Minitab® & Design of experiments (DoE)

Drug development case study

Milan, May 18th 2017

Almirall

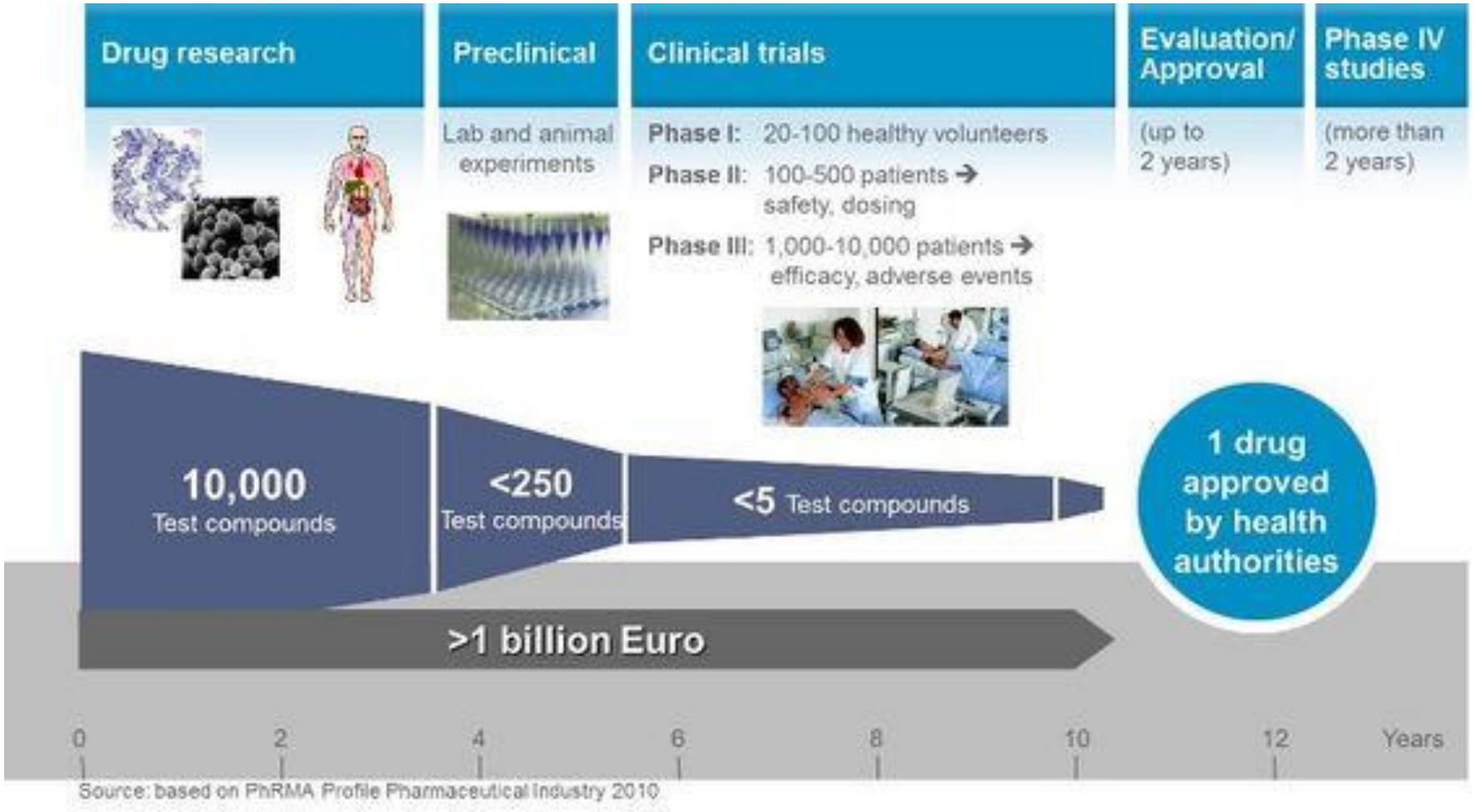
Solutions with you in mind

Dr Simone Sarno – Pharmaceutical Development Specialist - Polichem, an Almirall company, Lugano

