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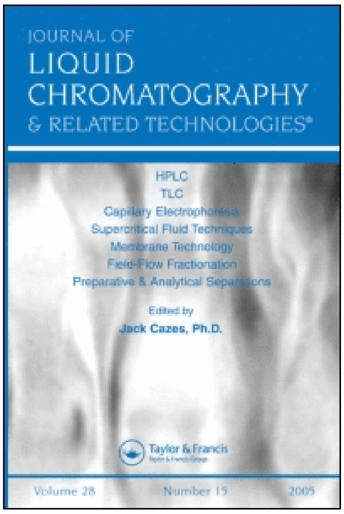

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Rapid Determination of Nitrofurantoin, Furazolidone and Furaltadone in Formulations, Feed and Milk by High Performance Liquid Chromatography

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RAPID DETERMINATION OF NITROFURANTOIN, FURAZOLIDONE AND FURALTADONE IN FORMULATIONS, FEED AND MILK BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A new and rapid method is described to determine nitrofurantoin, furazolidone and furaltadone in formulations, feed and milk by reversed phase high performance liquid chromatography. A high-speed C_{18} 3x3 column is used and a mobile phase of HAc/NaAc 0.1 M (pH 3.2):acetonitrile, 90:10, was found to be the optimum to carry out the analytical separation. A photometric detection at 360 nm was selected.

INTRODUCTION

Nitrofuran derivatives are highly effective chemotherapeutic drugs well known as antibacterial agents from Dodd and Stillman studies (1). Some

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of them are widely used to fight common infections to humans and animals or characteristic infections of domestic animals or poultry. Hence, among these compounds, nitrofurantoin (1-[[5-nitro-2-furanyl]methylene]amino-2,4-imidazolidinedione), furazolidone (3-[5-nitrofurfurylideneamino]-2-oxazolidinone) and furaltadone (5-morpholinomethyl-3-[5-nitrofurfurylideneamino]-2-oxazolidinone) are formulated together in our country (Tribactina Premix from Esteve Lab.) (2). The formulation is of great utility in the control of the bacterian origin infectious processes most frequent in the intensive stock exploitation, and is administered together with feeds.

In the bibliography, there are numerous references about the analytical determination of these compounds by high performance liquid chromatography. However, nitrofurantoin and furazolidone are the subject of a higher number of studies than furaltadone. About the determination of this compound by HPLC only four references have been found, in which its determination, together with nitrofurantoin, furazolidone and other nitrofurans, is described. In two of these, columns of ciano have been used (3, 4) and reversed phase chromatography has been used in the others (5, 6). The methods are applied to the determination of these compounds in milk, meat, eggs or biological fluids (urine or plasma).

In this paper, we describe a simple and rapid method to determine any of these compounds or their mixture in its formulations, feed and milk by using high speed liquid chromatography. For this purpose, a C_{18} 3x3 column, with aqueous acetonitrile as mobile phase, has been used, and the chromatographic separation is attained in less than four minutes.

MATERIALS

HPLC system

A Perkin Elmer Series. 4 high performance liquid chromatograph, equipped with a constant flow pump, together with a Diode-Array detector (LC-235) was used. The detector was interfaced with an Olivetti PCS-286

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personal computer, and an Epson LQ-570 printer was used for the graphical representation of chromatographic data. The analogue signal was taken from the output of the detector and the interface uses a 12-bits AD/DA card from Sapphire (Diamond System Corp. V.1.1), for the acquisition and digitization of the chromatographic data (7).

A program was written in BASIC that allows the representation of the chromatogram on the VDU screen, storage on diskettes and post-run manipulation, evaluation and graphical representation of the data. A convert program has been also developed with the object of transferring the files obtained with the acquisition data program to an ASCII XY format which allows the manipulation of these files with the "Data Leader" Software package from Beckman.

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The chromatographic separation was performed on a Perkin-Elmer Pecosphere 3x3 CR C_{18} column (0.46 cm ID x 3.3 cm). The mobile phase was HAc/NaAc 0.1 M (pH 3.2):acetonitrile 90:10. The solvents were degassed and filtered, through a 0.45 μm cellulose acetate or PTFE membrane filter, daily before use. Samples were filtered through a Millipore swinney syringe adapter, containing a 0.45 μm cellulose regenerated membrane filter, before injection. Samples of 10 μl were injected through a Rheodyne 7125 injector with the solvent flow-rate maintained at 2 $ml \cdot min^{-1}$. Photometric detection was performed at 360 nm.

