

EXPO&more International Workshop

Quantifying API polymorphs in solid formulations

Alessandro Zappi¹, Lucia Maini¹, Dora Melucci¹, Rocco Caliandro²

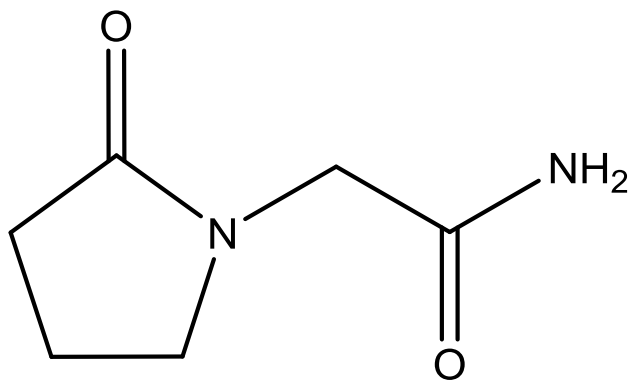
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²IC-CNR, Bari, Italy

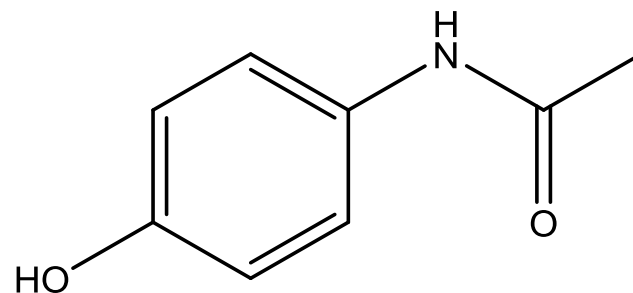
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Aim of the work

To use RootProf for the quantification of a specific polymorphs in solid mixtures



Piracetam F-II



Paracetamol F-I



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Quantifying API polymorphs in formulations using X-ray powder diffraction and multivariate standard addition method combined with net analyte signal analysis



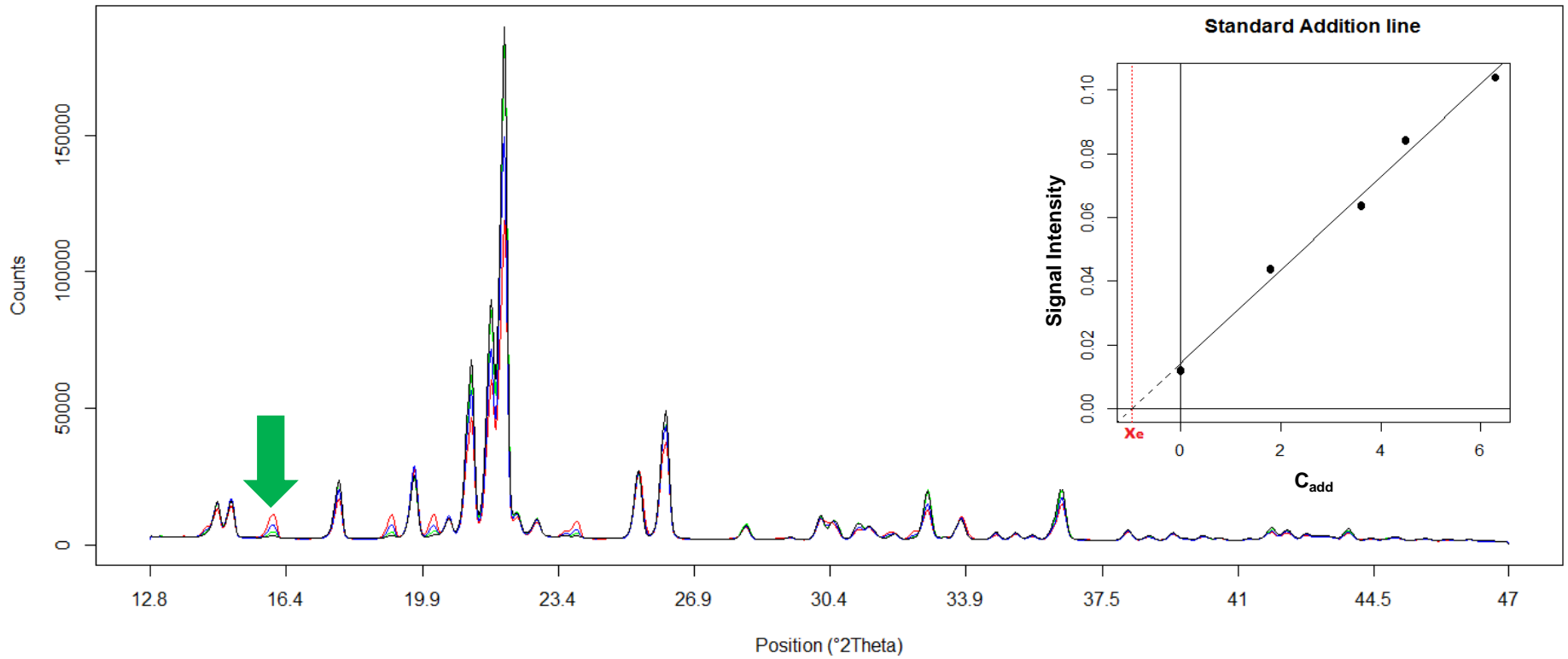
Alessandro Zappi^a, Lucia Maini^a, Giuliano Galimberti^b, Rocco Caliandro^c, Dora Melucci^{a,*}

