KOREA

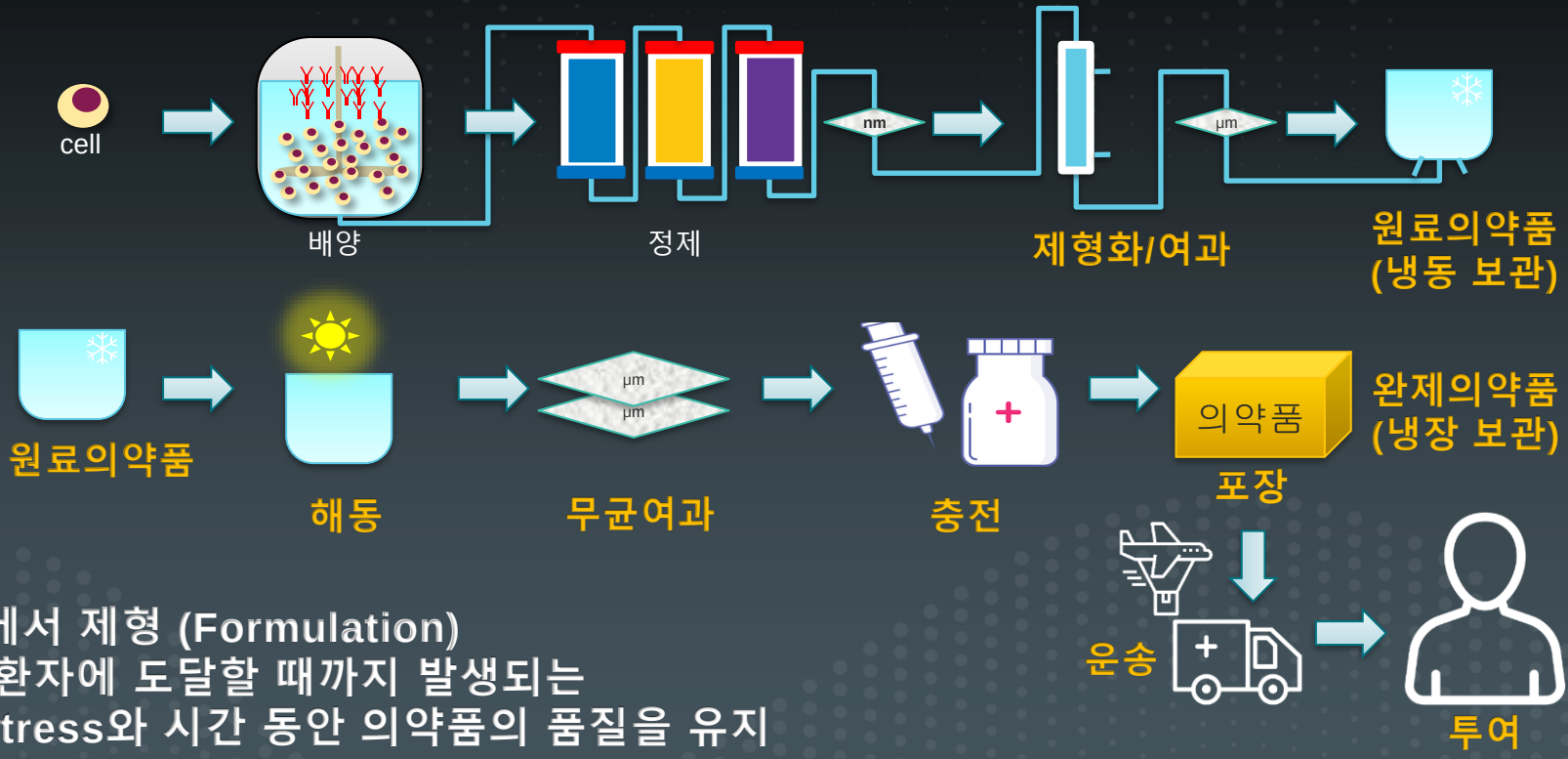
DISCOVERY SUMMIT

EXPLORING DATA
INSPIRING INNOVATION

권상오, 종근당

바이오의약품 액상 제형 개발에서의 DoE 활용

일반적인 유전자재조합의약품의 제조 공정



의약품에서 제형 (Formulation)
: 제조~환자에 도달할 때까지 발생되는
각종 stress와 시간 동안 의약품의 품질을 유지

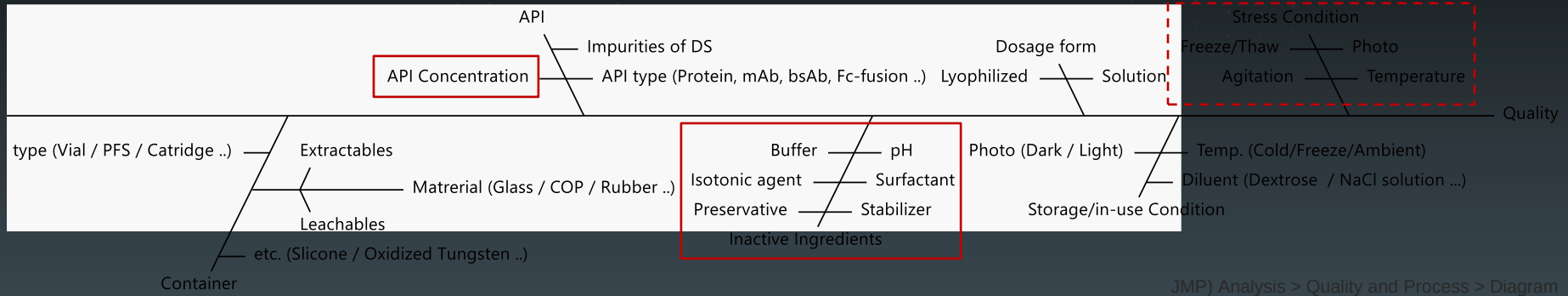
바이오의약품의 제형개발의 목적

- 안정성 (Stability)
- 편의성 (Patient friendly)

- 투여 경로와 형태
- 첨가제 조성, pH, 주성분 함량 → 제형 연구

바이오의약품의 제형연구의 특징

- 바이오의약품 품질에 영향을 미치는 요인 (완제의약품 관점)



