

“Dissolution – Moving Beyond Quality Control”

January 26, 2006

Philadelphia, PA

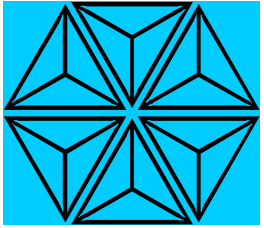


Evaluation of Rohm and Haas’ Novel In-Vitro Testing Technology for Dissolution

Ruben Lozano¹, Lyn Hughes², Pankaj A. Shah¹, Douglas Both¹

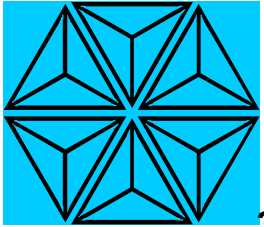
¹ Bristol-Myers Squibb Pharmaceutical Research Institute; New Brunswick, NJ

² Rohm and Haas Research Laboratories; Spring House, PA

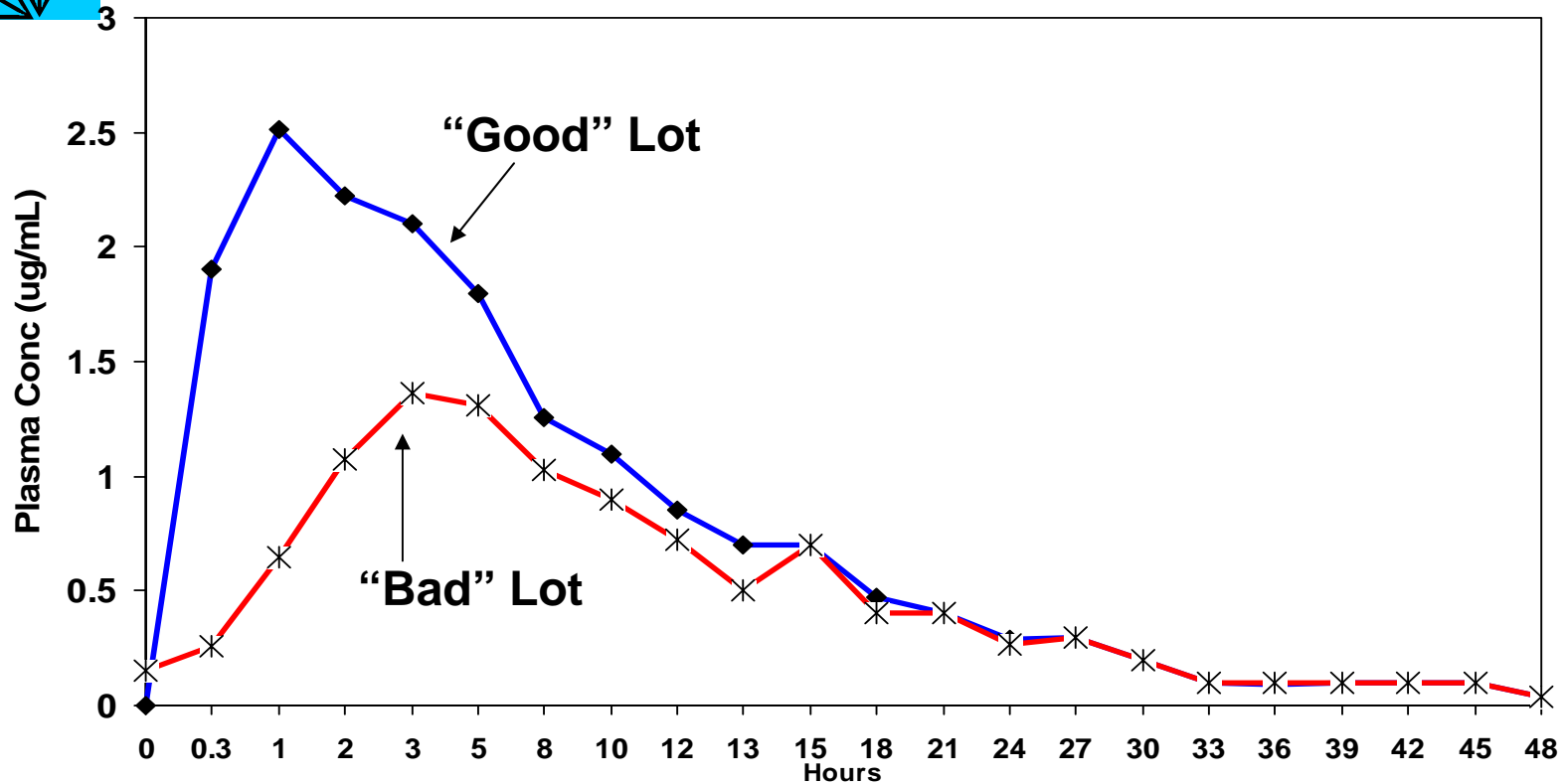


Evaluation Samples

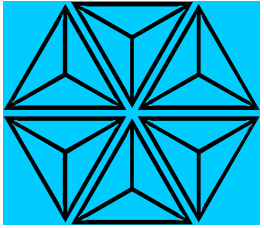
- **“A”:** Tablets Made with BCS ‘Class 1’ Drug
 - Evaluate:
 - Repeatability of analyses
 - Ability to distinguish between bio-inequivalent tablet lots
 - Effect of analyzing whole tablet vs. “partial” tablet ($\frac{1}{2}$ or $\frac{1}{4}$)
- **“B”:** Tablets Made with BCS ‘Class 2’ Drug
 - Evaluate ability to demonstrate “pH effect” of gastric media on dissolution
- **“C”:** Formulations Made with BCS “Class 4” Drug
 - Compare: tablet, tablet w/ tartaric acid, semisolid capsule