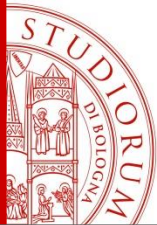
^a Department of Chemistry “G. Ciamician”, University of Bologna, Bologna, Italy

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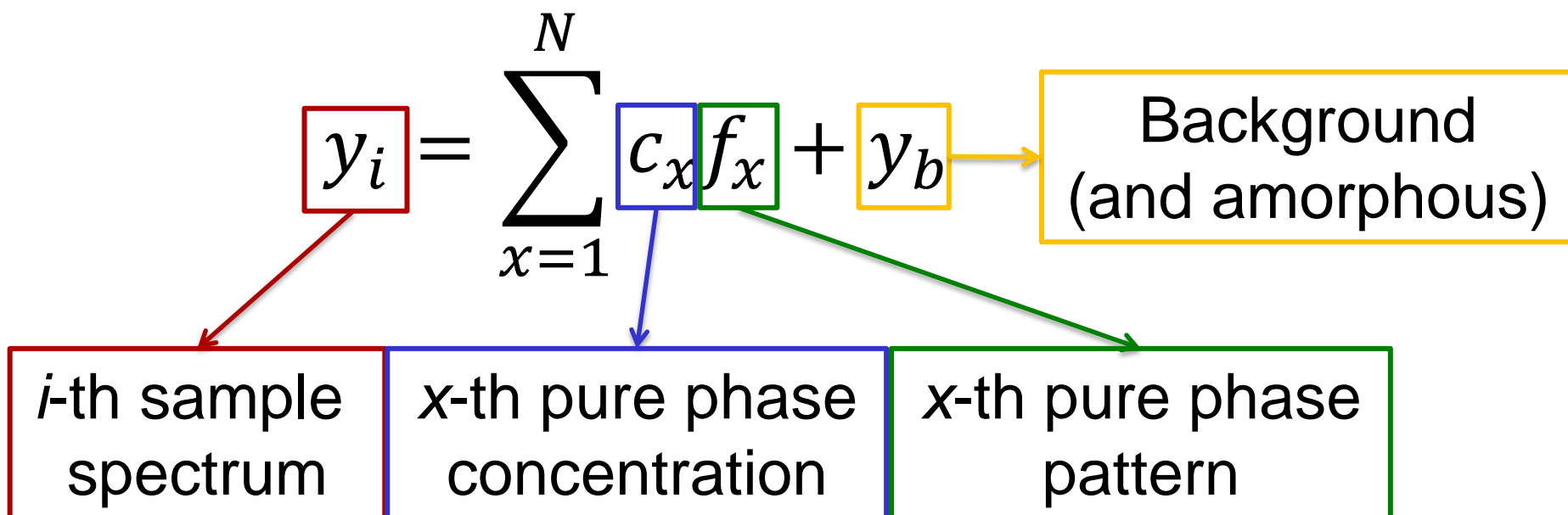
^c Institute of Crystallography, CNR, Bari 70126, Italy

RootProf approach

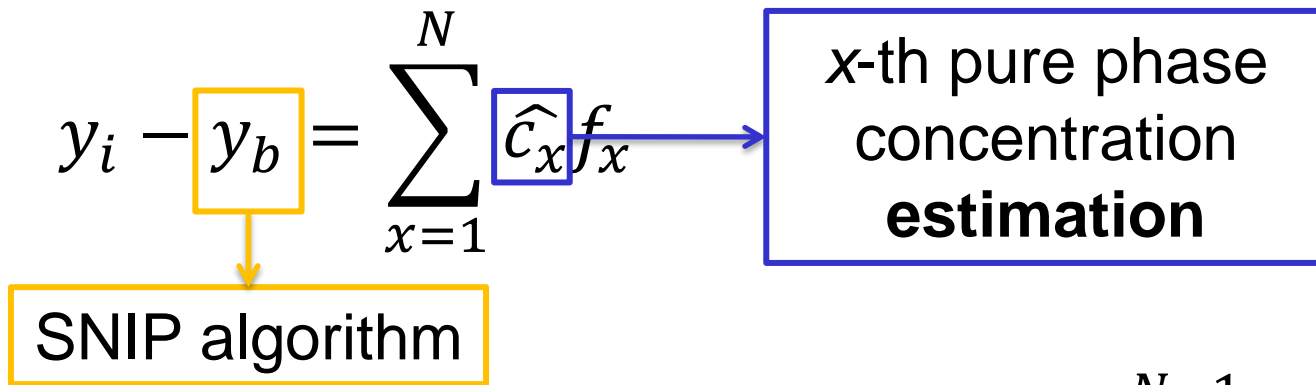




RootProf approach



RootProf approach



$$y_{corr,i} = y_M + \hat{c}_x f_x$$

$$\mathbf{y} = \mathbf{a} + \hat{\mathbf{c}}\mathbf{x}$$

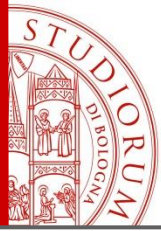
$$y_M = \mathbf{a} = \sum_{j=1}^{N-1} c_j f_j$$

