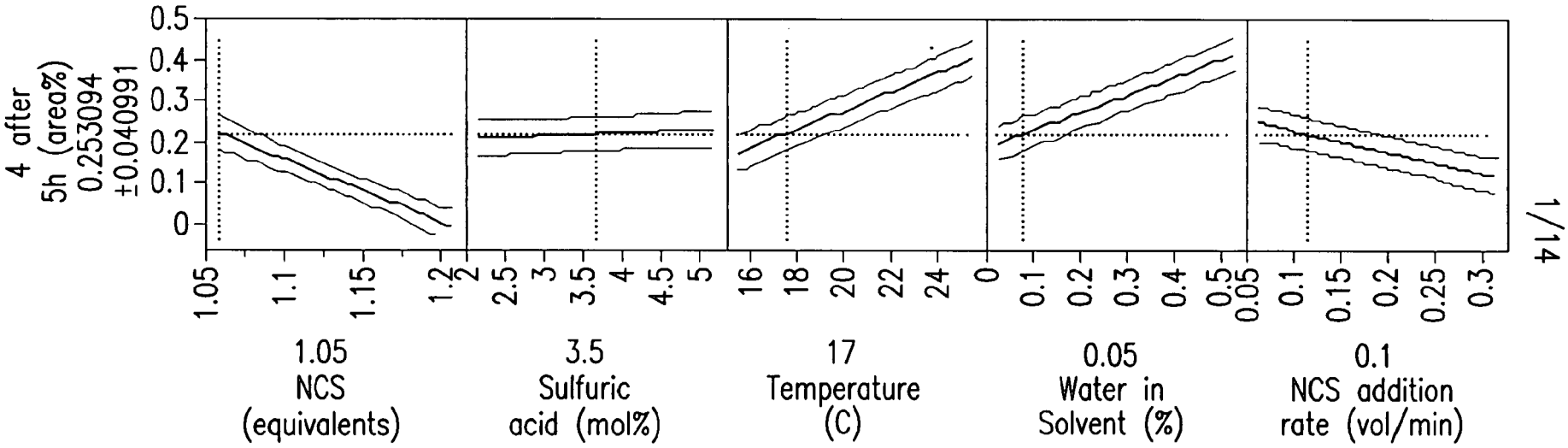

4 after
5h (area%)
0.253094
±0.040991
0.5
0.4
0.3
0.2
0.1
0
1.05
1.1
1.15
1.2
2
2.5
3
3.5
4
4.5
5
16
18
20
22
24
0
0.1
0.2
0.3
0.4
0.5
0.05
0.1
0.15
0.2
0.25
0.3
1.05
NCS
(equivalents)
3.5
Sulfuric
acid (mol%)
17
Temperature
(C)
0.05
Water in
Solvent (%)
0.1
NCS addition
rate (vol/min)

FIG. 1

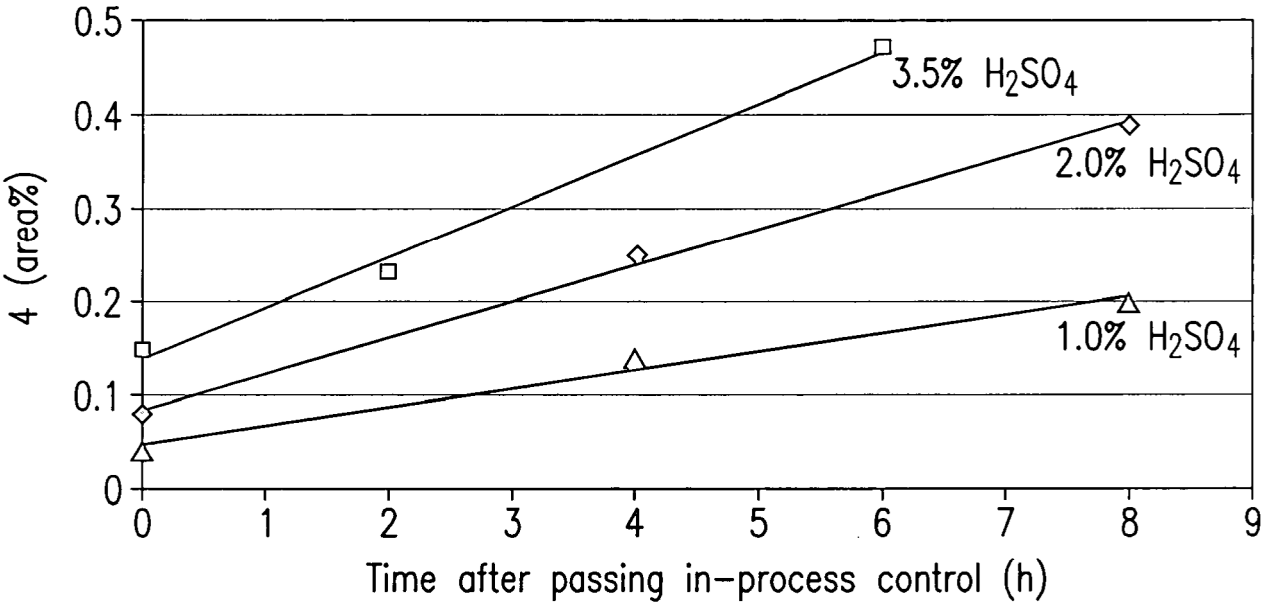

0.5
0.4
0.3
0.2
0.1
0
4 (area%)
0
1
2
3
4
5
6
7
8
9
Time after passing in-process control (h)
3.5% H_2SO_4
2.0% H_2SO_4
1.0% H_2SO_4

