Variability in Dissolution Testing

Results from a Collaborative Study

Mainz, October 5, 2005

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Agenda

- Aim
- Study protocol & Test design
- Participation, Laboratory dissolution apparatus & Experience
- Profiles obtained
- Calibrator tablets
- Earlier study
- Typical variability
- Value of Dissolution technique

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Objectives

- FIP -study with quite high variability
- Understand the variability among the laboratories in one company
- Understand the variability for an immediate- release solid drug product
- Evaluate Intra- Laboratory variability
- Evaluate Inter- Laboratory variability
- Statistics

Study Protocol

- Control test, General control test, Result sheet, List of participants
- Different to routine testing
- Procedure to be repeated by a second analyst (same lab) on a different day using freshly prepared media
- Steps: Preparing media- Weighing tablets- Collecting data- Calculating - Calibrator tablets
- Samples and reference standard shipment

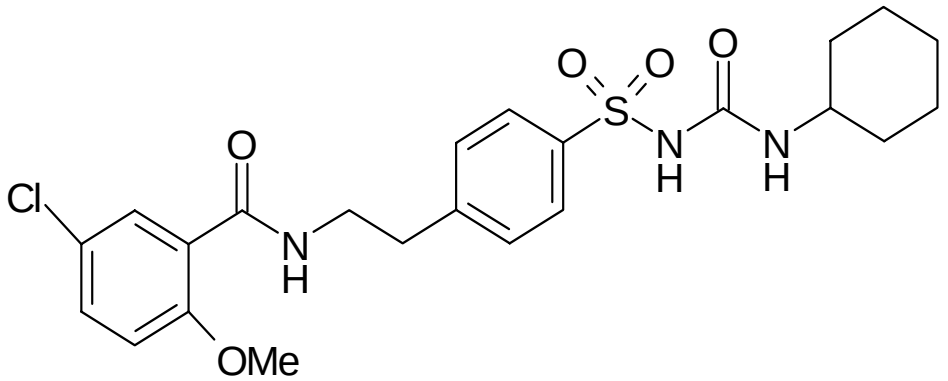
Control Test

- Immidiate Release Solid Form - 5 mg of Glibenclamide
- Paddle, Apparatus 2, USP
- Buffer, phosphate, pH 7.4 , 900 ml/vessel
- Media dearation: local approaches accepted
- Rotation speed: 75 rpm
- Test design: 10, 20, 30, 45, 60, 120 min
- Detector wavelength: 225 nm

Daonil™ (INN Glibenclamide)

Therapeutic Area:

Non-insulin-dependant (type II) diabetes mellitus, whenever blood sugar levels cannot be controlled adequately by diet, physical exercise, or weight reduction alone.



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Sample distribution

- Samples out End of May - analyses scheduled for Mid/End of June
- Routine production lot
- 20 Tablets sent out in the routine packaging material (PVC blister)
- Storage at room temperature ≤ 30°C
- Analytical Reference Standard – same lot valid sent out to all

Participation & Lab Experience

Worldwide 29 Laboratories reported data

Participants from 19 different countries

Operations (25) and R&D (4)

No experience over the last two years	11 Labs
Less experience < 100 analysis per year	14 Labs
Broad experience > 100 analyses per year	4 Labs

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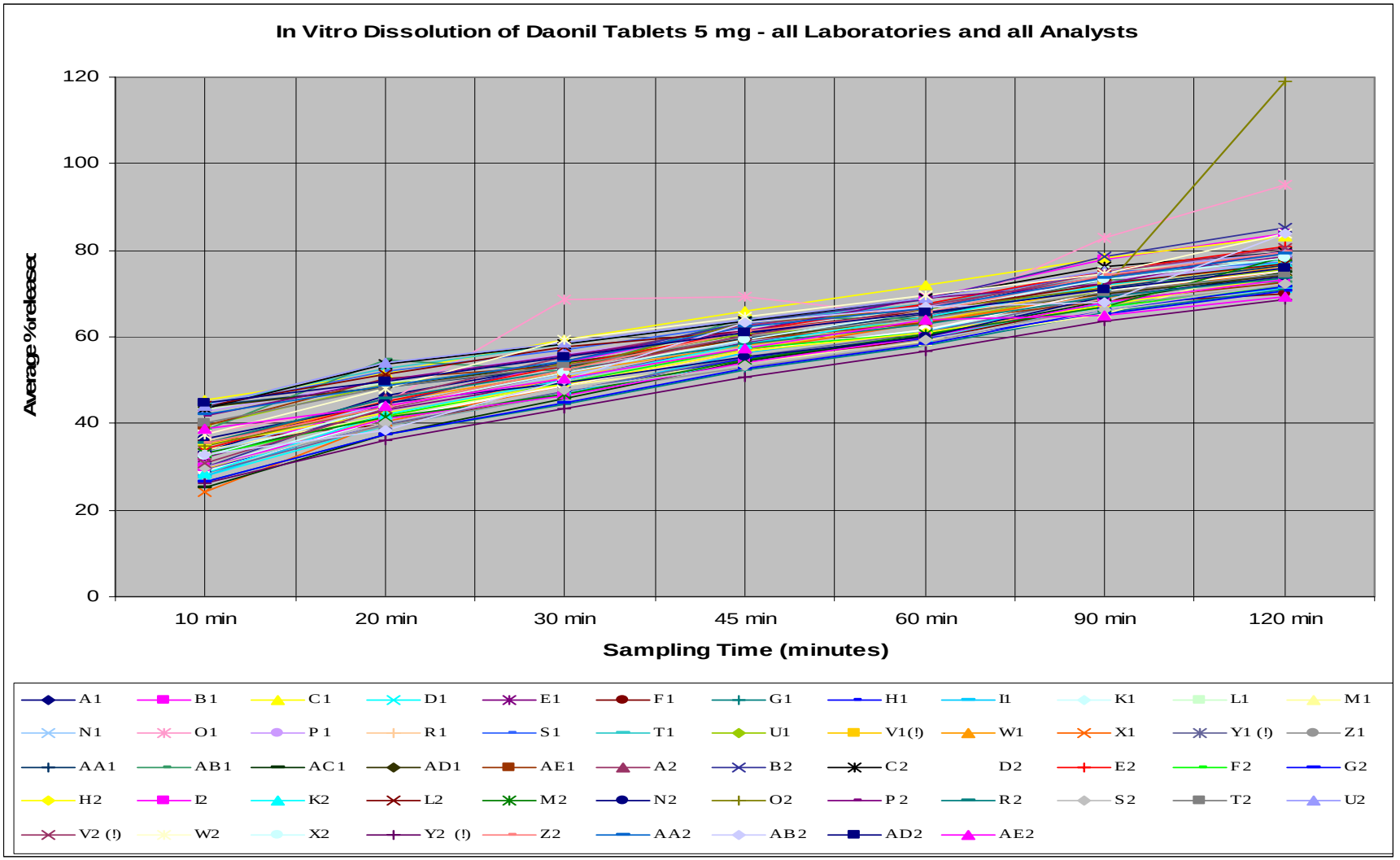
Laboratory Equipment

Brand name of Dissolution tester/ UV	Number of Laboratories
Sotax Dissolution Tester	8
Hanson	5
Distek	4
Toyama	2
Nippon Bunkou or Erweka	1
Other (ElektroLab!)	3
Hewlett Packard UV Detector	8
Perkin Elmer UV	7
Hitachi UV	4
Others, Uvikon, Beckmann	