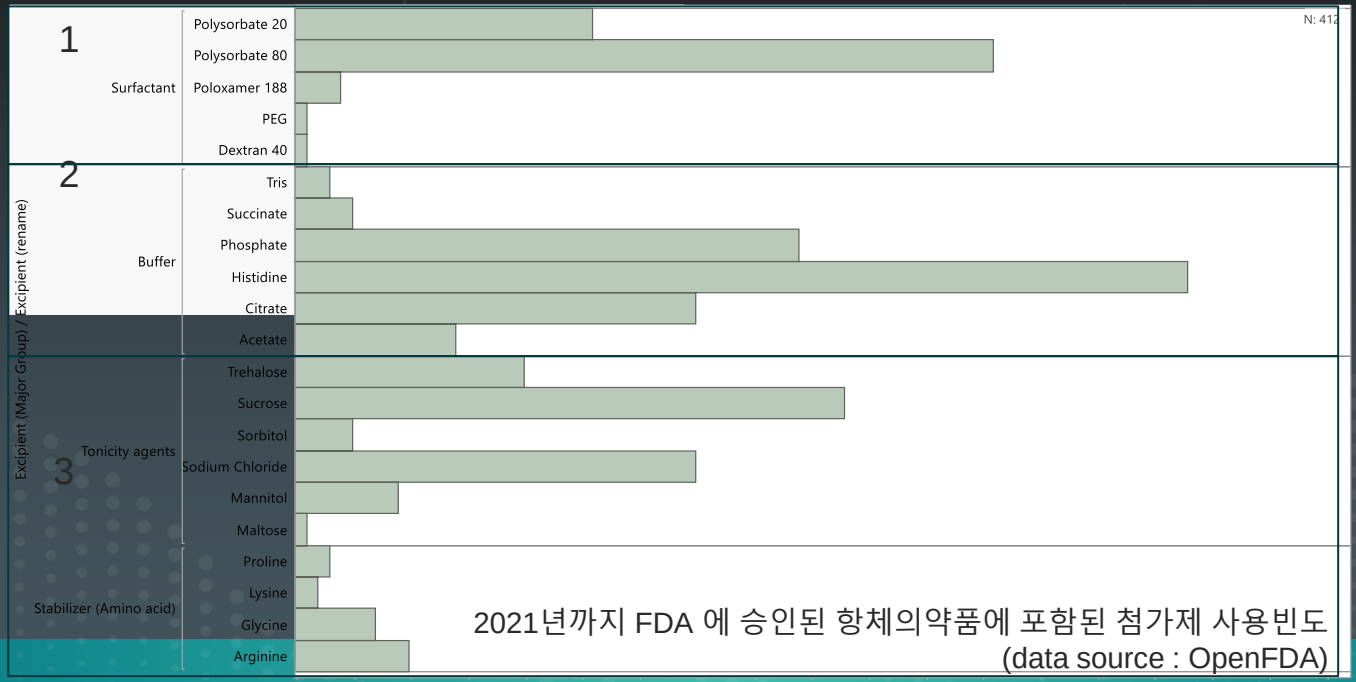
JMP) Analysis > Quality and Process > Diagram

- 제형 (formulation) 연구에서 main factor
  - API Concentration
  - Type / Concentration of Inactive Ingredients
  - Stress condition (Time)

} Factors for Design

바이오의약품의 제형 연구 - Screening

- 일반적인 조성 : API + Buffer (pH) + Isotonic agent/stabilizer + surfactant
- 각 그룹별로 OFAT or DoE 시험을 통해 가장 안정한 첨가제 조합 screening



바이오의약품의 제형 연구 – 최적화 (Case study)

- Custom Design (D-optimal)

Responses

Add Response | Remove | Number of Responses...

Response Name	Goal	Lower Limit	Upper Limit	Importance
Osmolarility	Match Target	240	360	1
pH	Match Target	-0.2	0.2	1
Impurity A (%)	Minimize	.	5	1
Impurity B (%)	Minimize	.	3	1
Variants A (%)	Minimize	.	.	1
Variants B (%)	Minimize	.	.	1

Factors

Add Factor | Remove | Add N Factors 1

Name	Role	Changes	Values	
pH	Continuous	Easy	5	7
API conc. (mg/mL)	Continuous	Easy	50	150
Buffer (mM)	Continuous	Easy	5	20
Isotonic agent (mg/mL)	Continuous	Easy	30	90
Surfactant (mg/mL)	Continuous	Easy	0.05	0.02

Minimum 5 Factor

Model

Main Effects | Interactions | RSM | Cross | Powers | Remove Term

Name	Estimability	
Intercept	Necessary	
pH	Necessary	Main
API conc. (mg/mL)	Necessary	Main
Buffer (mM)	Necessary	Main
Isotonic agent (mg/mL)	Necessary	Main
Surfactant (mg/mL)	Necessary	Main
pH*API conc. (mg/mL)	Necessary	Interaction
pH*Buffer (mM)	Necessary	Interaction
pH*Isotonic agent (mg/mL)	Necessary	Interaction
pH*Surfactant (mg/mL)	Necessary	Interaction
API conc. (mg/mL)*Buffer (mM)	Necessary	Interaction
API conc. (mg/mL)*Isotonic agent (mg/mL)	Necessary	Interaction
API conc. (mg/mL)*Surfactant (mg/mL)	Necessary	Interaction
Buffer (mM)*Isotonic agent (mg/mL)	Necessary	Interaction
Buffer (mM)*Surfactant (mg/mL)	Necessary	Interaction
Isotonic agent (mg/mL)*Surfactant (mg/mL)	Necessary	Interaction
pH*pH	Necessary	Power
API conc. (mg/mL)*API conc. (mg/mL)	Necessary	Power
Buffer (mM)*Buffer (mM)	Necessary	Power
Isotonic agent (mg/mL)*Isotonic agent (mg/mL)	Necessary	Power
Surfactant (mg/mL)*Surfactant (mg/mL)	Necessary	Power

바이오의약품의 제형 연구 – 최적화 (Case study)

- Custom Design vs. Classic design for Optimization

No. of Factor	Custom Design	½ RSM	RSM	Box-Behnken
5	21~28 (≒24)	≒32	≒52	≒46
6	28~32 (≒31)	≒53	≒90	≒54
7	36~40 (≒39)	≒88	≒152	≒62

- Custom Design 에서 적절한 run 수는 ??

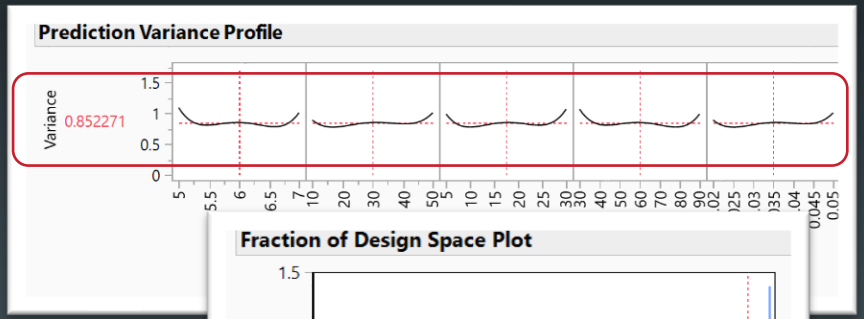
바이오의약품의 제형 연구 – 최적화 (Case study)

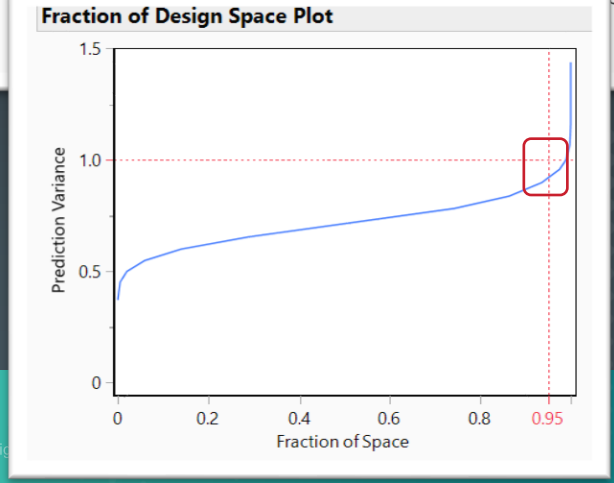
- Design Evaluation으로 Custom Design 의 적절한 run 수와 factor range를 판단
  - Power - Anticipated Coefficient / Prediction Variance Profile / Fraction of Design Space Plot
  - Thomas A. Little, BioPharm International, (2017), Volume 30, Issue 3
    Process Characterization Essentials: : Process Understanding and Health Authorities Guidance