Matrix contribution

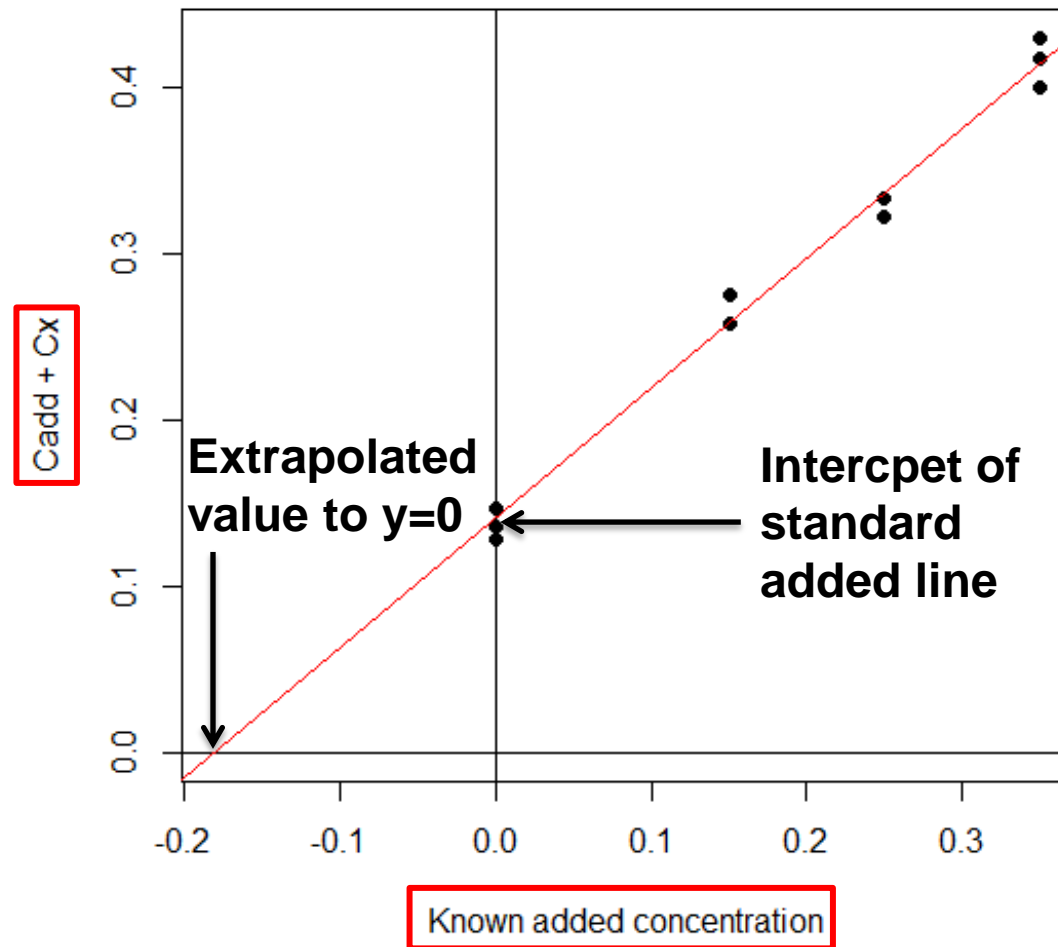
RootProf
Single Profile

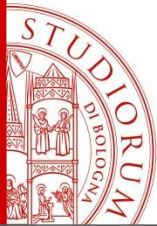
$$y_{corr,i} = y_M + (c_x + c_{add,i}) f_x$$

RootProf
SAM



RootProf NAS: C_x estimation



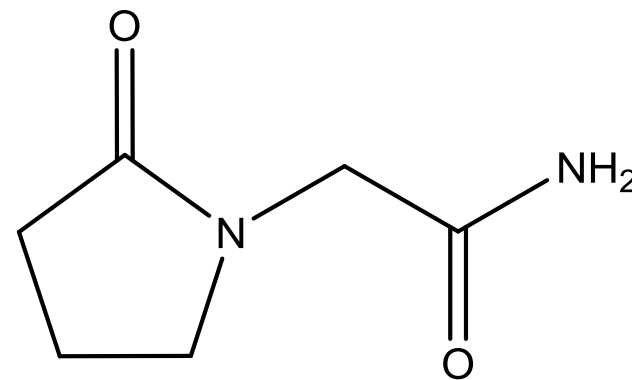


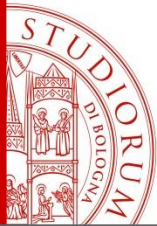
Case study

- Quantification of Piracetam II in a mixture containing both Piracetam II and Piracetam III (homemade)
- Quantification of Paracetamol in commercial formulation Tachifludec[®]

Piracetam

- It is a drug acting on cognitive disfunctions (dementia, Alzheimer, depression, etc.)
- Five polymorphs and at least two hydrate forms are known.
- The FIII (monoclinic) is stable, while FII (triclinic) is meta-stable at room conditions, the others are unstable.