FIG.2

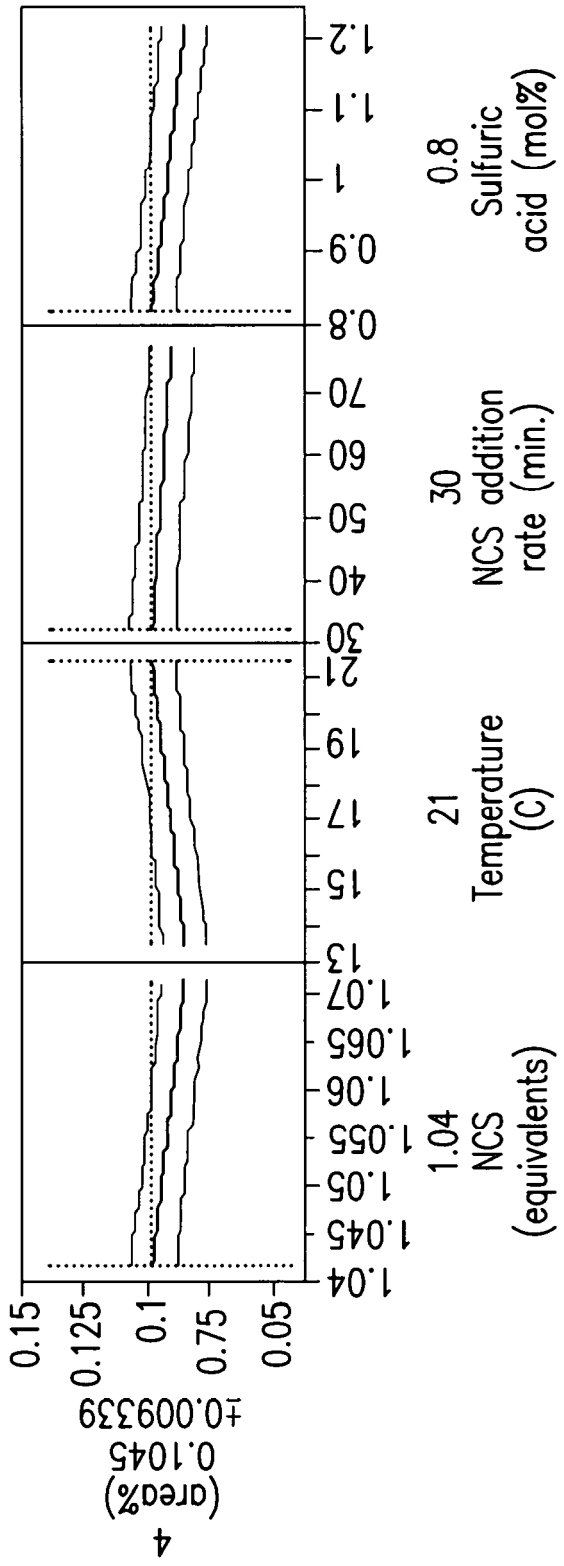

4
(σred%)
0.1045
±0.009339
0.15
0.125
0.1
0.75
0.05
1.04
1.045
1.05
1.055
1.06
1.065
1.07
NCS
(equivalents)
1.04
13
15
17
19
21
Temperature
(C)
21
30
40
50
60
70
NCS addition
rate (min.)
30
0.8
0.9
1
1.1
1.2
Sulfuric
acid (mol%)
0.8

FIG. 3

Experimental Table

Initial Design of Experiment

Experiment	Pattern	NCS (equivalents)	Sulfuric acid (mol%)	Temp. (C)	Solvent (volume)	Water in solvent (%)	NCS addition rate (vol/min)	Solvent	4 after 5h (area%)
1	−−++−−+	1.05	2	25	3	0	0.05	MeOAc	0.239
2	++−−++−	1.2	5	15	2	0.5	0.3	EtOAc	0.05
3	−++−−++	1.05	5	25	2	0	0.3	MeOAc	0.139
4	2	1.125	3.5	20	2.5	0.25	0.175	MeOAc	0.247
5	+−−++−−	1.2	2	15	3	0.5	0.05	EtOAc	0.068
6	−+−+−+−	1.05	5	15	3	0	0.3	EtOAc	0.095
7	+++−−−−	1.2	5	25	2	0	0.05	EtOAc	0.125
8	1	1.125	3.5	20	2.5	0.25	0.175	EtOAc	0.192
9	−+−−+−+	1.05	5	15	2	0.5	0.05	MeOAc	0.234
10	−−−−−−−	1.05	2	15	2	0	0.05	EtOAc	0.185
11	−−+−++−	1.05	2	25	2	0.5	0.3	EtOAc	0.475
12	+−++−+−	1.2	2	25	3	0	0.3	EtOAc	0.123
13	+−+−+−+	1.2	2	25	2	0.5	0.05	MeOAc	0.322
14	+−−−−++	1.2	2	15	2	0	0.3	MeOAc	0.129
15	++−+−−+	1.2	5	15	3	0	0.05	MeOAc	0.168
16	−−−++++	1.05	2	15	3	0.5	0.3	MeOAc	0.11
17#	1	1.125	3.5	20	2.5	0.25	0.175	EtOAc	0.372
18	+++++++	1.2	5	25	3	0.5	0.3	MeOAc	0.472
19	−++++−−	1.05	5	25	3	0.5	0.05	EtOAc	0.68