Profiles Plot



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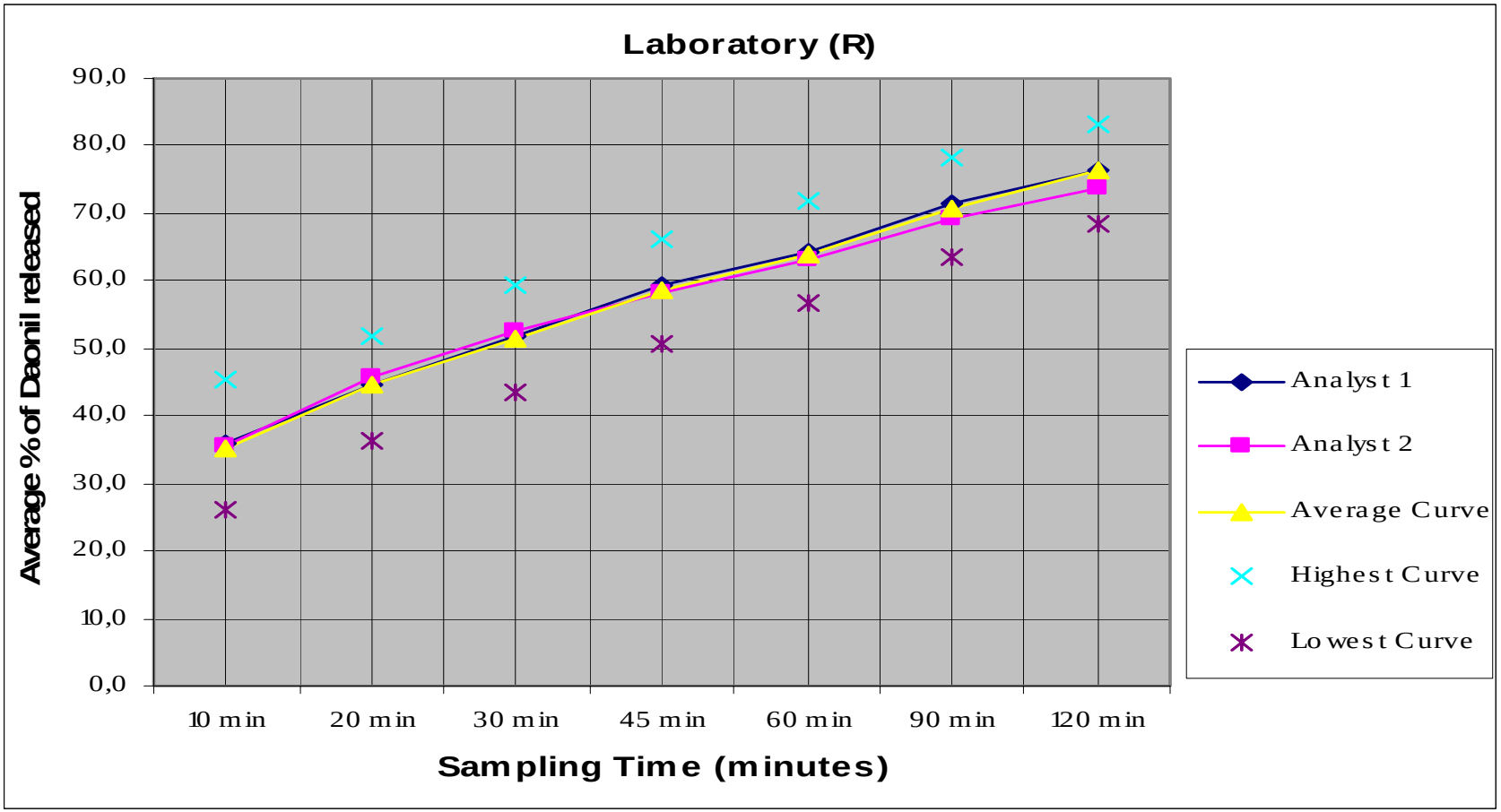
Dissolution Profile – perfect match



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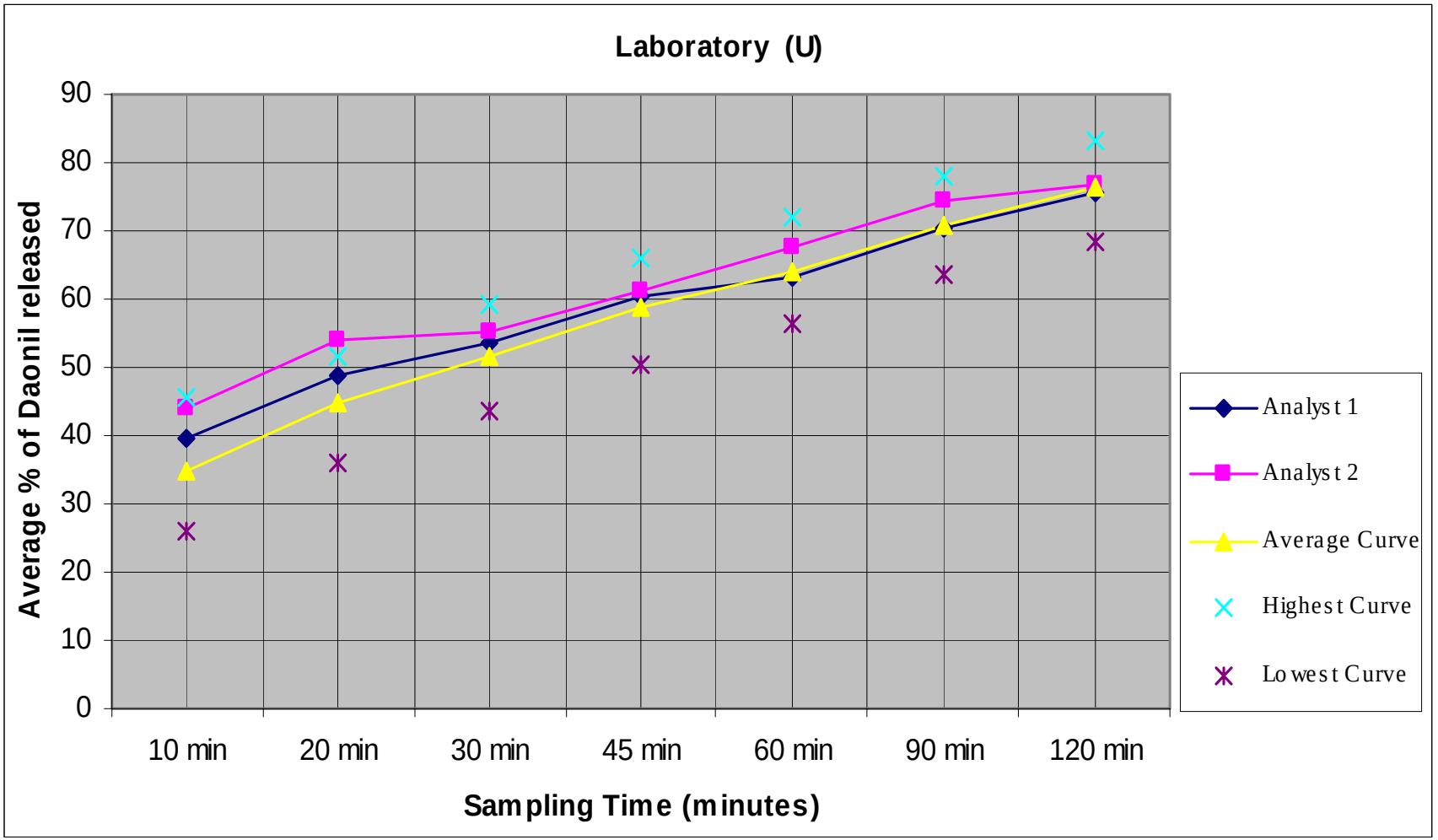
Dissolution Profile



