Fundamentos de QbD e DOE no desenvolvimento farmacêutico

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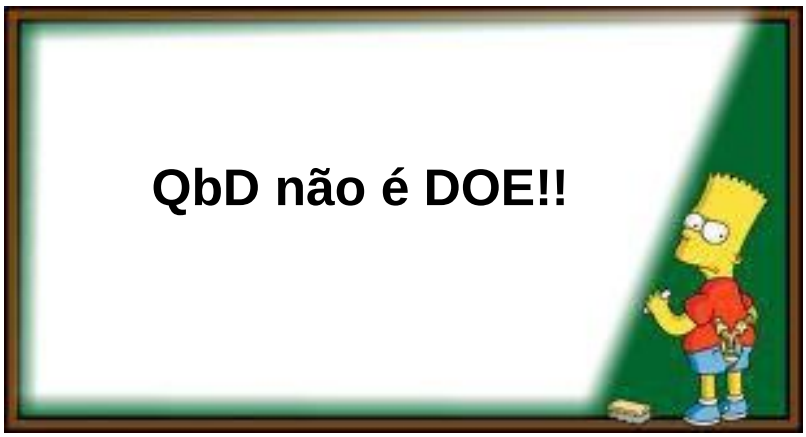
QbD não é DOE!!



✓ QbD: uma estratégia racional de desenvolvimento que envolve várias etapas; **DOE é uma etapa.**

✓ DOE: **ferramenta multivariada** de tratamento de dados que apresenta vantagens em relação à metodologia *One-Factor-at-a-Time* (OFAT).

2

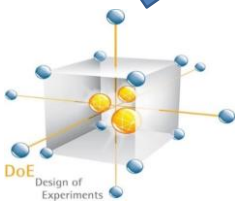
Elementos de *Quality by Design*

Construir QTPP — QTTP = *Quality Target Product Profile*

Identificar CQAs — CQAs = *Critical Quality Attributes*

Analise de risco: CMAs e CPPs — CMAs = *Critical Material Attributes*; CPPs = *Critical Parameter Parameteres*

Conduzir DOE e realizar tratamento estatístico dos resultados

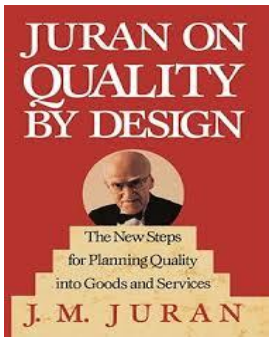


Definir o *Design Space*

Estabelecer estratégias de controle

O conceito de *Quality by Design*

- Conceito primeiramente introduzido por Joseph M. Juran (Quality Expert, 1904-2008);
- ✓ Utilizados há muito tempo em outras áreas.



A maior parte dos problemas relacionados à qualidade estavam relacionadas com a maneira como a qualidade estava ***definida***.

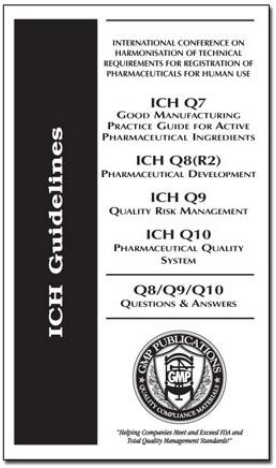
A qualidade do produto deve ser **construída** e não **testada** no mesmo

~~**Quality by Testing**~~

O conceito de *Quality by Design*

➢ **Definição:** "*A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control,* ***based on sound science and quality risk management***"

Atual	Proposta QbD
Minimal Approaches	**Enhanced, Quality by Design Approaches**
• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised



The Quality Target Product Profile

➢ "***A prospective summary*** *of the quality characteristics of a drug product that ideally will be achieved to ensure the desired* ***quality"***

Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms

- ✓ Empresa;
- ✓ Agência regulatória;
- ✓ Farmacopéia;
- ✓ Paciente.

Table 4. Quality Target Product Profile (QTPP) for Generic Acetriptan Tablets, 20 mg

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes Identification Assay Content Uniformity Dissolution Degradation Products Residual Solvents Water Content Microbial Limits	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

Critical Quality Attributes

- *"A critical quality attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality".*

Matérias-primas
Formulação
Processo

→ **Produto** →

Atributos de qualidade do produto finais ou intermediários

*Os CQAs afetam a **segurança e eficácia** do medicamento e são afetados pelos **atributos de materiais e variáveis de processo***

Table 5. Critical Quality Attributes (CQAs) of Generic Acetriptan Tablets, 20 mg

Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the acetriptan tablet.
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for acetriptan	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content Uniformity (CU)		Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.
Dissolution		NLT 80% at 30 minutes in 900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.

