

Linearity

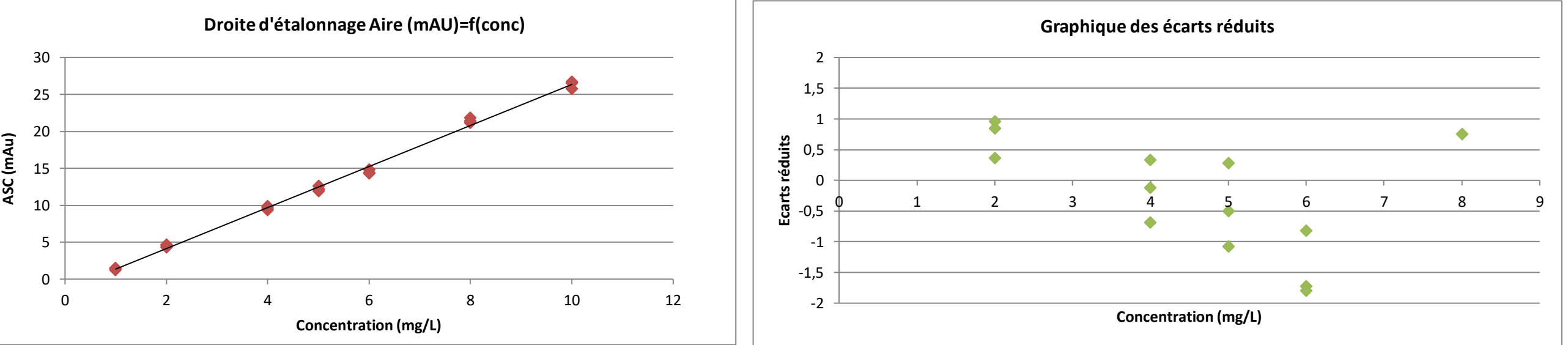
KETAMINE drug product.						
Essay	Observed AUC (mAu)	Concentration (µg/L)	Variance s²	Estimated AUC	Adjusted AUC	Confidence interval
D1 25%	1,46400913	1	0,00947754	1,360667954	1,46400913	0,20452703
D2 25%	1,278485634	1		1,360667954	1,278485634	-0,162650616
D3 25%	1,422417631	1		1,360667954	1,422417631	0,12221148
D1 50%	4,6212	2		4,136776219	4,6212	0,586744247
D2 50%	4,317925558	2	0,025829936	4,136776219	4,317925558	0,358520562
D3 50%	4,561803051	2		4,136776219	4,561803051	0,841189154
D1 100%	9,3436	4		9,688992748	9,3436	-0,633918693
D2 100%	9,626704715	4		9,688992748	9,626704715	-0,122278965
D3 100%	9,8574	4	0,117895544	9,688992748	9,8574	0,333302142
D1 125%	12,2109	5		12,46510201	12,2109	-0,30310032
D2 125%	12,06817335	5		12,46510201	12,06817335	0,278302415
D3 125%	11,9224	5		12,46510201	11,9224	-1,074083261
D1 150%	14,8235	6	0,074742023	15,24120628	14,8235	-0,826706662
D2 150%	14,3713	6		15,24120628	14,3713	-1,27256418
D3 150%	14,3312	6		15,24120628	14,3312	-1,80039078
D1 200%	21,7282967	8	0,112430365	20,79342581	21,7282967	0,75089475
D2 200%	21,83151003	8		20,79342581	21,83151003	2,654517795
D3 200%	21,3931	8		20,79342581	21,3931	1,186841367
D1 250%	26,33069975	10	0,253484928	26,34564234	26,33069975	0,366255196
D2 250%	26,07098278	10		26,34564234	26,07098278	0,643095548
D3 250%	25,73738477	10		26,34564234	25,73738477	-1,203987436

