Reconstitution volume	0.30–0.40 mL	Stable analytical response
Mixing time	5–15 min	No significant differences observed
Membrane type	PVDF / Nylon / PTFE	PVDF provided the most stable performance

PVDF – polyvinylidene fluoride; PTFE – polytetrafluoroethylene

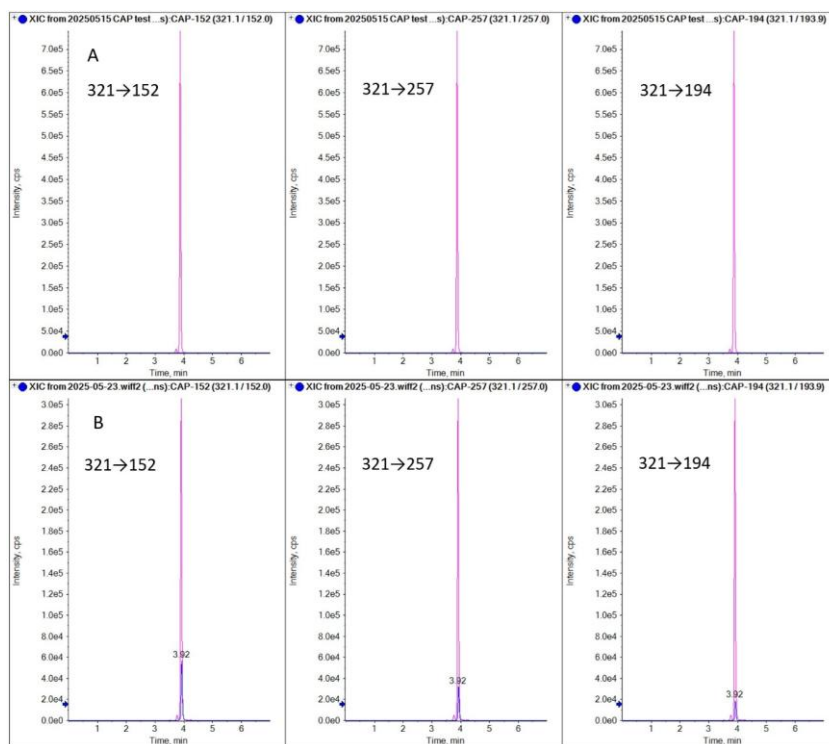


Fig. 1. Multiple-reaction monitoring LC-MS/MS chromatograms of blank (A) and fortified milk samples (B) at the level of $0.15 \mu\text{g kg}^{-1}$. The navy blue trace (the trace peaking directly below the given value 3.92 min) corresponds to chloramphenicol (CAP), while the pink trace (the trace extending higher) corresponds to the internal standard (CAP-D5 at the level of $1.5 \mu\text{g kg}^{-1}$)