Summary

- ✓ Pharmaceutical development steps
- ✓ The new paradigma
- ✓ Quality by Design (QbD) for pharmaceuticals (overview)
- ✓ Design of Experiments (DoE)
- ✓ Drug development case study
- ✓ Overall results & Conclusions
- ✓ Next Steps
- ✓ Q&A

Pharmaceutical development steps



Source: based on PhRMA Profile Pharmaceutical Industry 2010

Almirall

The new paradigma

*From **quality by testing** (i.e. compliance with final specifications)...*

*...to **Quality by Design (QbD)***

Quality by Design (QbD) for pharmaceuticals - overview

- QbD keypoint:

"Quality cannot be tested in products, i.e. quality should be built in by design".

"La qualità non può essere valutata sul prodotto, ma deve essere costruita insieme al prodotto".

- QbD is a systematic and multidisciplinar approach, based on prefixed objectives (Target Product Profile, TTP). It is focused on the understanding of the final product, its manufacturing process and the relations between quality and biopharmaceutical performance. Final attributes of finish product should be identified and monitored, in order to understand the direct impact on the quality and on the performance: CRITICAL QUALITY ATTRIBUTES (CQAs).

QbD tools

- ✓ Quality Target Product Profile (QTPP)
- ✓ Quality Risk Management (QRM)
- ✓ Design of Experiments (DoE)
- ✓ Critical Quality Attribute (CQA)
- ✓ Knowledge Management (KM)
- ✓ Critical Process Parameter (CPP)
- ✓ Control Strategy (CS)
- ✓ Process Analytical Technology (PAT)
- ✓ Lifecycle Management (LCM)
- ✓ Continuous Improvement (CI)

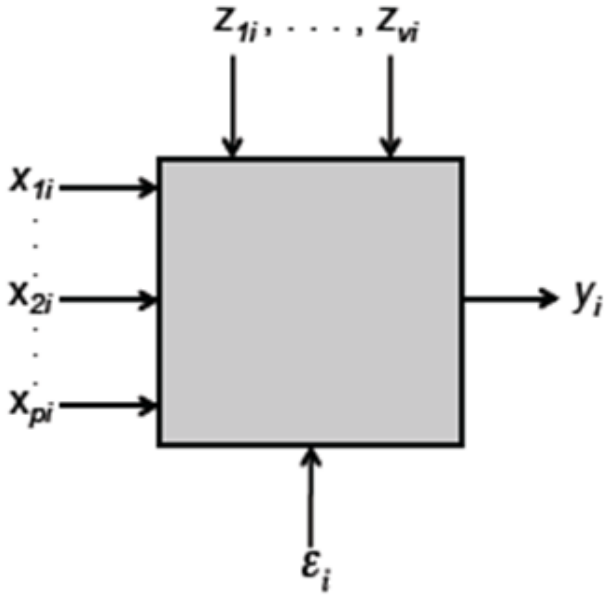
Almirall

Design of Experiments – DoE

- ✓ DoE, together with Risk Assessment and PAT, represents one of the main tools in the application of QbD
- ✓ At the end of 90's there was a change in the concept of quality. We moved from quality as compliance with final specifications to quality by design
- ✓ There are several factors and interactions between factors to be monitored during a manufacturing process for a drug product
- ✓ An efficient plan of activities is essential to hit the target and avoid waste
- ✓ DoE allows to define the «design space», in order to better understand the robustness of a process and its relation with the quality of the final product

DoE

- ✓ X_i → FACTORS
- ✓ Z_i → VARIABLES (LEVELS) that can contribute to the final result
- ✓ ε_i → Experimental error
- ✓ y_i → RESPONSE



DoE

✓ Phases:

1. Planning → Factors and levels selection
2. Execution → Analytical data collection
3. Analysis → Statistical data analysis

ANOVA

- Statistical methodology developed in order to verify the level of significance of means between groups.
- It is also called F test, in honour of Sir Ronald Aylmer Fisher (1890- 1962), considered the father of modern statistic.
- Current ANOVA is nevertheless attributed to Mr George W. Snedecor, that in 1934 improved the model previously generated by Fischer.