Power Analysis

Significance Level	0.05
Anticipated RMSE	1

Term	Anticipated Coefficient	Power
Intercept	1	0.122
pH	1.5	0.986
API conc. (mg/mL)	1.5	0.978
Buffer (mM)	1.5	0.979
Isotonic agent (mg/mL)	1.5	0.979
Surfactant (mg/mL)	1.5	0.978
pH*API conc. (mg/mL)	1.5	0.974
pH*Buffer (mM)	1.5	0.978
pH*Isotonic agent (mg/mL)	1.5	0.978
pH*Surfactant (mg/mL)	1.5	0.974
API conc. (mg/mL)*Buffer (mM)	1.5	0.975
API conc. (mg/mL)*Isotonic agent (mg/mL)	1.5	0.972
API conc. (mg/mL)*Surfactant (mg/mL)	1.5	0.967
Buffer (mM)*Isotonic agent (mg/mL)	1.5	0.971
Buffer (mM)*Surfactant (mg/mL)	1.5	0.972
Isotonic agent (mg/mL)*Surfactant (mg/mL)	1.5	0.975
pH*pH	4.5	0.969
API conc. (mg/mL)*API conc. (mg/mL)	3.5	0.959
Buffer (mM)*Buffer (mM)	4.5	0.973
Isotonic agent (mg/mL)*Isotonic agent (mg/mL)	4.5	0.973
Surfactant (mg/mL)*Surfactant (mg/mL)	3.5	0.959

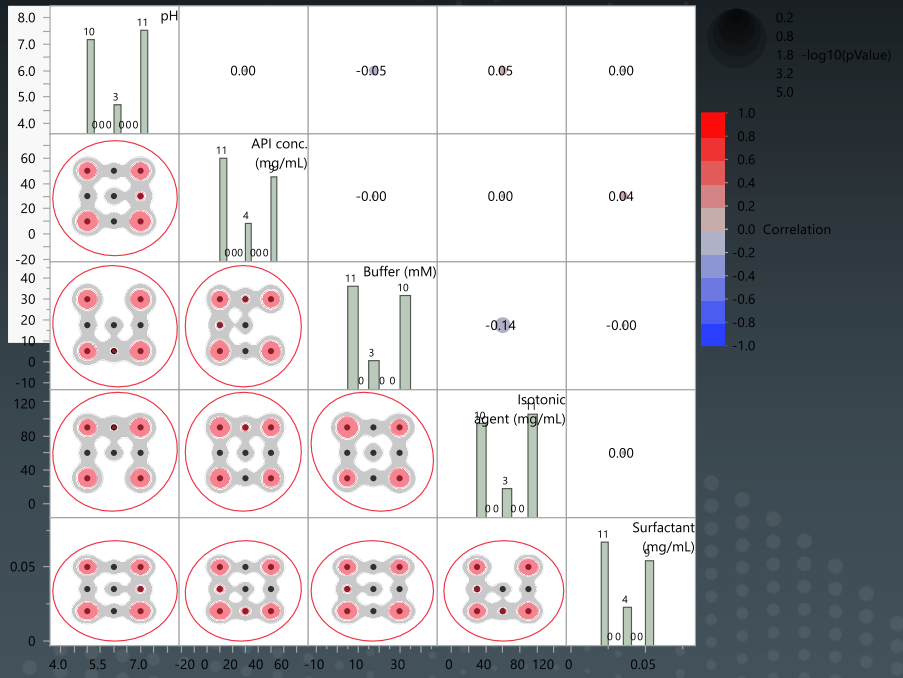




바이오의약품의 제형 연구 – 최적화 (Case study)

- 24 run → Stress condition (40 ºC , ~6 week)

	Sample No.	pH	API conc. (mg/mL)	Buffer (mM)	Isotonic agent (mg/mL)	Surfactant (mg/mL)
1	F1	5.0	10	5.0	30	0.02
2	F2	5.0	10	5.0	90	0.05
3	F3	5.0	10	17.5	30	0.035
4	F4	5.0	10	30.0	30	0.05
5	F5	5.0	10	30.0	90	0.02
6	F6	5.0	30	30.0	60	0.02
7	F7	5.0	50	5.0	30	0.05
8	F8	5.0	50	5.0	90	0.02
9	F9	5.0	50	30.0	30	0.02
10	F10	5.0	50	30.0	90	0.05
11	F11	6.0	10	5.0	90	0.02
12	F12	6.0	30	17.5	90	0.05
13	F13	6.0	50	5.0	60	0.035
14	F14	7.0	10	5.0	30	0.05
15	F15	7.0	10	5.0	90	0.035
16	F16	7.0	10	17.5	60	0.02
17	F17	7.0	10	30.0	30	0.02
18	F18	7.0	10	30.0	90	0.05
19	F19	7.0	30	5.0	90	0.02
20	F20	7.0	30	30.0	30	0.035
21	F21	7.0	50	5.0	30	0.02
22	F22	7.0	50	5.0	90	0.05
23	F23	7.0	50	30.0	30	0.05
24	F24	7.0	50	30.0	90	0.02



바이오의약품의 제형 연구 – 최적화 (Case study)

Factor (X)
API Conc
Buffer
pH
Ingredient A
Ingredient B

	Sample No.	pH	API conc. (mg/mL)	Buffer (mM)	Isotonic agent (mg/mL)	Surfactant (mg/mL)
1	F1	5.0	10	5.0	30	0.02
2	F2	5.0	10	5.0	90	0.05
3	F3	5.0	10	17.5	30	0.035
4	F4	5.0	10	30.0	30	0.05
5	F5	5.0	10	30.0	90	0.02
6	F6	5.0	30	30.0	60	0.02
7	F7	5.0	50	5.0	30	0.05
8	F8	5.0	50	5.0	90	0.02
9	F9	5.0	50	30.0	30	0.02
10	F10	5.0	50	30.0	90	0.05
11	F11	6.0	10	5.0	90	0.02
12	F12	6.0	30	17.5	90	0.05
13	F13	6.0	50	5.0	60	0.035
14	F14	7.0	10	5.0	30	0.05
15	F15	7.0	10	5.0	90	0.035
16	F16	7.0	10	17.5	60	0.02
17	F17	7.0	10	30.0	30	0.02
18	F18	7.0	10	30.0	90	0.05
19	F19	7.0	30	5.0	90	0.02
20	F20	7.0	30	30.0	30	0.035
21	F21	7.0	50	5.0	30	0.02
22	F22	7.0	50	5.0	90	0.05
23	F23	7.0	50	30.0	30	0.05
24	F24	7.0	50	30.0	90	0.02

Custom Design

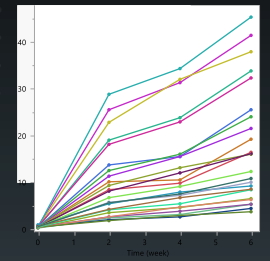
Stress

Time 0 / 2 / 4 / 6 ..

