

Annex D1b:

Reconciliation of N,N-Dimethylformamide in the Fosinopril
Sodium Process


RECONCILIATION OF
N,N-DIMETHYLFORMAMIDE
IN THE
FOSINOPRIL SODIUM PROCESS

Written by:

 26-10-07

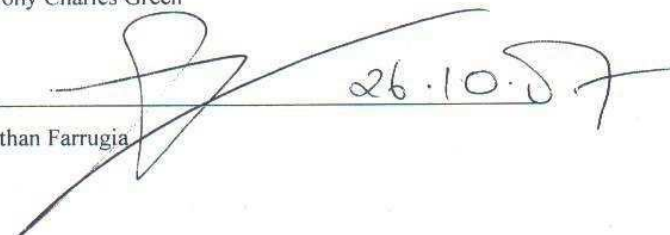
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Table Of Contents

1.1 Introduction	3
2.1 Sampling.....	4
3.1 Measurement	5
3.1.1 Reference standard:	6
3.1.2 Samples analysis.....	7
Appendix A –Block Diagram of FOS-2	9
Appendix B – Chromatograms of Samples	10

1.1 Introduction

N,N-Dimethyl formamide (DMF) is considered a volatile solvent (vapour pressure @ 20°C = 2.7 mm Hg → 0.36 Kpa @ 293.15°K)

The method used for the analysis of the determination of the DMF in the outcoming solution from the Fosinopril process is the gas-chromatography.

The analysis results are used to calculate the flow rate of DMF during the Fosinopril sodium process.

Five solutions (solution A,B,C,D,E) were analyzed for GC. The solution A,B,C are aqueous solution separated during the synthesis from the organic phase and they contain most of the DMF used in the process. The solution D is the mother liquor obtained after the filtration in the centrifuge of the Fosinopril sodium precipitate. The solution E consists of Toluene distilled of from the organic phase.

Each of all these solutions is collected in 1000 litres tank calculating the volume of each solution.

2.1 Sampling

The sampling was taken directly from each container using a glass pipette.

3.1 Measurement

The analysis of the samples are carried out using a GC instrument using the following method:

GC Instrument:	SHIMADZU GC 17 A
Injector Temperature:	200°C
Detector temperature:	230°C
Column:	30 m , 0.53mm , 1.5µm (thickness)
Column Flow:	3.4 ml/min
Column Program:	80°C for 10 minutes
Makeup Flow (Helium):	30ml/min
Hydrogen Flow:	35ml/min
Air Flow:	300ml/min
Solvent Used:	Methanol

3.1.1 Reference standard:

The reference standard is performed by preparing standard of the solvent under investigation (DMF) with 50% w/w concentration.

DMF 50% w/w	Standard 1	Standard 2	Standard 3	Standard 4	Standard 5	Average
Area%	500218	560386	558762	568130	562228	561858

3.1.2 Samples analysis

Sample preparation

Sample solution (A, B, C, E): 1 ml of sample solution is diluted to 50 ml using Methanol

Sample solution (D): 10 ml of sample solution is diluted to 50 ml using Methanol

Results

Solution A: Assay: 48.295% w/v

Solution B: Assay: 8.67% w/v

Solution C: Assay: 1.40% w/v

Solution D: Assay: 0.047%

Solution E: not detected

3.1.2 Calculation

FOSINOPRIL SODIUM SYNTHESIS

DMF used per batch of Fosinopril sodium (100 kg batch size): **594kg**

Solution containing DMF coming out from the process:

- A) Aqueous phase I separation: 1145 L(d=0.9973)=1142 kg
Assay: 48.295% w/v → Amount DMF= **553.0 kg**
- B) Aqueous phase II separation: 380 L (d=0.9828)= 373.5 kg
Assay: 8.67% w/v → Amount DMF= **32.9kg**
- C) Aqueous phase III separation: 330 L (d=0.9835) = 324.5kg
Assay: 1.40% w/v → Amount DMF= **4.6 kg**
- D) Mother liquors FOS-2: 1125 L (d= 0.890)= 1001 kg
Assay: 0.047% → Amount DMF= **0.5 kg**
- E) Toluene distilled : 364 L (0.866)= 315.4 kg

Assay: not detected

Remarks: other solutions obtained from the same process but successive steps which can contain only small amount of DMF (traces) were not analysed