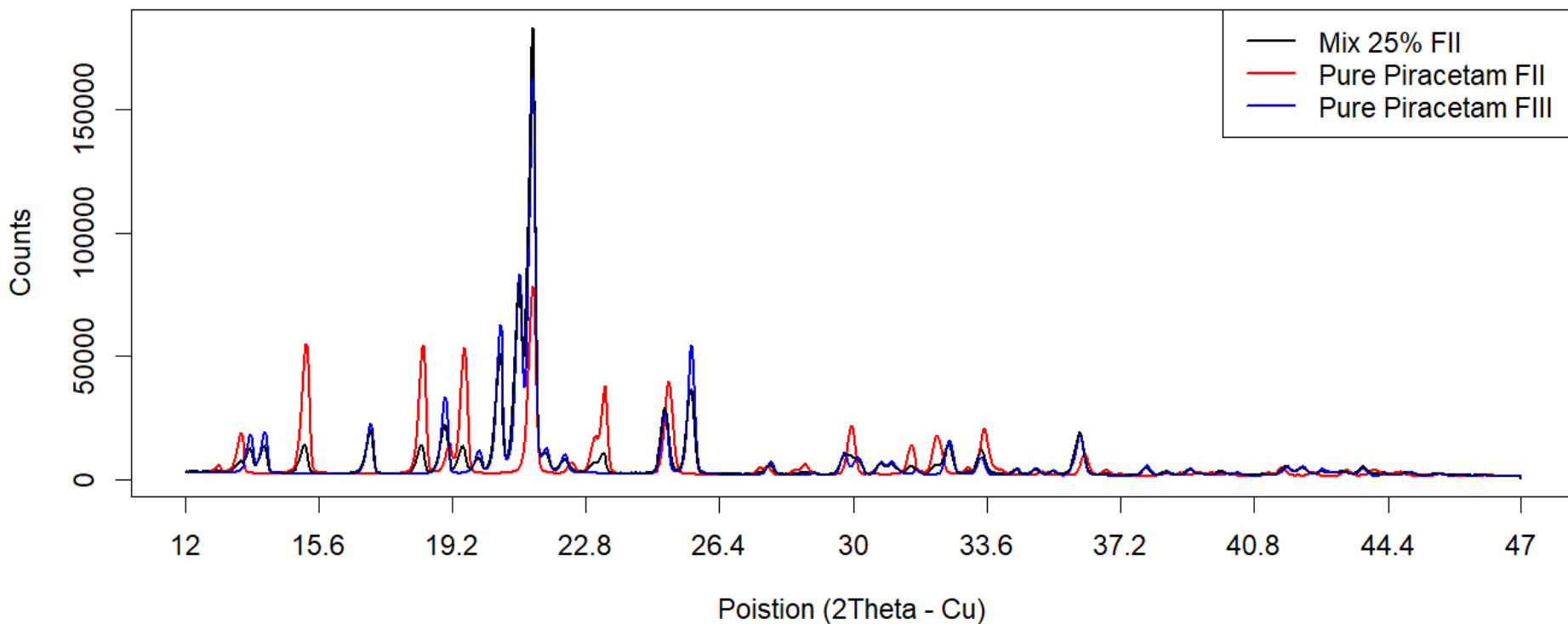


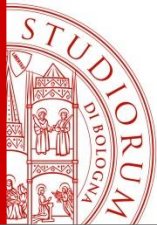
Working procedure

Sample	FII concentration (%w/w)	Added concentration (%w/w)
1	2	0
2	3	1
3	5	3
4	10	8
5	15	13
6	20	18
7	25	23
8	100	Pure Piracetam FII

- *Three replicates per sample*
- *Diffraction angle range: 12-47° (2θ – Cu)*

Piracetam





Piracetam RootProf input

whichanalysis 3

Analysis type: quantitative analysis (3)

range 0 21 22 100

Diffraction range: exclude 2θ range 21-22°
(peak of both forms or preferential orientation)

preprocess 0 3 30

Pre-treatment:

- 0: No signal modification
- 3: Area Normalization
- 30: Background subtraction with SNIP algorithm with a clipping window of 30 variables

```
file /home/alessandro/piracetam/output_1.txt  
msa 0
```

```
file /home/alessandro/piracetam/output_2.txt  
msa 0
```

```
file /home/alessandro/piracetam/output_3.txt  
msa 0
```

```
file /home/alessandro/piracetam/output_4.txt  
msa 0.01
```

```
file /home/alessandro/piracetam/output_5.txt  
msa 0.01
```

```
file /home/alessandro/piracetam/output_6.txt  
msa 0.01
```

```
file /home/alessandro/piracetam/output_7.txt  
msa 0.03
```

...

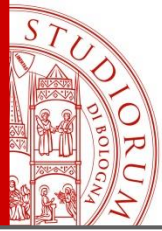
```
file /home/alessandro/piracetam/output_26.txt  
purephase
```