Linear regression (LINEST function)				
Slope b	2,776108265	-1,41544031	Intercept a	
S slope	0,037394375	0,0221679131	S Intercept	
R²	0,99636443	0,505269035	S res	
F	9511,378579	19	DOF	
Regression sum of squares	1407,037304	4,850639164	esidual sum of squares	

CHECKING THE FIT TO THE LINEAR MODEL n=3 k=7		
Cochran's C test: Study of the homogeneity of a series of variances		
C test	0.384051872	k : number of samples per test
Cochran's critical C, $\alpha = 5\%$	0.561	C test = $\max s^2 / \sum s^2$
Maximum S^2	0.253484928	
Sum s^2	0.660027841	
The variances are homogeneous at the risk of 0.05% because 0.384<0.561		

Calculation of experimental variance s²exp	0,094289692			
Calculation of mistfit variance				
SCC.ALE	3,907742248			
s².ALE	1,302580749			
Fisher Test				
H0:	not significantly different			
H1:	significantly different			
F exp	13,81456767	F threshold limit 5% (5, 14)	2,958248913	p-value
Conclusion	p-value > 5%, therefore no rejection of H0. Fit to the validated linear model.			0,000181489

DEPENDENCE VERIFICATION F(1, n - 2)				
H0:	The variances are not significantly different			
H1:	The variances are significantly different			
F exp	5511,378579	F threshold limit 5% (1, 19)	4,38	p-value
Conclusion	Dependence is validated as H0 is rejected, p-value<5%			7,07E-25



VALIDATION OF THE PROPORTIONAL MODEL

Regression of KETAMINE within the mixture: Comparison of the y-intercept to 0				KETAMINE Pure drug Product Regression: Comparing the Intercept to 0			
H0:		1,41544031		H0:		0,8721640855	
H1:		0,221679131		H1:		3,35151414	
Standard deviation of the intercept Sa		0,221679131		standard deviation		0,246711032	
Student Test				Student Test			
H0:		The y-intercept is equal to 0		H0:		The y-intercept is equal to 0	
H1:		The y-intercept is different from 0		H1:		The y-intercept is different from 0	
t exp		6,839085971		t exp		3,35151414	
Nb of DOF (N-2)		19		Nb of DOF (N-2)		19	
t threshold (5%, student)		2,093		t threshold (5%, stude		2,093	
Conclusion				Conclusion			
teexp > threshold→ Rejection of H0 at 5% risk. The y-intercept is significantly different from 0				teexp > threshold→ Rejection of H0 at 5% risk. The y-intercept is significantly different from 0			
the correlation line does not pass through the origin				the correlation line does not pass through the origin			

CALCULATED LIMIT OF DETECTION	1,82066243
CALCULATED LIMIT OF QUANTIFICATION	0,606626602

COMPARISON OF CLONIDINE IN THE MIXTURE AND THE PUR DRUG PRODUCT REGRESSIONS

Comparison of Student slopes	
H0:	No difference between the two slopes
H1:	Difference between the two slopes
teexp	4,612656913
Nb of DOF (N1+N2-4)	38
t threshold (5%, student à 38 dof)	2,042
Conclusion	teexp > t threshold→ Rejection of

COMPARISON OF STUDENT INTERCEPTS

H0:	No difference between the two intercepts
H1:	Difference between the two intercepts
teexp	1,637989847
Nb of DOF (N1+N2-4)	38
t threshold (5%, student à 38 dof)	2,042
Conclusion	teexp > t threshold→ Rejection of H0 at 5% risk, therefore no

SIGNIFICANCE TEST OF KETAMINE IN THE MIXTURE FORM CORRELATION COEFFICIENT (Pearson correlation coefficient test)			
H0 :	R=0	R reconstituted form:	0,998280737
H1 :	R different from 0		
teexp	74,2386596		
Nb of DOF:	19		
t threshold (5%, student)	2,093		
Conclusion	teexp > t threshold → Rejection of H0 at 5% risk, existence of a significant linear link between the variables		
SIGNIFICANCE TEST OF KETAMINE PURE PRODUCT CORRELATION COEFFICIENT (Pearson correlation coefficient test)			
H0 :	R=0	R pure product	0,997415039
H1 :	R different from 0		
teexp	60,50504009		
Nb of DOF:	19		
t threshold (5%, student)	2,093		
Conclusion	teexp > t threshold → Rejection of H0 at 5% risk, existence of a significant linear link between the variables		