Drug development case study

Desired target product profile

✓ **Route of admin.:**	topical
✓ **Release type:**	immediate
✓ **Form:**	semi solid
✓ **Critical attribute:**	stratum corneum permeation
✓ **Subjective properties:**	no unpleasant smell
	good spreadability/squeezing properties
✓ **API content:**	1.25 to 10% (TBD)
✓ **Impurities profile*:**	unknown ≤ 0.1%
	specified known ≤ 0.5 to 1%
✓ **Stability:**	≥ 24 months (world wide long term=30°C)
✓ **Pack size:**	40 to 100 g (TBD)

*Based on >2 g/die of API (worst case)

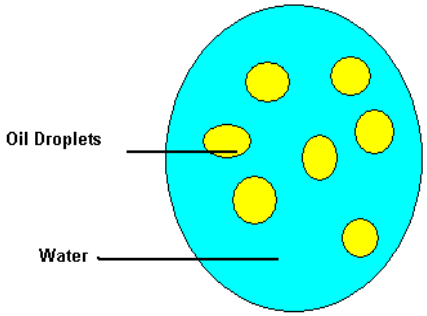
Preliminary feasibility studies

Emulsion was the preferred topical delivery system:

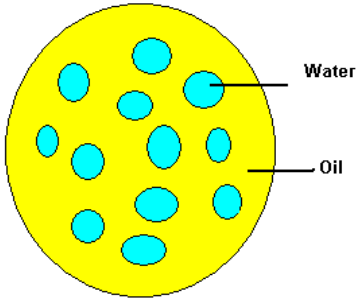
- ✓ Enables variety of ingredients to promote delivery of the API;
- ✓ Aids to restore protective barrier function in damaged skin, providing emollients and hydration.

Three different platforms of emulsion have been formulated to evaluate stability and delivery of the API, distributed differently in the water compartment of the emulsion:

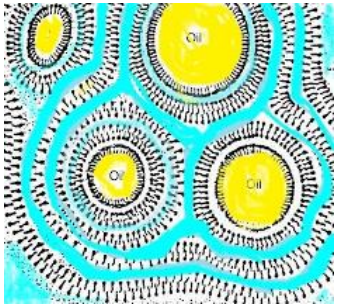
- **Oil-in-Water (O/W)**: API in external phase
- **Water-in-Oil (W/O)**: API in internal phase
- **Multi-lamellar system (LS)**: API in external phase and lamellar system



O/W



W/O



O/W Multi-lamellar

STEP 1: DoE for Qualitative composition evaluation

FACTORS AND LEVELS

A full factorial design has been chosen. A matrix with 24 prototype formulations has been generated. Prototypes have been stressed under accelerated stress conditions.

✓ 4 Factors investigated:

I. Platform (Emulsifier) - 3 levels:
   1. O/W Emulsion **(Platform 1)**
   2. W/O Emulsion **(Platform 2)**
   3. O/W Lamellar Emulsion **(Platform 3)**