File directory

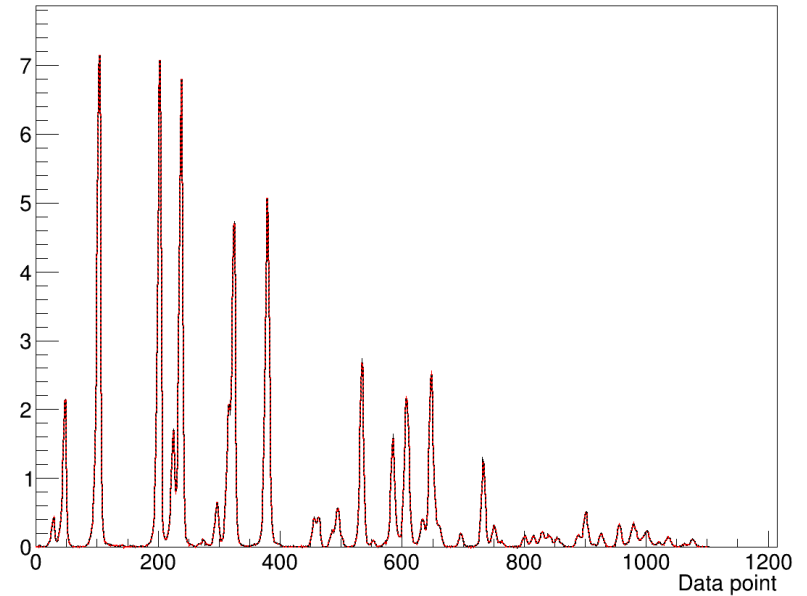
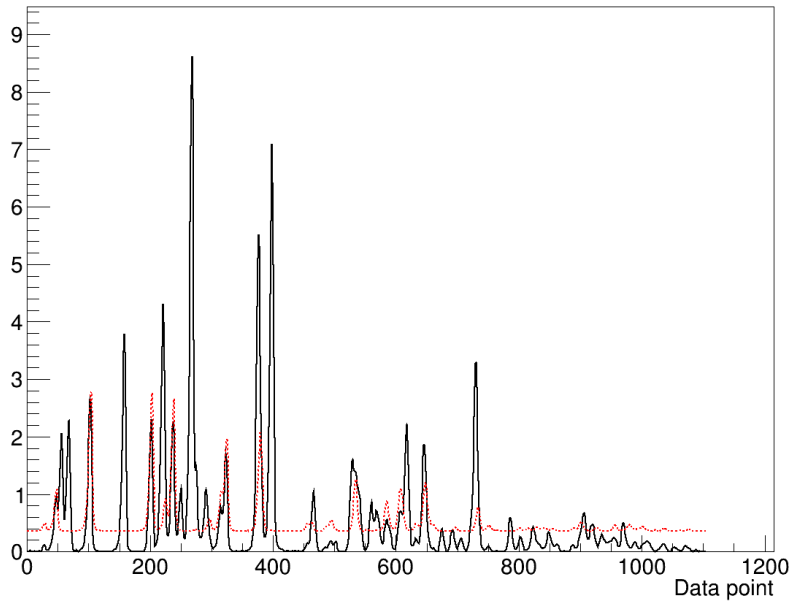
Input files (diffractograms)

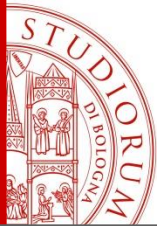
Known added concentration

Pure analyte (piracetam)
diffractogram

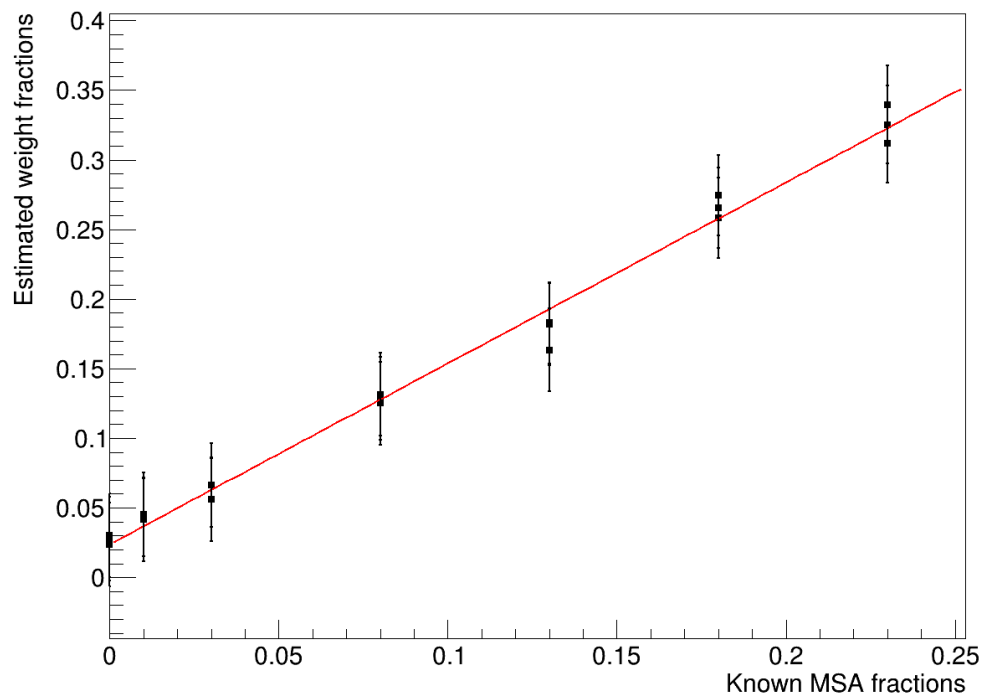


Piracetam RootProf output





RootProf results – Piracetam



Line parameters

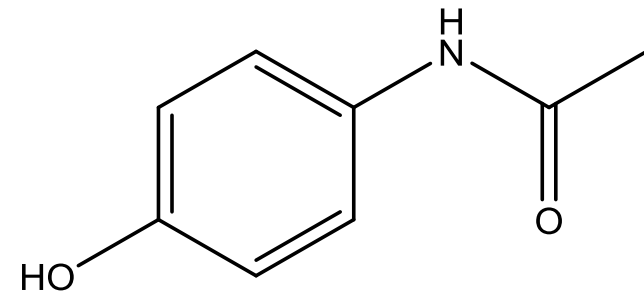
Slope	1.30
Intercept	0.024
R²	0.991
RMSE	0.0001
C_{extrapolated}	2.1
Std dev. C_E	0.6
LoD	0.82

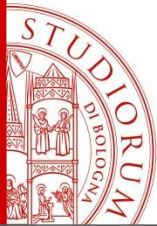
- *Expected Piracetam II content: 2 %_{w/w}*

Paracetamol – Tachifludec

- Paracetamol is a compound used to treat moderate pain and fever
- Tachifludec[®] is an antipyretic containing paracetamol within the following formulation