Linearity

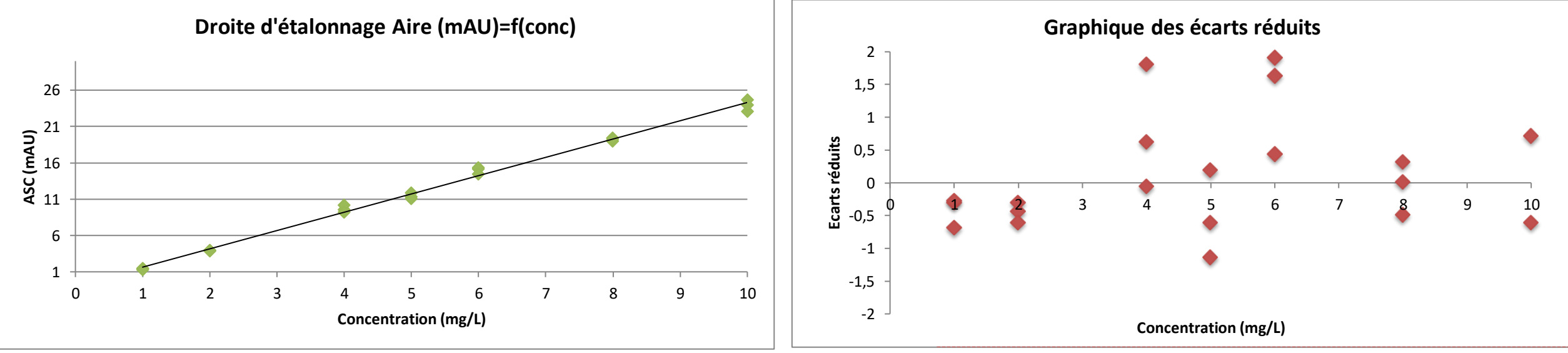
KETAMINE within the mixture						
Essay	Observed AUC (mAu)	Concentration (µg/L)	Variance s²	Estimated AUC	Adjusted AUC	Confidence interval
D1 25%	1,476925796	1	0,017397656	1,645873146	1,476925796	-0,300444972
D2 25%	1,494472837	1		1,645873146	1,494472837	-0,269240456
D3 25%	1,257747468	1		1,645873146	1,257747468	-0,690217446
D1 50%	3,914898234	2		4,163907148	3,914898234	-0,442821245
D2 50%	3,996755732	2	0,007603481	4,163907148	3,996755732	-0,297515199
D3 50%	3,822466737	2		4,163907148	3,822466737	-0,607195405
D1 100%	9,54711592	4		9,19997515	9,54711592	0,630875767
D2 100%	10,21598237	4		9,19997515	10,21598237	1,80680111
D3 100%	9,170945685	4	0,140366747	9,19997515	9,170945685	-0,05162412
D1 125%	11,17880915	5		11,17880915	8,858811545	-0,600259823
D2 125%	11,82368674	5		11,17880915	11,82368674	0,18759015
D3 125%	11,07964472	5		11,17880915	11,07964472	-1,135225759
D1 150%	15,15411853	6	0,194004473	14,23604315	15,15411853	1,632645506
D2 150%	15,30818545	6		14,23604315	15,30818545	1,806628077
D3 150%	14,48001222	6		14,23604315	14,48001222	0,433858706
D1 200%	18,5967	8	0,052977507	19,27211116	18,5967	-0,489773275
D2 200%	19,45211651	8		19,27211116	19,45211651	0,302027637
D3 200%	19,282	8		19,27211116	19,282	0,017585677
D1 250%	23,0973608	10	0,651955534	24,30817916	23,0973608	-2,153240566
D2 250%	24,71053849	10		24,30817916	24,71053849	0,715529593
D3 250%	23,96805877	10		24,30817916	23,96805877	-0,64847964