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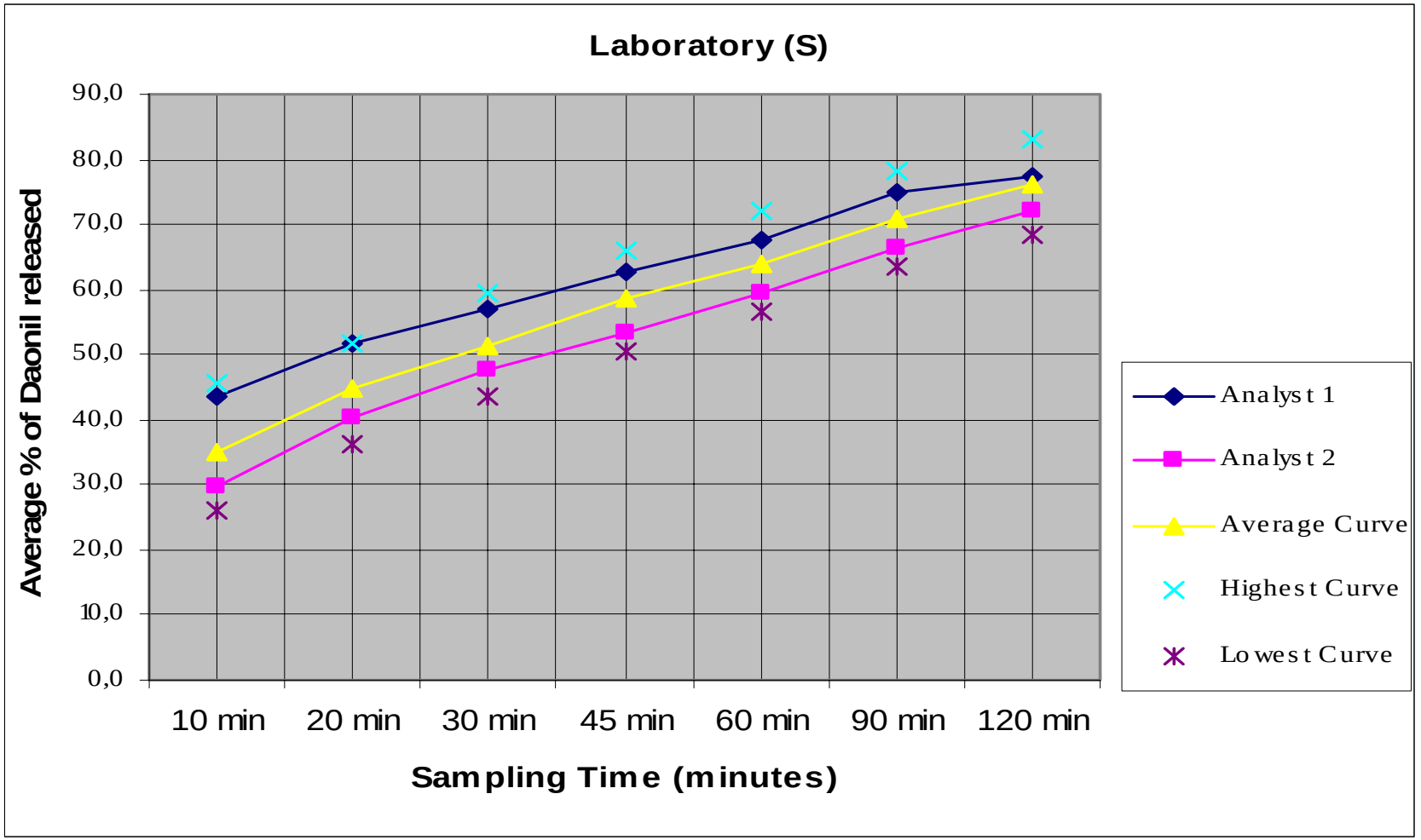
Dissolution Profile- difference A1- A2



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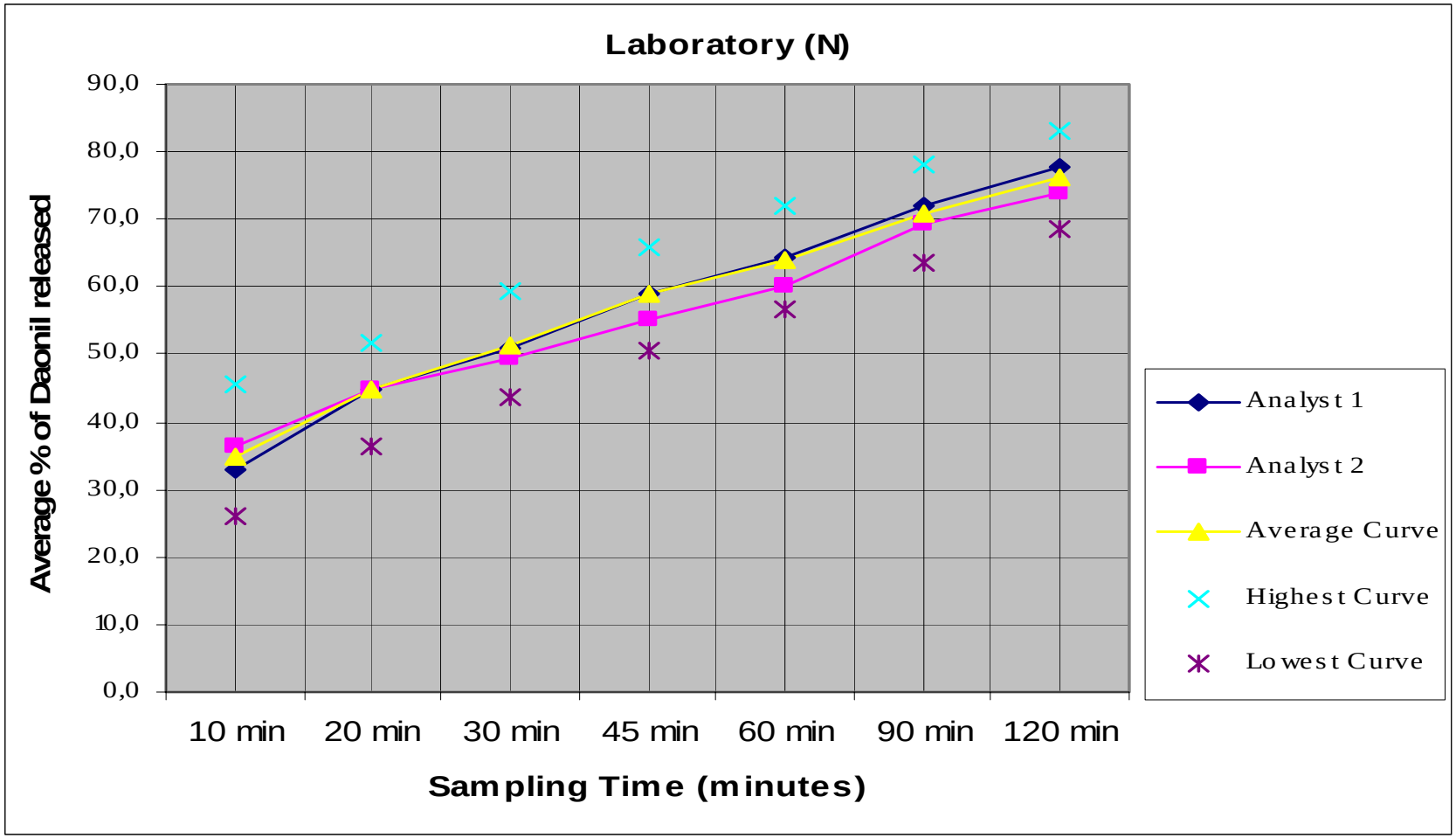
Dissolution Profile – ‚no brand‘- dissotester