Qaulity A	Qaulity B	Qaulity C
90	0.001	5
99	0.01	4
85	0.01	2
69	0.001	4
48	0.01	2
56	0.001	6
58	0.001	8
85	0.01	4
60	0.01	9
90	0.001	5
99	0.001	10
85	0.01	2
69	0.001	5
48	0.01	2
56	0.01	6
58	0.001	8
85	0.0055	4
60	0.0055	10
90	0.0055	11
99	0.0055	6
85	0.0055	9
69	0.0055	8
48	0.0055	6
56	0.0055	5
58	0.001	3
58	0.01	2
60	0.0055	1
60	0.0055	2

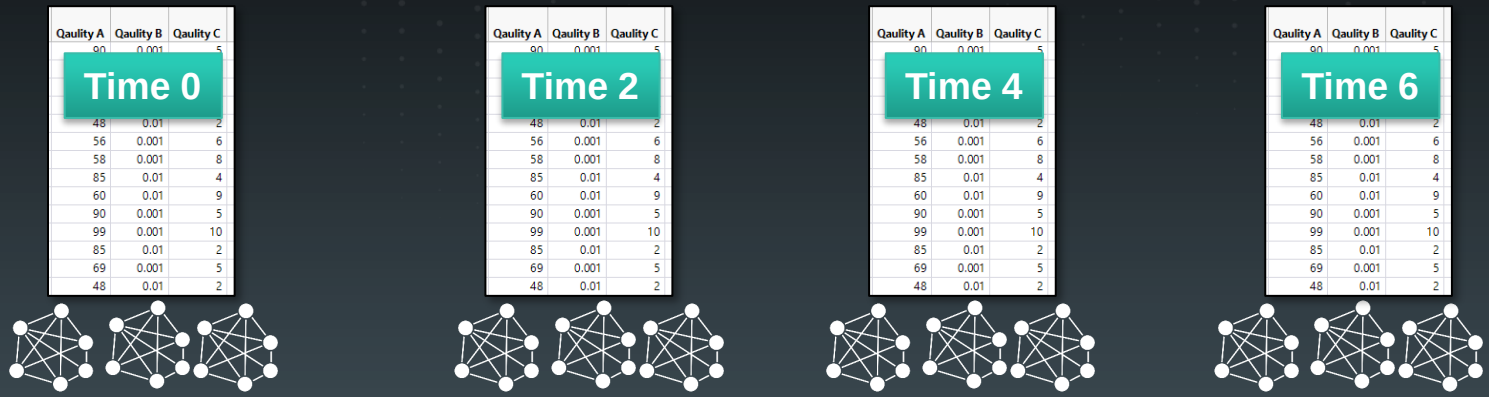
Analysis

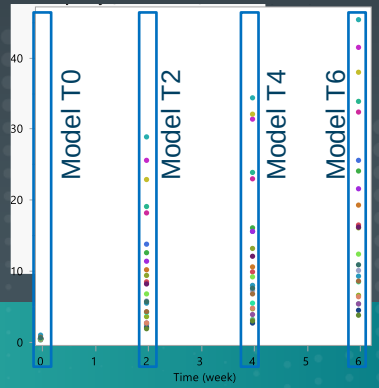
Modeling



바이오의약품의 제형 연구 – Time 의 처리?

- time point 마다 modeling? (Time point x analysis)





바이오의약품의 제형 연구 – Time 의 처리?

- 특정 time point 만 modeling? (1개 Time point 만 modeling 에 사용)

Time 0

Qaulity A	Qaulity B	Qaulity C
90	0.001	5
48	0.01	2
56	0.001	6
58	0.001	8
85	0.01	4
60	0.01	9
90	0.001	5
99	0.001	10
85	0.01	2
69	0.001	5
48	0.01	2

Time 2

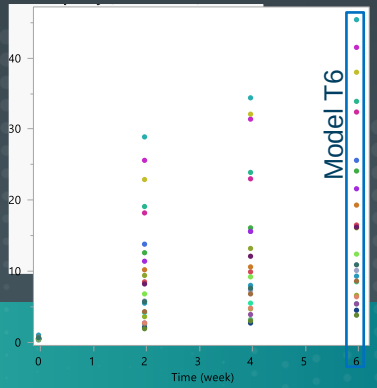
Qaulity A	Qaulity B	Qaulity C
90	0.001	5
48	0.01	2
56	0.001	6
58	0.001	8
85	0.01	4
60	0.01	9
90	0.001	5
99	0.001	10
85	0.01	2
69	0.001	5
48	0.01	2

Time 4

Qaulity A	Qaulity B	Qaulity C
90	0.001	5
48	0.01	2
56	0.001	6
58	0.001	8
85	0.01	4
60	0.01	9
90	0.001	5
99	0.001	10
85	0.01	2
69	0.001	5
48	0.01	2

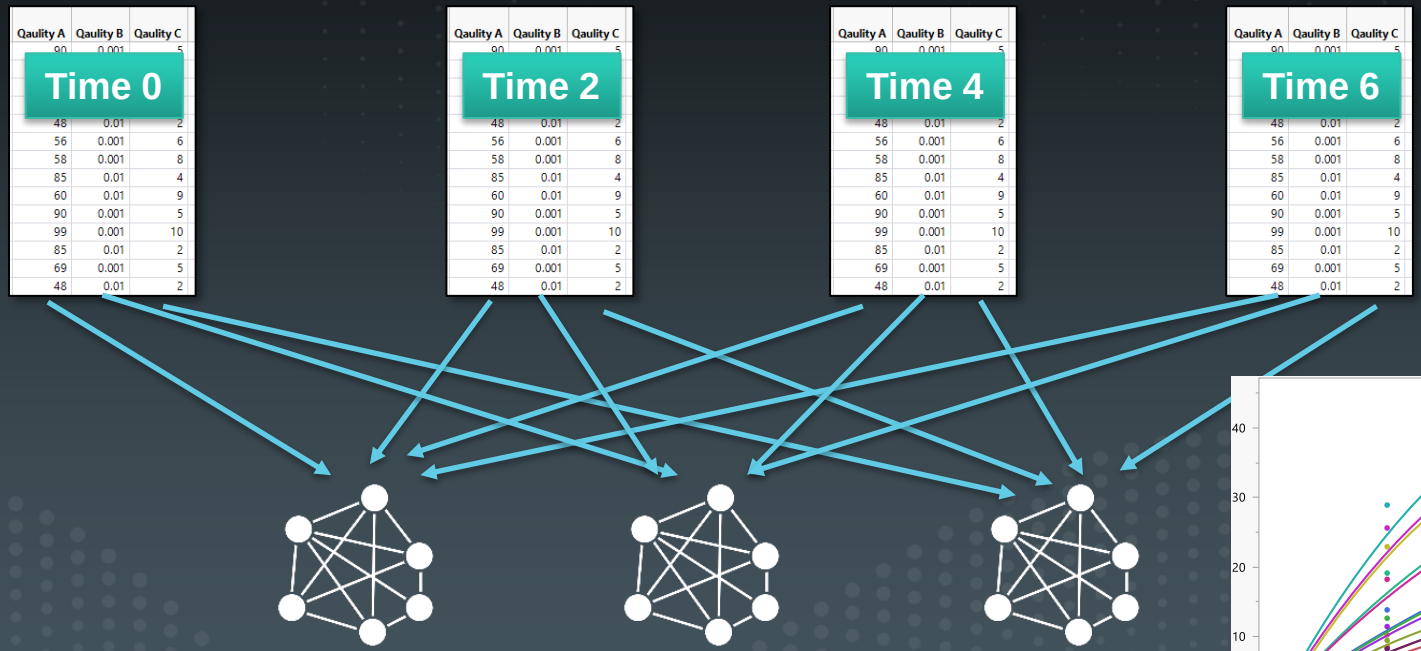
Time 6

Qaulity A	Qaulity B	Qaulity C
90	0.001	5
48	0.01	2
56	0.001	6
58	0.001	8
85	0.01	4
60	0.01	9
90	0.001	5
99	0.001	10
85	0.01	2
69	0.001	5
48	0.01	2



바이오의약품의 제형 연구 – Time 의 처리?