#Experiment 17 was deemed an outlier and was ignored for the analysis

FIG.4

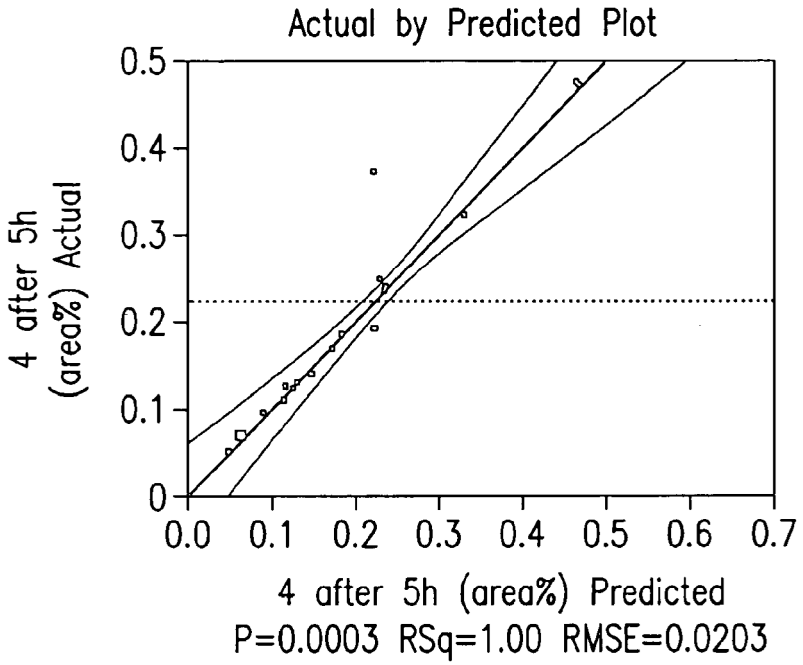


FIG.5A

Summary of Fit	
RSquare	0.9965
RSquare Adj	0.985126
Root Mean Square Error	0.020258
Mean of Response	0.225167
Observations (or Sum Wgts)	18

FIG.5B

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	13	0.46741489	0.035955	87.6090
Error	4	0.00164161	0.00410	Prob>F
C. Total	17	0.46905650		0.0003*

FIG.5C

Parameter Estimates				
Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.2251667	0.004775	47.16	<.0001*
NCS (equivalents)(1.05,1.2)	−0.04375	0.005065	−8.64	0.0010*
Sulfuric acid (mol%)(2,5)	0.0195	0.005065	3.85	0.0183*
Temperature (C)(15,25)	0.096	0.005065	18.96	<.0001*
Solvent (vol)(2,3)	0.0185	0.005065	3.65	0.0217*
Water in Solvent (%)(0,0.5)	0.0755	0.005065	14.91	0.0001*
NCS addition rate (vol/min)(0.05,0.3)	−0.02675	0.005065	−5.28	0.0062*
Solvent[EtOAc]	−0.003722	0.004775	−0.78	0.4792*
NCS (equivalents)*Temperature (C)	−0.017625	0.005065	−3.48	0.0254*
NCS (equivalents)*Solvent (vol)	0.007125	0.005065	1.41	0.2322*
NCS (equivalents)*Water in Solvent (%)	−0.029625	0.005065	−5.85	0.0043*
NCS (equivalents)*NCS addition rate (vol/min)	0.038125	0.005065	7.53	0.0017*
NCS (equivalents)*Solvent[EtOAc]	−0.089875	0.005065	−17.75	<.0001*
Sulfuric acid (mol%)*Temperature (C)	0.012625	0.005065	2.49	0.0673