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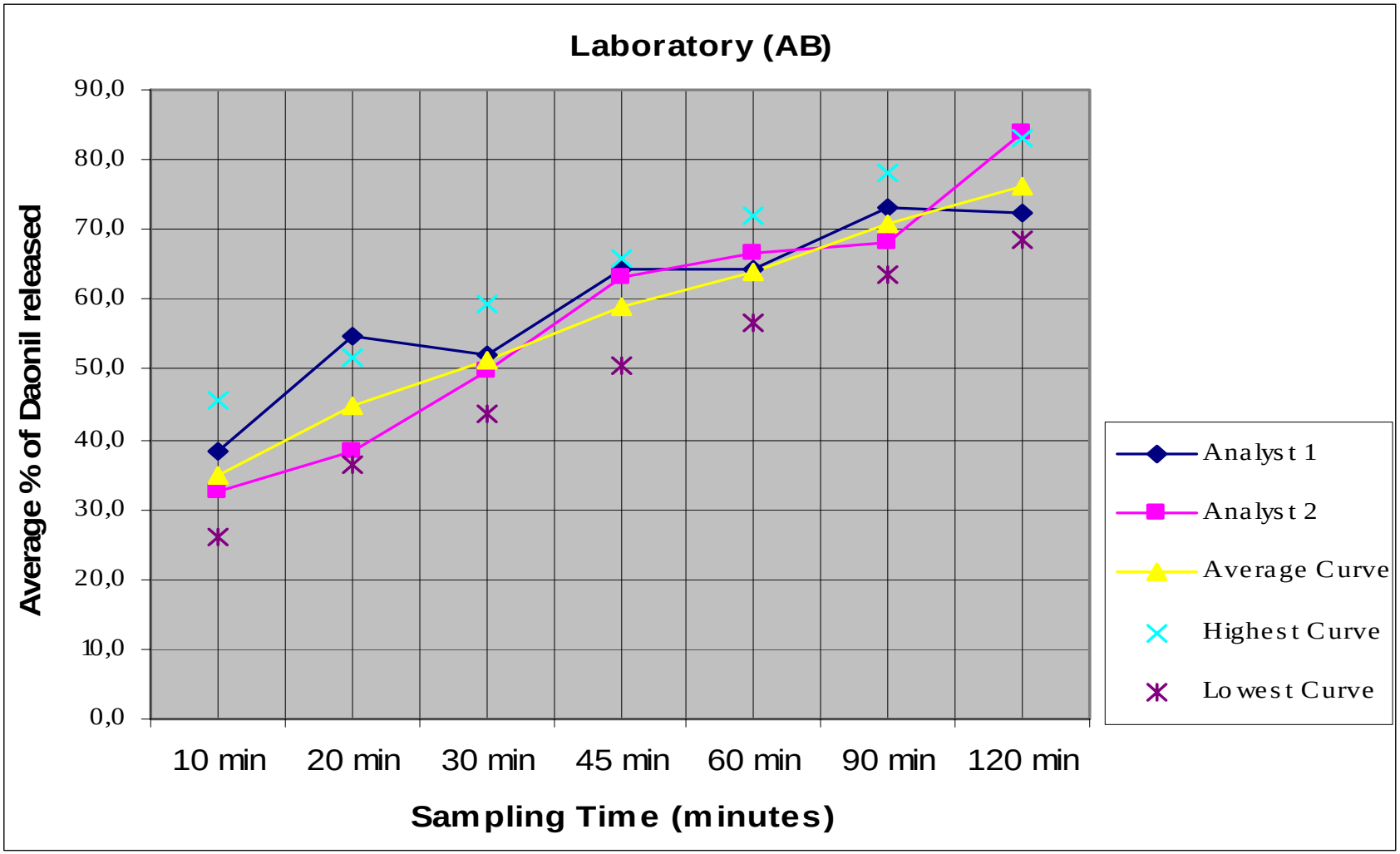
Profile - inconsistent