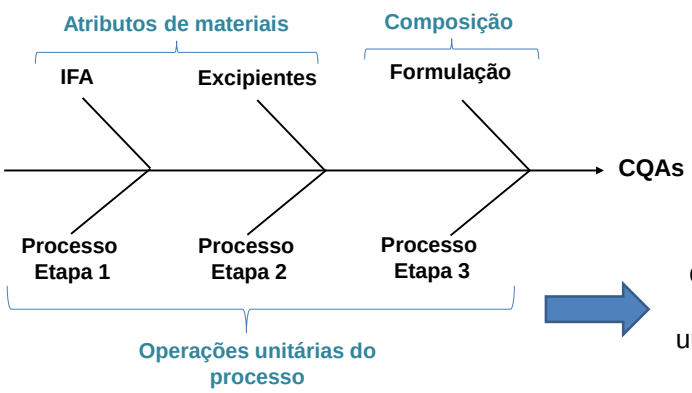
CQAs do produto final

✓ **Dependem da forma farmacêutica**

Análise de risco (AR)

1) Identificar os atributos de **materiais, formulação e processo** que podem afetar os atributos críticos de qualidade do produto (CQAs):

Diagrama de Ishikawa:



Atenção: Estamos falando de ***inputs*** agora!

Quando o processo envolve varias etapas é interessante dividi-lo em suas operações unitárias e trabalhar com CQAs intermediários

Análise de risco (AR)

2) Atribuir um risco aos inputs de acordo com o impacto esperado nos CQAs;

✓ Não é *mandatório* o uso de uma ferramenta formal de AR (p.e FMEA).

➢ **Formulação:** Obenção de uma formulação inicial (ou deformulação).

Exemplo:
Formulation Development Study #1

Table 17. Initial risk assessment of the formulation variables

Drug Product CQA	Formulation Variables				
	Drug Substance PSD	MCC/Lactose Ratio	CCS Level	Talc Level	Magnesium Stearate Level
Assay	Medium	Medium	Low	Low	Low
Content Uniformity	High	High	Low	Low	Low
Dissolution	High	Medium	High	Low	High
Degradation Products	Low	Low	Low	Low	Medium

Análise de risco (AR)

- **Processo de fabricação**

1) análise de risco para CQAs ***finais***

Exemplo:
 # Manufacturing process development

Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms

Table 32. Initial risk assessment of the manufacturing process for Generic Acetriptan Tablets, 20 mg

Drug Product CQAs	Process Steps				
	Pre-RC* Blending and Lubrication	Roller Compaction	Milling	Final Blending and Lubrication	Compression
Assay	Medium	Low	Medium	Low	Medium
Content Uniformity	High	High	High	Low	High
Dissolution	Medium	High	Medium	High	High
Degradation Products	Low	Low	Low	Low	Low

Análise de risco (AR)

- Análise de risco para ***CQAs intermediários de processo:***

Atributos de materiais

Table 34. Initial risk assessment of the pre-roller compaction blending and lubrication process variables

Process Step: Pre-Roller Compaction Blending and Lubrication		
Output Material CQA: Blend Uniformity		
Variables	Risk Assessment	Justification and Initial Strategy
Input Material Attributes		
Acetriptan PSD	High	The pilot BE study indicated that a $d_{90} \leq 30$ µm is needed for bioequivalence. Based on several lots of acetriptan analyzed during preformulation, the drug substance meeting this d_{90} criterion has poor flowability (ffc < 3.50) which may impact BU. The risk is high.
Acetriptan cohesiveness	Medium	The specific energy of acetriptan Lot #1-4 indicated that acetriptan is moderately to highly cohesive which will make achieving BU more challenging. The risk is medium.
Acetriptan flowability	Medium	The ffc value of acetriptan Lot #1-4 suggested poor flow which could impact BU. The risk is medium.
Excipient flowability	Low	Filler comprises the majority (~ 80%) of the formulation. MCC grade B02 and lactose monohydrate grade A01 are used in a 1:1 ratio because this ratio demonstrated good flowability (ffc ≈ 7). Glidant and lubricant are used in small quantities and are unlikely to impact BU. The risk is low.
Excipient PSD	Low	Experience with previously approved ANDA 123456 and ANDA 456123 demonstrated that when the selected grades of MCC and lactose monohydrate are used in a 1:1 ratio, the flowability is good. This suggests that the PSD of the fillers will not impact BU. Because the quantities of glidant and lubricant used are small, their PSD are unlikely to impact BU. The risk is low.
Excipient bulk density	Low	The 1:1 ratio of MCC to lactose monohydrate has a comparable bulk density to acetriptan. Glidant and lubricant are used in small quantities and their bulk densities are unlikely to impact BU. The risk is low.
Excipient moisture content	Low	The moisture content of the excipients is controlled per compendial/in-house specifications. Based on previous experience with approved ANDA 123456, excipient moisture content did not exhibit any significant impact on BU. The risk is low.
Excipient lot-to-lot variability	Low	Large variations in the PSD of the excipients could impact BU; however, previous experience with the chosen excipient grades has shown that the lot-to-lot variability within grade is minimal. The risk is low.