II. pH - 2 levels:
   1. 4.5
   2. 6.5

III. %API - 2 levels:
   1. 5%
   2. 15%

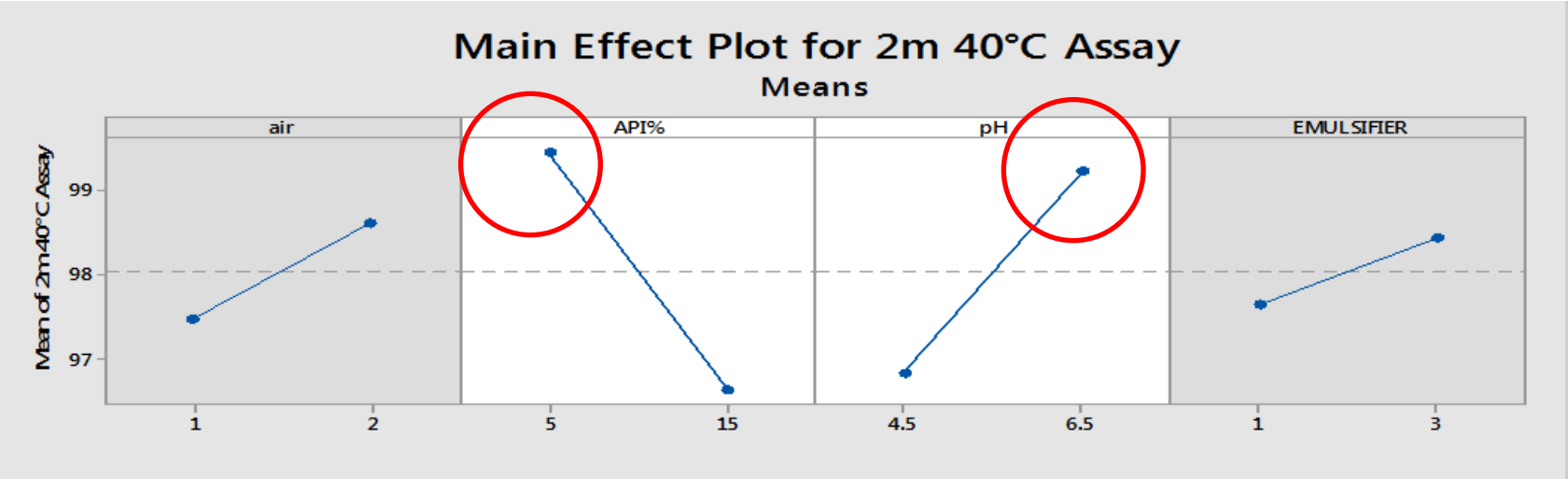
IV. Air Intake - 2 levels:
   1. Low
   2. High

DoE for qualitative optimization: Minitab® EXPANDED MATRIX

RunOrder	Emulsifier	pH	% API	AirIntake
1	2	2	1	2
2	1	2	2	2
3	1	1	1	1
4	3	2	2	1
5	3	2	2	2
6	2	1	1	2
7	2	1	2	1
8	1	1	1	2
9	2	2	1	1
10	3	1	2	1
11	2	2	2	1
12	2	1	1	1
13	1	2	1	1
14	3	1	1	2
15	3	1	1	1
16	3	1	2	2
17	1	1	2	2
18	2	2	2	2
19	3	2	1	2
20	2	1	2	2
21	1	1	2	1
22	1	2	2	1
23	3	2	1	1
24	1	2	1	2

STEP 1: DoE Minitab® RESULTS

(evaluation of API assay after 2 m @ 40°C)