Chemicals and supplies

Nitrofurantoin, furazolidone and furaltadone obtained from Sigma Chemicals Co. were used. Standard solutions of these compounds were prepared by dissolving the appropriate amounts, in acetonitrile or dimethylformamide (DMF). Acetate buffer (0.1 M, pH 3.2) was prepared from anhydrous sodium acetate (Panreac) and glacial acetic acid (Normalsolv) in Millipore Milli-Q purified water (HPLC-grade water). All other chemicals were of analytical-reagent grade or better.

METHODS

Procedure for the determination of nitrofurantoin, furazolidone and furaltadone in formulations

A suitable aliquot of the formulation (powdered, solution or emulsion) is accurately weighed or pipetted, dissolved in DMF (filtering and washing with DMF when necessary) and diluted to a known volume. Suitable aliquots of the obtained solutions are used to prepare appropriate samples in acetonitrile, and portions for analysis are filtered before injection (10 μl) into the HPLC system.

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Procedure for the determination of nitrofurantoin, furazolidone and furaltadone in feeds.

Amounts of about 10 g of finely ground feeds are accurately weighed and carefully stirred with 40 ml of DMF, during 30 minutes. The extracts are centrifuged and filtered and the residues are washed with DMF diluting to a final volume of 50 ml. Suitable aliquots of these solutions are used to proceed with the analysis.

Procedure for the determination of nitrofurantoin, furazolidone and furaltadone in milk

Aliquots of 200 ml of milk are pipetted, liophylized and washed with acetonitrile (about 75 ml) during 15 minutes. The residue is extracted with 15 ml of DMF stirring during 30 minutes, and subsequently washed with a mixture of 25 ml of acetonitrile and 5 ml of DMF. The different solutions are joined and evaporated to dryness in a rotavapor under diminished pressure. The residue is treated with DMF, filtered and diluted into a 25 ml volumetric flask with DMF. Portions for analysis are filtered before injection (10 μl) into the HPLC system.

RESULTS AND DISCUSSION

The analytical separation of nitrofurantoin, furazolidone and furaltadone in a 3x3 reversed phase C_{18} column has been investigated. Aqueous methanol or aqueous acetonitrile have been initially tested as mobile phases to perform the separation. In the Table 1 the retention times, capacity factors (k') and resolution values (R_S) for these compounds, obtained with different proportions of organic component in the mobile phase, have been summarized. It can be observed that nitrofurantoin and furazolidone are easily eluted by aqueous methanol or aqueous acetonitrile with just a 10% of organic modifier. Furaltadone, however, is strongly retained and it is necessary to use mobile phases with at less 30% of methanol or 70% of acetonitrile to obtain capacity factors lower than 10 for this compound. To improve these results, acetonitrile:water or methanol:water mobiles phases, in which the pH of the aqueous portion was modified by using acetate buffer solutions of different pH values, were assayed. The obtained results have been summarized in the Table 2. It can be appreciated that the behavior of nitrofurantoin and furazolidone do not significantly changes in the different mobile phases tested, whereas the furaltadone retention do it drastically. In the Table 3 the capacity factor values obtained for furaltadone with the various mobile phases are compared.

As can be observed, the furaltadone retention diminishes drastically when the mobile phase contains buffer solution and is generally lower when acetonitrile is used as organic modifier.

It is also interesting to denote that the retention-elution behavior of furaltadone is also strongly influenced by the ionic strength of the mobile phase, as has been proved by using different 0.05 M HAc-$NaClO_4$:acetonitrile, 90:10, mobile phases, in which the $NaClO_4$ concentration is changed, to elute the furaltadone. This fact could

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TABLE 1.