FIG.5D

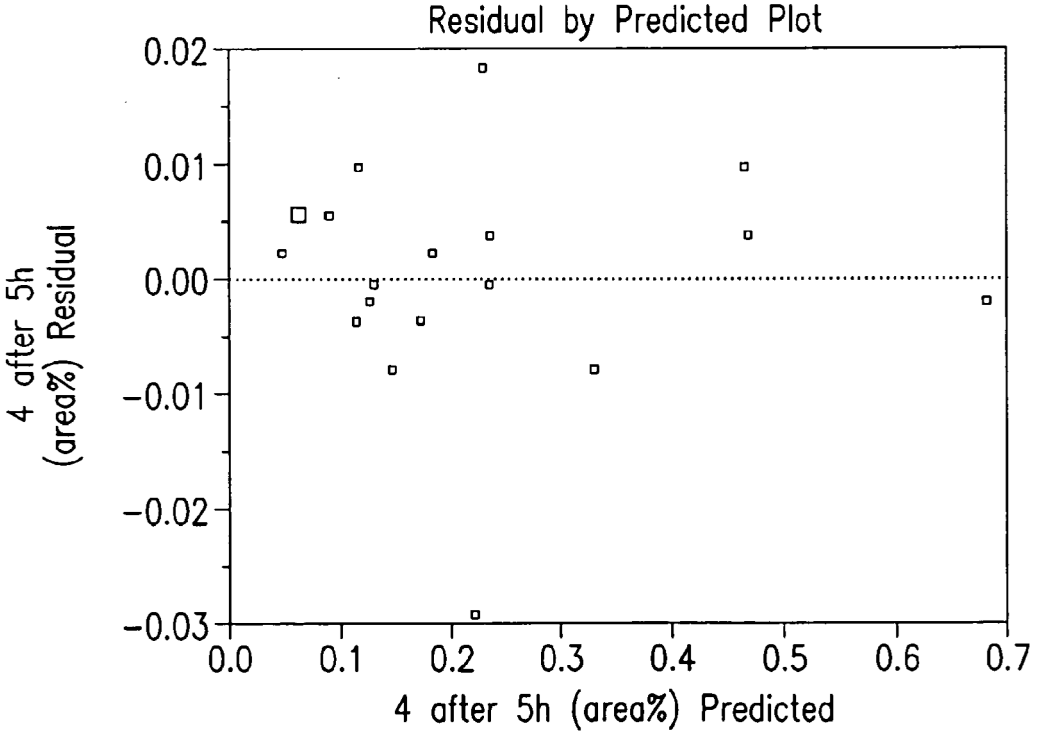


FIG.5E

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Temperature (C)(15,25)	0.096	0.005065	18.96	<.0001*
NCS (equivalents)*Solvent[EtOAc]	−0.089875	0.005065	−17.75	<.0001*
Water in Solvent (%)(0,0.5)	0.0755	0.005065	14.91	0.0001*
NCS (equivalents)(1.05,1.2)	−0.04375	0.005065	−8.64	0.0010*
NCS (equivalents)*NCS addition rate (vol/min)	0.038125	0.005065	7.53	0.0017*
NCS (equivalents)*Water in Solvent (%)	−0.029625	0.005065	−5.85	0.0043*
NCS addition rate (vol/min)(0.05,0.3)	−0.02675	0.005065	−5.28	0.0062*
Sulfuric acid (mol%)(2,5)	0.0195	0.005065	3.85	0.0183*
Solvent (vol)(2,3)	0.0185	0.005065	3.65	0.0217*
NCS (equivalents)*Temperature (C)	−0.017625	0.005065	−3.48	0.0254*
Sulfuric acid (mol%)*Temperature (C)	0.012625	0.005065	2.49	0.0673
NCS (equivalents)*Solvent (vol)	0.007125	0.005065	1.41	0.2322
Solvent[EtOAc]	−0.003722	0.004775	−0.78	0.4792