Total amount of DMF = 591 kg

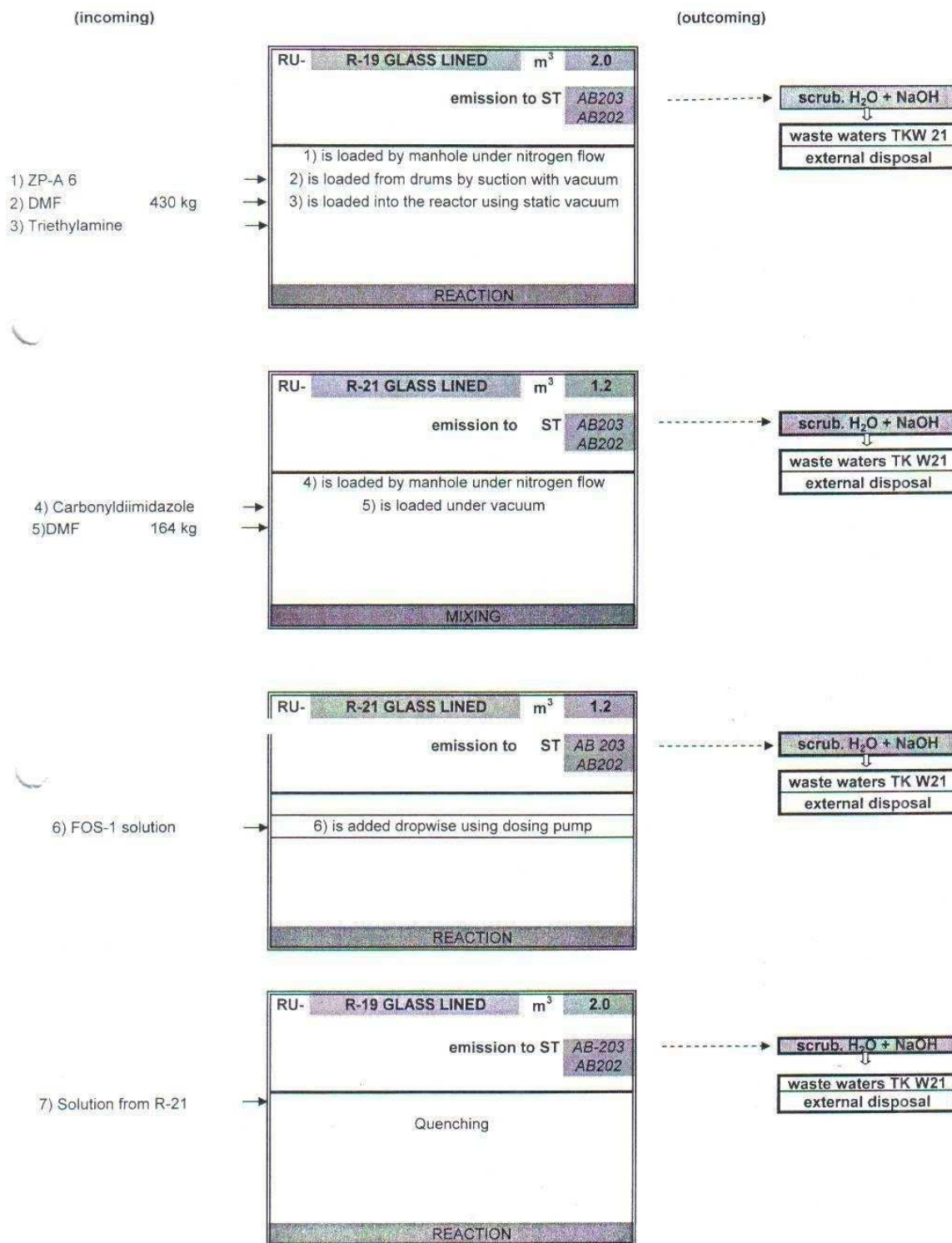
$$\text{Flow rate} = \frac{\text{Mass in} - \text{Mass out}}{\text{Production time}} = \frac{594-591}{\sim 32 \text{ hrs}} = 0.09 \text{ kg/ hr}$$

Appendix A –Block Diagram of FOS-2

BLOCK DIAGRAM

NOTES:

All the standard loading are done from drums under loading under vacuum and using air suction points in the manipulation area



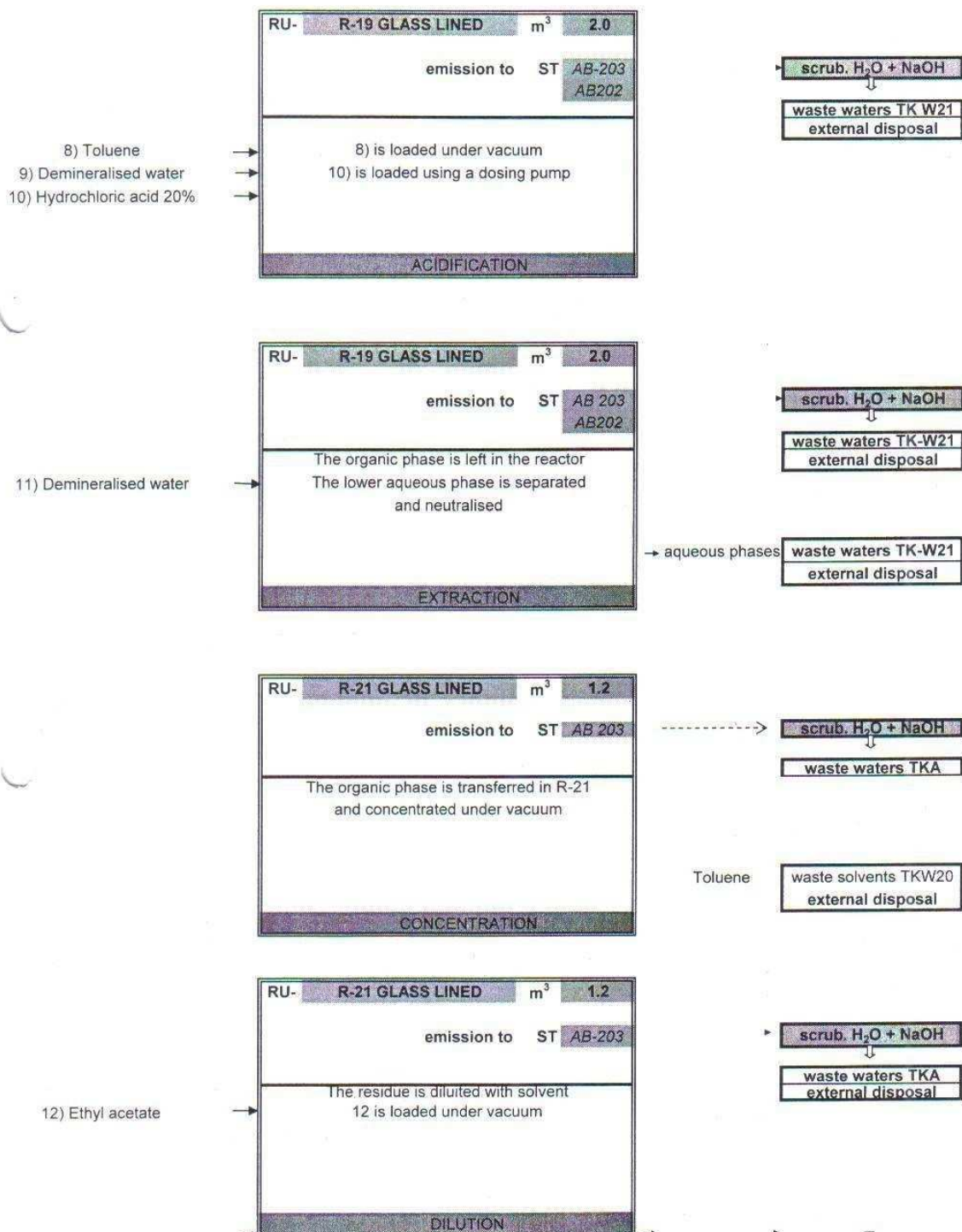
BLOCK DIAGRAM

NOTES:

All the standard loading are done from drums under loading under vacuum and using air suction points in the manipulation area

(incoming)

(outcomin)



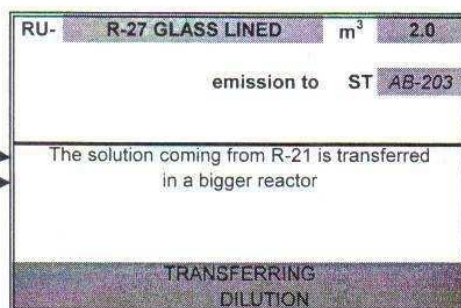
BLOCK DIAGRAM

NOTES:

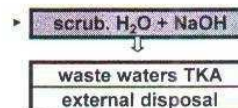
All the standard loading are done from drums under loading under vacuum and using air suction points in the manipulation area

(incoming)

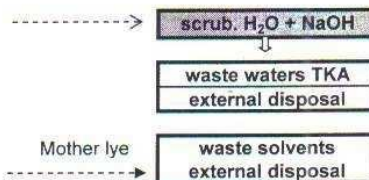
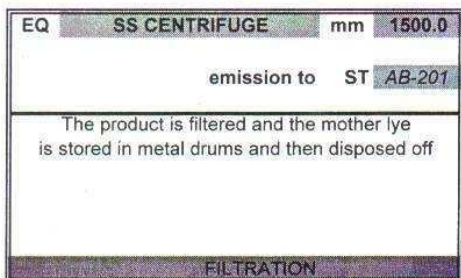
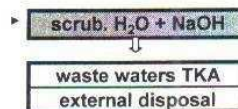
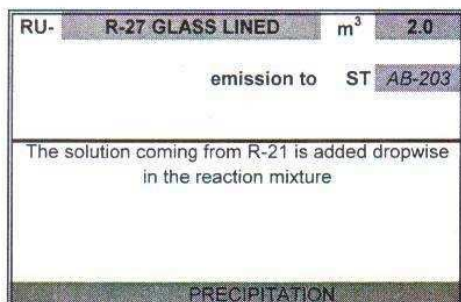
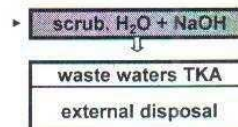
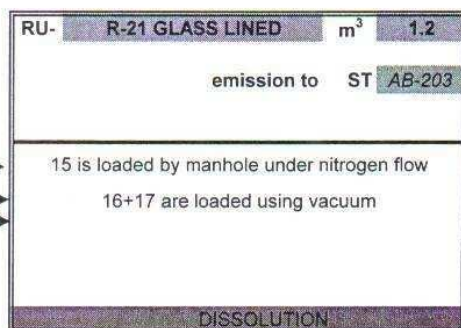
- 13) Ethyl acetate
14) Tetrahydrofuran



(outcomin)



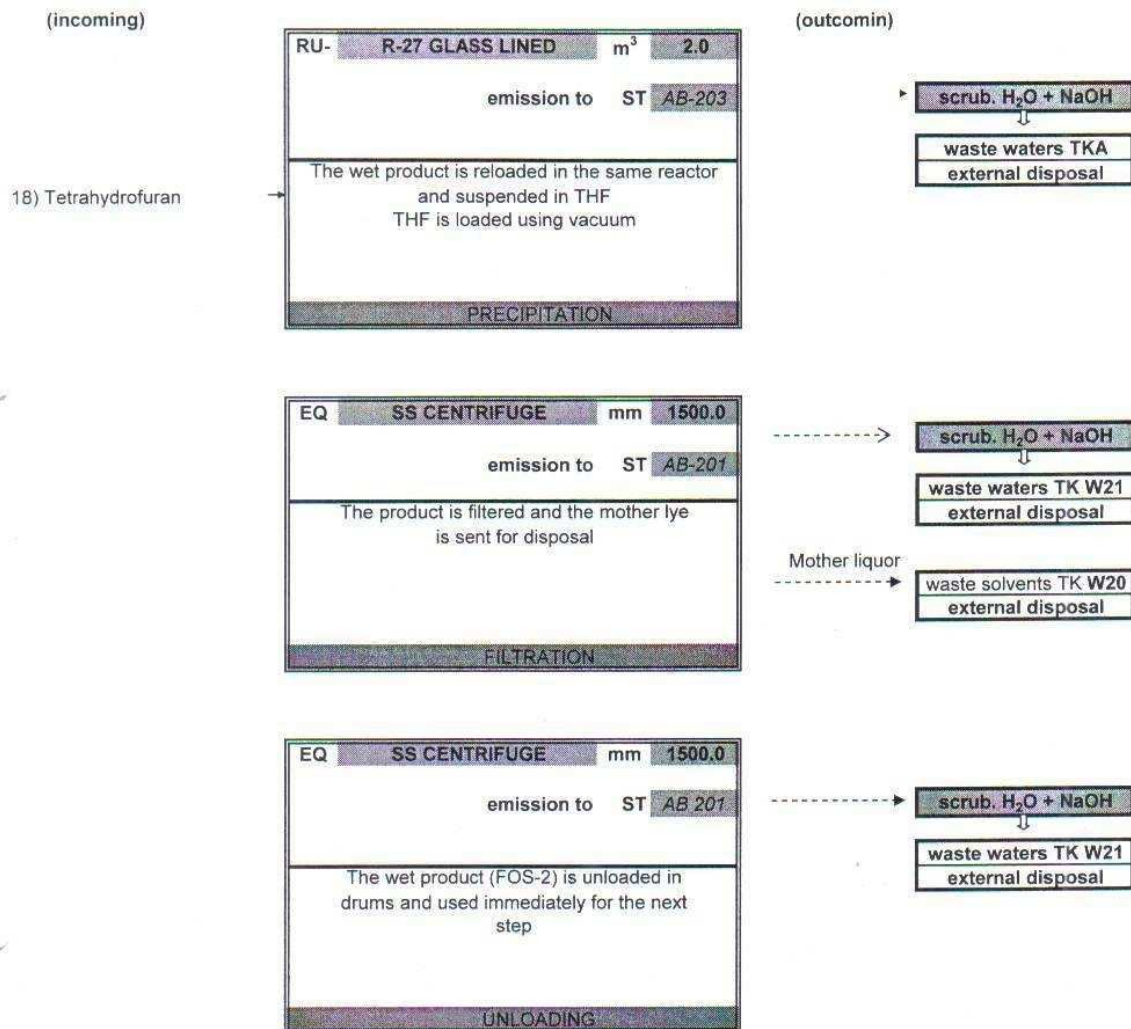
- 15) Sodium 2-ethyl hexanoate
16) Ethyl acetate
17) Tetrahydrofuran