Influence of the Organic Modifier Proportion on the Retention of Nitrofurantoin (NF), Furazolidone (FZ) and Furaltadone (FD)

a) Aqueous acetonitrile mobile phase

% AcCN	NF		FZ		FD		$R_{s_{1,2}}$
	t_R	k'	t_R	k'	t_R	k'	
5	3.67	14.29	4.09	16.04	---	---	0.840
10	1.49	5.21	1.74	6.25	---	---	0.930
20	0.58	1.42	0.74	2.08	19.20	79.00	0.533
30	0.36	0.50	0.43	0.79	9.39	38.13	
40					6.39	25.63	
50					4.82	19.08	
60					4.84	19.17	
70					4.14	16.25	

b) Aqueous methanol mobile phase

% MeOH	NF		FZ		FD		$R_{s_{1,2}}$
	t_R	k'	t_R	k'	t_R	k'	
10	3.05		3.14		---	---	0.180
15					13.12	61.48	
20					6.60	30.43	
25					3.71	16.67	
30					2.03	8.67	
35					1.47	6.00	
40					1.06	4.05	
50					0.51	1.43	

TABLE 2 a.

Influence of % Acetonitrile on the Mobile Phases HAc/NaAc 0.1 M:Acetonitrile, on the Retention of Nitrofurantoin (NF), Furazolidone (FZ) and Furaltadone (FD).

Buffer solution pH = 2.8

% AcCN	NF		FZ		FD		$R_{s_{1,2}}$
	t_R	k'	t_R	k'	t_R	k'	
5	4.40	17.3	4.74	18.75	7.40	29.83	----
10	1.55	5.46	1.90	6.92	4.25	16.71	0.88
15	0.81	2.38	1.04	3.33	2.72	10.33	0.74
20	0.55	1.29	0.70	1.92	2.29	8.54	0.56
25	0.40	0.67	0.50	1.08	2.08	7.67	0.36

Buffer solution pH = 3.2

% AcCN	NF		FZ		FD		$R_{s_{1,2}}$
	t_R	k'	t_R	k'	t_R	k'	
5	3.58	13.9	4.12	16.17	4.26	16.75	0.80
10	1.36	4.67	1.77	6.38	2.40	9.00	0.87
15	0.76	2.17	0.98	3.08	1.55	5.46	0.60
20	0.52	1.17	0.66	1.75	1.20	4.00	0.55

Buffer solution pH = 3.6

% AcCN	NF		FZ		FD	
	t_R	k'	t_R	k'	t_R	k'
5	3.89	15.2	4.44	17.5	3.51	13.6
10	1.51	5.29	1.88	6.83	1.55	5.46
15	0.81	2.38	1.04	3.33	1.02	3.25
20	0.56	1.33	0.70	1.92	0.74	2.08

Buffer solution pH = 4.1

% AcCN	NF		FZ		FD	
	t_R	k'	t_R	k'	t_R	k'
5	3.77	14.7	4.00	15.7	4.25	16.7
10	1.43	4.96	1.72	6.17	1.50	5.25
15	0.77	2.21	0.99	3.13	0.86	2.58
20	0.54	1.25	0.69	1.88	0.60	1.50

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TABLE 2 b.

Influence of % Methanol on the Mobile Phases HAc/NaAc 0.1 M: Methanol on the Retention of Nitrofurantoin (NF), Furazolidone (FZ) and Furaltadone (FD)

Buffer solution pH = 2.84

% MeOH	NF		FZ		FD		$R_{s_{1,2}}$
	t_R	k'	t_R	k'	t_R	k'	
5	7.11	32.9	7.45	34.5	7.80	36.1	0.39
10	2.89	12.8	3.06	13.6	3.52	15.8	0.41
15	1.37	5.52	1.52	6.24	2.18	9.38	0.54
20	0.80	2.81	0.89	3.24	1.60	6.62	0.45

Buffer solution pH = 3.19

% MeOH	NF		FZ		FD	
	t_R	k'	t_R	k'	t_R	k'
5	6.99	32.3	8.17	37.9	7.22	33.4
10	2.84	12.5	3.16	14.1	2.92	12.9
15	1.29	5.14	1.51	6.19	1.53	6.29
20	0.76	2.62	0.87	3.14	1.07	4.10

Buffer solution pH = 3.60

% MeOH	NF		FZ		FD		
	t_R	k'	t_R	k'	t_R	k'	
5	8.24	38	.2	8.82	41.0	7.83	36.3
10	3.07	13.6	3.36	15.0	3.01	13.3	
15	1.40	5.67	1.60	6.62	1.49	6.10	
20	0.82	2.90	0.94	3.48	0.97	3.62	

Buffer solution pH = 4.1

% MeOH	NF		FZ		FD	
	t_R	k'	t_R	k'	t_R	k'
5	8.07	37.4	8.80	40.9	13.12	61.48
10	3.02	13.4	3.29	14.7	4.26	19.29
5	1.42	5.70	1.62	6.71	1.90	8.05
20	0.83	2.95	0.95	3.52	1.09	4.19

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TABLE 3.