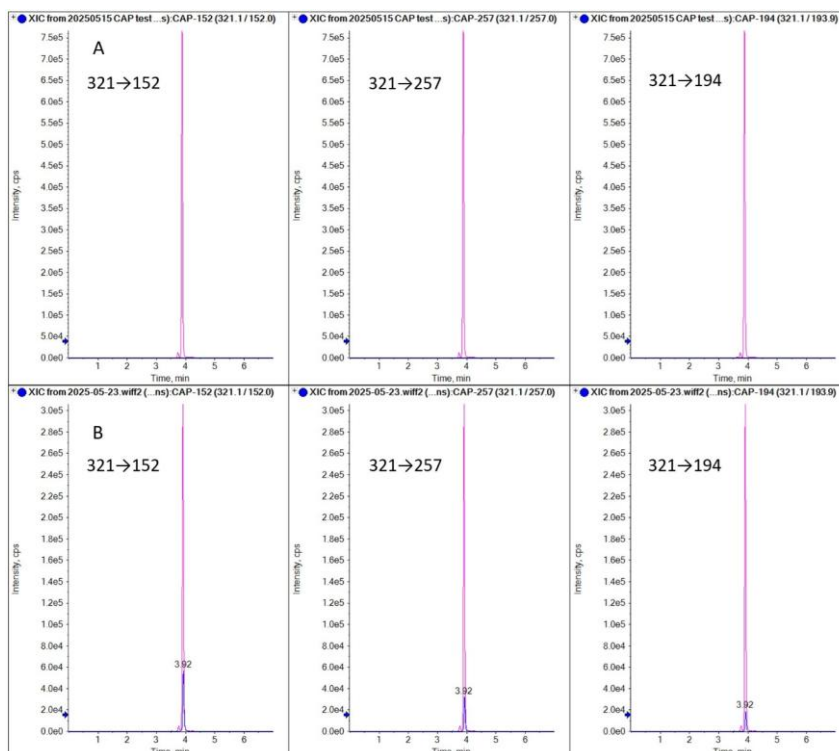


Fig. 2. Multiple-reaction monitoring LC-MS/MS chromatograms of blank (A) and fortified muscle samples (B) at the level of $0.15 \mu\text{g kg}^{-1}$. The navy blue trace (the trace peaking directly below the given value 3.92 min) corresponds to chloramphenicol (CAP), while the pink trace (the trace extending higher) corresponds to the internal standard (CAP-D5 at the level of $1.5 \mu\text{g kg}^{-1}$)

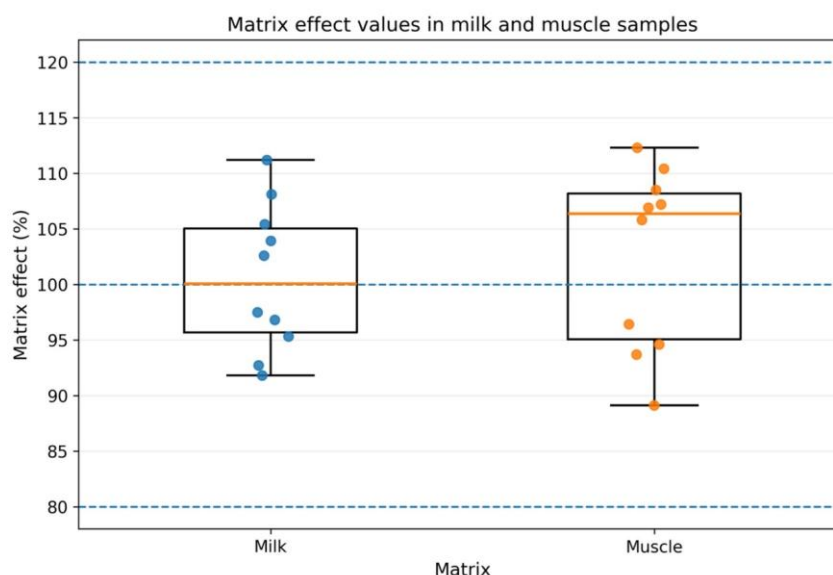


Fig. 3. Distribution of matrix effect values obtained for milk and muscle samples following the hybrid QuEChERS–micro-scale solid-phase extraction procedure. Dots show results for one blank sample each, boxes indicate the interquartile range, horizontal lines represent the median, and whiskers indicate the range of observed values

Discussion

The results obtained in this study demonstrate that the proposed hybrid QuEChERS–MSPE approach provides a reliable and simplified strategy for chloramphenicol determination in milk and muscle matrices. The method fulfilled the validation criteria specified in Commission Implementing Regulation (EU) 2021/808, confirming its suitability for routine LC–MS/MS analysis at trace concentration levels (2). Several LC–MS/MS methods for chloramphenicol determination in milk and muscle matrices have been reported previously, including workflows based on SPE clean-up, multi-matrix extraction procedures and QuEChERS-based approaches (10, 11, 13, 14). Earlier workflows were commonly based on solvent extraction combined with SPE or additional clean-up procedures, particularly in multi-matrix applications. Selected examples of previously published methods are summarised in Table 4.