BLOCK DIAGRAM

NOTES:

All the standard loading are done from drums under loading under vacuum and using air suction points in the manipulation area



Appendix B – Chromatograms of Samples



Amino Chemicals

Quality Control

Sample ID: DMF St 50% P-P Inj 1

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P

Inj 1 25-10-2007 13-34-03.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF

Fosinopril\DMF St 50% P-P Inj 1 25-10-2007 13-34-03.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

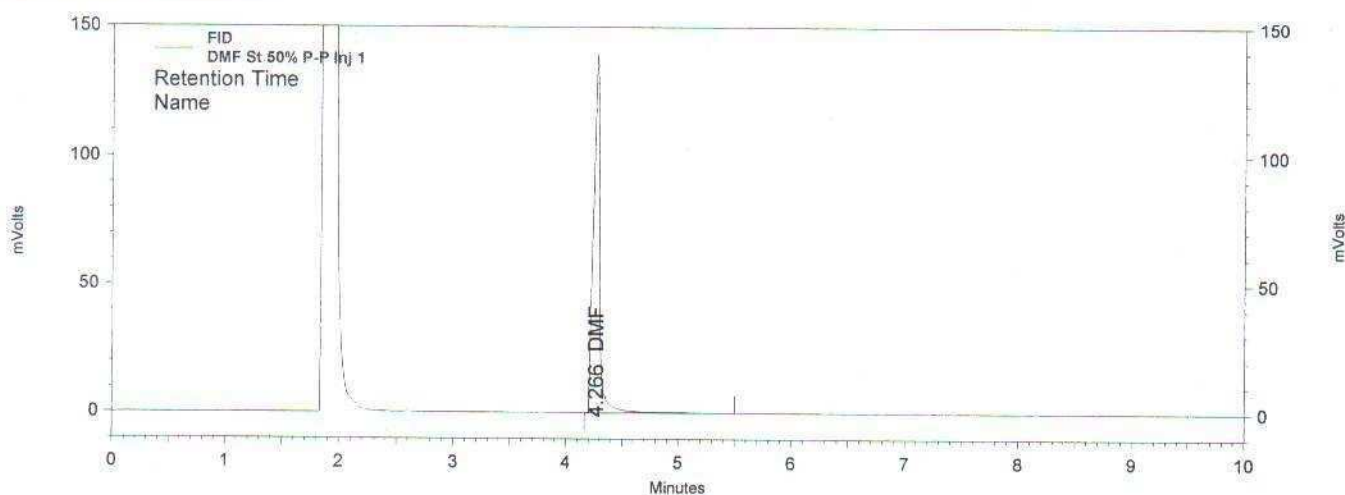
Volume inj: 1 µl

Vial: 2

Run time: 25/10/2007 13:36:05

Operator: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.266	560218	100.000	DMF
Totals				
		560218	100.000	

$\bar{M}_w \text{ det} = 561.858$



Amino Chemicals

Quality Control

Sample ID: DMF St 50% P-P Inj 2

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P Inj 2 25-10-2007 13-46-07.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P Inj 2 25-10-2007 13-46-07.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

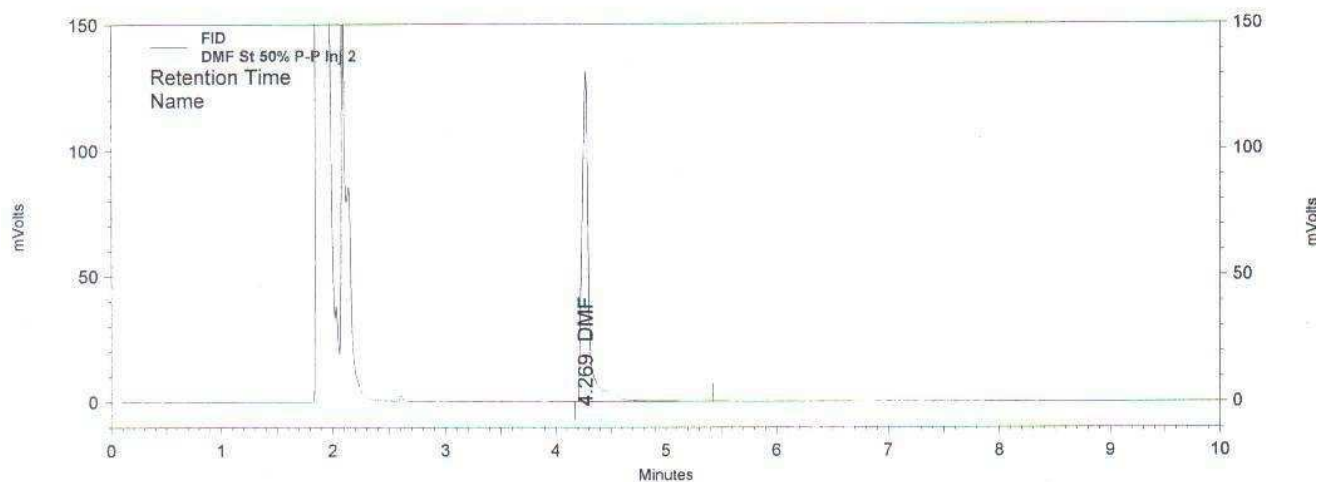
Volume inj: 1 µl

Vial: 2

Run time: 25/10/2007 13:48:11

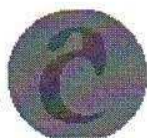
Operatore: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.269	560386	100.000	DMF
Totals				
		560386	100.000	