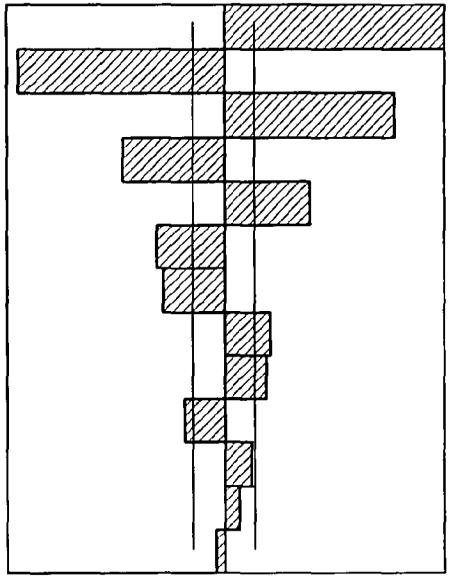


FIG.5F

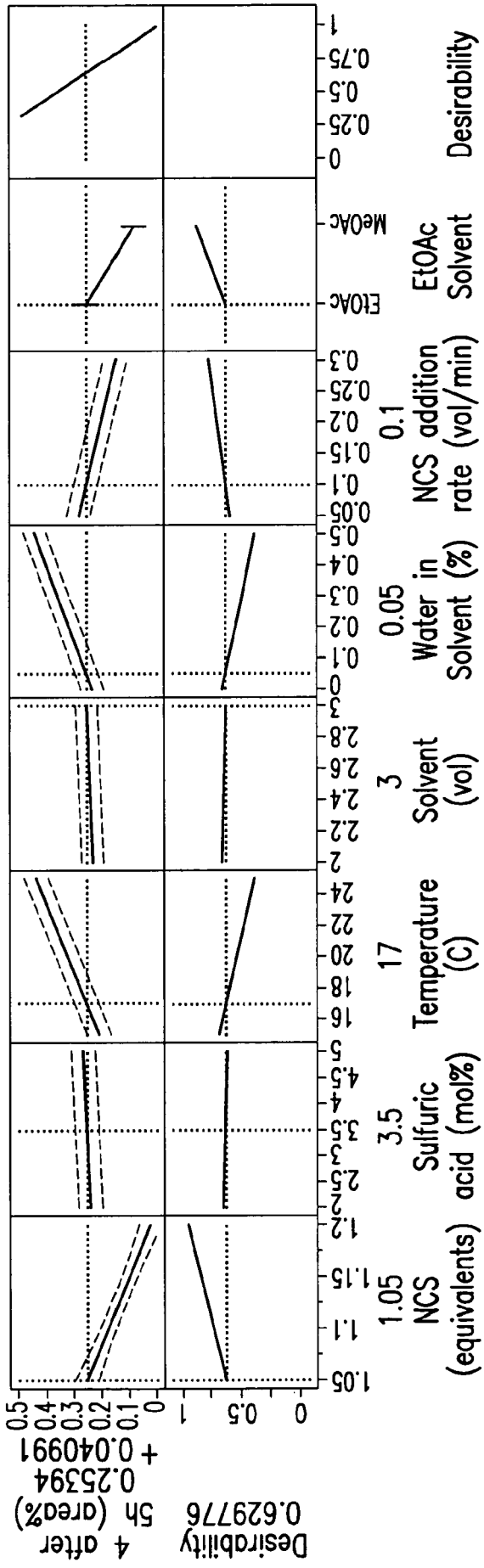

Prediction Profiler
4 after 5h (area%)
0.25394
+ 0.040991
Desirability
0.629776
NCS (equivalents)
1.05
Sulfuric acid (mol%)
3.5
Temperature (C)
17
Solvent (vol)
3
Water in Solvent (%)
0.05
NCS addition rate (vol/min)
0.1
EtOAc
MeOAc
EtOAc Solvent
Desirability