Classical QuEChERS procedures are widely used because of their simplicity and high throughput; however, insufficient removal of co-extracted matrix components may negatively affect LC–MS/MS performance (5, 8). The incorporation of MSPE clean-up enabled preparation of cleaner extracts while maintaining a relatively simple analytical workflow. The additional MSPE clean-up step most likely partially removed co-extracted matrix components that can affect ionisation efficiency during electrospray processes (3, 7). This effect appears particularly relevant for muscle samples, which contain

elevated levels of phospholipids and other endogenous compounds known to interfere with LC–MS/MS (11, 13). Importantly, reliable analytical performance was achieved without additional preparation steps such as defatting or extensive clean-up procedures (4, 6). The optimisation study demonstrated that membrane type was a critical parameter influencing method performance. The PVDF membranes provided stable extract flow and reproducible elution behaviour, whereas the nylon and PTFE membranes detracted from the method's robustness and made the analytical response less consistent. The favourable performance of PVDF membranes may be associated with their balanced hydrophobic properties and compatibility with aqueous–organic solvent systems, which likely contributed to stable extract flow and limited analyte adsorption during clean-up. These observations indicate that membrane properties may significantly affect analyte recovery and reproducibility during MSPE clean-up. The robustness study additionally confirmed that minor variations in solvent composition, elution volume and mixing time did not significantly affect analytical performance within the tested ranges. Only minor fluctuations in analytical response were observed at lower methanol content in the elution solvent, although these changes did not affect overall method performance or quantitative reliability. This indicates that the proposed workflow is resistant to small procedural deviations, which is important for routine laboratory application (2).

Table 4. Comparison of selected LC-MS/MS methods for chloramphenicol determination in milk and muscle matrices

Reference	Matrix	Extraction / Clean-up strategy	Analytical performance	Main characteristics
14	Bovine milk	SPE (C18) + alumina clean-up	Recovery ~90%, RSD 2.8 –4.3%, CC β 0.03 μ g/kg	SPE and alumina-based clean-up workflow
10	Multiple food and biological matrices	ACN extraction + chloroform clean-up	RSD < 25%, CC β 0.03 –0.04 μ g/kg	Multi-matrix LC-MS/MS workflow
13	Liquid milk, milk powder, bovine muscle	Ethyl acetate extraction with additional clean-up	Accuracy 89–107%, RSD 4–15%	Simultaneous CAP and florfenicol determination
12	Multiple food matrices including milk and muscle	QuEChERS	Recovery 86–111%, RSDr < 11.2%	Simplified QuEChERS workflow
	Milk and muscle	QuEChERS + PVDF- MSPE microspin clean-up	Recovery 97.5–101.8%, RSDr < 10%	Additional microspin clean-up and matrix effect control

Compared with conventional SPE-based approaches, the proposed workflow reduces the number of preparation steps while maintaining satisfactory analytical performance for CAP determination in milk and muscle samples. The method was developed for single-residue chloramphenicol analysis; therefore, further studies would be required to evaluate its applicability to multi-residue methods (5). Limitations of the study are the relatively small number of analysed samples, the lack of detailed information regarding the anatomical origin and species of some muscle samples, and the limited direct comparability of results between milk and muscle matrices arising from their different physicochemical properties and consequent differences in matrix effect behaviour. Nevertheless, the obtained results confirm that the proposed hybrid QuEChERS-MSPE procedure provides a practical and robust approach for chloramphenicol determination in complex biological matrices

Conclusion

A hybrid QuEChERS-MSPE method for the determination of chloramphenicol in milk and muscle matrices was successfully developed and validated using LC-MS/MS. The proposed workflow provided satisfactory recovery, precision and robustness while maintaining a relatively simple sample preparation workflow without extensive additional clean-up or hydrolysis procedures (6). The use of PVDF-based MSPE clean-up improved analytical stability and reproducibility, confirming its suitability as

a practical and robust approach for routine residue analysis in complex veterinary matrices.

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