- time point 를 변수(factor)로 포함하여 modeling? (모든 데이터를 포함)



바이오의약품의 제형 연구 – 최적화 (Case study)

- time point 를 별도의 변수(factor)로 포함

Factors A~E	Response Q (Time = 0)	Response Q (Time = 1)	Response Q (Time = 2)	Response Q (Time = 4)
Sample 1	0	1	2	3
Sample 2	0	1.5	3	4.5
Sample 3	1.5	2.5	3.5	4.5
…	…	…	…	…

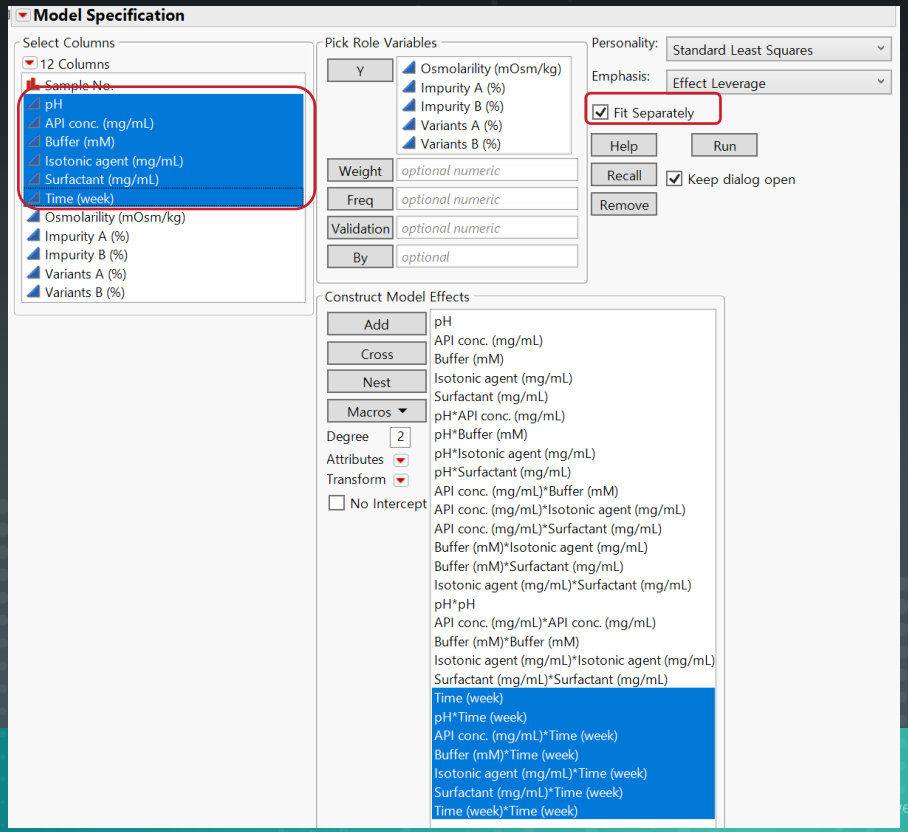
Factors A~E	Time	Response Q
Sample 1	0	0
Sample 2	0	0
Sample 3	0	1.5
Sample 1	1	1
Sample 2	1	1.5
Sample 3	1	2.5
…	…	…

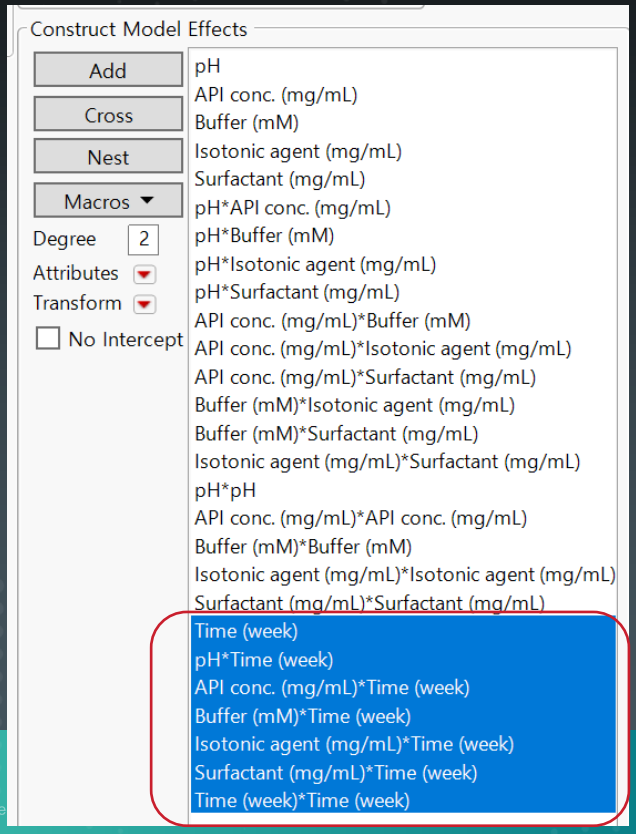
바이오의약품의 제형 연구 – 최적화 (Case study)

	Sample No.	pH	API conc. (mg/mL)	Buffer (mM)	Isotonic agent (mg/mL)	Surfactant (mg/mL)	Time (week)	Osmolarility (mOsm/kg)	Impurity A (%)	Impurity B (%)
1	F1	5.0	10	5.0	30	0.02	0	171	0.4	1.3
2	F2	5.0	10	5.0	90	0.05	0	286	0.5	1.6
3	F3	5.0	10	17.5	30	0.035	0	179	0.4	1.2
4	F4	5.0	10	30.0	30	0.05	0	189	0.4	1.7
5	F5	5.0	10	30.0	90	0.02	0	300	0.4	0.9
6	F6	5.0	30	30.0	60	0.02	0	256	0.4	0.9
7	F7	5.0	50	5.0	30	0.05	0	182	0.6	1.4
8	F8	5.0	50	5.0	90	0.02	0	313	0.5	0.8
9	F9	5.0	50	30.0	30	0.02	0	205	0.5	0.5
10	F10	5.0	50	30.0	90	0.05	0	331	0.6	0.9
11	F11	6.0	10	5.0	90	0.02	0	246	0.4	1.1
12	F12	6.0	30	17.5	90	0.05	0	268	1	1
13	F13	6.0	50	5.0	60	0.035	0	238	0.5	0.9
14	F14	7.0	10	5.0	30	0.05	0	197	0.3	1.4
15	F15	7.0	10	5.0	90	0.035	0	349	0.5	0.9
16	F16	7.0	10	17.5	60	0.02	0	283	0.5	0.9
17	F17	7.0	10	30.0	30	0.02	0	218	0.4	0.7
18	F18	7.0	10	30.0	90	0.05	0	367	0.5	1.2
19	F19	7.0	30	5.0	90	0.02	0	353	0.5	1
20	F20	7.0	30	30.0	30	0.035	0	225	0.5	0.8
21	F21	7.0	50	5.0	30	0.02	0	208	0.5	1
22	F22	7.0	50	5.0	90	0.05	0	376	0.7	0.6
23	F23	7.0	50	30.0	30	0.05	0	229	0.5	1.4
24	F24	7.0	50	30.0	90	0.02	0	372	0.6	0.8
25	F1	5.0	10	5.0	30	0.02	1	•	8.2	1
26	F2	5.0	10	5.0	90	0.05	1	•	4.9	1.5
27	F3	5.0	10	17.5	30	0.035	1	•	6.9	1.5
28	F4	5.0	10	30.0	30	0.05	1	•	6.2	1
29	F5	5.0	10	30.0	90	0.02	1	•	5.3	0.8
30	F6	5.0	30	30.0	60	0.02	1	•	10.3	2.4
31	F7	5.0	50	5.0	30	0.05	1	•	16.3	3
32	F8	5.0	50	5.0	90	0.02	1	•	13.5	2.6
33	F9	5.0	50	30.0	30	0.02	1	•	17.8	3.2
34	F10	5.0	50	30.0	90	0.05	1	•	10.2	2
35	F11	6.0	10	5.0	90	0.02	1	•	2.1	0.8
36	F12	6.0	30	17.5	90	0.05	1	•	3.5	0.8
37	F13	6.0	50	5.0	60	0.035	1	•	5.3	1.2
38	F14	7.0	10	5.0	30	0.05	1	•	1.5	0.8
39	F15	7.0	10	5.0	90	0.035	1	•	1.2	0.9
40	F16	7.0	10	17.5	60	0.02	1	•	1.6	1.3