Compound	Quantity (mg)
Suchrose	2000
Paracetamol	600
Ascorbic acid	40
Phenylephrine chloridrate	10
Citric acid, Sodium citrate, Cornstarch, etc. (8 other excipients)	Not declared



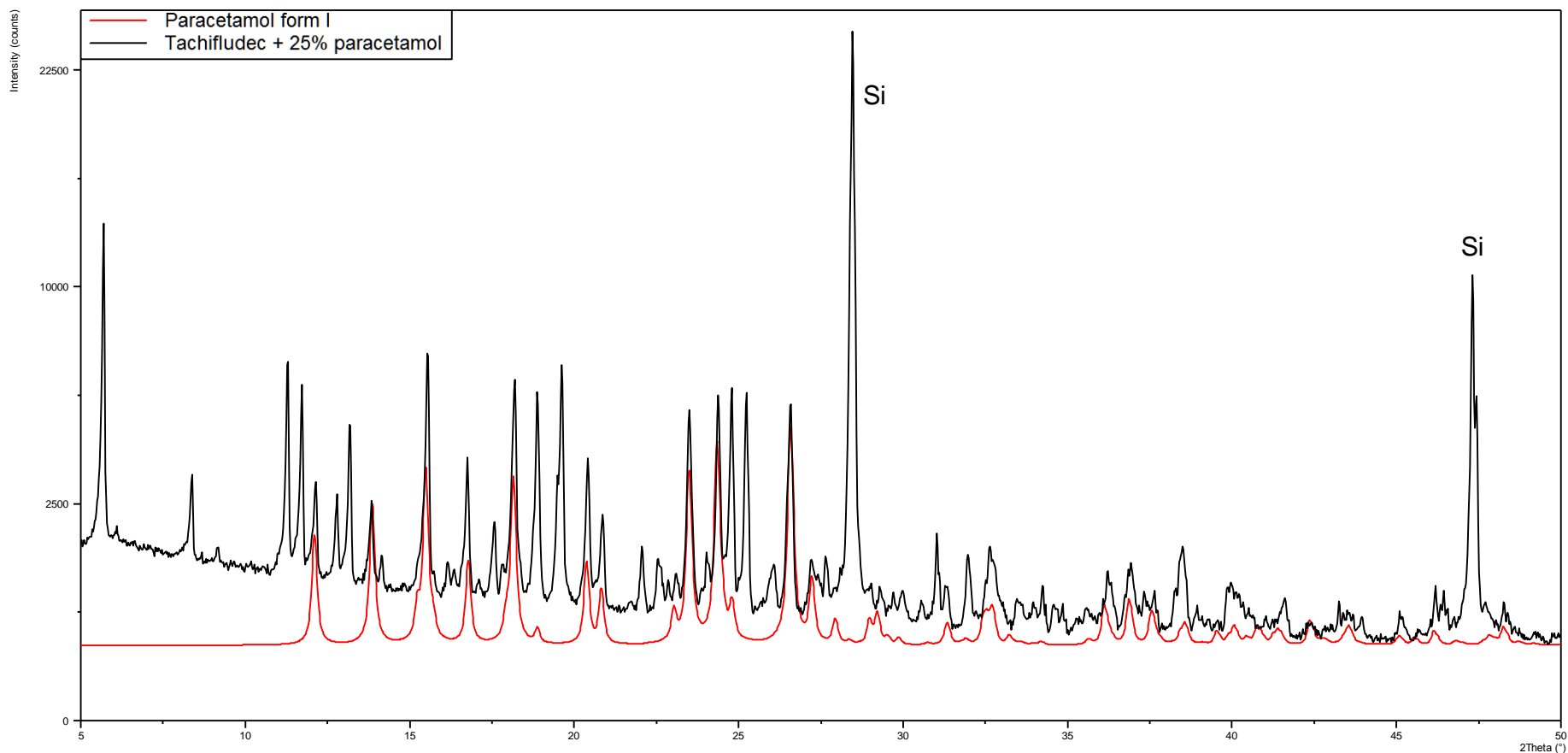


Working procedure

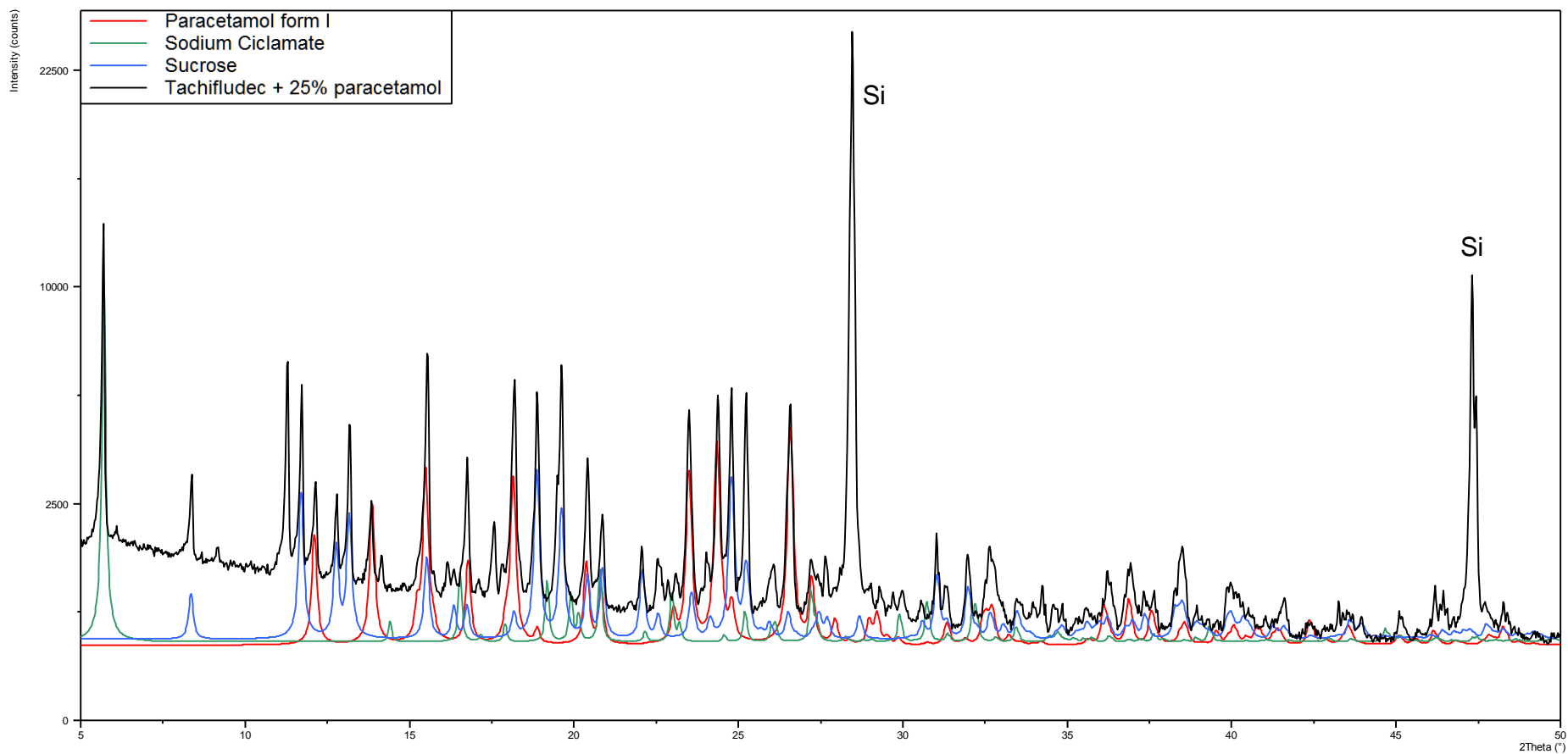
Sample	Added concentration (%w/w)
1	0
2	15
3	25
4	35
5	Pure Paracetamol

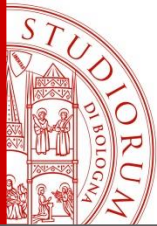
- *Three replicates per sample*
- *Diffraction angle range: 5-60° (2θ – Cu)*

Paracetamol – Tachifludec



Paracetamol – Tachifludec





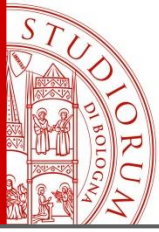
Paracetamol RootProf input

```
whichanalysis 3

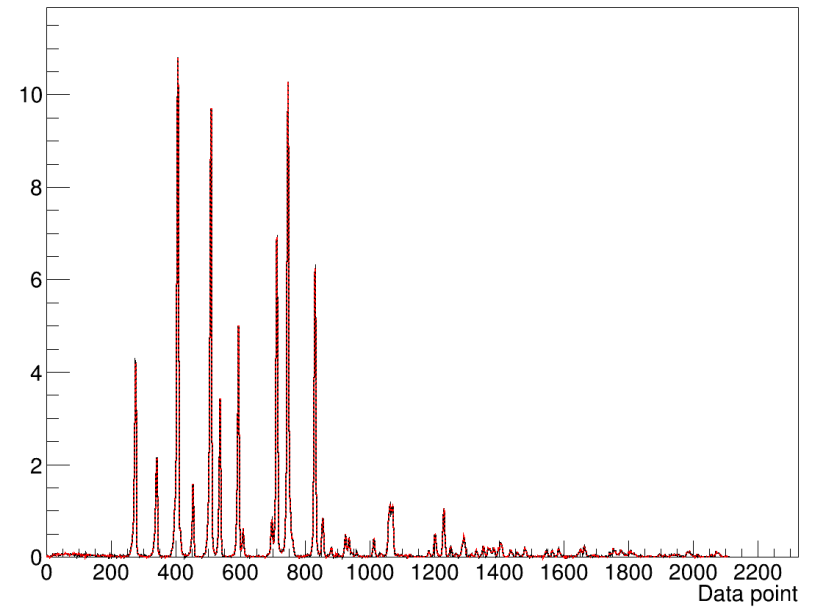
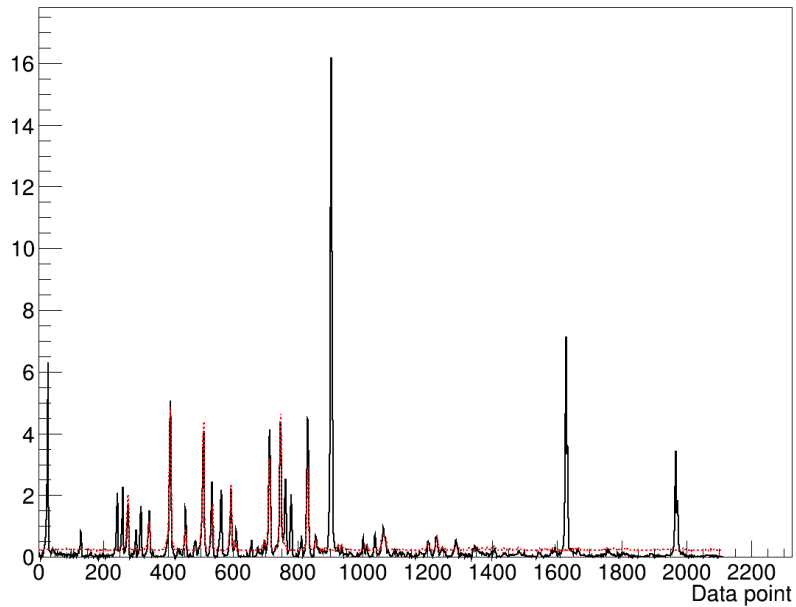
figpaper 1

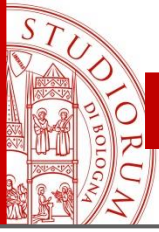
preprocess 0 3 30

file /home/alessandro/paracetamolo/agg0_1.ASC
msa 0
file /home/alessandro/paracetamolo/agg0_2.ASC
msa 0
file /home/alessandro/paracetamolo/agg0_4.ASC
msa 0
file /home/alessandro/paracetamolo/agg1_1.ASC
msa 0.15
file /home/alessandro/paracetamolo/agg1_2.ASC
msa 0.15
file /home/alessandro/paracetamolo/agg1_3.ASC
msa 0.15
file /home/alessandro/paracetamolo/agg2_1.ASC
msa 0.25
file /home/alessandro/paracetamolo/agg2_2.ASC
msa 0.25
file /home/alessandro/paracetamolo/agg2_3.ASC
msa 0.25
file /home/alessandro/paracetamolo/agg3_1.ASC
msa 0.35
file /home/alessandro/paracetamolo/agg3_2.ASC
msa 0.35
file /home/alessandro/paracetamolo/agg3_3.ASC
msa 0.35
file /home/alessandro/paracetamolo/paracetamolo_1.ASC
purephase
```