Linear regression (LINEST function)				
Slope b	2,518034001	-0,872160855	Intercept a	
S slope	0,04161693	0,246711032	S Intercept	
R²	0,99483876	0,562323779	S res	
F	3660,809876	19	DOF	
Regression sum of squares	1157,593272	6,00795248	Residual sum of squares	

CHECKING THE FIT TO THE LINEAR MODEL n=3 k=7		
Cochran's C test: Study of the homogeneity of a series of variances.		
C test	0.485177519	k: number of samples per test
Cochran's critical C, α = 5%	0.561	C test = max s²/sum s²
Maximum S²	0.651955534	
Sum s²	1.343746376	
The variances are homogeneous at the risk of 0.05% because 0.4851<0.561		

Calculation of experimental variance s²exp	0,191963768			
Calculation of mistfit variance				
SCC.ALE	4,08892148			
s².ALE	1,3627716			
Fisher Test				
H0:	not significantly different			
H1:	significantly different			
F exp	7,09910841	F threshold limit 5% (5, 14)	2,958248913	p-value
Conclusion	p-value > 5%, therefore no rejection of H0. Fit to the validated linear model.			0,003918571

DEPENDENCE VERIFICATION F(1, n - 2)				
H0:	The variances are not significantly different			
H1:	The variances are significantly different			
F exp	3660,809876	F threshold limit 5% (1, 19)	4,38	p-value
Conclusion	Dependence is validated as H0 is rejected, p-value<5%			2,53879E-17



Precision

KETAMINE drug product

Assay Number	AUC (mAu*min)	Concentration (µg/mL)	Observed concentration (µg/mL)	Recovery Rate	
Day 1-1	11,1643	5	4,780102591	104%	Average:
Day 1-2	11,2314	5	4,806750365	104%	103%
Day 1-3	11,0329	5	4,727919023	105%	Variance:
Day 1-4	12,0338	5	5,125411167	97%	0,000857776
Day 1-5	11,0886	5	4,750039455	105%	
Day 1-6	11,2528	5	4,815249059	104%	
Day 2-1	11,8274	5	5,043442959	99%	Average :
Day 2-2	11,9117	5	5,076921459	98%	100%
Day 2-3	11,0395	5	4,730540115	105%	Variance :
Day 2-4	11,6646	5	4,978789344	100%	0,000840733
Day 2-5	11,964	5	5,097691631	98%	
Day 2-6	12,0275	5	5,122909718	98%	
Day 3-1	10,7564	5	4,618111133	108%	Average:
Day 3-2	11,7393	5	5,008455346	100%	102%
Day 3-3	11,101	5	4,754963932	105%	Variance:
Day 3-4	11,4303	5	4,885740561	102%	0,001362522
Day 3-5	11,8952	5	5,070368727	99%	
Day 3-6	11,8938	5	5,069812738	99%	

2,518034001-0,872160855Average recovery:102%

Cochran's C test: study of the homogeneity of a series of variances C (m,p)

s² max	0,003061031	m : number of days for 1 test: 6
sum s²	0,7071	p: number of tests for validation: 3
Cochran's critique C, α = 5%	0,5685	
C test	0	

C test < C 5% : The variances are homogeneous (No rejection of H0)

Estimation of repeatability

Average calculation:	102%
s² intra :	0,001020344
SD repeatability:	0,031673546
	3,17%

Estimation of intermediate precision

Average calculation:	102%
Average s² :	8,78873E-08
s²IG :	5,27324E-07
s² facteur :	-0,000169969
s²RI:	0,000850374
SD intermediate precision:	0,028915354
	2,89%