바이오의약품의 제형 연구 – 최적화 (Case study)

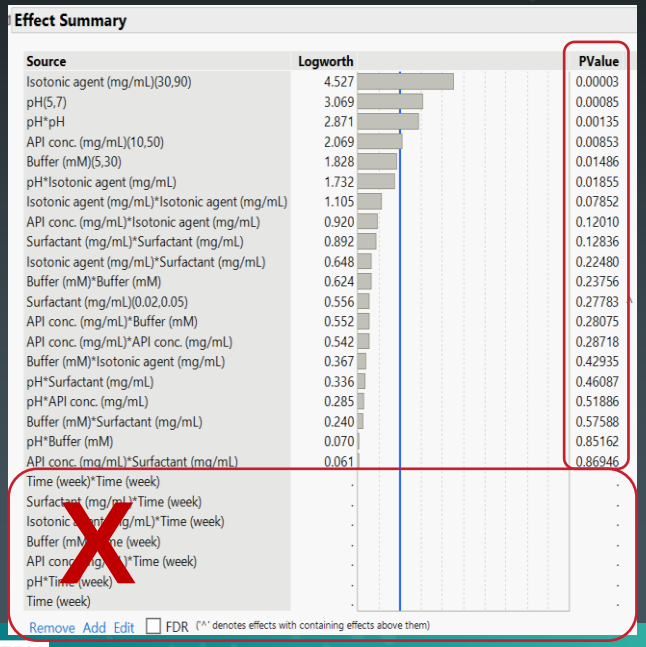
- Modeling – Time 포함 (Main effect / Interaction / Power)

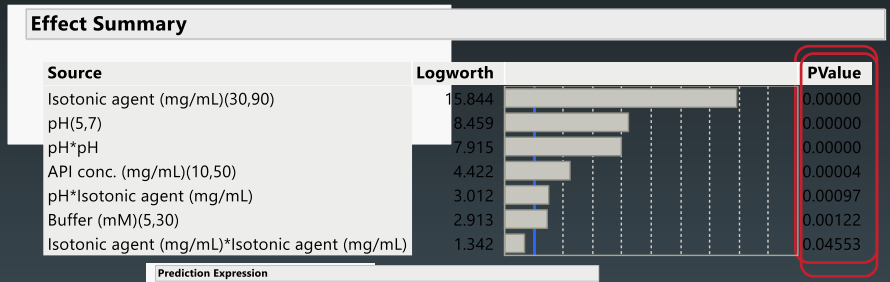


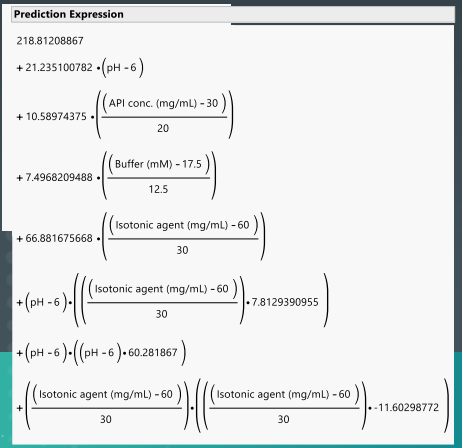


바이오의약품의 제형 연구 – 최적화 (Case study)

- 단일 point 평가 (Initial point, T0) – Stress / Time 에 따라 변화가 없는 Quality Attributes
- 예) 삼투압 – 목표범위 약 260 ~ 320 mOsm/kg 의 model 최적화

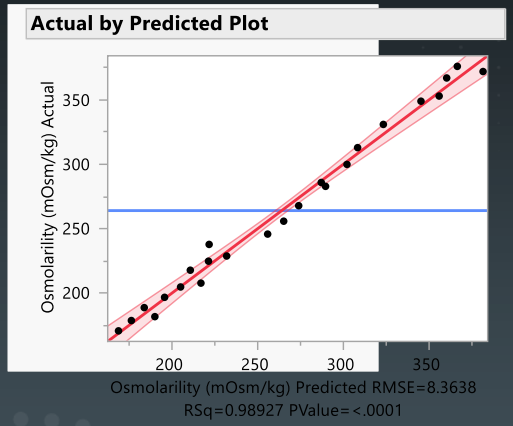


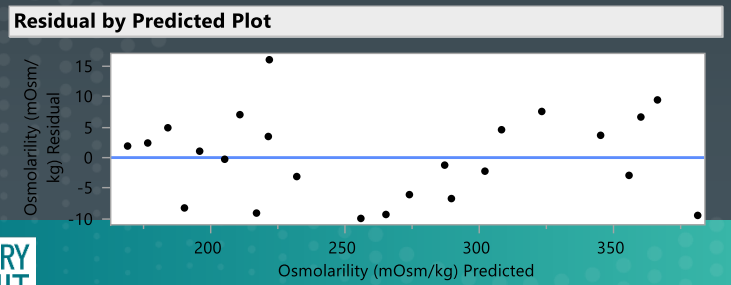




바이오의약품의 제형 연구 – 최적화 (Case study)

- 단일 point 평가 (Initial point, T0) – Stress / Time 에 따라 변화가 없는 Quality Attributes
- 예) 삼투압 – 목표범위 약 260 ~ 320 mOsm/kg 의 model 최적화





Summary of Fit

RSquare	0.989265
RSquare Adj	0.984569
Root Mean Square Error	8.363814
Mean of Response	264.2083
Observations (or Sum Wgts)	24

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	7	103144.70	14735.0	210.6397
Error	16	1119.25	70.0	Prob > F
C. Total	23	104263.96		<.0001 *