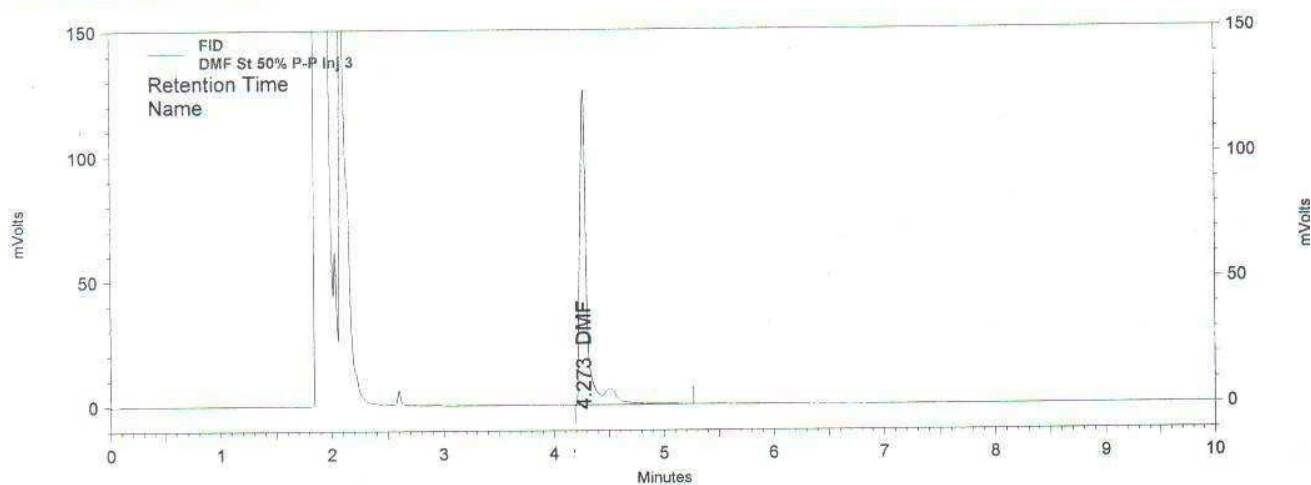


Amino Chemicals

Quality Control

Sample ID: DMF St 50% P-P Inj 3
File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P Inj 3 25-10-2007 13-58-13.dat
Fosinopril\DMF St 50% P-P Inj 3 25-10-2007 13-58-13.dat
Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met
Volume inj: 1 µl
Vial: 2
Run time: 25/10/2007 14:00:17
Operator: Roberto (VPDomain\Roberto)

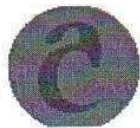
UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.273	558762	100.000	DMF

Totals		558762	100.000	
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Amino Chemicals

Quality Control

Sample ID: DMF St 50% P-P Inj 4

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P

Inj 4 25-10-2007 14-10-18.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF

Fosinopril\DMF St 50% P-P Inj 4 25-10-2007 14-10-18.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

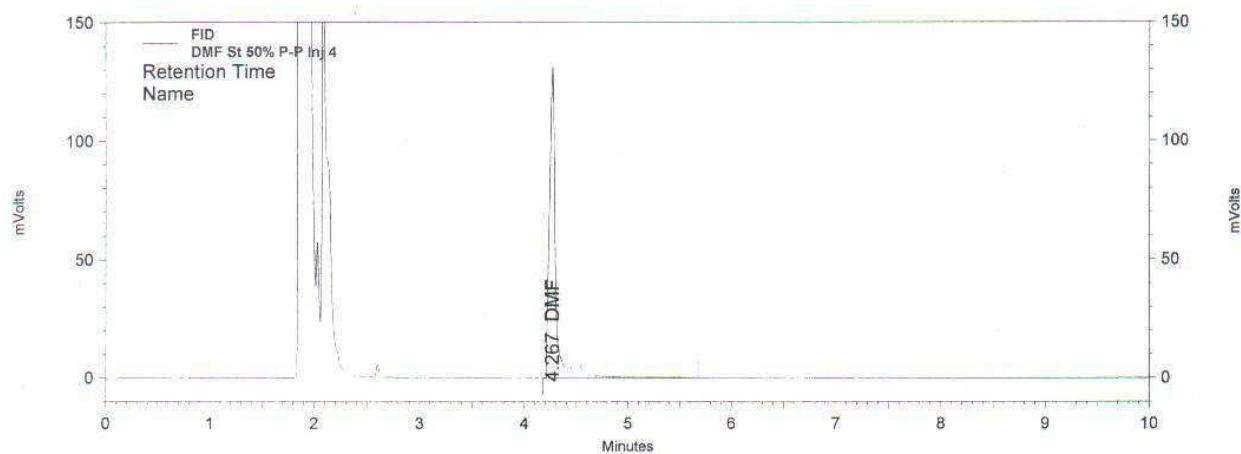
Volume inj: 1 µl

Vial: 2

Run time: 25/10/2007 14:12:23

Operatore: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.267	568130	100.000	DMF
Totals				
		568130	100.000	



Amino Chemicals

Quality Control

Sample ID: DMF St 50% P-P Inj 5

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P

Inj 5 25-10-2007 14-22-24.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF

Fosinopril\DMF St 50% P-P Inj 5 25-10-2007 14-22-24.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