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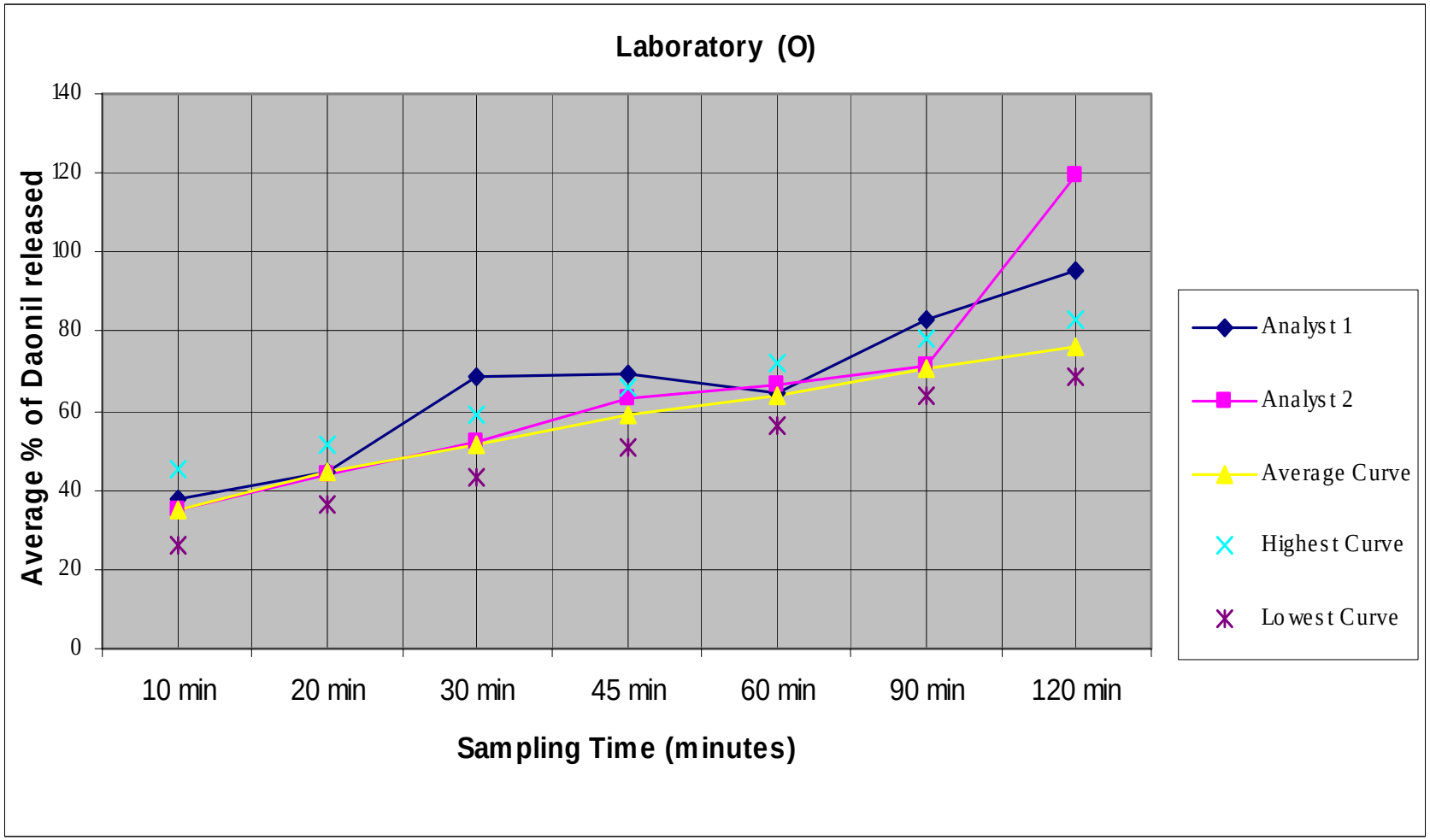
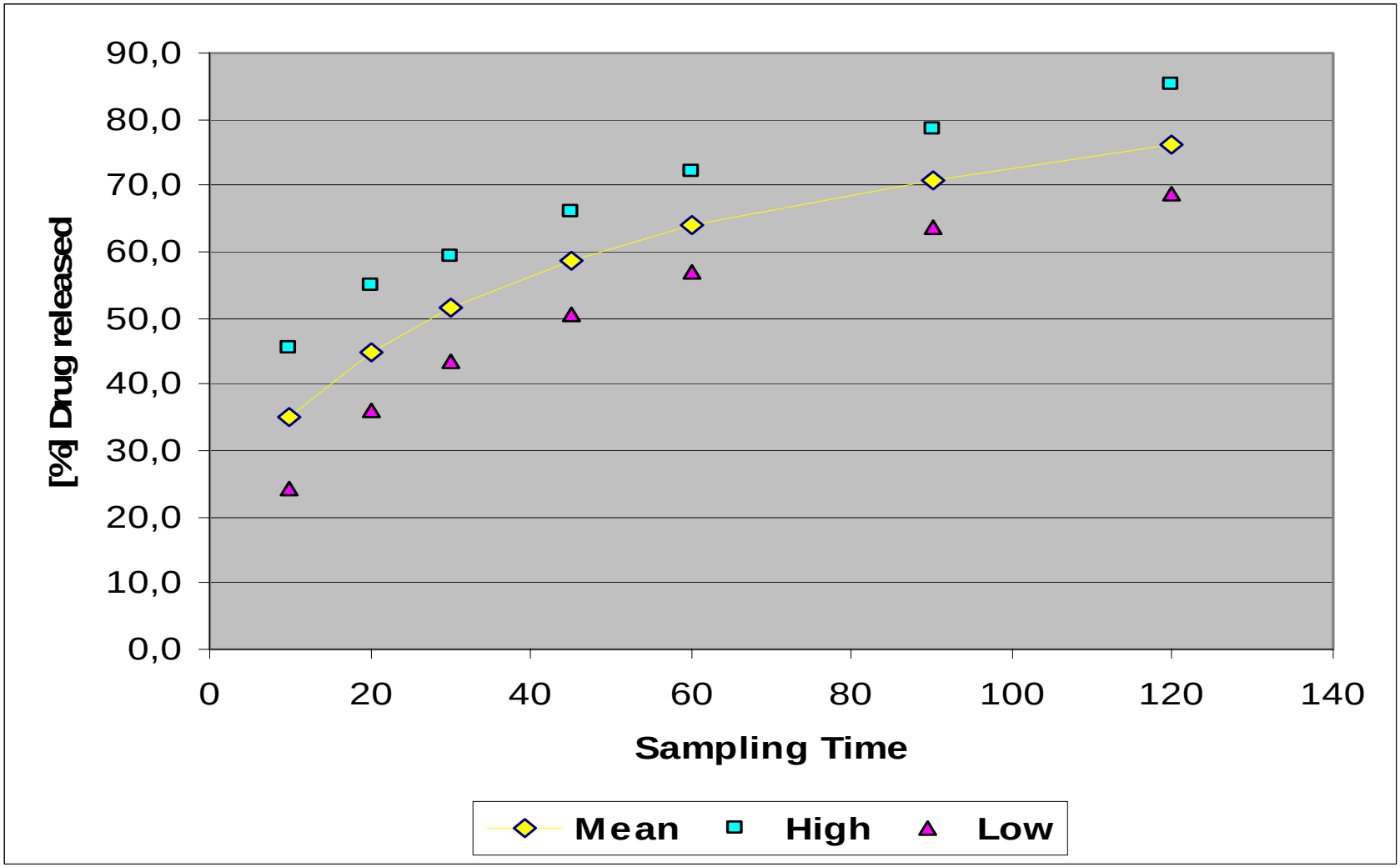
Profile – inconsistent



[%] Drug dissolved (n = 27)



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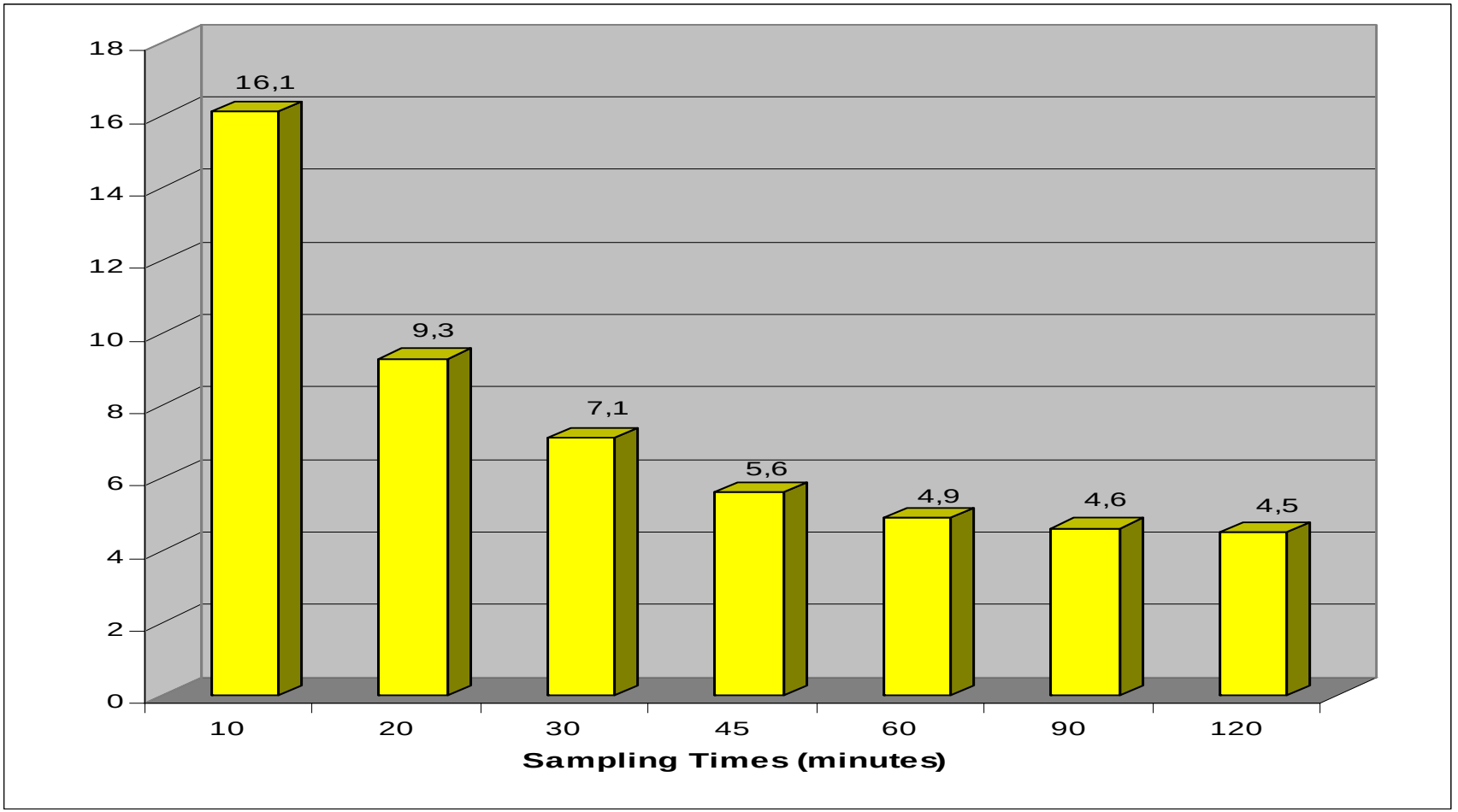
RSD [%] per sampling interval