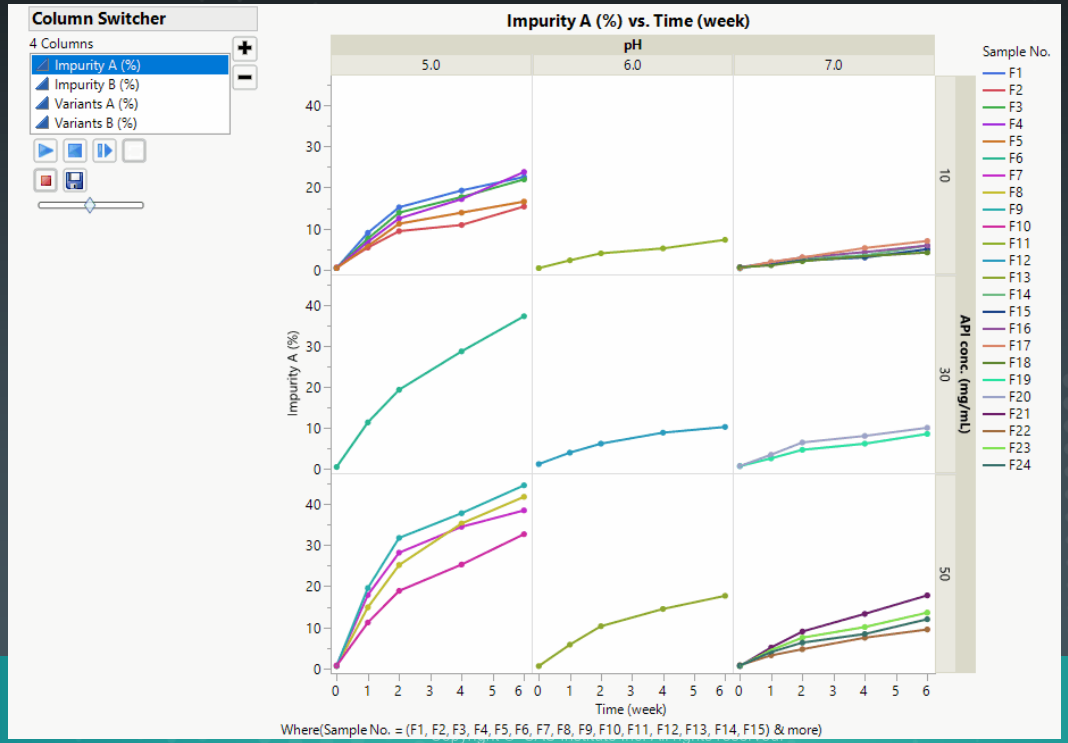
Press

Residual	SSE	RMSE	RSquare
Press	3632.1648413	12.3020406	0.9652
Ordinary	1119.254072	8.36381369	0.9893

Predicted R^2

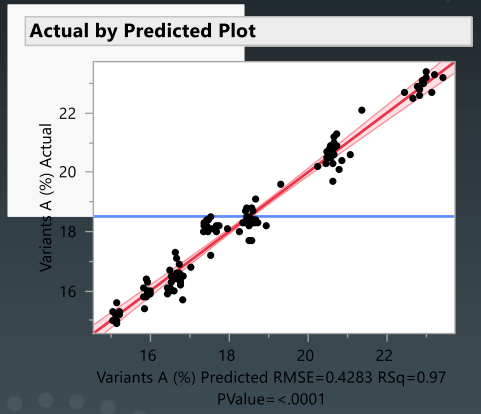
바이오의약품의 제형 연구 – 최적화 (Case study)

- TIme point 평가 – Stress / Time 에 따라 경향을 보이는 Quality Attributes
- 예) Product-related Impurities / Variants



바이오의약품의 제형 연구 – 최적화 (Case study)

- TIme point 평가 – Stress / Time 에 따라 경향을 보이는 Quality Attributes
- 예) Product-related Impurities / Variants



Summary of Fit

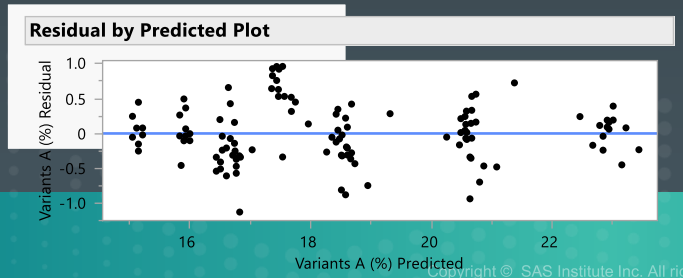
RSquare	0.970037
RSquare Adj	0.967586
Root Mean Square Error	0.428335
Mean of Response	18.51417
Observations (or Sum Wgts)	120

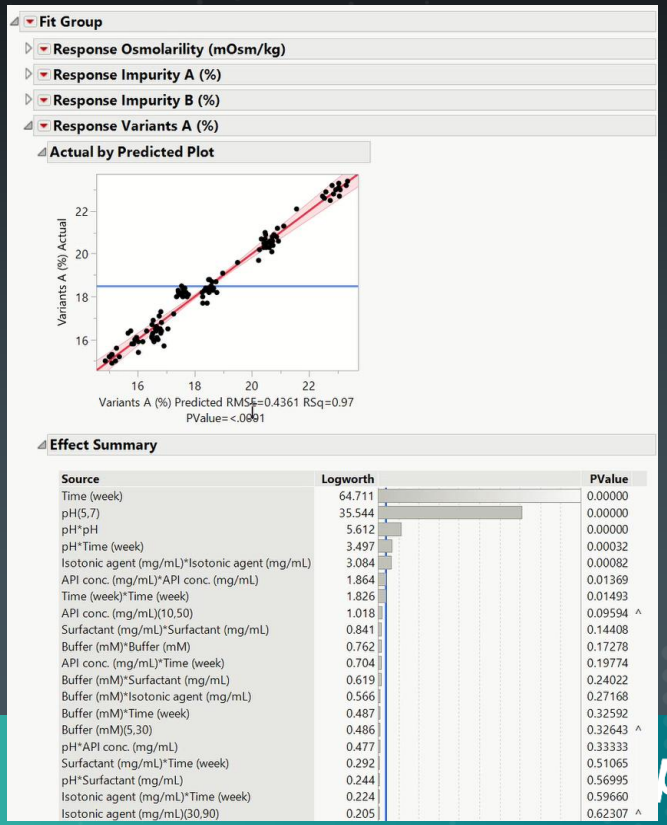
Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	9	653.38412	72.5982	395.6935
Error	110	20.18180	0.1835	Prob > F
C. Total	119	673.56592		<.0001 *

Press

Residual	SSE	RMSE	RSquare
Press	24.332954904	0.45030503	0.9639
Ordinary	20.181798923	0.42833503	0.9700





Source	Logworth	PValue
Time (week)	64.711	0.00000
pH(5,7)	35.544	0.00000
pH*pH	5.612	0.00000
pH*Time (week)	3.497	0.00032
Isotonic agent (mg/mL)*Isotonic agent (mg/mL)	3.084	0.00082
API conc. (mg/mL)*API conc. (mg/mL)	1.864	0.01369
Time (week)*Time (week)	1.826	0.01493
API conc. (mg/mL)(10,50)	1.018	0.09594 ^
Surfactant (mg/mL)*Surfactant (mg/mL)	0.841	0.14408
Buffer (mM)*Buffer (mM)	0.762	0.17278
API conc. (mg/mL)*Time (week)	0.704	0.19774
Buffer (mM)*Surfactant (mg/mL)	0.619	0.24022
Buffer (mM)*Isotonic agent (mg/mL)	0.566	0.27168
Buffer (mM)*Time (week)	0.487	0.32592
Buffer (mM)(5,30)	0.486	0.32643 ^
pH*API conc. (mg/mL)	0.477	0.33333
Surfactant (mg/mL)*Time (week)	0.292	0.51065
pH*Surfactant (mg/mL)	0.244	0.56995
Isotonic agent (mg/mL)*Time (week)	0.224	0.59660
Isotonic agent (mg/mL)(30,90)	0.205	0.62307 ^