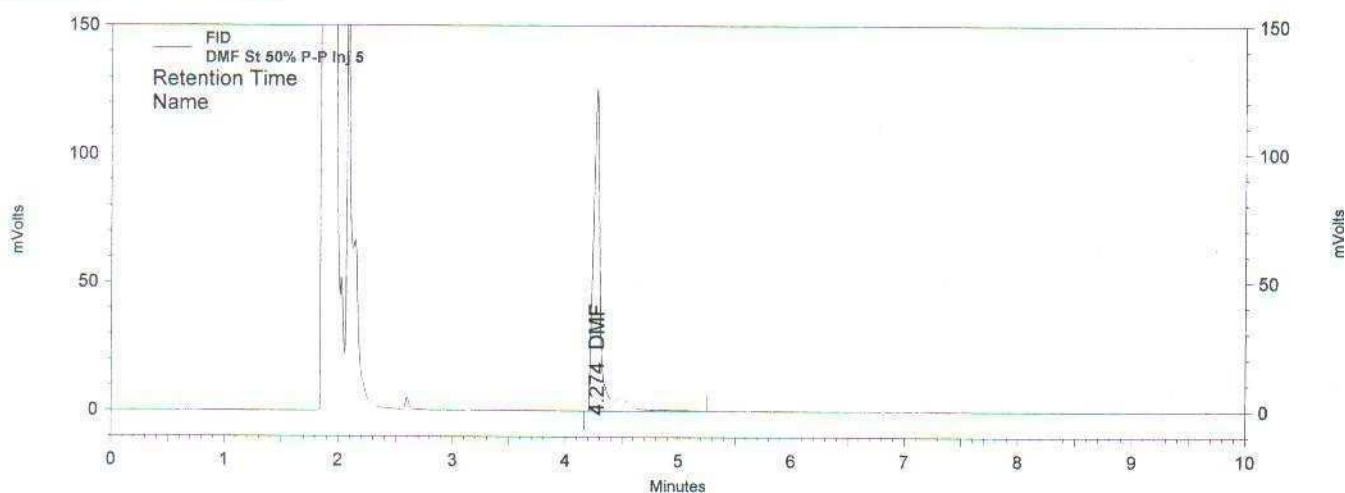
Volume inj: 1 µl

Vial: 2

Run time: 25/10/2007 14:24:28

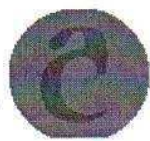
Operator: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.274	562228	100.000	DMF
Totals		562228	100.000	



Amino Chemicals

Quality Control

Sample ID: DMF St 50% P-P Inj 6

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P Inj 6 25-10-2007 14-34-30.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\DMF St 50% P-P Inj 6 25-10-2007 14-34-30.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

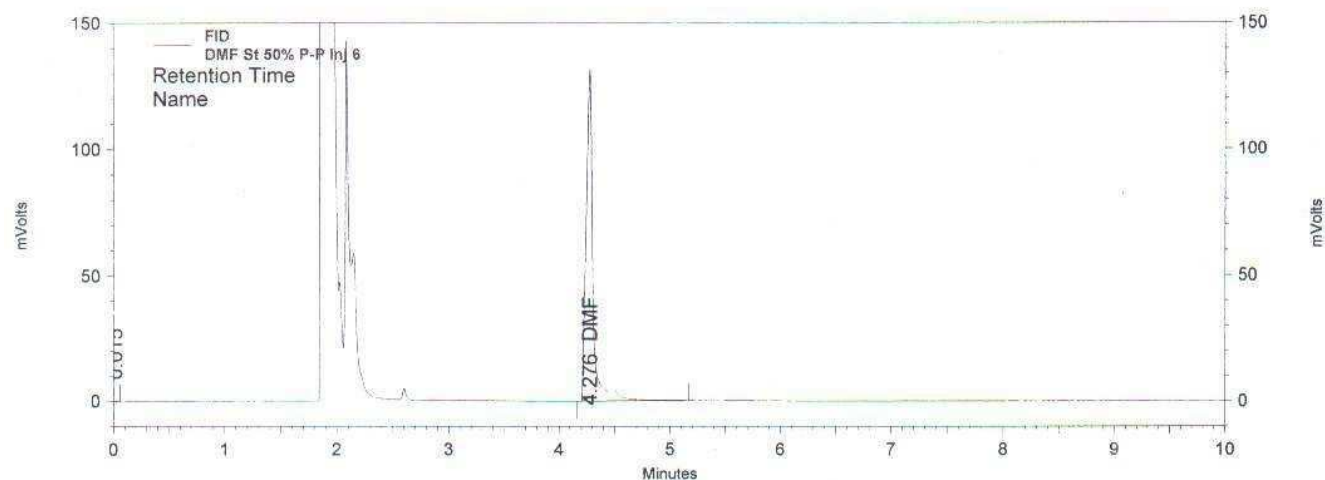
Volume inj: 1 μ l

Vial: 2

Run time: 25/10/2007 14:36:33

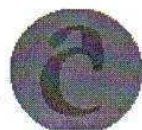
Operatore: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	0.015	788	0.140	
2	4.276	561424	99.860	DMF
Totals		562212	100.000	



Amino Chemicals

Quality Control

Sample ID: Sample A

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\Sample A

25-10-2007 14-46-36.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\Sample A 25-10-2007 14-46-36.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

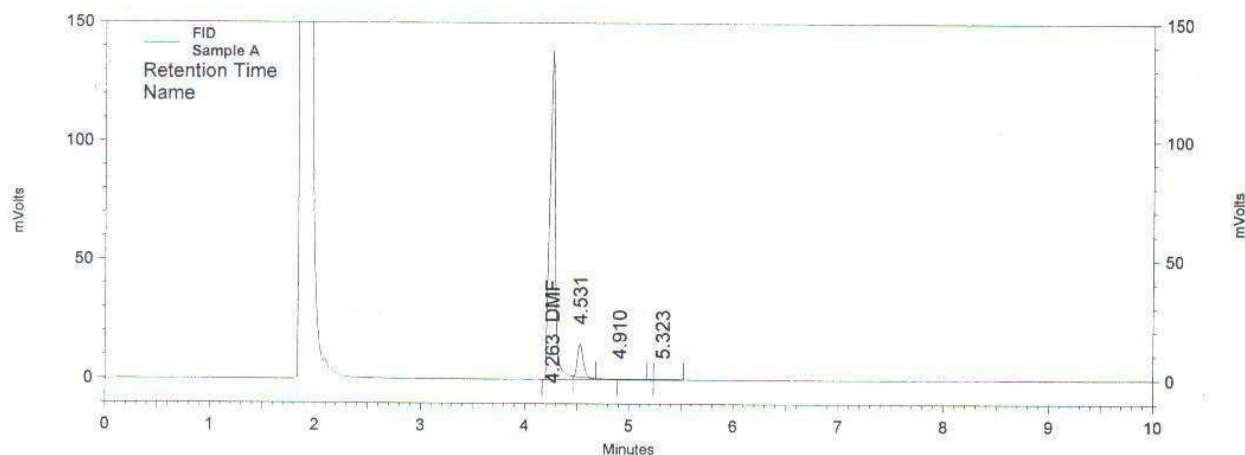
Volume inj: 1 µl

Vial: 3

Run time: 25/10/2007 14:48:42

Operatore: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.263	542704	90.877	DMF
2	4.531	53002	8.875	
3	4.910	440	0.074	
4	5.323	1041	0.174	
Totals		597187	100.000	