Capacity Factor (k') of Furaltadone in Several Aqueous Methanol or aqueous Acetonitrile Mobile Phases

Aqueous portion composition	5% AcCN	5% MeOH	10% AcCN	10% MeOH	15% AcCN	15% MeOH	20% AcCN	20% MeOH
HAc/NaAc 0,1 M pH 2.84	29.8	36.1	16.7	15.8	10.3	9.38	8.54	6.62
HAc/NaAc 0,1 M pH 3,19	16.8	33.4	9.00	12.9	5.46	6.29	4.00	4.10
HAc/NaAc 0,1 M pH 3,60	13.6	36.3	5.46	13.3	3.25	6.10	2.08	3.62
HAc/NaAc 0,1 M pH 4,20	16.7	61.5	5.25	19.3	2.58	8.05	1.50	4.19
Water						61.50	79.0	30.43

indicate the participation of some kind of polar interaction between the stationary phase and the furaltadone.

According with these results it has been chosen, as optimum, a mobile phase of 0.1 M HAc/NaAc (pH 3.2):acetonitrile, 90:10, due to the acceptable values obtained for the capacity factors (k'_{NF} = 4,7; k'_{FZ} = 6,4 and k'_{FD} = 9,0) and the resolution next to the unity, for the nitrofurantoin and furazolidone peaks.

The mobile phase caudal, in the interval of values assayed (1.0-2.3 ml/min), do not significantly affect to peak width neither to analytical signals (peak area or peak height). Only an slight diminution on k' values is observed. A 2 ml/min caudal has been selected in order to reduce the analysis time.

With the mobile phase composition and caudal chosen, the resolution between peaks of nitrofurantoin and furazolidone has a value lower than the unity.

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We have tried to improve these results by time-domain differentiation of the chromatograms. Derivative techniques have been increasing in popularity for improving the resolution of overlapping spectra in other analytical methodologies such as spectrophotometry and spectrofluorimetry, and, recently, the fundamental properties, limitations, and some applications of time-domain derivatives in liquid chromatography have been evaluated (7-10). Derivative peaks are characterized by reduced peak widths in comparison with the original, which implies a potential improvement in resolution. In figure 1 the conventional chromatogram and the first and second derivative of the two peaks of nitrofurantoin and furazolidone are shown. These have been obtained by means of a Basic program which allows storage on diskettes and post-run manipulation of the data. A CONVER program has been used to translate the initial format files to ASCII format files which can be manipulated by the "Data Leader" Software package from Beckman. The smoothing and differentiation of the chromatographic peaks with respect to time is done according to the Savitzky and Golay method (11, 12). Due to the low sensititivity obtained in the second derivative chromatograms, we have selected as analytical signals those obtained in the first maximum of the first derivative chromatogram for nitrofurantoin, ${}^1D_{máx}$, and in the last minimum for furazolidone, ${}^1D_{min}$. These signals correspond to the inflexion points of the ascending and descending lengths of nitrofurantoin and furazolidone peaks, respectively. At these points, the one to other contribution of these two peaks is lower than in the peak maxima. The optimization of smoothing and band widths used for the calculation of the derivative chromatograms has been made according with their influence on the signal to noise ratio. Smoothing through 13 experimental points and a band width of 13 experimental points have been selected.

Calibration graphs for the three compounds have been established, in the chromatographic conditions mentioned and for the different analytical signals (area or height of chromatographic peaks or ${}^1D_{máx}$ for nitrofurantoin and ${}^1D_{min}$ for furazolidone). The obtained results are summarized in Table 4.