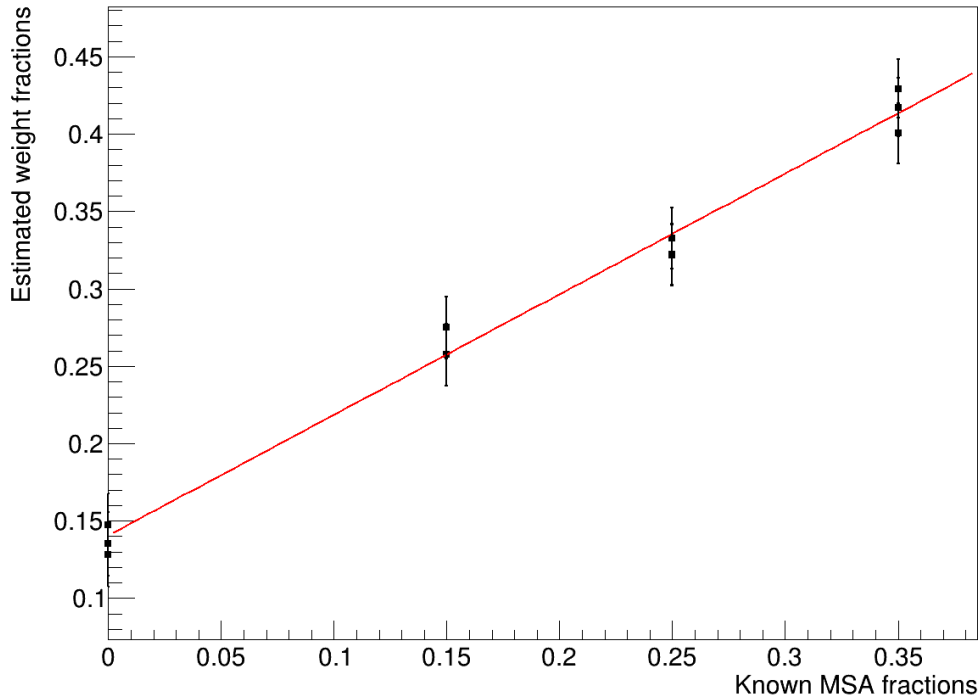


Paracetamol RootProf output





RootProf results – Paracetamol



Line parameters

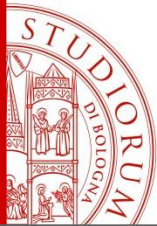
Slope	0.78
Intercept	0.14
R ²	0.987
RMSE	0.0001
C_{extrapolated}	15.2
Std dev. C_E	0.1
LoD	0.50

- *Expected Paracetamol content. 14.5 %_{w/w}*



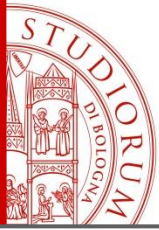
RootProf – NAS results

	Piracetam	Paracetamol
Expected value	2	14.5
RootProf SAM	2.1 ± 0.6	15.2 ± 0.1
RootProf Single Profile	2.7 ± 2	14 ± 1
NAS	1.7 ± 0.2	15 ± 2



Conclusions

- The multivariate standard addition method improved by RootProf procedure proved to be suitable for accurate quantification of one polymorph of Piracetam in a mixture and Paracetamol in Tachifludec[®].
- RootProf can be used for **rapid** quantification of crystal forms in solid mixtures by XRPD.



THANK YOU!

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