FIG.6A

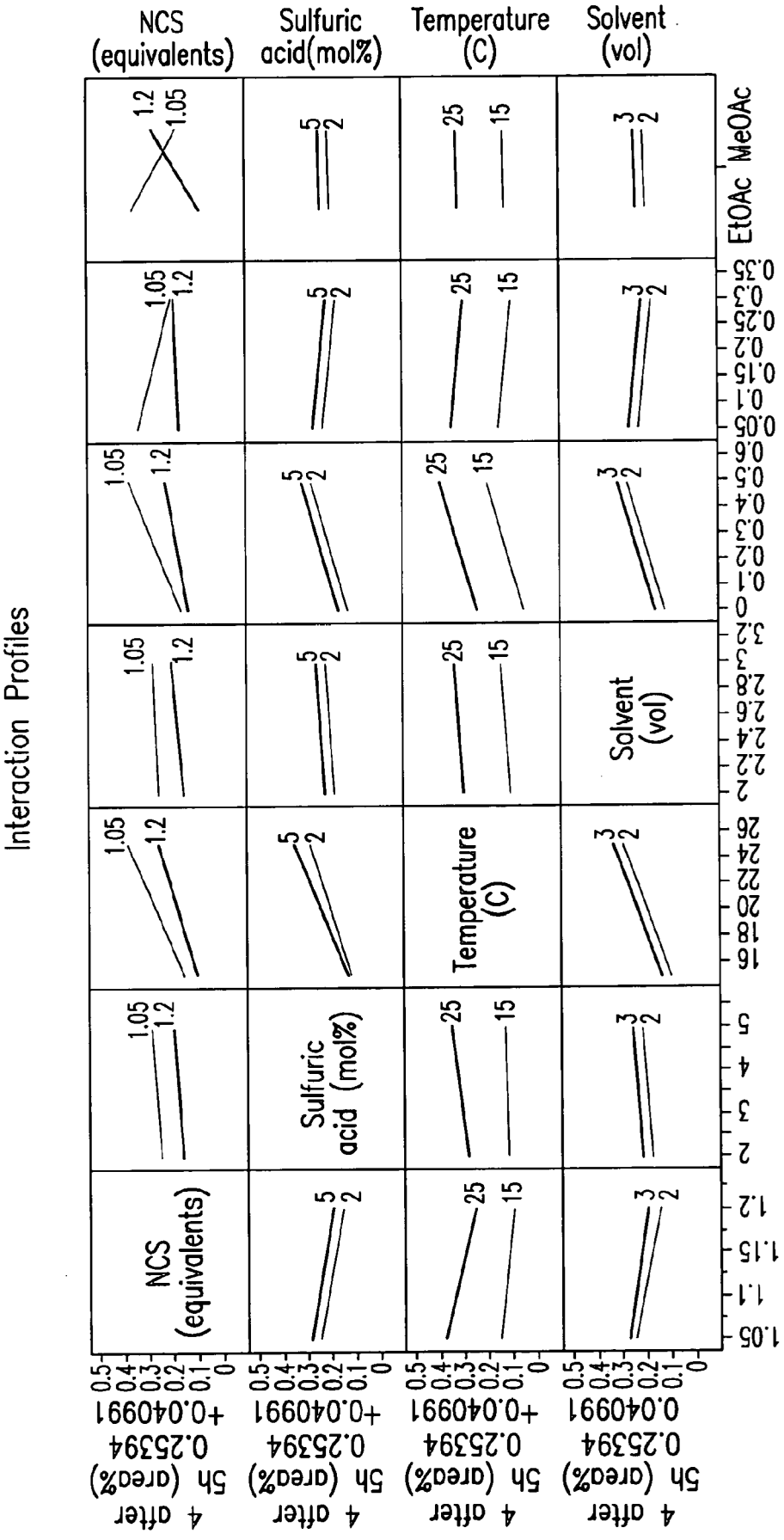

Interaction Profiles
NCS (equivalents)
Sulfuric acid(mol%)
Temperature (C)
Solvent (vol)
4 after 5h (area%) 0.25394 +0.04091
4 after 5h (area%) 0.25394 +0.04091
4 after 5h (area%) 0.25394 +0.04091
4 after 5h (area%) 0.25394 +0.04091
EtOAc MeOAc

FIG. 6B

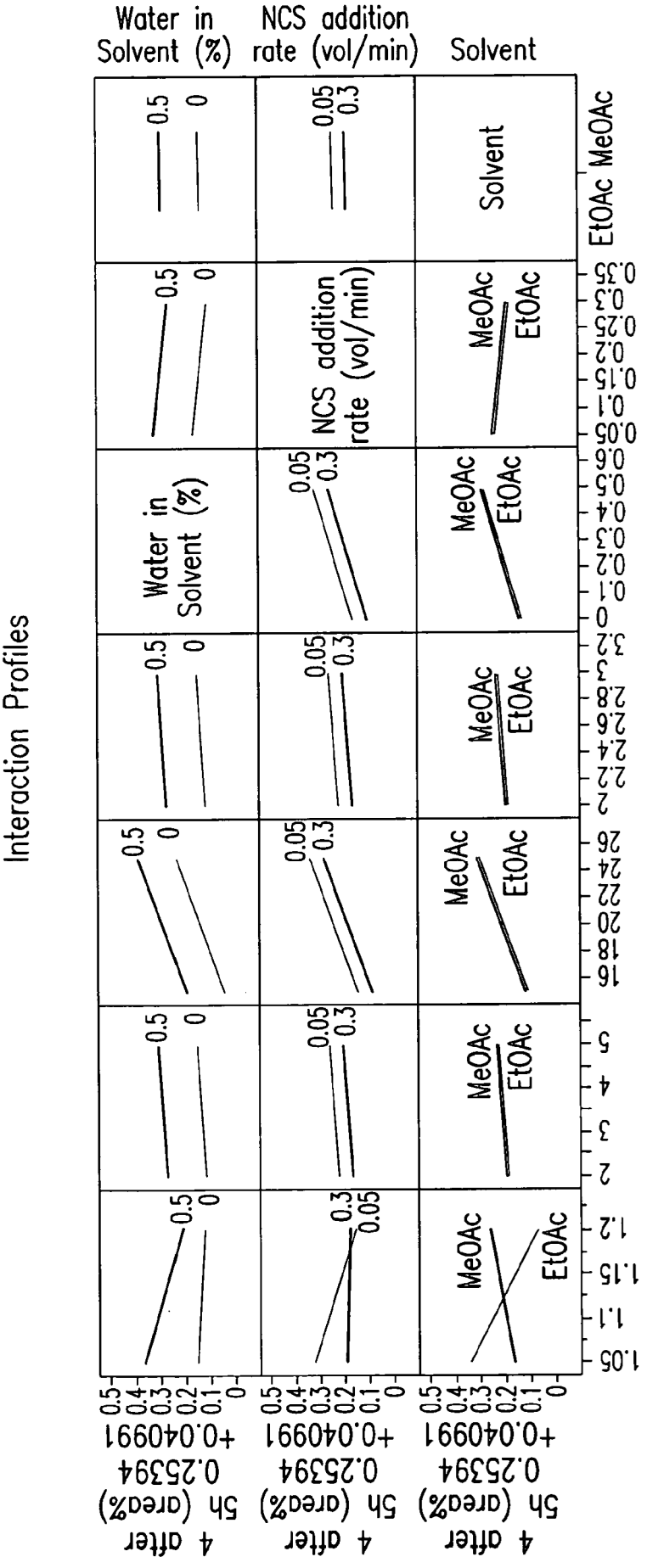

Interaction Profiles
Water in Solvent (%)
NCS addition rate (vol/min)
Solvent
4 after 5h (area%) +0.04091 0.25394
MeOAc
EtOAc
0.5
0
0.05
0.3