Subsequently, we have prepared synthetic mixtures of nitrofurantoin/furazolidone (weight to weight ratio between 0.1 and 7.5) to

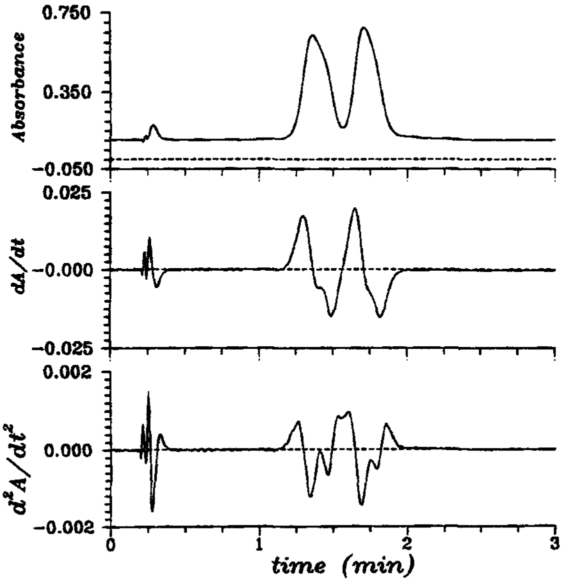

Figure 1. Conventiona chromatogram, and first and second derivative of it, corresponding to a mixture of a 500 ng of nitrofurantoin and 500 ng of furazolidone.

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compare the obtained recoveries by using the selected analytical signal on the first derivative chromatogram with those obtained by integration of the conventional chromatogram with diverse criteria (baseline drawn from valley to valley; baseline drawn horizontally until a base point or baseline draw between base points).

We have found similar results by differentiation of the chromatograms or by integration of the conventional chromatograms with a baseline drawn between base points, and these results are better than those obtained with the other integration criteria. On the other hand, differentiation only slightly improve the recoveries obtained by integration of the furazolidone peaks in presence of a great excess of nitrofurantoin. Because of this, the integration to the baseline between base points have been selected. The precision of the assay was checked, by performing eleven replicate runs of the three substances. In Table 5, the results obtained by measuring the peak area or the peak height are compared. It can be appreciated that

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Table 4.

Calibration Graphs for the Chromatographic Determination of Nitrofurantoin, Furazolidone and Furaltadone, as well as for Nitrofurantoin and Furazolidone Determination after Differentiation of the Chromatograms.

	Nitrofurantoin (20-900 ng)		Furazolidone (20-900 ng)		Furaltadone (20-250 ng)	
Analytical signal (y)	Straight line equation	r	Straight line equation	r	Straight line equation	r
Peak area	$y=13{,}7\times10^3\ X+6.30\times10^5$	0.9993	$y=14.2\times10^3\ X+5.87\times10^5$	0.9991	$y=10.7\times10^3\ X+8.05\times10^5$	0.9981
Peak height	$y=1.11\ X-3.70$	0.9994	$y=1.09\ X+2.99$	0.9997	$y=0.725\ X+4.44$	0.9992
$^1D_{max}$	$y=0.344\times10^{-4}\ X-7.70\times10^{-4}$	0.9982				
$^1D_{min}$			$y=0.281\times10^{-4}\ X-5.12\times10^{-6}$	0.9998		

X: analyte amounts (ng); r: linear regression coefficient

TABLE 5.

Precision of the Methods of Determination of Nitrofuratoin, Furazolidone and Furaltadone.

Analytical signal	Nitrofurantoin		Furazolidone		Furaltadone	
	Area x10^{-4}	Height	Area x10^{-4}	Height	Area x10^{-4}	Height
$\bar{X}$	692.3	492.2	746.7	543.7	52.31	81.21
S	2.94×10^5	9.53	2.81×10^5	9.77	3.73	1.95
S_m	8.85×10^4	2.88	8.87×10^4	2.95	1.18	0.58
% error (95% confidence level)	2.85	1.31	2.69	1.21	5.10	1.61

better results are obtained when the peak height is the analytical signal. In this instance, the detection and determination limits for the three compounds, calculated on the basis of analyte response at low concentration (13) are, respectively: 4.7 ng and 15.8 ng for nitrofurantoin, 4.2 ng and 13.8 ng for furazolidone and 8.2 ng and 27.3 ng for furaltadone.