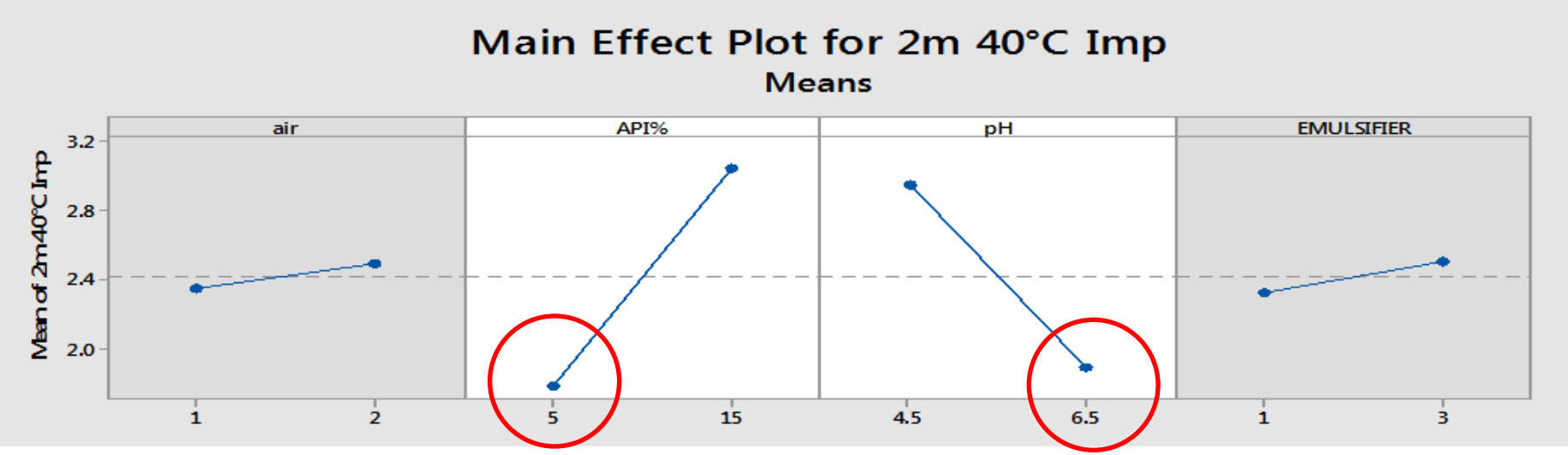


The higher the observed API assay %, the better the performance.

Almirall

STEP 1: DoE Minitab® RESULTS

(evaluation of API related substances after 2 m @ 40°C)



The lower the observed level of total impurities %, the better the performance.

Almirall

STEP 1: Overall Results

Confidential

ATTRIBUTE STUDIED	BEST PERFORMANCE	NEUTRAL	WORST PERFORMANCE
API Assay %	pH 6.5 API% = 5	Platform (1 and 3 are statistically equivalent) Air Intake	pH 4.5 API% = 15
TOTAL % RELATED SUBSTANCES	pH 6.5 API% = 5	Platform (1 and 3 are statistically equivalent) Air Intake	pH 4.5 API% = 15
TECHNOLOGICAL PROPERTIES (viscosity and pH variations, phases separation)		Platform (1 and 3 are equivalent)	Platform 2

BEST OVERALL PERFORMANCES	
Platform:	1 or 3
%API:	5%
pH:	6.5
Air Intake:	Neutral

Almirall

STEP 2: DoE for Quantitative formula optimization

✓ DoE for QUANTITATIVE FORMULA OPTIMIZATION **(with platforms 1 and 3)**

- Important for the fine tuning of the formulation
- For each platform, a full factorial design matrix with central point has been generated
- Prototype formulations have been stressed under accelerated stability conditions

Platform 1

2^4 Full factorial design:

I. Emollient **(Penetration enhancer)**; 2 levels:
   1. 3.5%
   2. 8%

II. Buffer, 2 levels:
   1. NO
   2. YES

III. % API, 2 levels:
   1. 1.25%
   2. 10%

IV. Antioxidant, 2 levels:
   1. 0.05%
   2. 0.1%

Platform 3

2^3 Full factorial design:

I. Emollient **(Penetration enhancer)**; 2 levels:
   1. 3.5%
   2. 8%

II. % API, 2 levels:
   1. 1.25%
   2. 10%

III. Antioxidant, 2 levels:
   1. 0.05%
   2. 0.1%

DoE for quantitative optimiz Platform 1: EXPANDED MATRIX

Run	EMOLLIENT	%API	ANTIOX	BUFFER
1	3.5	1.25	0.05	-1
2	8	1.25	0.05	-1
3	3.5	10	0.05	-1
4	8	10	0.05	-1
5	3.5	1.25	0.1	-1
6	8	1.25	0.1	-1
7	3.5	10	0.1	-1
8	8	10	0.1	-1
9	3.5	1.25	0.05	1
10	8	1.25	0.05	1
11	3.5	10	0.05	1
12	8	10	0.05	1
13	3.5	1.25	0.1	1
14	8	1.25	0.1	1
15	3.5	10	0.1	1
16	8	10	0.1	1
17	5.75	5.625	0.075	0

DoE for quantitative optimiz Platform 3: EXPANDED MATRIX

Run	EMOLLIENT	%API	ANTIOX	BUFFER
1	3.5	1.25	0.05	1
2	8	1.25	0.05	1
3	3.5	10	0.05	1
4	8	10	0.05	1
5	3.5	1.25	0.1	1
6	8	1.25	0.1	1
7	3.5	10	0.1	1
8	8	10	0.1	1
9	5.75	5.625	0.075	1