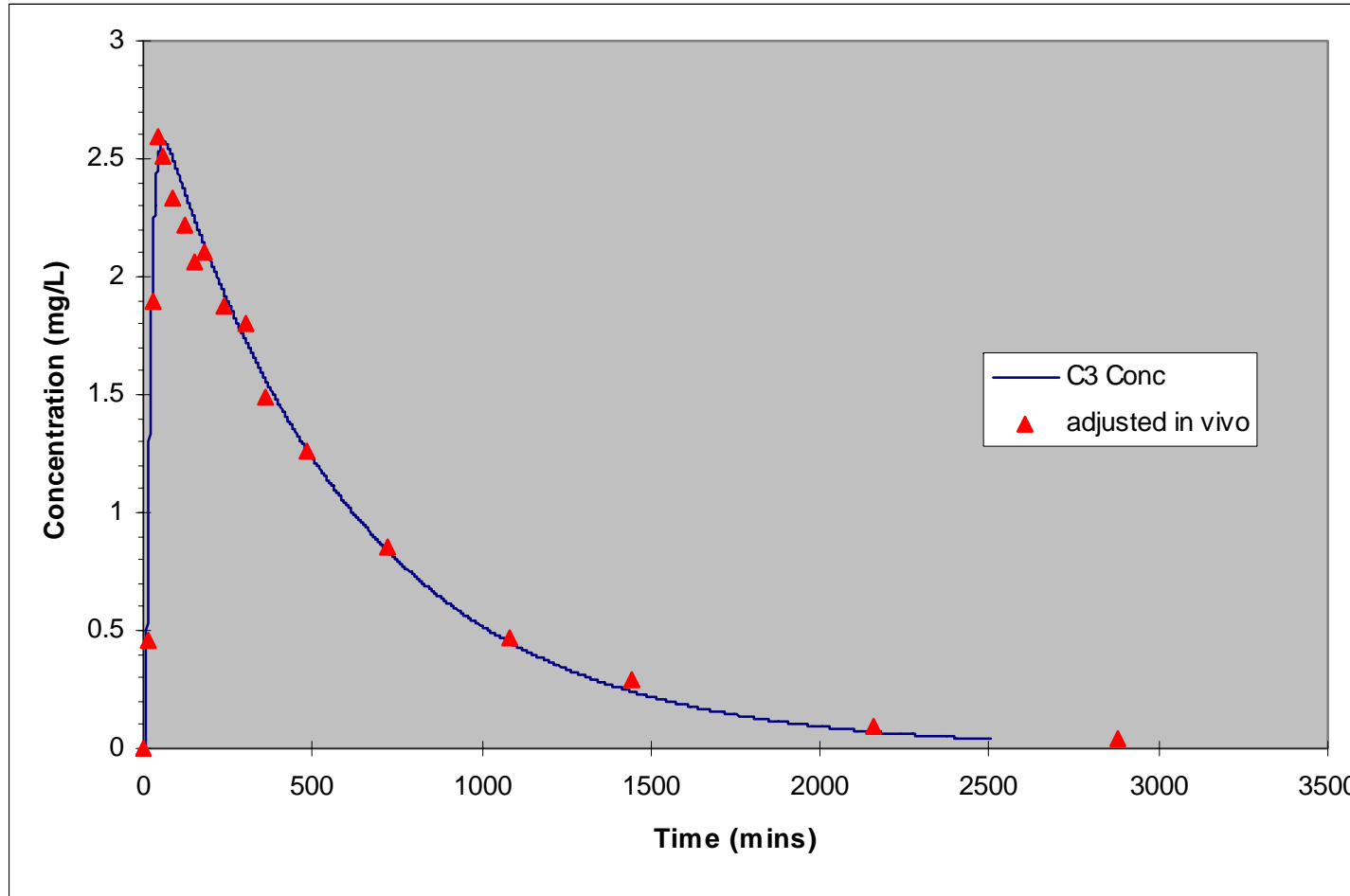
PK Plot for Sample "A" 400-mg Tablets (BCS Class 1)



Extrapolation	t_{\max} (minutes)	C_{\max} (ug/L)
'Good' Lot	53	3.37
'Bad' Lot	180	1.72

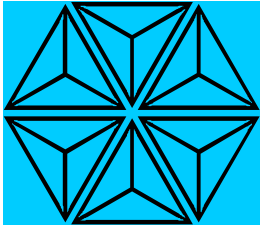


Sample "A" Tablets: In-Vitro Test System Algorithm



Estimated Cell Residence Times:

- Cell 1: 12 min
- Cell 2: 7 min
- Cell 3: 580 min



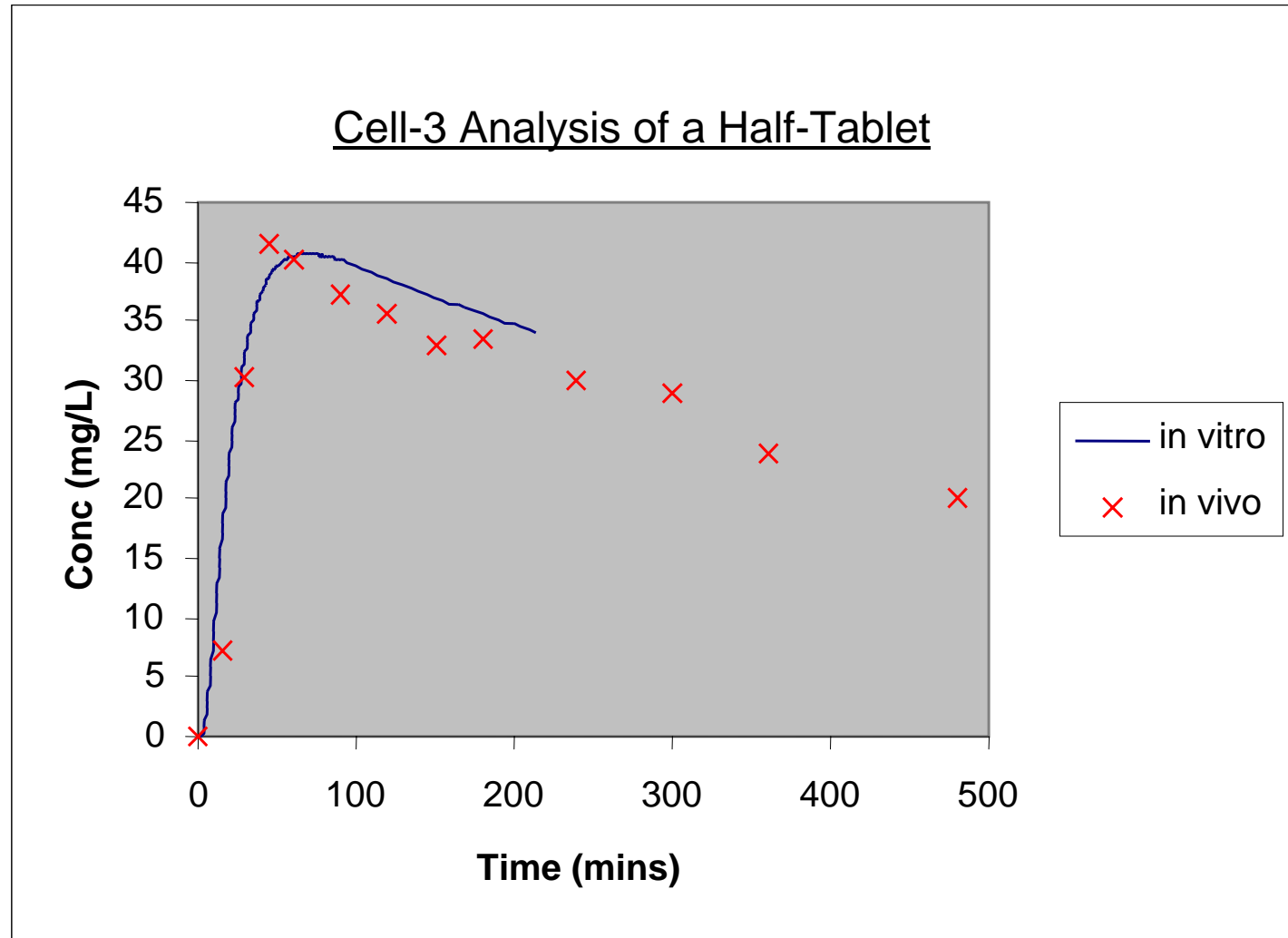
Sample "A" Tablets - In-Vitro Test System: First Evaluation Run

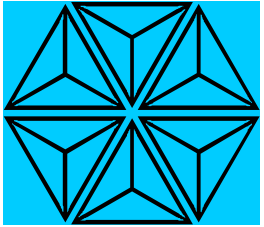
Media:

- Cell 1: SGF
- Cell 2: SIF
- (no enzymes)

Cell Residence Times:

- Cell 1: 12 min
- Cell 2: 8.2 min
- Cell 3: 580 min

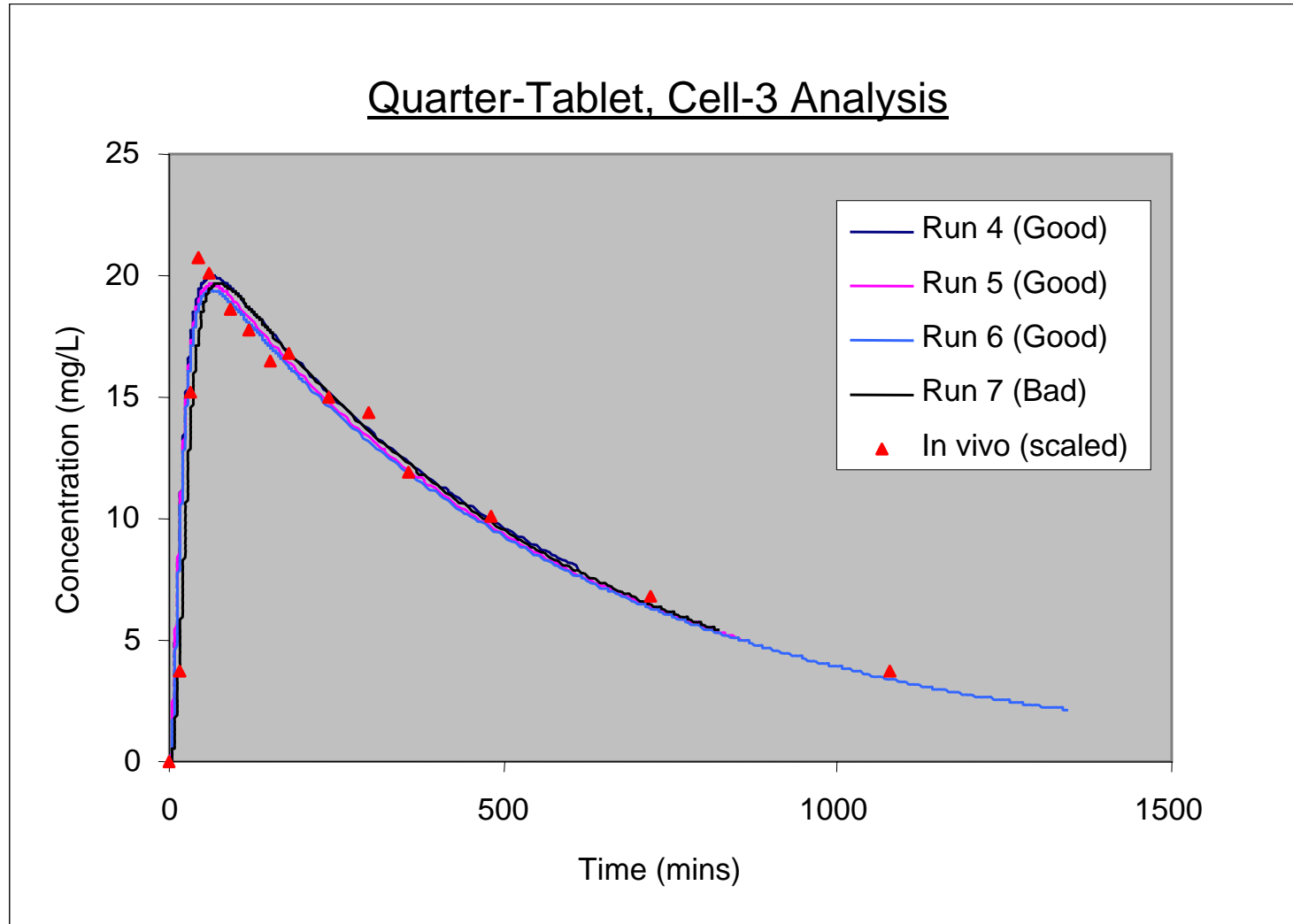


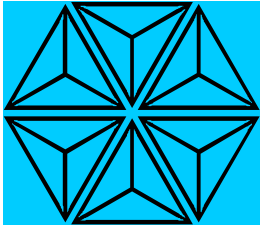


Sample "A" Tablets - In-Vitro Test System: Analysis After Parameter Optimization

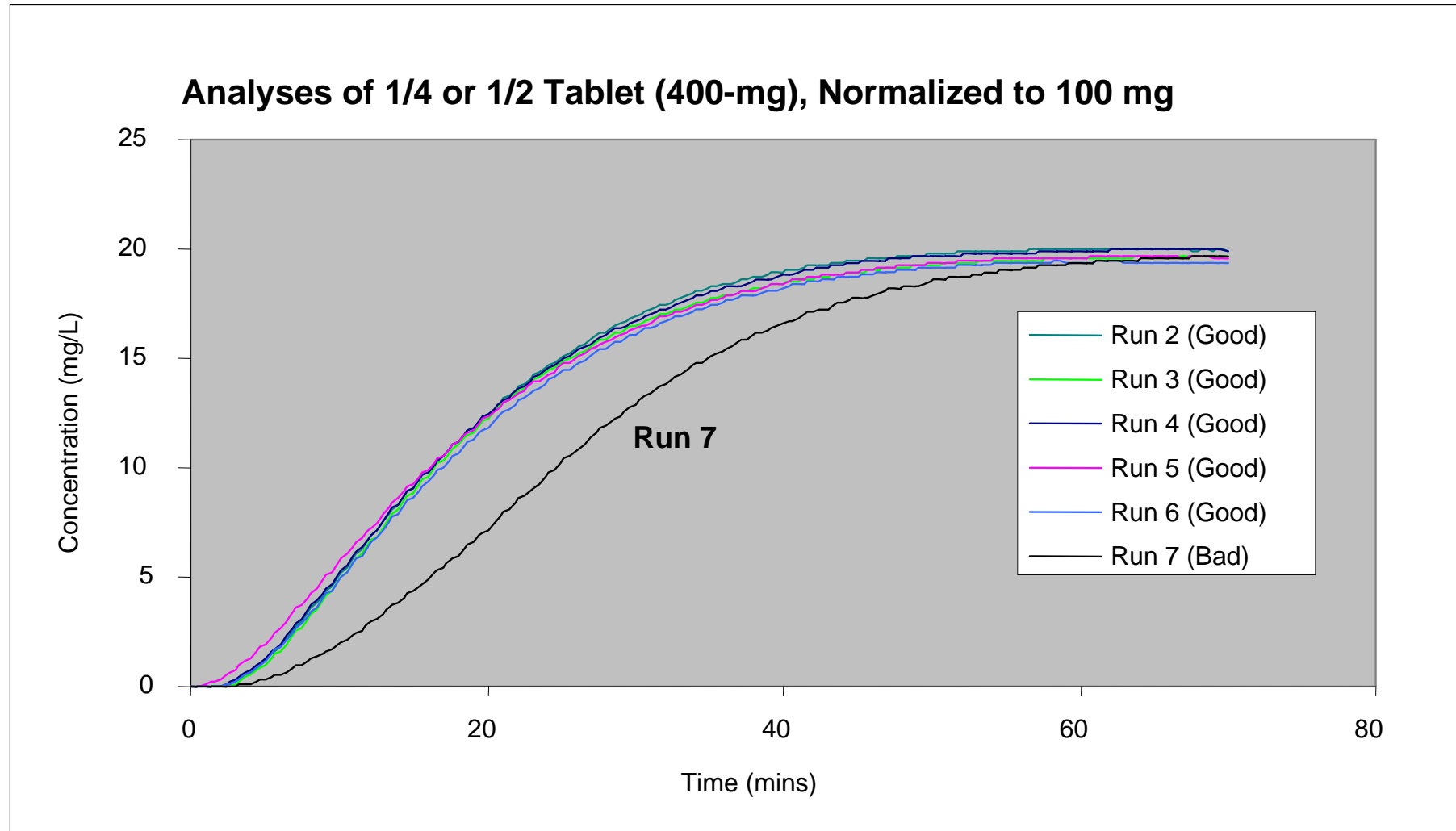
Cell Residence Times

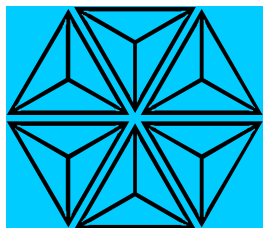
- Cell 1: 12 min
- Cell 2: 5.8 min
- Cell 3: 580 min





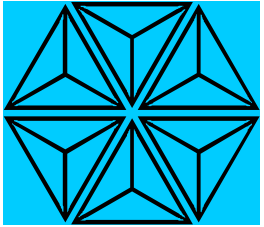
Sample “A” Tablets - In-Vitro Test System: Expansion of Analysis from 0 – 70 Minutes