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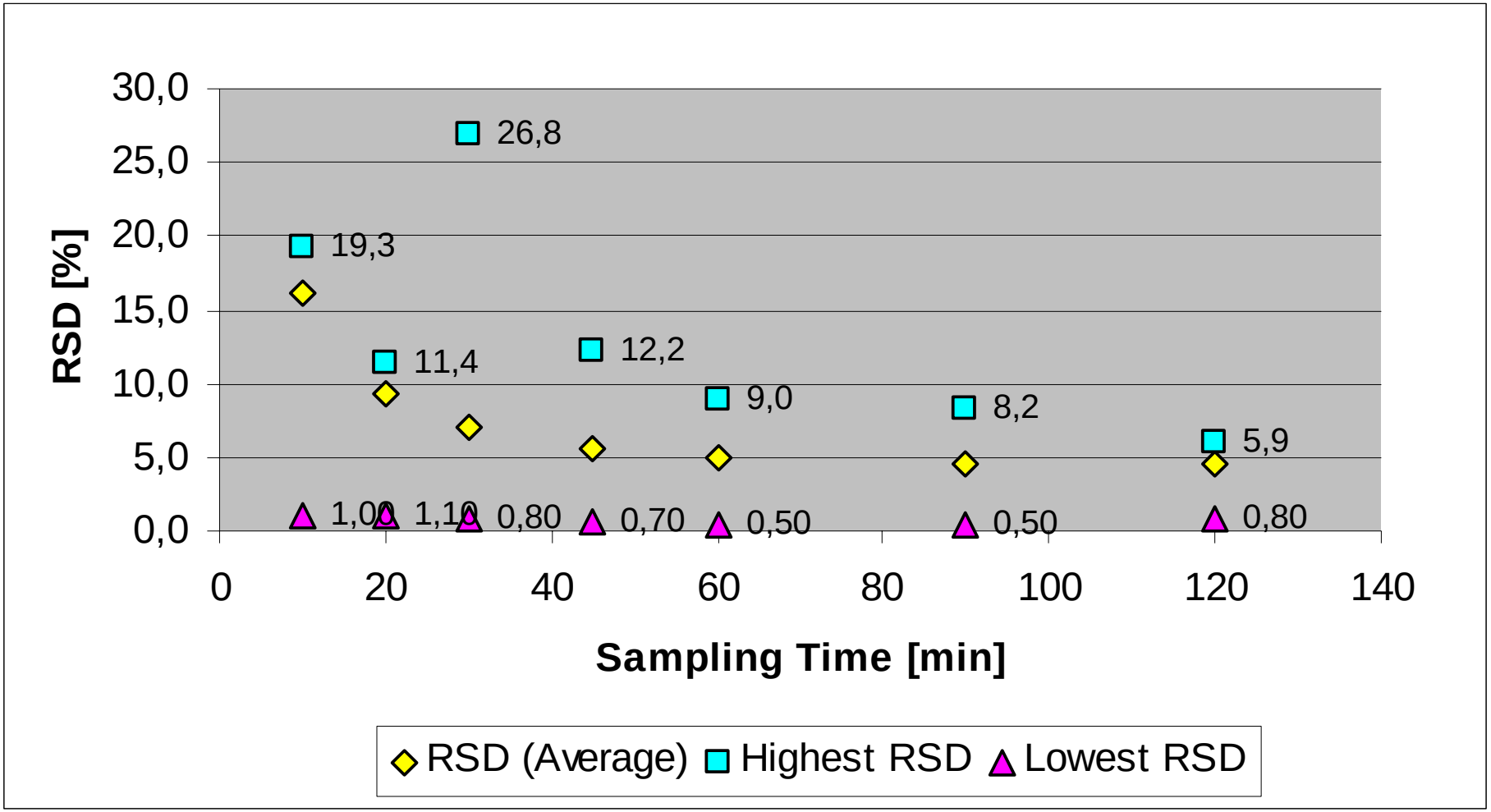
RSD per Sampling interval



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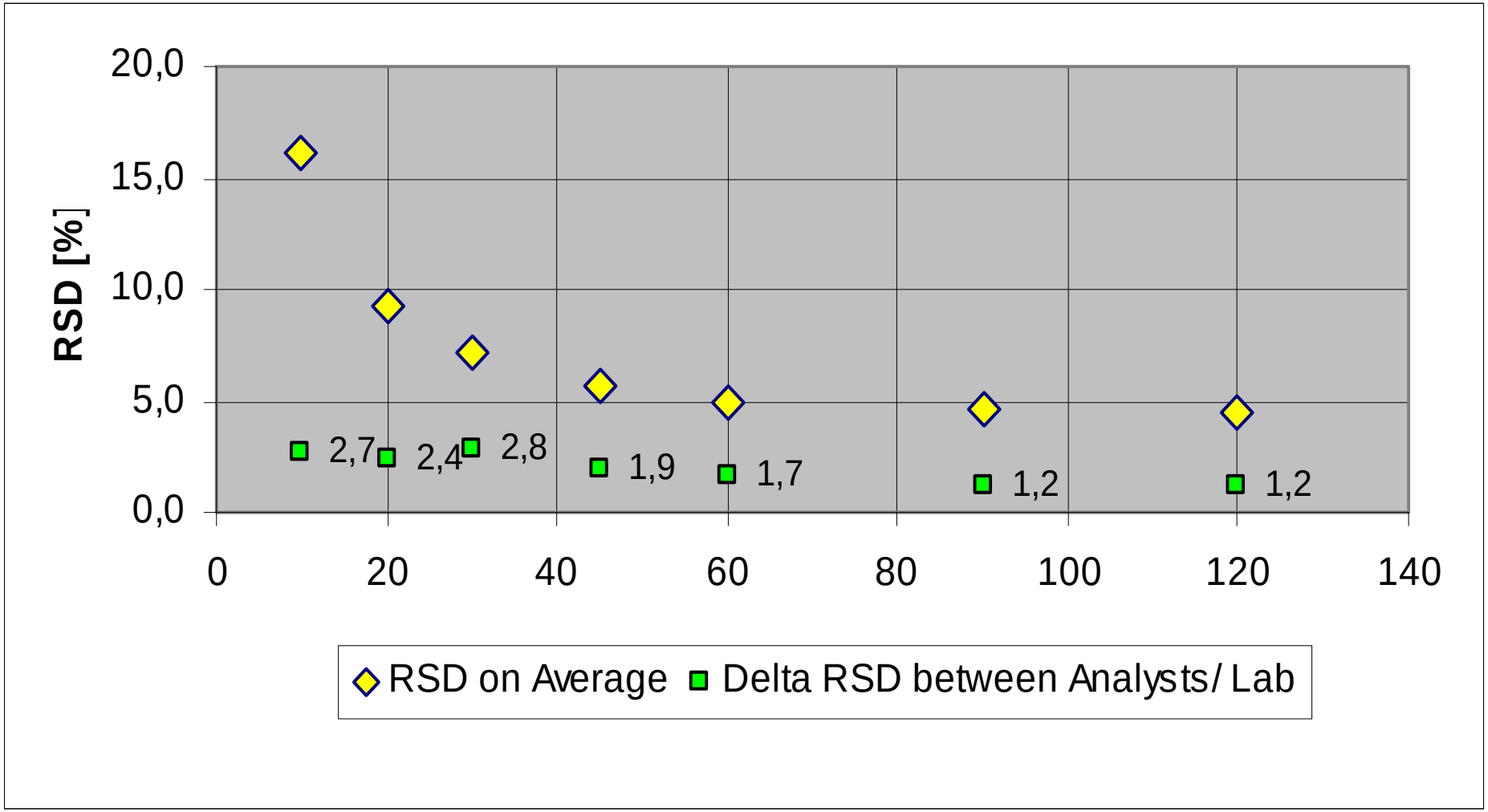
Difference (% RSD) between the two Analysts in one Lab