Precision

KETAMINE within the mixture

Assay Number	AUC (mAu*min)	Concentration (µg/mL)	Observed concentration (µg/mL)	Recovery Rate	
Day 1-1	12,7083	5	5,107222876	98%	Average:
Day 1-2	12,63	5	5,159525585	97%	97%
Day 1-3	12,346	5	5,156586785	97%	Variance:
Day 1-4	12,4507	5	5,159724153	97%	0,00010402
Day 1-5	12,4978	5	5,173306178	97%	
Day 1-6	12,0473	5	5,03951132	99%	
Day 2-1	11,988	5	5,107222876	98%	Average :
Day 2-2	12,1197	5	5,159525585	97%	97%
Day 2-3	12,1123	5	5,156586785	97%	Variance :
Day 2-4	12,1202	5	5,159724153	97%	0,00010402
Day 2-5	12,1544	5	5,173306178	97%	
Day 2-6	11,8175	5	5,03951132	99%	
Day 3-1	11,8564	5	5,054959881	99%	Average:
Day 3-2	11,7621	5	5,017510029	100%	100%
Day 3-3	11,991	5	5,108414282	98%	Variance:
Day 3-4	11,4393	5	4,889314778	102%	0,000421534
Day 3-5	11,3155	5	4,840149437	103%	
Day 3-6	11,5691	5	4,94086293	101%	

2,518034001-0,872160855Average recovery:98%

Cochran's C test: study of the homogeneity of a series of variances C (m,p)

s² max	0,000629575	m : number of days for 1 test: 6
sum s²	0,7071	p: number of tests for validation: 3
Cochran's critique C, α = 5%	0,5685	
C test	0	

C test < C 5% : The variances are homogeneous (No rejection of H0)

Estimation of repeatability

Average calculation:	98%
s² intra :	0,000209858
SD repeatability:	0,014604035
	1,46%

Estimation of intermediate precision

Average calculation:	98%
Average s² :	3,3605E-08
s²IG :	2,0163E-07
s² facteur :	-3,49428E-05
s²RI:	0,000174916
SD intermediate precision:	0,01333288
	1,33%

Accuracy

ketamine drug product						
Essai	Observed AUC (mg*min)	Concentration (mg/L)	observed concentration (mg/L)	Recovery rate (%)	Variance of recoveries	Average recovery
Day 1 25%	1.476925796	1	0.93290506	93.290506	4.549403094	93.63893301
Day 2 25%	1.494472837	1	0.93873604	93.873604		
Day 3 25%	1.577474682	1	0.972938661	97.286606		
Day 1 50%	3.914898234	2	1.901109789	95.0548946		
Day 2 50%	3.986757122	2	1.933618385	96.48091425	2.097983862	94.981501
Day 3 50%	3.822466737	2	1.864401886	93.22009928		
Day 1 100%	9.554731593	4	4.14886079	103.522157		
Day 2 100%	10.21598237	4	4.403492255	110.0873064		
Day 3 100%	9.17094585	4	3.988471377	99.7178442	27.54526364	104.4824119
Day 1 125%	11.37584555	5	4.88217564	97.27453388		
Day 2 125%	11.82388874	5	5.04196824	100.8393659		
Day 3 125%	11.07664472	5	4.76682998	94.32965995		
Day 1 150%	15.15413853	6	6.36400073	100.076679	8.93524662	98.11128264
Day 2 150%	15.58838545	6	6.42578847	107.064545		
Day 3 150%	14.48091222	6	6.066480709	101.6148118		
Day 1 200%	18.5967	8	7.89024529	98.83280661		
Day 2 200%	18.45211651	8	8.07152618	100.8940772	1.30551452	99.85865799
Day 3 200%	19.282	8	8.003927208	100.0490901		
Day 1 250%	21.0973608	10	9.519141379	96.59141379		
Day 2 250%	24.71053846	10	10.15979105	101.5979105		
Day 3 250%	23.9682677	10	9.86492613	98.6492613	10.28240713	98.47952881
				Sum of variances	94.035304	99.18478062
				Average of recovery averages		
				6.628011726 Total standard deviation of the recovery		
2.518024001	0.872160855					

Cochran's C test C(7,3)

C test	0.490158129
C threshold (cochran table) 5%	0.561
y*max	27.54536354
y*sum	64.035204
C test < C table, no rejection of H0, the variances are homogeneous at the 5% risk.	