Applications

Under the optimum conditions already established, the proposed method has been applied to the determination of nitrofurantoin, furazolidone and furaltadone in several formulations, pig feed and milk, according to the above mentioned procedures. Due to the great solubility of these compounds in DMF (>50 g/l), considerably higher than in other solvents (14), this solvent has been used to extract nitrofurantoin, furazolidone and furaltadone from their formulations as well as from feed. The analysed formulations contain the three mentioned compounds (Tribactina Premix), two of them (Trionic) or one of the nitrofuran mixed with other kind of drugs.

The proposed procedure to analyse feeds has been applied to the determination of the three compounds in pig feed samples that have been

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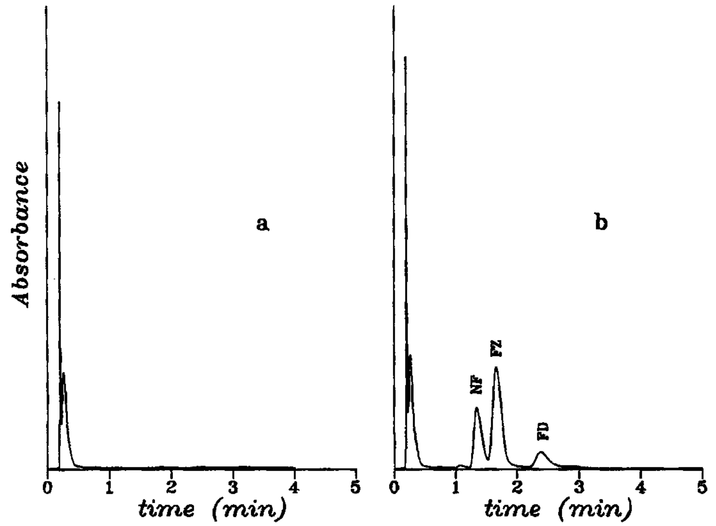

Figure 2. Chromatograms of feed samples contaminated with 0.1% Tribactine premix (b) and without Tribactine premix (a).

previously mixed with 0.1% of Tribactina Premix. This is the lowest level of dosage in which this formulation is used.

The obtained results are summarized in Tables 6 and 7 and in figure 2 the chromatograms corresponding to the analysis of a feed sample contaminated with Tribactina Premix and of a feed sample without these compounds are shown.

To execute the analysis of milk samples, previously contaminated with these compounds, different procedures have been assayed. At first, extraction of milk samples, deproteinized in acid medium, with ethylacetate has been tried. This solvent was chosen according to the solubility data (14) and the bibliographic references about the extraction of these compounds (15, 16). However, negative results were found. Because of this, the liophylization of milk samples previous to the solution of the analyte in a suitable solvent, as other alternative procedure to get preconcentration of analytes, has been assayed. As a previous experience, we have performed the analysis of powdered milk, contaminated with the nitrofurans, by using ethylacetate or acetonitrile as solvent to extract

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TABLE 6.

Determination of Nitrofurantoin, Furazolidone and Furaltadone in Formulations.

a) Determination of nitrofurantoin

Formulation	Composition	Nitrofurantoin claimed (mg/g)	Nitrofurantoin found* (mg/g)
Tribactina Premix Polvo	(per 100 mg) Nitrofurantoin 60 g. Furazolidone 120 g. Furaltadone 60 g. (2,3-dihydroxibutane-dioate)	60	60.43±0.80
Furantoin comp.	(per tablet) Nitrofurantoin 50 mg.	158.8	165.09±0.24

b) Determination of furazolidone

Formulation	Composition	Furazolidone claimed (mg/g)	Furazolidone found* (mg/g)
Tribactina Premix polvo		120	124.00±0.89
Saleton	(per tablet) Furazolidone 50 mg Difenoxilate hydrochloride 2.5 mg Neomycin sulfate 3.5 mg Atropine sulfate 0.025 mg	272	270.84±0.39
Enteromicina	(per tablet) Furazolidone 250 mg Neomycin sulfate 250 mg Electrolytes Cl^- 474 mg Na^+ 346 mg K^+ 52 mg Ca^{2+} 18 mg Mg^{2+} 15 mg	84.6	84.46±0.44