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First evaluation

29 Laboratories delivered their data

3 profiles considered inconsistent

Variability (RSD) among participating labs larger than inside one Lab

- Difference [%] drug dissolved inside one lab smaller than among the participants

Higher RSD observed at earlier dissolution time- points

No significant observation for labs with less experience

No significant observation for brand of dissotester

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Prednisone Calibrator - Lot L - Hanson

Lab	Prednisone [%] dissolved	Range	Spec	Diss Apparatus // 50 rpm
X	39.2	38.8-39.5	38-48	Hanson SR8
Y1	42.6	40.0-44.1	38-48	Hanson SR8
Z	43.2	43.0-43.3	38-48	Hanson SR8 plus
S	41.3	38.1-44.3	38-48	Hanson 1094-0306
AC	46.5	43.5-47.9	38-48	Hanson SR2
Mean	42.6			
s	2.4			
RSD%	5.6			

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Prednisone Calibrator - Lot L - Sotax

Lab	Prednisone [%] dissolved	Range	Spec	Diss Apparatus // 50 rpm
A	41.0	39 - 43	38-48	Sotax AT 7
B	44.0	43 - 46	38-48	Sotax AT 6
F	41.7	40.5 - 44.9	38-48	Sotax AT 7
P	40.1	39.4 - 41.1	38-48	Sotax AT 7
R	43.0	41 - 44	38-48	Sotax AT 7
AD	41.3	38 - 43	38-48	Sotax AT 7
AE	46.8	46.4 - 48.0	38-48	Sotax AT 7
Mean	42.6			
s	2.3			
RSD%	5.3			

Salicylic Acid Calibrator - Lot N - Hanson

Lab	Salicylic acid [%] dissolved	Range	Spec	Diss Apparatus // 100 rpm
X	19.0	18.2-20.0	17-26	Hanson SR8
Y1	22.0	19.1-23.6	17-26	Hanson SR8
Z	22.7	22.1-23.2	17-26	Hanson SR8 plus
S	20.4	19.3-22.7	17-26	Hanson 1094-0306
AC	19.3	18.3-21.0	17-26	Hanson SR2
Mean	20.7			
s	1.6			
RSD%	7.9			

Salicylic Acid Calibrator - Lot N - Sotax

Lab	Salicylic acid [%] dissolved	Range	Spec	Diss Apparatus // 100 rpm
A	20.0	19 -22	17-26	Sotax AT 7
F	24.9	22.3 -26	17-26	Sotax AT 7
R	19.0	18-20	17-26	Sotax AT 7
B	20.0	18 -23	17-26	Sotax AT 6
AB	20.9	20.2- 21.8	17-26	Sotax AT 6
AD	20.0	19 –21	17-26	Sotax AT 7
AE	24.5	21.9-25.6	17-26	Sotax AT 7
Mean	21.3			
s	2.4			
RSD%	11.1			

Calibrator tablets

Product	Time [min]	Mean [%] Drug released	Variability [%] RSD Min-Max	Variability [%] RSD Mean
Prednisone USP Tablets Lot L 50 mg (n=28)	30 min/ 50 rpm	42.6	5.2 – 6.0	5.7
Salicylic Acid USP Tablets Lot N 300 mg (n=21)	30 min / 100 rpm	21.3	8.6 –10.8	9.9
Glibenclamide (Aventis) Tablets Lot U740 5 mg (n = 55)	30 min/ 75 rpm	51.5	0.8 - 26.8	7.1
	45 min/ 75 rpm	58.8	0.7 – 12.2	5.6
Tablet mass (n= 55) 158.99 mg				RSD 0.8 %

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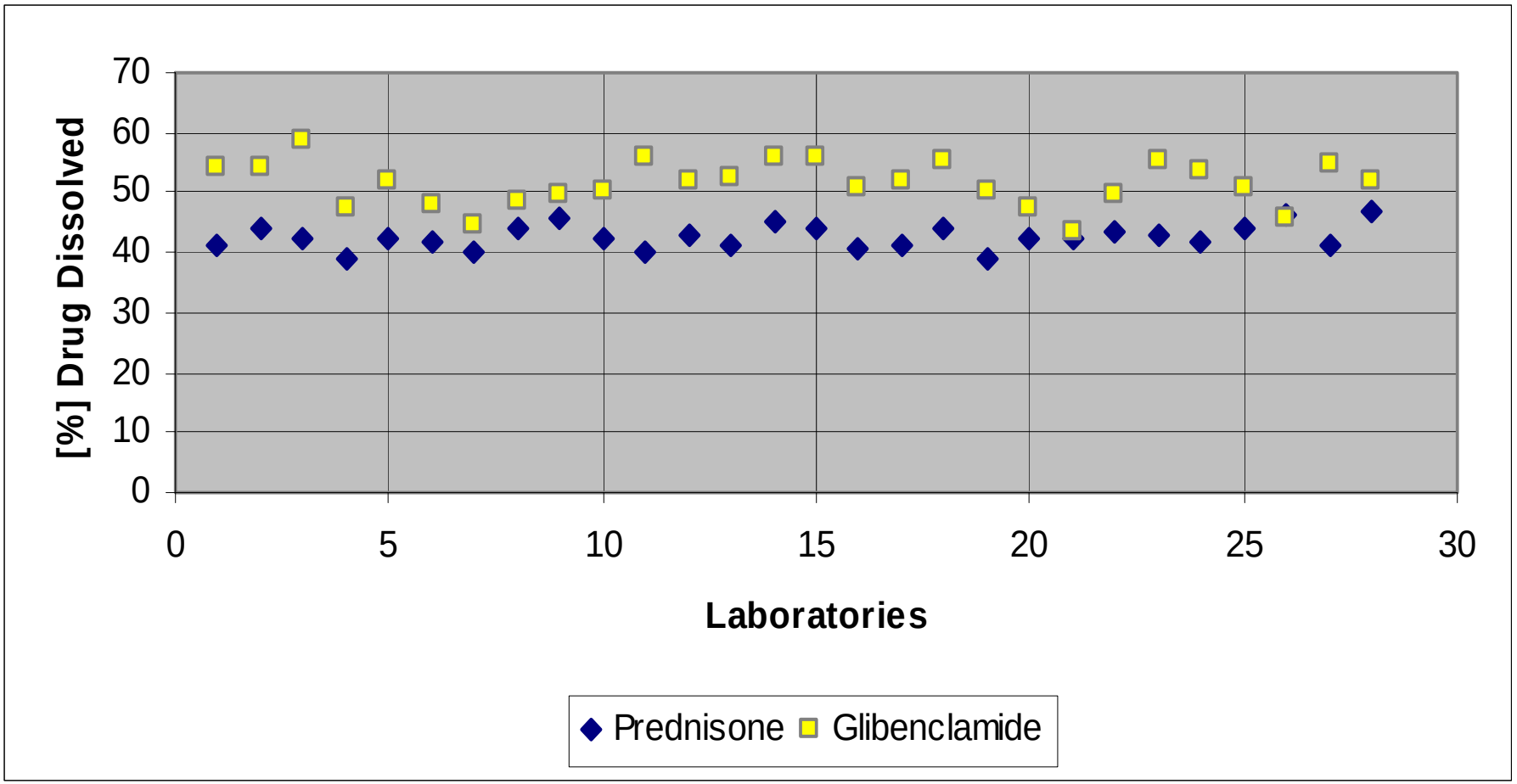
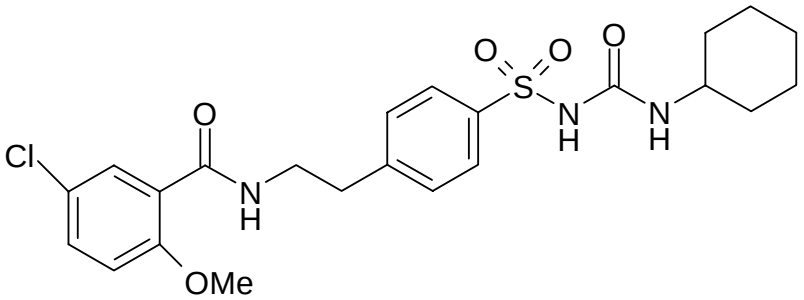
[%] Dissolved - Glibenclamide vs Prednisone