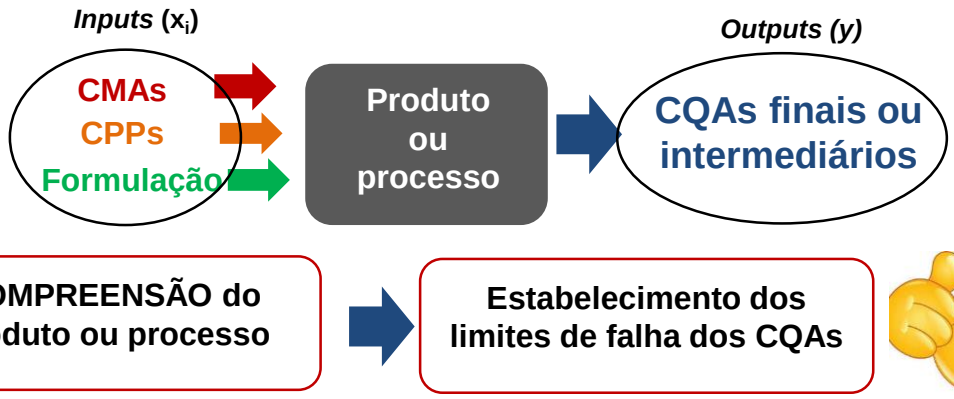
Variáveis de processo

Process Step: Pre-Roller Compaction Blending and Lubrication		
Output Material CQA: Blend Uniformity		
Variables	Risk Assessment	Justification and Initial Strategy
Blending Variables		
Blender type	Low	Different blender types have different mixing dynamics. V-blender is selected based on equipment availability. The risk is low. However, if the blender type is changed during scale-up or commercialization, the risk should be re-evaluated.
Order of addition	Low	Order of addition may impact the ease of evenly dispersing ingredients charged in lower quantities. Materials are added in the following order: lactose monohydrate, CCS, acetriptan, talc, and MCC. The risk is low.
Rotation speed (rpm)	Medium	Rotation speed is often fixed by equipment constraint. Different size blenders have different rotation speeds. The rotation speed for the 16 qt blender is fixed at 20 rpm. The risk is medium.
Number of revolutions	High	Under- or over-blending will result in suboptimal BU. The risk is high.
Intensifier bar (on/off)	Low	The intensifier bar is often not needed to improve BU. In addition, the intensifier bar may interfere with BU measurements if an NIR probe is used. The intensifier bar is fixed in the off position. The risk is low.
Blender fill level	High	The blender fill level depends on equipment capacity, blend bulk density (0.43-0.48 g/cc) and batch size. Since the blender fill level may affect mixing dynamics, the risk is high.
Holding time	Medium	Even if adequate BU is achieved, the drug substance may segregate prior to granulation during holding, discharge or transfer. The risk is medium.
Blender discharge	Medium	
Drum-to-hopper transfer	Medium	
Environment (temperature and RH)	Low	If not controlled, fluctuations in the facility temperature and RH could impact BU. Routine environment temperature and RH set point in the cGMP manufacturing facility is fixed at 25 °C ± 5% and 40%-60% RH, respectively, and will be monitored during manufacturing. The risk is low.

Design of Experiments (DOE)

- Estabelecimento de **modelos matemáticos** para entender as relações de causa e efeito entre *Inputs* e *Outputs*:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{11}{x_1}^2 + b_{22}{x_2}^2 + b_{33}{x_3}^2 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 + b_{123}x_1x_2x_3$$



COMPREENSÃO do produto ou processo → **Estabelecimento dos limites de falha dos CQAs**

Planejamento de Experimentos

- ❑ **DOE é a parte mais "difícil" dentro do contexto de QbD:**
  - ✓ Pouco (ou nada) ensinado na Faculdade/Cursos técnicos;
  - ✓ Cultura do procedimento univariado de "otimização";
  - ✓ Dificuldade ou trauma com métodos estatísticos.