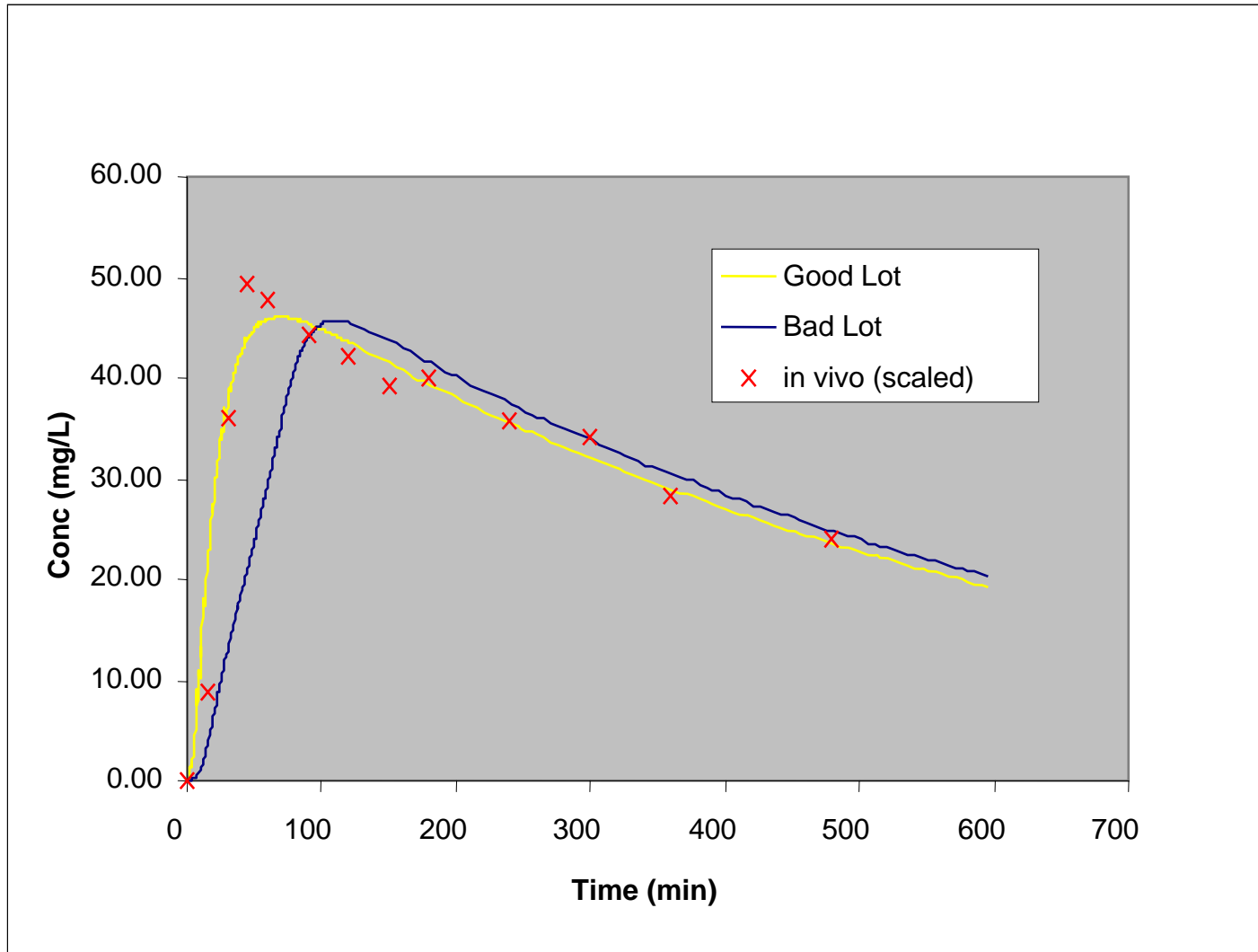


Sample “A” Tablets - In-Vitro Test System: Analysis of 0 - 70 Minute Interval

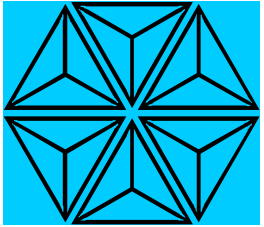
Run #	Tablet Type	t_{\max} (min)	C_{\max} (mg/L)	Conc. at 20 min (mg/L, normalized)
2	1/2 “Good”	----	----	12.4
3	1/2 “Good”	----	----	12.3
4	1/4 “Good”	65.5	20.0	12.4
5	1/4 “Good”	64.5	19.7	12.3
6	1/4 “Good”	62.0	19.4	11.8
7	1/4 “Bad”	73.5	19.7	7.1



Sample "A" Tablets – In-Vitro Test System: Analysis of Whole Tablet



	t_{max}	C_{max}
Good Lot	70	46.1
Bad Lot	109	45.6



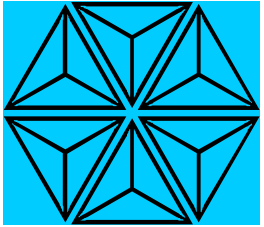
Testing of Sample “B” Tablets (BCS Class 2)

- Two forms of Sample “B” tablets:
 - Free base
 - Hydrochloride salt
- pKa: ~3.1
- Gastric pH/food effect:
 - Free base: No effect of food or famotidine on PK
 - HCl salt: pH effect on PK

Sample “B” Tablets – HCl salt

Effect of High-Fat Meal (“Fed”)				
Dose (mg)	C _{max} (ng/mL)		t _{max} (hr)	
	(-)	(+)	(-)	(+)
30	198	207	2	3
100	525	508	1.5	2.5
400	1489	985	1.0	3.5

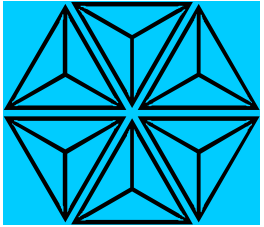
Effect of Famotidine				
Dose (mg)	C _{max} (ng/mL)		t _{max} (hr)	
	(-)	(+)	(-)	(+)
50	356	57	1.5	0.75