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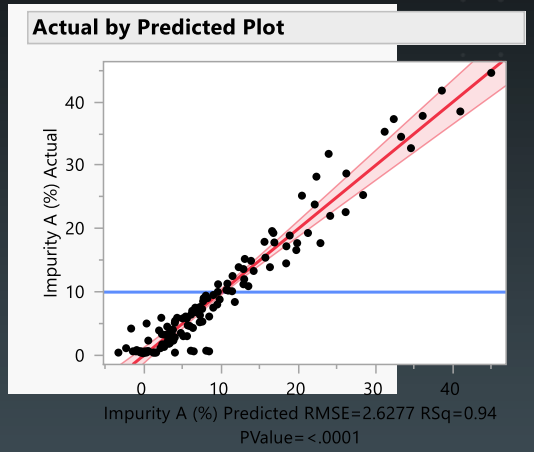
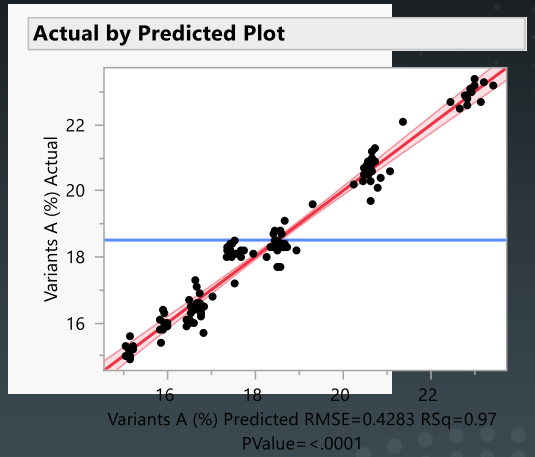
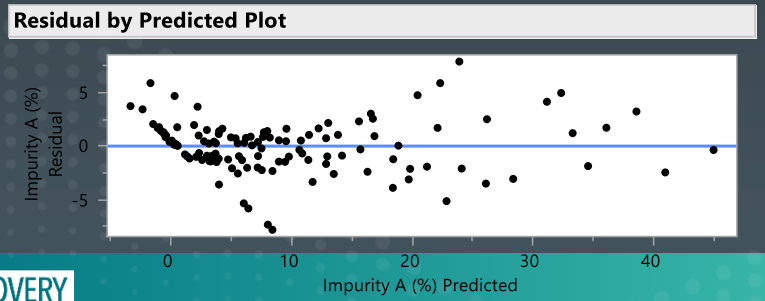
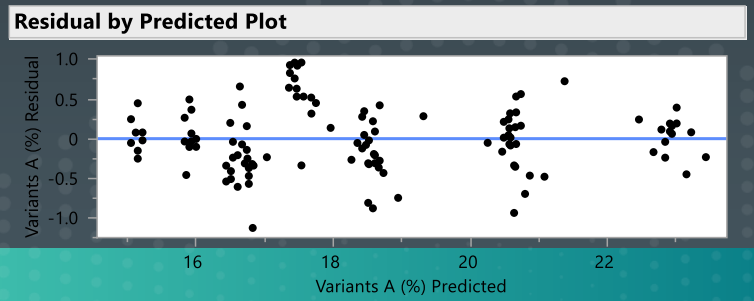
바이오의약품의 제형 연구 – 최적화 (Case study)

- TIme point 평가 – Stress / Time 에 따라 경향을 보이는 Quality Attributes



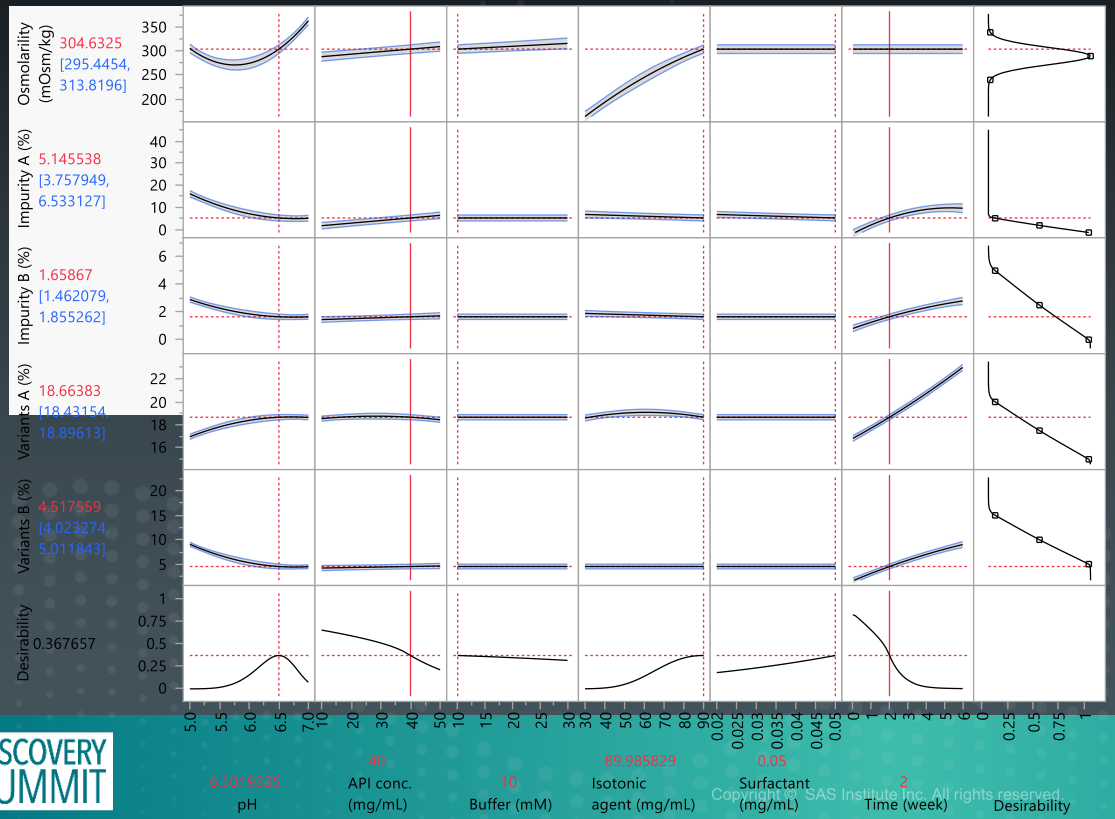






바이오의약품의 제형 연구 – 최적화 (Case study)

- Profiler를 활용한 최적화 도출



- 삼투압 – Mixture design으로 설계 가능하나, 최적화에서 범위 탐색으로도 설정 가능
- API conc. – QTPP (dosage form / strength 등)에 맞게 적절히 설정
- Time point 는 Initial 이 아닌 적절한 point를 고정하여 최적화
- 각 첨가제들의 농도는 적절한 범위 / 용례에 맞추어 제한된 범위에서 최적화 수행

바이오의약품 액상 제형 개발에서의 DoE 활용

- 의약품에서 제형 (Formulation)
  : 제조~환자에 도달할 때까지 발생되는 각종 stress와 시간 동안 의약품의 품질을 유지
- 제형연구에서의 시험계획법 적용의 어려움
  - 일반적인 제형의 경우 5 factor 이상으로 많은 시험 run 수가 필요
    → Custom Design 을 활용하여 적은 시험 수로 효율적인 시험 진행 가능
  - Stress 경과 "시간"에 따라 분석 결과 (Response) 가 증가함. → 결과 해석 (modeling) 난해
    → Time을 factor로 처리: 단일 point 해석보다 정확도 높고, 복수의 point 해석보다 간단한 modeling 구축 및 결과 해석
- 기타 활용 영역
  - 대부분의 안정성 연구 결과의 해석에 적용 가능
  - Formulation robustness study (Long-term stability)
    → Simulation을 통한 첨가제 / pH 등의 제형 robustness 범위 검증 및 control strategy 확립
  - 제형 외에 시험 point 가 존재하는 연구 결과의 해석 (배양기간별 시험 결과 해석)

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restc1235@gmail.com

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