FIG.6B-1

Robustness Design of Experiment

Experimental Table

Experiment	Pattern	NCS (equivalents)	Temp. (C)	NCS addition rate (vol/min)	Sulfuric acid (mol%)	4 (area%)
1	+−+−	1.07	13	75	0.8	0.07
2	0	1.055	17	52.5	1	0.09
3	−−−−	1.04	13	30	0.8	0.09
4	−+−+	1.04	21	30	1.2	0.09
5	−−++	1.04	13	75	1.2	0.07
6	++++	1.07	21	75	1.2	0.07
7	+−−+	1.07	13	30	1.2	0.07
8	0	1.055	17	52.5	1	0.08
9	−++−	1.04	21	75	0.8	0.1
10	++−−	1.07	21	30	0.8	0.09

FIG.7

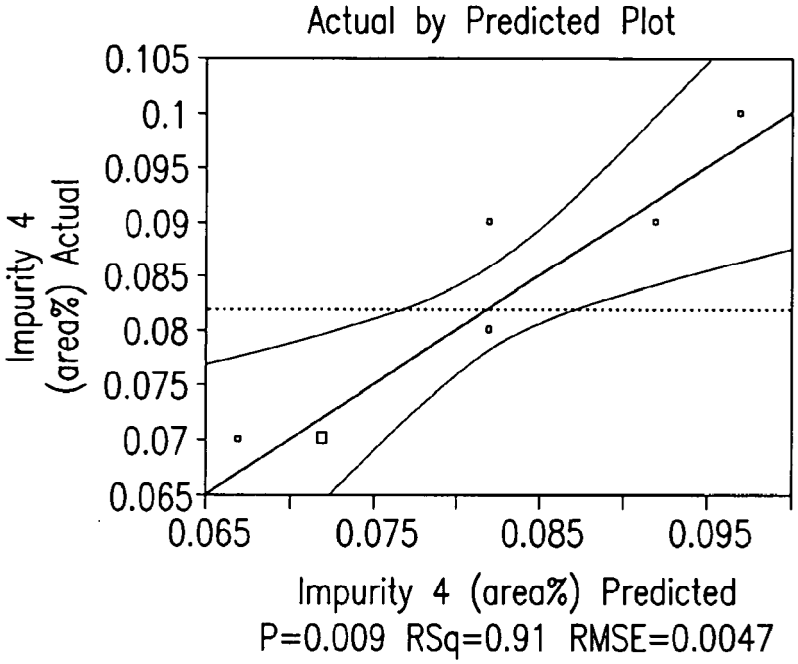


FIG.8A

Summary of Fit	
RSquare	0.905172
RSquare Adj	0.82931
Root Mean Square Error	0.00469
Mean of Response	0.082
Observations (or Sum Wgts)	10

FIG.8B

Analysis of Variance				
Source	DF	Sum of Squares	Mean Square	F Ratio
Model	4	0.00105000	0.000262	11.9318
Error	5	0.00011000	0.000022	Prob>F
C. Total	9	0.00116000		0.0090*

FIG.8C

Lack Of Fit

Source	DF	Sum of Squares	Mean Square	F Ratio 0.3000
Lack Of Fit	4	0.00006000	0.000015	Prob>F
Pure Error	1	0.00005000	0.000050	0.8581
Total Error	5	0.00011000		Max RSq
				0.9569

FIG.8D

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	0.082	0.001483	55.28	<.0001*
NCS (equivalents)(1.04,1.07)	−0.00625	0.001658	−3.77	0.0130*
Temperature (C)(13,21)	0.00625	0.001658	3.77	0.0130*
Addition Rate (min.)(30,75)	−0.00375	0.001658	−2.26	0.0732
Sulfuric acid (mol%)(0.8,1.2)	−0.00625	0.001658	−3.77	0.0130*