(continued)

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TABLE 6 *(continued)*

c) Determination of furaltadone

Formulation	Composition	Furaltadone claimed (mg/g or mg/ml)	Furaltadone found* (mg/g or mg/ml)
Tribactina Premix polvo		41	37.34±0.34
Trionic	(per gram) Chloroamphenicol 25 mg Neomycin base 40 mg Furazolidone 40 mg Furaltadone 40 mg Methylescopolamine bromine 0,2 mg Nicontinamide 20 mg	20	19.98±0.15
Panotile sol.	(per ml) Furaltadone hydrochloride 4.5 mg Polymixin B sulfate 10,000 U.I. Neomycin sulfate 3.5 mg Fluorocortisone acetate 1.0 mg Didocaine hydrochloride 40.0 mg	4.5	4.40±0.04
Altabactina	(per 200 ml) Furaltadone 4.16 g. Chloroamphenicol 4.16 g. Noemycine sulfate 10.0 g. Valeramide sulfate 41.50 g. Magnesium chloride 16.66 g.	19.6	18.40±0.74

* Each value is mean of three determinations.

TABLE 7.

Determination of Nitrofurantoin, Furazolidone and Furaltadone in Pig Feed.

Compound	Added (mg/g)	Found (mg/g)	% Recovery
Nitrofurantoin	0.0604	0.0579	95.9
		0.0591	97.8
		0.0589	97.5
	0.121	0.118	97.5
		0.121	100.0
		0.111	91.7
Furazolidone	0.124	0.119	96.0
		0.119	96.0
		0.122	98.4
	0.248	0.242	97.6
		0.245	98.8
		0.234	94.4
Furaltadone	0.0373	0.0303	81.2
		0.0326	87.4
		0.0319	85.5
	0.0746	0.0721	96.6
		0.0721	96.6
		0.0705	94.5

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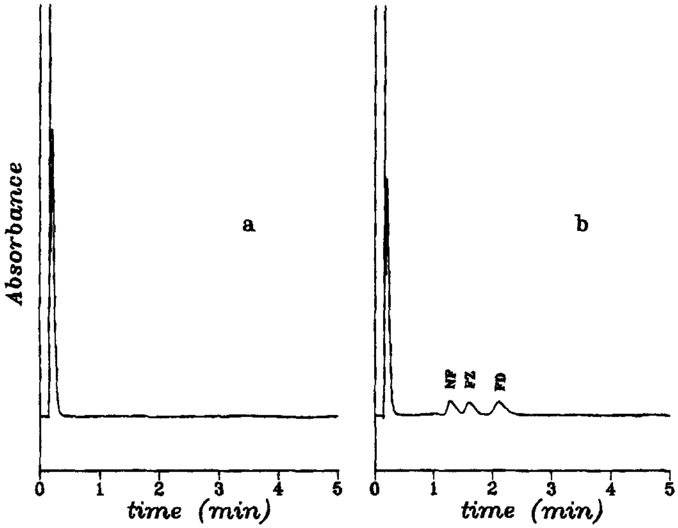

Figure 3. Chromatograms of milk samples contaminated with nitrofurantoin (0.25 ppm), furazolidone (0.25 ppm) and furaltadone (0.5 ppm) (b) and without addition of these compounds (a).

TABLE 8.

Determination of Nitrofurantoin, Furazolidone and Furaltadone in Milk

Compound	Added (μg/g)	Found* (μg/g)	% Recovery
Nitrofurantoin	0.25	0.198	79.2
		0.202	80.8
		0.211	84.4
Furazolidone	0.25	0.210	84.0
		0.214	85.6
		0.219	87.6
Furaltadone	0.50	0.405	81.0
		0.409	81.8
		0.413	82.6

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these compound. Very good results were obtained with acetonitrile as extractant (recoveries greater than 95% for nitrofurantoin and furazolidone and greater than 90% for furaltadone). However, these results are not reproduced when natural milk samples, contaminated with these substances, are analysed. Because of this we have assayed a mixture of DMF-acetonitrile as the extractant according to the described procedure. The obtained results are shown in Table 8. In figure 3 the chromatograms of milk samples with and without the nitrofurans are shown.

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