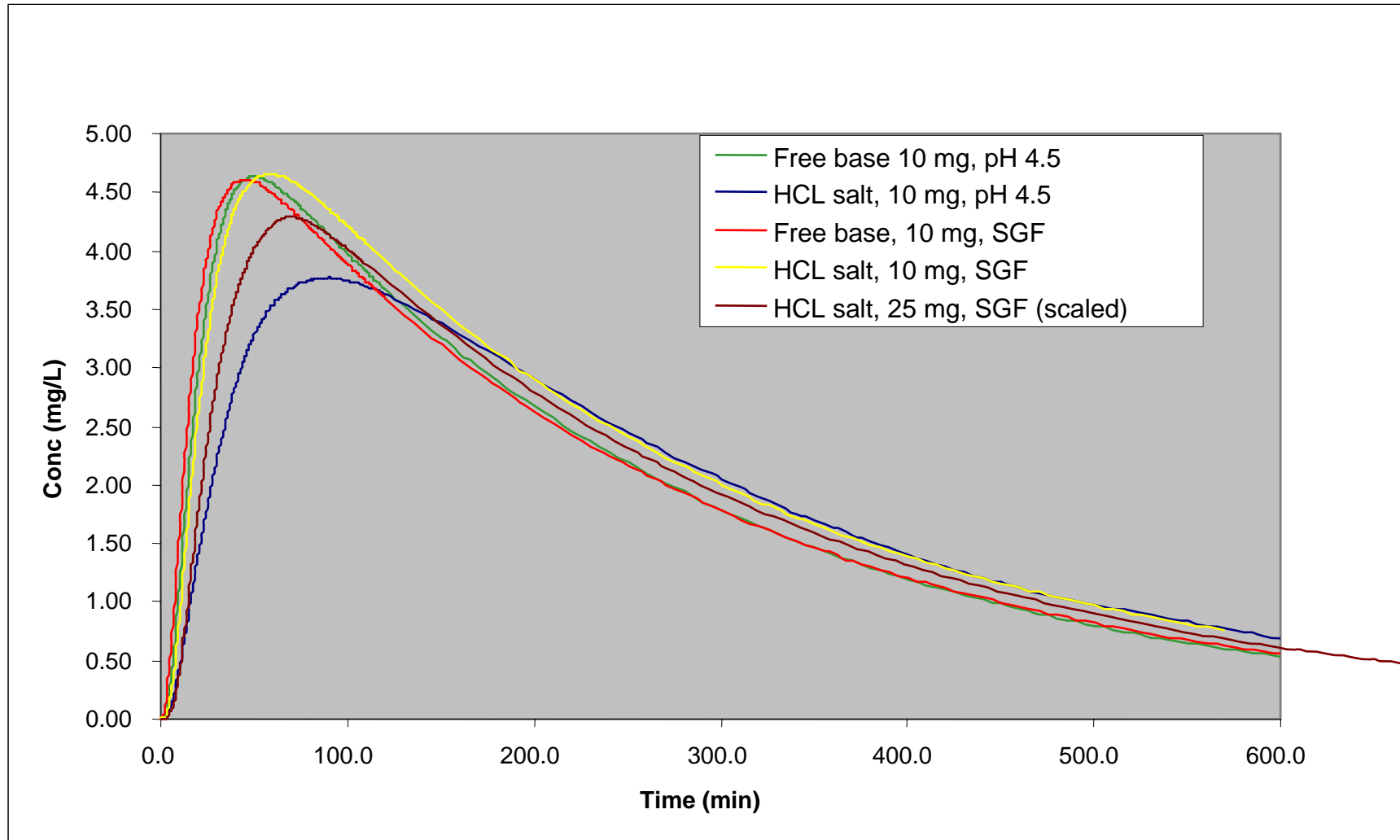
Testing of Sample “B” Tablets

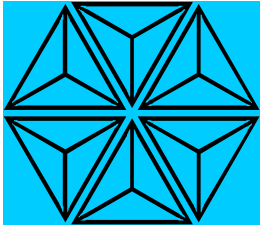
- Each tablet form (free base and HCl salt) was tested in-vitro in 2 different “gastric” (Cell 1) media:

	Cell-1 Medium	Cell-2 Medium
“Fasted” State	USP SGF + 0.5% SLS	USP SIF (sodium phosphate, no enzyme)
“Fed” State	Acetate buffer (pH 4.5) + 0.5% SLS	USP SIF (sodium phosphate, no enzyme)