FIG.8E

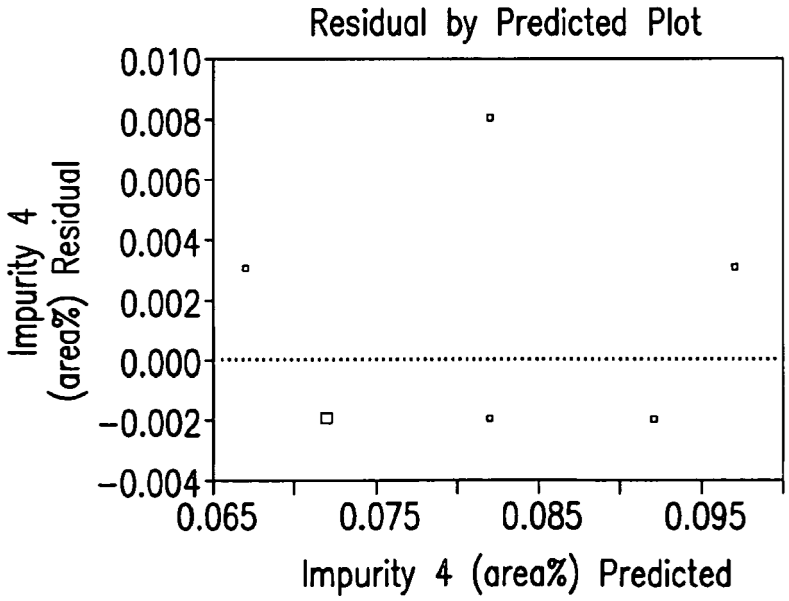


FIG.8F

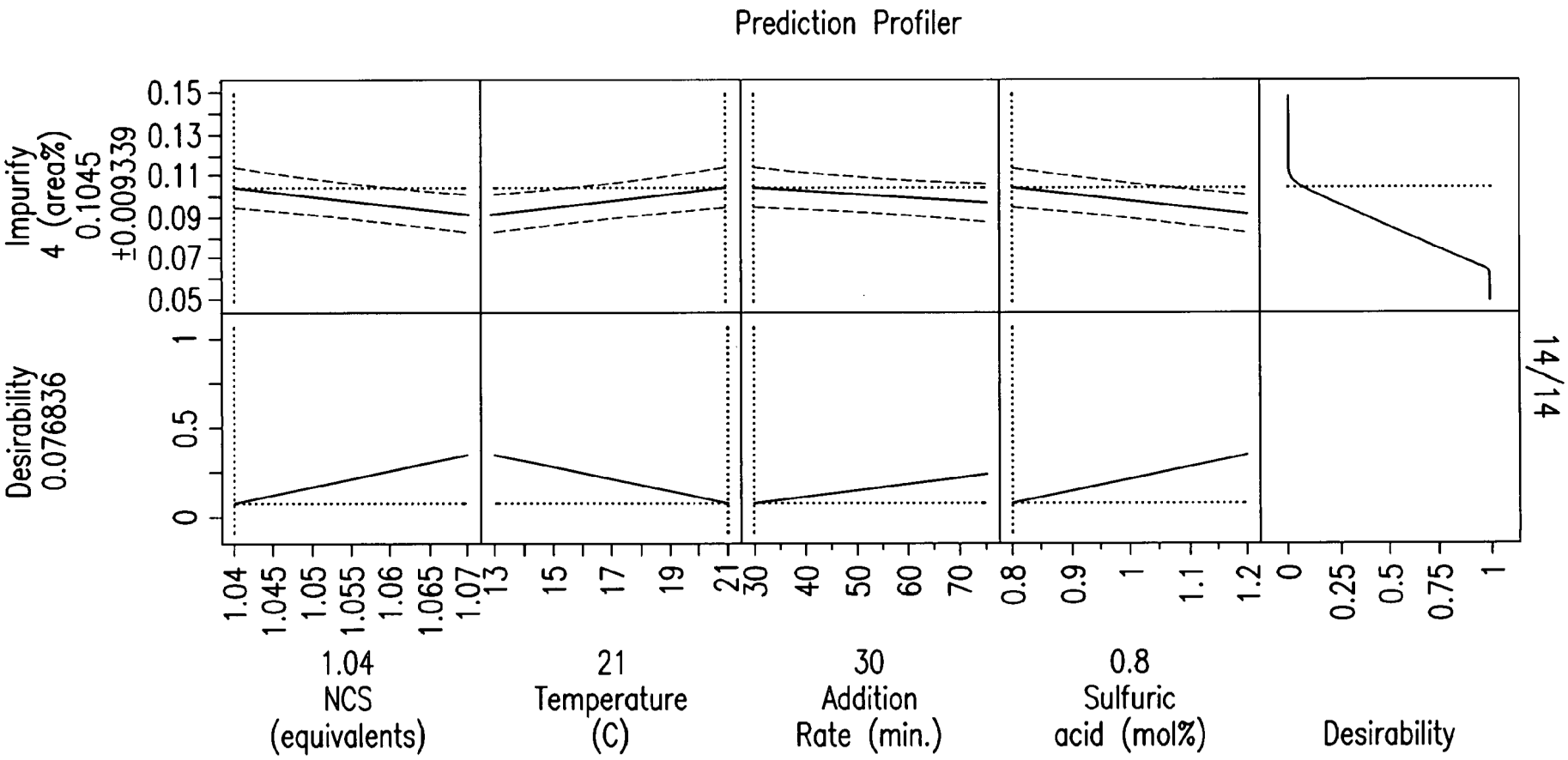

Prediction Profiler
Impurity
4 (area%)
0.1045
±0.009339
0.15
0.13
0.11
0.09
0.07
0.05
Desirability
0.076836
1
0.5
0
1.04
1.045
1.05
1.055
1.06
1.065
1.07
13
15
17
19
21
30
40
50
60
70
0.8
0.9
1
1.1
1.2
0
0.25
0.5
0.75
1
1.04
NCS
(equivalents)
21
Temperature
(C)
30
Addition
Rate (min.)
0.8
Sulfuric
acid (mol%)
Desirability
14/14

FIG.8G