STEP 2: Results

- ✓ DoE for QUANTITATIVE FORMULA OPTIMIZATION **(Platform 1 and 3)**
  - *Prototype formulations with Platform 3:*
    - Suspended because of the physical instability of some of designed prototypes
  - *Prototype formulations with Platform 1:*
    - Statistical data analysis on physico-chemical properties by Minitab® software
    - Skin permeation study
      - *Permeation trials and analytical phase for API retained amount*
      - *Statistical data anaylsis by Minitab® software*

Skin permeation study

- ✓ In collaboration with University of Milan
- ✓ Performed on a matrix having 11 prototype formulations chosen from Platform 1, which differ for:
  - API concentration (1.25% and 10%)
  - Emollient concentration (3.5% and 8%)
  - Buffer (with and without)
- ✓ API acqueous solutions as control
- ✓ Antioxidant effect has not been considered in this test
- ✓ Franz cells technology and human skin have been used

Formulation	Matrix		
	EMOLLIENT	%API	BUFFER
RUN 1 *(1.25% API)*	3.5	1.25	-1
RUN 2 *(1.25% API)*	8	1.25	-1
RUN 3 *(10% API)*	3.5	10	-1
RUN 4 *(10% API)*	8	10	-1
RUN 9 *(1.25% API)*	3.5	1.25	1
RUN 10 *(1.25% API)*	8	1.25	1
RUN 11 *(10% API)*	3.5	10	1
RUN 12 *(10% API)*	8	10	1
RUN 17* *(5.625% API)*	5.75	5.625	0

*RUN 17 is the central point of the full factorial matrix designed for this study.

Skin permeation study – Results

Confidential

Formulations	Matrix			
	EMOLLIENT	%API	BUFFER	R24*
RUN 1 (1.25% API)	3.5	1.25	-1	**463 ± 254.1**
RUN 2 (1.25% API)	8	1.25	-1	**1170 ± 380**
RUN 3 (10% API)	3.5	10	-1	**7022 ± 4758**
RUN 4 (10% API)	8	10	-1	**3500 ± 3296**
RUN 9 (1.25% API)	3.5	1.25	1	**257 ± 74**
RUN 10 (1.25% API)	8	1.25	1	**311 ± 190**
RUN 11(10% API)	3.5	10	1	**5525 ± 3317**
RUN 12 (10% API)	8	10	1	**3962 ± 2618**
RUN 17 (5.625%)	5.75	5.625	0	**5210 ± 2402**

*R24: Retained amount of API into the skin after 24 h experiment.