ANOVA

	Sum of SES	DOF	s²	Fexp	p-value
Intragroup	128.070408	14	9.147886286	6.565438807	0.002413872
Intergroup	300.2994427	5	60.05988853		
Total	428.3698507	19			

SES : Sum of standard errors squared

Mean Recovery Confidence Interval

Average R:	99.53181388
Total variance:	21.54578185
Number of DOF:	n-1 = 20
15% 20 DOF:	2.085933441
lower bound :	96.760968
Upper bound :	101.8757997

So the mean overlap confidence interval is : [96.8035 ; 101.8239]
The average recovery rate is 98.7137
It is included in the confidence interval: ok.

Accuracy

ketamine within the mixture						
Essai	Observed AUC (mg.h/mL)	Concentration (mg/L)	reved concentration (n)	Recovery rate (%)	Variance of recoveries	Average recovery
Day 1 25%	1.46600913	1	1.017225196	101.7225196	1.122293251	100.3810884
Day 2 25%	1.27885634	1	0.970390572	97.03905724		
Day 3 25%	4.42317631	1	0.02243192	100.2442572		
Day 1 50%	4.6713	2	2.174497438	108.7449719		
Day 2 50%	4.317025508	2	2.005257981	105.2625649	8.378968221	106.5475149
Day 3 50%	4.561803051	2	2.153101628	107.6552839		
Day 1 100%	9.3436	4	8.47583883	96.8959583		
Day 2 100%	9.676704725	4	9.97562823	99.43907057		
Day 3 100%	9.8076	4	4.006619771	101.5165768	5.370808099	99.28174772
Day 1 125%	12.2105	5	4.90842601	98.14885202		
Day 2 125%	12.60617335	5	5.05816583	101.0163317		
Day 3 125%	11.8224	5	4.806510101	96.09030282		
Day 1 150%	14.8135	6	5.848532226	97.85223711	2.693950128	
Day 2 150%	14.2713	6	5.888444325	96.77746242		
Day 3 150%	14.3312	6	5.672109544	94.55660973		
Day 1 200%	21.17282967	8	8.136667932	101.7083482		
Day 2 200%	21.83151003	8	8.373332605	104.6741883	2.279454075	103.0275631
Day 3 200%	21.3931	8	8.216012538	100.7001567		
Day 1 250%	26.52699979	10	10.06666073	100.6666073		
Day 2 250%	26.67098278	10	10.117193	101.171393		
Day 3 250%	25.73730477	10	9.7886677	97.8086677	3.289117157	99.88140367
				Sum of variances	26.52697976	100.29759663
				Average of recovery averages		
				3.878842378 Total standard deviation of the recovery		
2.776108265	-1.41544031					

Cochran's C test C(7,3)

C test	0.189133488
C threshold (cochra	0.561
y*max	1.37880099
y*sum	29.25057976
C test < C table, no rejection of H0, the variances are homogeneous at the 5% risk.	

ANOVA

	Sum of SES	DOF	s²	Fexp	p-value
Intragroup	58.50119982	14	4.198054252	11.60290875	0.000141301
Intergroup	242.4227189	5	48.48454399		
Total	300.9238795	19			

SES : Sum of standard errors squared

Mean Recovery Confidence Interval

Average R:	100.5374159
Total variance:	15.838090892
Number of DOF:	n-1 = 20
15% 20 DOF:	2.085933441
lower bound :	98.39336392
Upper bound :	102.6808621

So the mean overlap confidence interval is : [98.3940 ; 102.6809]
The average recovery rate is 100.5374
It is included in the confidence interval: ok.