$$\frac{542704}{561858} \cdot 100 = 48,295\% \quad P/V$$



Amino Chemicals

Quality Control

Sample ID: Sample B

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\Sample B
25-10-2007 14-58-44.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF
Fosinopril\Sample B 25-10-2007 14-58-44.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

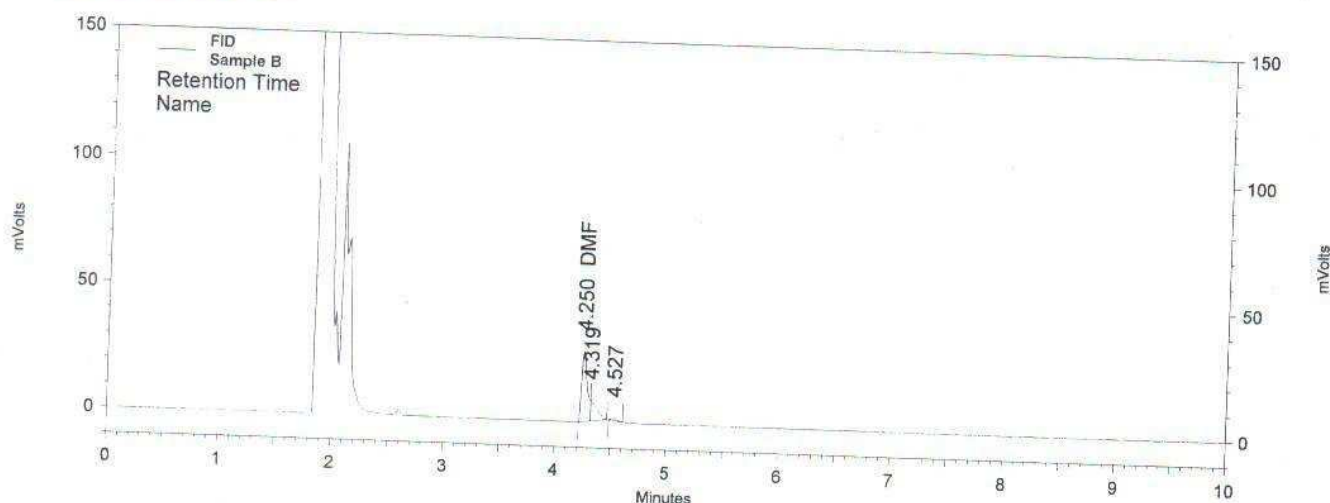
Volume inj: 1 µl

Vial: 4

Run time: 25/10/2007 15:00:52

Operatore: Roberto (VPDomain\Roberto)

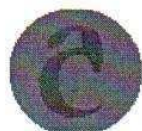
UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.250	97399	74.223	DMF
2	4.319	30971	23.602	
3	4.527	2854	2.175	
Totals		131224	100.000	

$$\frac{97399}{561858} \cdot 100 = 8.64\% \quad P/V$$



Amino Chemicals

Quality Control

Sample ID: Sample C

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\Sample C

25-10-2007 15-10-54.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF

Fosinopril\Sample C 25-10-2007 15-10-54.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Prove\Metodi\Prova.met

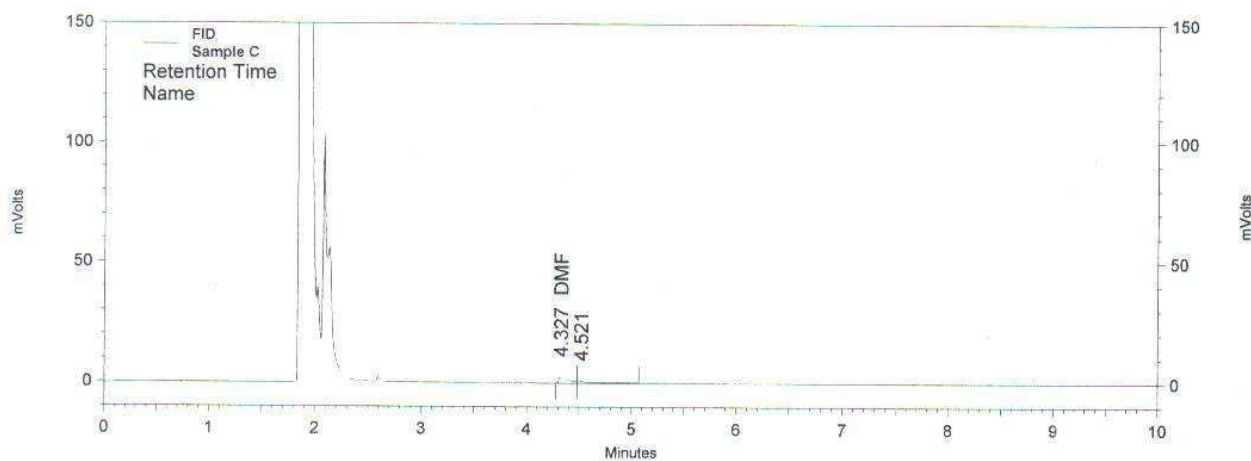
Volume inj: 1 µl

Vial: 5

Run time: 25/10/2007 15:13:05

Operator: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.327	15701	72.162	DMF
2	4.521	6057	27.838	
Totals		21758	100.000	

$$\frac{15701}{561858} \cdot 50 = 1.40\% \text{ 9/5}$$



Amino Chemicals

Quality Control

Sample ID: Sample D

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\Sample D

25-10-2007 16-20-38.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF

Fosinopril\Sample D 25-10-2007 16-20-38.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\Metodi\DMF in Fos.met