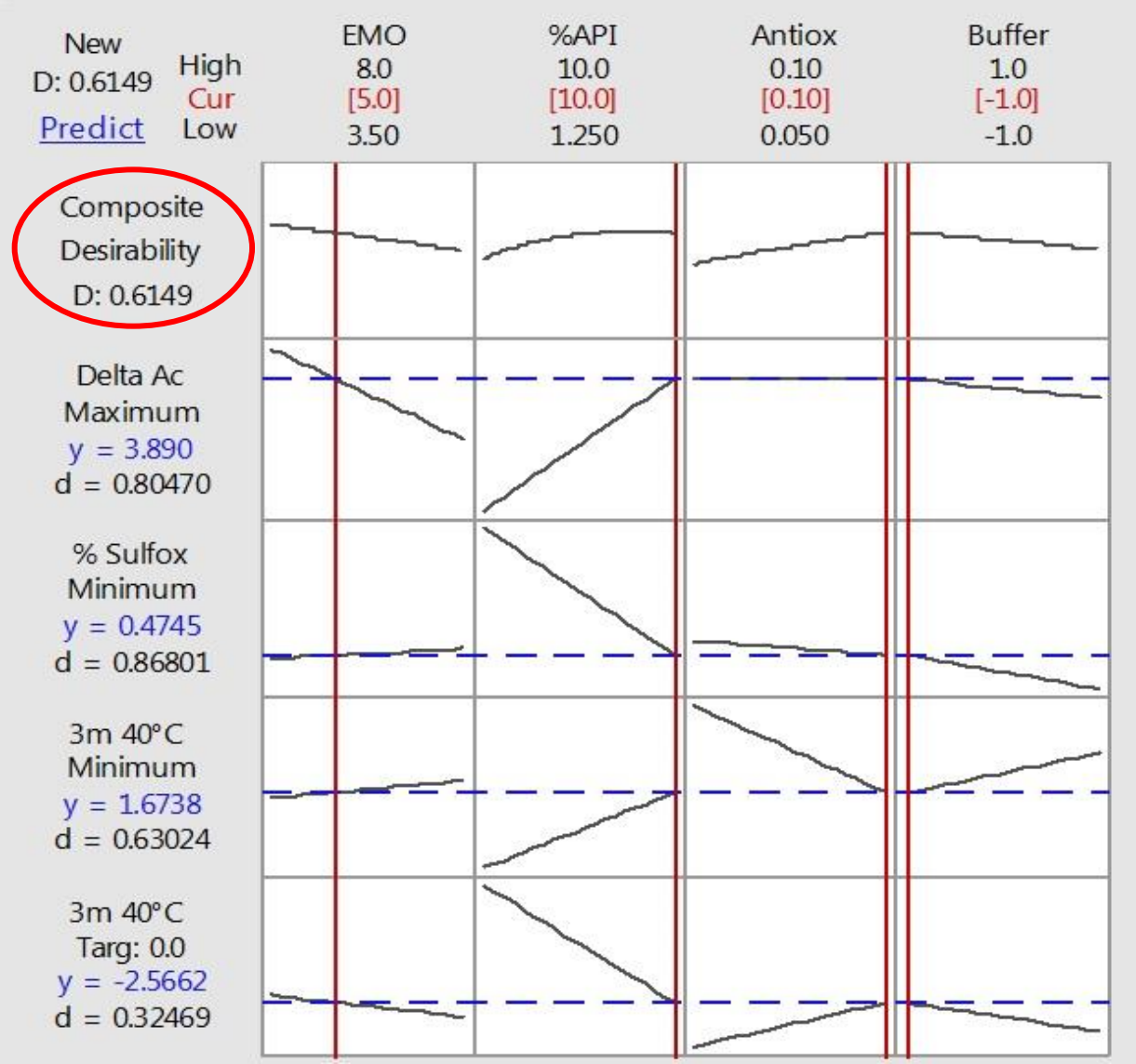
Solutions (Reference)	R24* (µg/g)
API Sol. 1.25%	793 ± 189.10
API Sol. 5.625 %	1640 ± 616.7
API Sol. 10%	2054 ± 657.6

- ✓ Permeation of API through human epidermis appears dependent by drug concentration
- ✓ From a statistical point of view, there is no difference between formulations at 10% of API and formulations at 5.625% of API, in terms of retained amount
  - This suggests that no advantage in using semisolid formulations having 10% of API would be probably observed
- ✓ Permeation of API through human epidermis appears also dependent by the presence of the buffer in the formulation
  - Buffer seems to decrease the ability of the human epidermis to retain the API

Almirall

DoE – Choice of quali-quantitative best formulation - Minitab® Optimization Plot -

Confidential



Almirall

Step 2: DoE Overall Results & Conclusions

Overall results have been obtained from the statistical data analysis of the experimental designs, generated for this study, using Minitab® software. Table below shows the best candidate formulation, considering the following responses:

- ✓ API Assay %
- ✓ Related substances formation
- ✓ Oxide impurity formation
- ✓ Retained amount of API after 24h (R24)

Best Overall Results	
Emollient	5%
API	10%
Antioxidant	0.1%
Buffer	NO

Next steps

- ✓ Container/closure system choice (DoE), using Minitab® software for:
  - study setup
  - statistical data analysis

Thank you for your attention!

Q & A