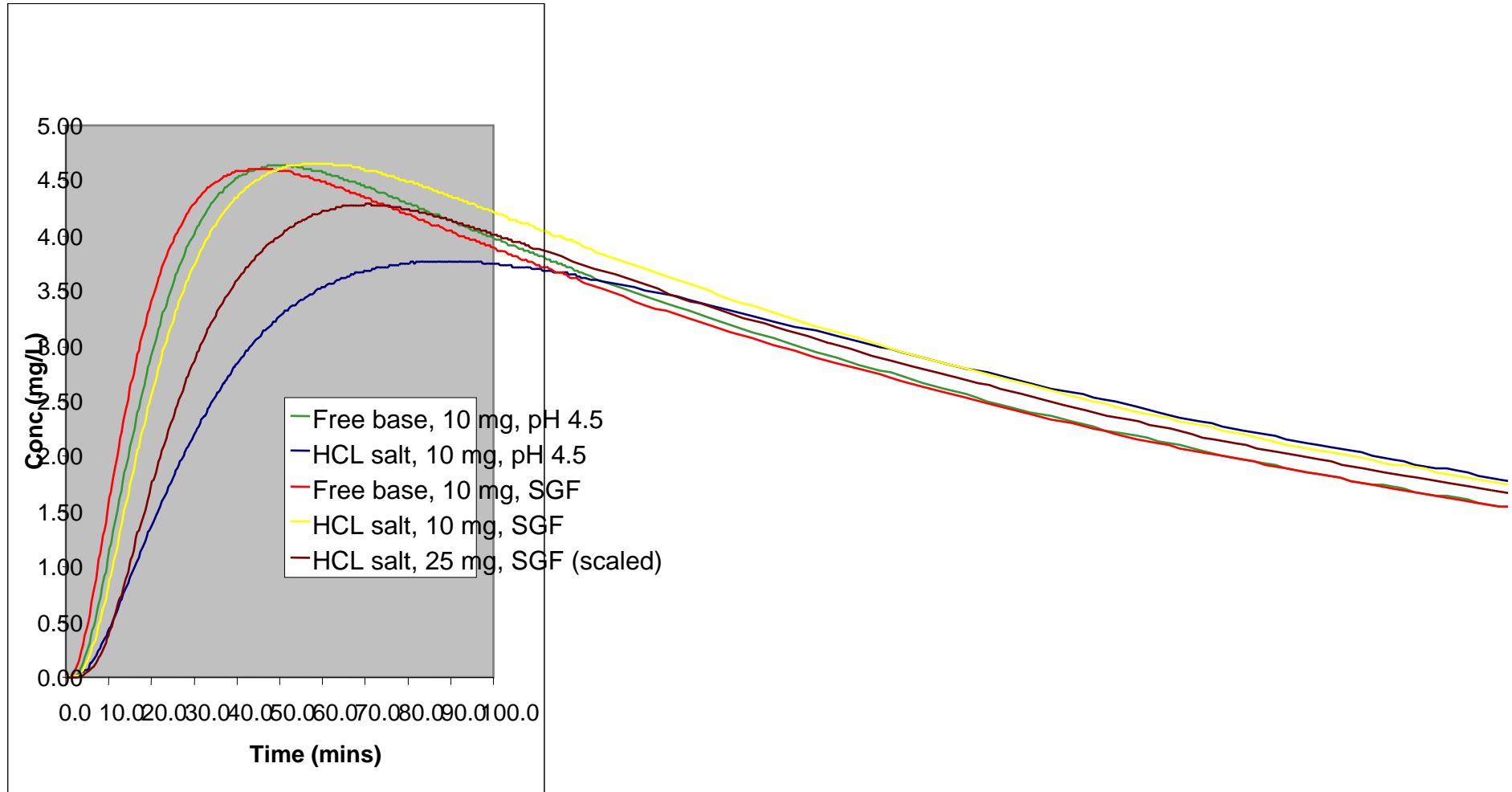


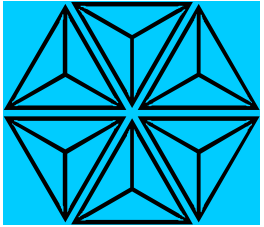
Sample “B” Tablets – In-Vitro Test Analyses:
Free Base vs. HCl Salt; pH 4.5 (“Fed”) vs. SGF (“Fasted”)





Sample “B” Tablets – In-Vitro Test Analyses: Free Base vs. HCl Salt; pH 4.5 (“Fed”) vs. SGF (“Fasted”)





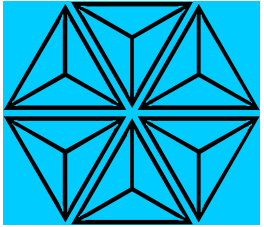
Sample “B” Tablets – In-Vitro Test Analyses:
Free Base vs. HCl Salt; pH 4.5 (“Fed”) vs. SGF (“Fasted”)

“(+)” = increase; “(++)” = larger Increase; “(-)” = decrease; “0” = no change

Changing from “Fasted” to “Fed” State:			
Free Base		HCl Salt	
tmax	Cmax	tmax	Cmax
(+)	0	(+++)	(--)

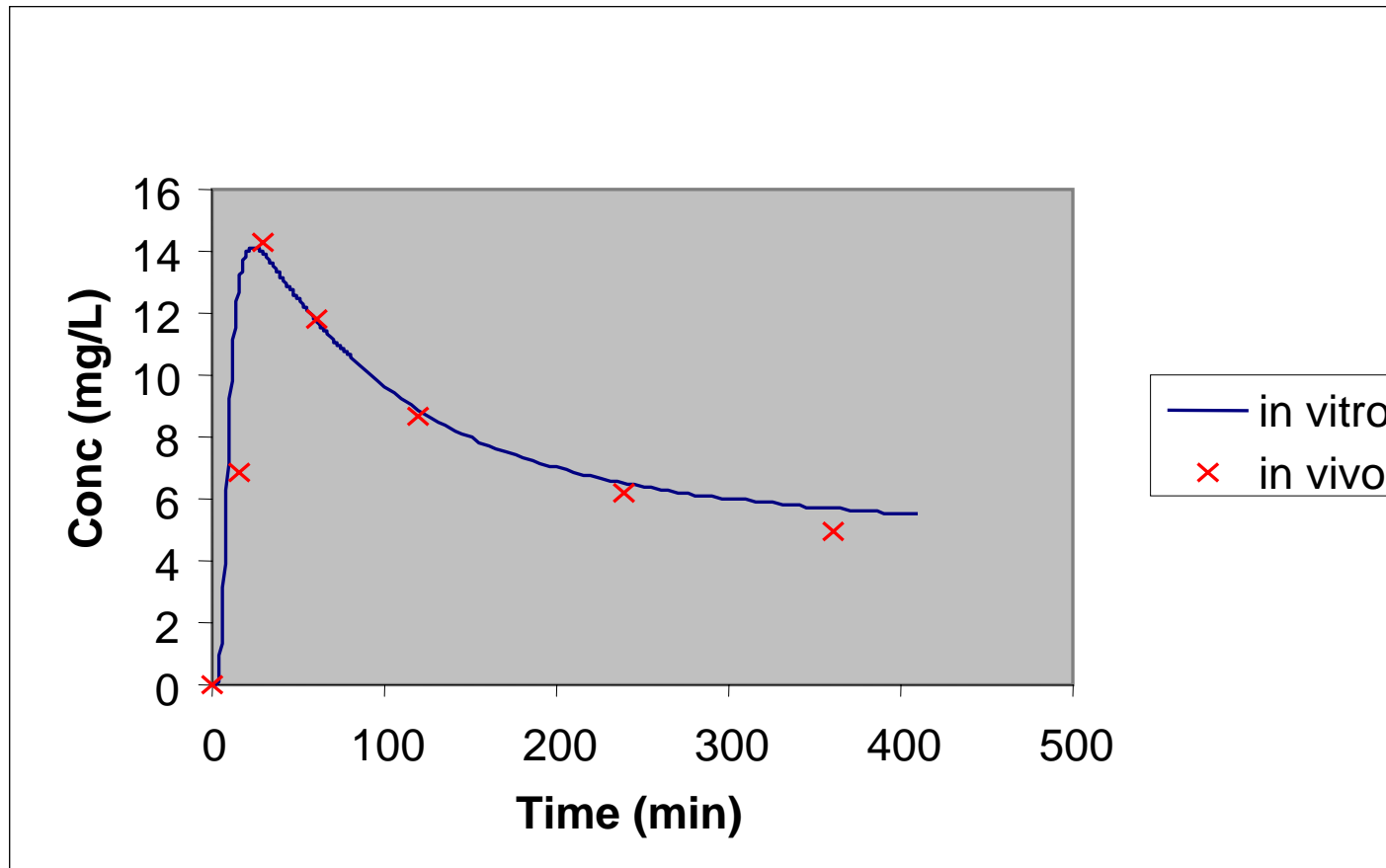
Changing from Free Base to HCl Salt:			
“Fasted” State		“Fed” State	
tmax	Cmax	tmax	Cmax
(++)	0	(++++)	(--)

➤ For better assessment, test parameters should be developed separately for fed and fasted states, to account for absorption characteristics.