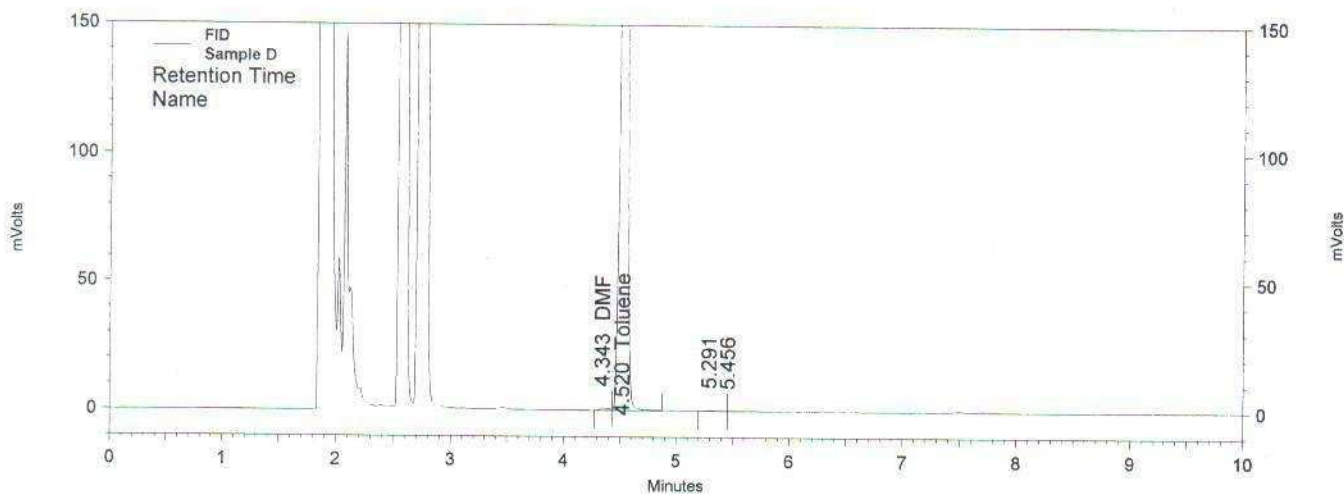
Volume inj: 1 µl

Vial: 7

Run time: 25/10/2007 16:22:54

Operator: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

Pk #	Retention Time	Area	Area Percent	Name
1	4.343	5318	0.382	DMF
2	4.520	1385355	99.538	Toluene
3	5.291	1115	0.080	
4	5.456	0	0.000	

Totals		1391788	100.000	
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10 µl → 50
1 µl

$$\frac{5318}{561858} \cdot \frac{50}{10} = 0.047\% \text{ p/v}$$

(10 µl)



Amino Chemicals

Quality Control

E

Sample ID: Sample *E*

File: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF Fosinopril\Sample T
25-10-2007 15-23-07.dat \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\DMF
Fosinopril\Sample T 25-10-2007 15-23-07.dat

Method: \\Vp7server\VP7Data\Projects\Default\2007\GC\Riconciliazione Solventi\Metodi\DMF in Fos.met

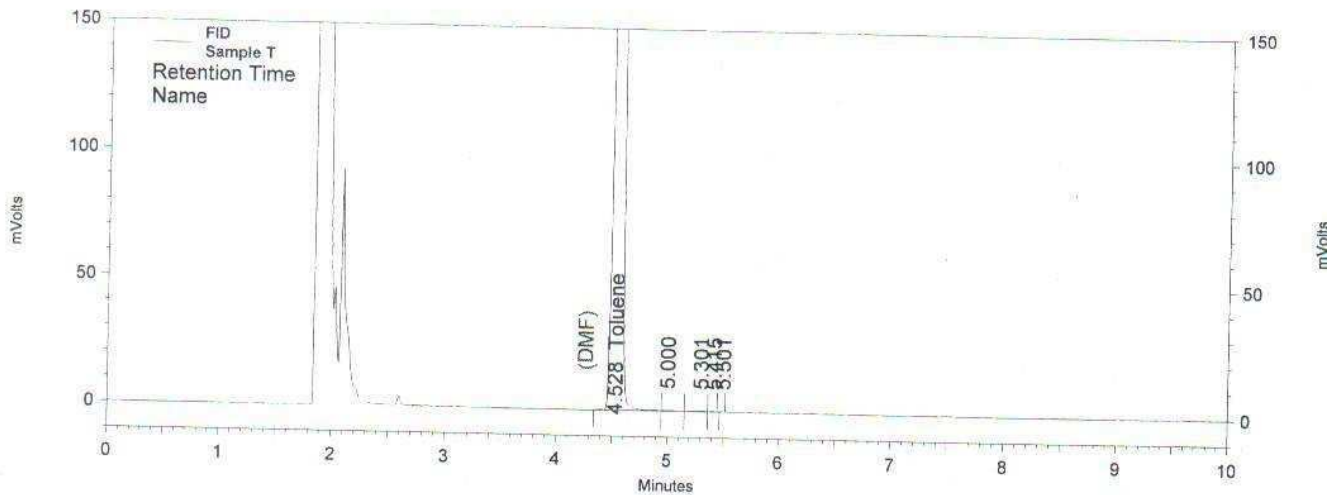
Volume inj: 1 µl

Vial: 6

Run time: 25/10/2007 15:25:21

Operator: Roberto (VPDomain\Roberto)

UV Detector 220nm



FID Results

PK #	Retention Time	Area	Area Percent	Name
1	4.528	3372566	99.912	DMF
2	5.000	1729	0.051	Toluene
3	5.301	910	0.027	
4	5.415	209	0.006	
5	5.501	112	0.003	
Totals				
		3375526	100.000	