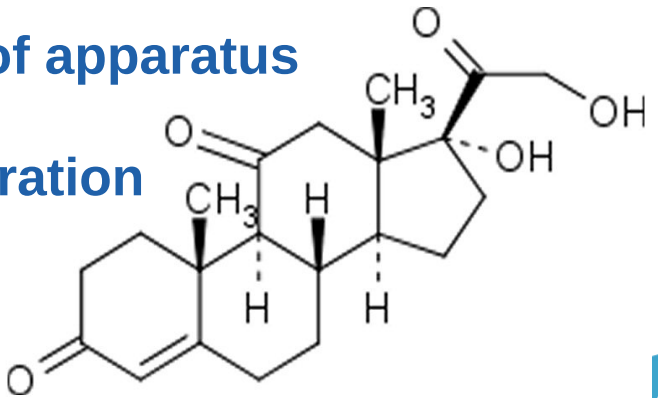


Glibenclamide vs Prednisone Tablets



Glibenclamide

- **Release profile from Glibenclamide tablets similar to Prednisone**
  - **after 30 minutes 52 % released (up to 9 % higher on average)**
- **Time interval before 30 minutes not advisable (disintegration effects)**
- **Variability is similar, RSD for both is close to 6 %**
- **No significant observation made for brand of apparatus**
- **Glibenclamide could serve for internal calibration**



Prednisone

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Earlier Study

Performed by Qureshi/McGilveray, Health Protection Branch, Canada, under the auspices of the FIP (1997)

RSD observed, n = 30 Labs - up to 30 % (37 % for paddle)

Conclusions drawn

- **20 – 40 % of variability arises from dissolution technique itself ?**
- **Lack of discriminating ability ?**
- **In vitro-dissolution technique questionable in itself ?**
- **Changes in manufacturing or formulation not predictable ?**

Comparison to FIP study

Time-point [min]	Aventis Study Average percent Gliben-clamide Dissolved Paddle 75 rpm	Earlier FIP Study Average percent Glibenclamide Dissolved Basket 50 rpm	RSD (%)* Aventis Glibenclamide Study	RSD (%) Earlier FIP Study
10	**34.85**	**39.7**	**18.96**	**29.93**
20	**44.62**	**50.2**	**11.31**	**20.64**
30	**51.43**	**59.2**	**9.09**	**19.72**
60	**63.88**	**72.6**	**6.49**	**16.89**
90	**70.82**	**80.8**	**5.94**	**15.64**
120	**76.18**	**85.8**	**5.78**	**13.70**

* calculated from variance component analysis

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Statistics

ANOVA variance component analysis

Within analysts - Between analysts - Between laboratories

s^2 total = s^2wA + s^2bA + s^2bL

Basis 95 % CI (interval of confidence)

- **Inconsistencies identified and eliminated**

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Variances observed

Interval [min]	[%] Drug Dissolved	Source	df	Variance s^2	RSD [%]
10		Between Labs	26	31,20	
		Between Analyst	27	7,09	
		Within Analyst	269	5,23	
	34,85	Total	322	43,52	18,96
20		Between Labs	26	15,66	
		Between Analyst	27	4,86	
		Within Analyst	269	4,96	
	44,62	Total	322	25,48	11,31
30		Between Labs	26	10,99	
		Between Analyst	27	5,27	
		Within Analyst	270	5,60	
	51,43	Total	323	21,86	9,09
60		Between Labs	26	7,06	
		Between Analyst	27	4,88	
		Within Analyst	270	5,25	
	63,88	Total	323	17,19	6,49
90		Between Labs	26	7,50	
		Between Analyst	27	5,26	
		Within Analyst	270	4,95	
	70,82	Total	323	17,71	5,94
120		Between Labs	26	8,56	
		Between Analyst	27	5,22	
		Within Analyst	270	5,59	
	76,18	Total	323	19,37	5,78

Discernable difference

Detectable difference = Standard error of the mean difference x 1.645

- **Smallest detectable difference is 6 to 7 dissolution percentage points**
  - One analyst per laboratory (total of 2 laboratories)

- **4 to 5 percentage points (two analysts at each of the two laboratories)**

Rel. Standard Deviations (RSD) observed in analytical testing

Analysis from a solution (approx.)

- Titration, potentiometric < 0.5 %
- Titration, visual 0.5 %
- UV/ VIS 1.0 %
- HPLC 1.5 %

Analysis from a solid form (approx.)

- type Immediate release

  UV/VIS (~ sampling time) > 6 - 9 %

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Conclusion

Dissolution technique is quite robust

- No evidence found for variability up to 30 % (RSD) or more
- Labs with less or no experience deliver similar curves
- Labs having non- brandname equipment deliver similar curves
- Multiple point testing is as easy as single point measuring

Between laboratories variability contributes most

Higher RSD at earlier dissolution time- points (10, 20, 30)

Comparison of profiles/ Select small number of laboratories

Drivers for Performance

Study design

Labs having some common understanding of

- Dissolution technique in general
- Labs doing physical calibration of dissotesters
- Labs using USP calibrator tablets
- Labs having training programs in place

Reference Standards/Samples handling

Dissolution Technique is measuring Performance

Consistency of batches

Homogeneity of dosage forms

Impact of changes in formulation

ACKNOWLEDGEMENTS

- Laboratories participating
- Dr. Martin Siewert and FIP Dissolution Working Group
- Dr. Catherine Judkins
- Dr. David Whiteman

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