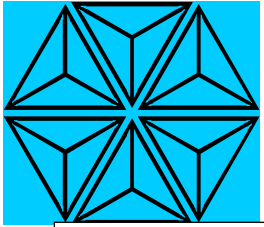
Testing of Sample “C” Formulations

- Compare 3 formulations: tablet, tablet w/ tartaric acid, semisolid capsule
- BCS Class 4; pKa at 2.2
- Cell-1 medium: USP SGF

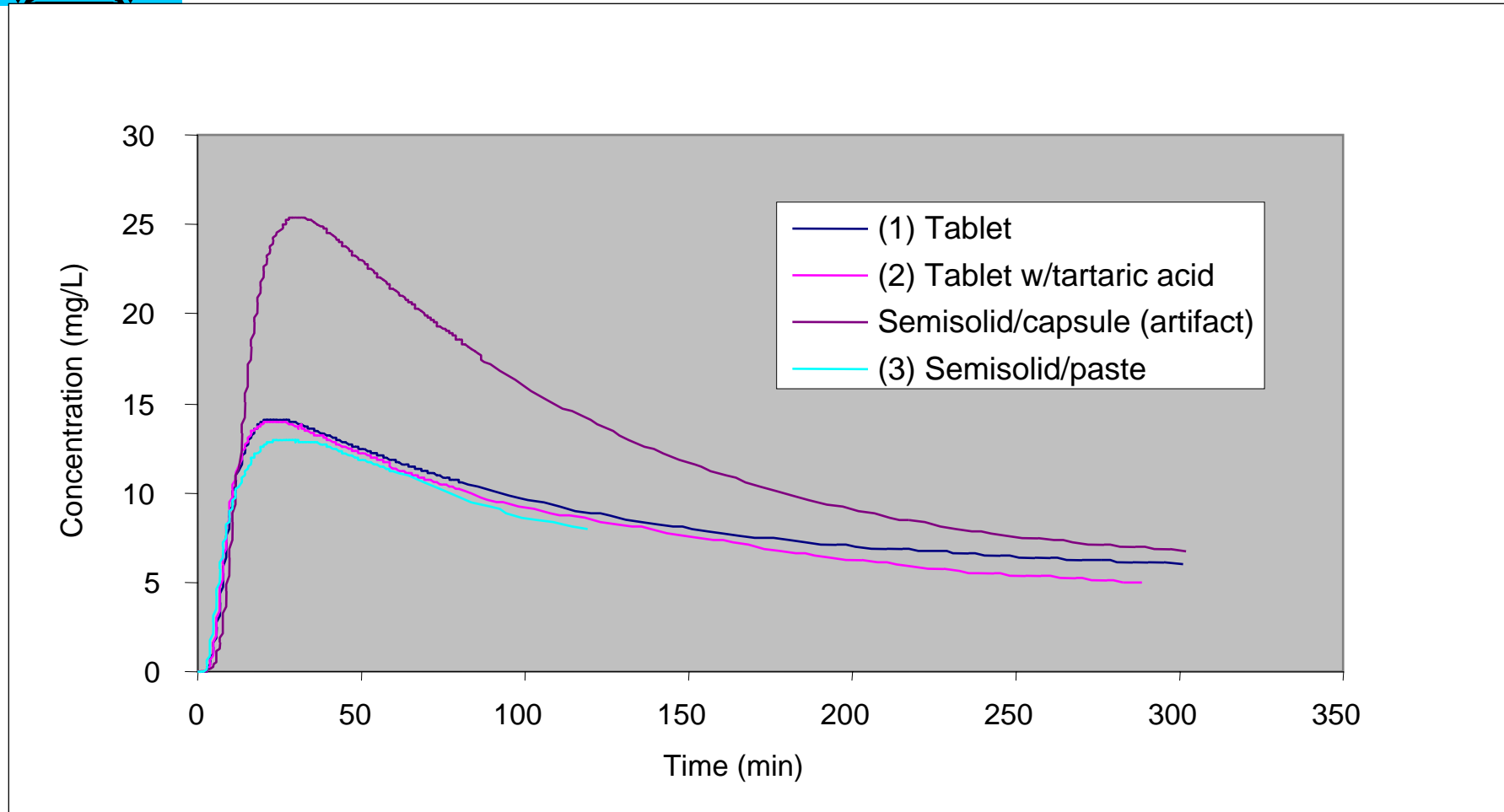


Estimated Cell Residence Times:

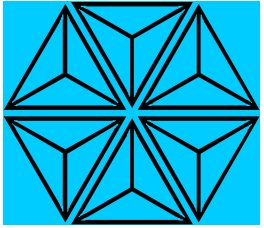
- Cell 1: 3 min
- Cell 2: 4 min
- Cell 3: 120 min



Comparison of Sample “C” Formulations



➤ No significant differences among the 3 formulations, in agreement with *in vivo* data.



Observations From In-Vitro Test Evaluations

- Good IVIVC obtained with the three drugs (BCS 1, 2, and 4)
- Good repeatability within one tablet lot
- 'Good' and 'bad' lots could be differentiated
- UV interference (e.g. from gelatin capsule shells) could confuse analysis
- Algorithm gives good starting point, even for poorly soluble drugs
- Test parameters can be optimized further
 - Optimization to achieve better correlation with *in vivo* C_{\max} data
- Able to compare different formulations of same drug and demonstrate agreement with *in vivo* performance
 - No effect from addition of tartaric acid to tablets
 - In-vitro dissolution of semisolid solubilized drug was same as tablet