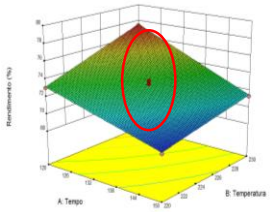
Treinamento e prática

Tipos de Planejamentos

LabFarQui Laboratório de Pesquisas Farmacêuticas e Químiometria

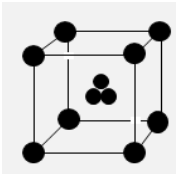
➢ DOE é um **conjunto** de métodos. Como escolher?

- ✓ Qual seu objetivo? Triagem/Previsão/Otimização?
- ✓ Quantas variáveis você tem para estudar?

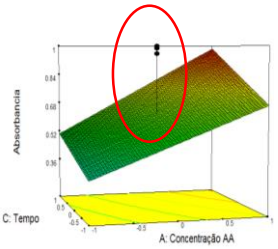


➢ **Número de variáveis: 2 < k < 3**

Planejamentos fatoriais completos em dois níveis

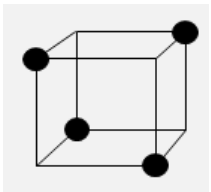


- ✓ Construção de **superfícies lineares;**
- ✓ Estimativa de efeitos principais ***e interações;***
- ✓ *Importante ter uma medida da* ***variância experimental (replicatas);***
- ✓ ***Checar a curvatura*** antes de fazer previsões!



Tipos de Planejamentos

LabFarQui Laboratório de Pesquisas Farmacêuticas e Químiometria



➢ **Número de variáveis k > 4**

Planejamentos fatoriais fracionários

Estimativa de efeitos principais e (algumas) interações

2_{IV}^{4-1}

Term	Generator
D	ABC

Factorial Effects Aliases

Estimated Term	Aliased Terms
Intercept	= Intercept
A	= A + BCD
B	= B + ACD
C	= C + ABD
D	= D + ABC
AB	= AB + CD
AC	= AC + BD
AD	= AD + BC

Efeito de interação estarão confundidos = ***é preciso conhecer a Resolução do Planejamento***

Interações ternarias não são importantes =Triagem de efeitos principais OK ☺

Não permite estimar modelos na presença de interações binárias significativas! ☹

Tipos de Planejamentos

2_V^{5-1}

Factorial Effects Aliases

Estimated Term	Aliased Terms
Intercept	= Intercept
A	= A
B	= B
C	= C
D	= D
E	= E
AB	= AB + CDE
AC	= AC + BDE
AD	= AD + BCE
AE	= AE + BCD
BC	= BC + ADE
BD	= BD + ACE

Term	Generator
E	ABCD

Resultados equivalentes a um planejamento completo

Mas cuidado:

2_{III}^{5-2}

Factorial Effects Aliases

Estimated Term	Aliased Terms
Intercept	= Intercept + ABD + ACE
A	= A + BD + CE
B	= B + AD + CDE
C	= C + AE + BDE
D	= D + AB + BCE
E	= E + AC + BCD
BC	= BC + DE + ABE + ACD
BE	= BE + CD + ABC + ADE

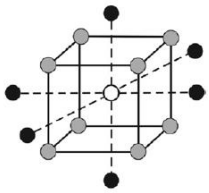
Jamais usar para previsão/construção de Design Space!

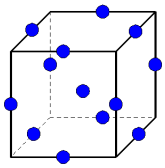
Term	Generator
D	AB
E	AC

Planejamentos saturados (Ex: Plackett Burman): triagem de um grande numero de fatores; Lembre-se que os efeitos principais estão misturados com as interações!

17

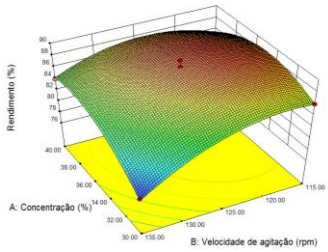
Tipos de Planejamentos

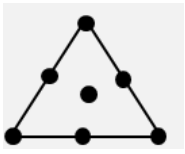




Planejamentos para Otimização e construção de modelos não lineares

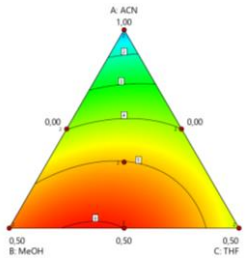
- ✓ Quando existe curvatura na superfície **(2 < k < 4)**
- ✓ Composto Central (CCD), Box-Behnken



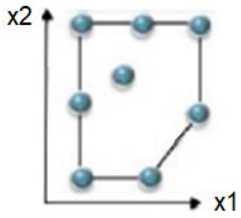


Planejamentos de misturas

- ✓ Quando os *outputs* dependem das **<u>proporções</u>** entre os *inputs*;
- ✓ Ex: componentes de uma formulação ou composição de FM em cromatografia



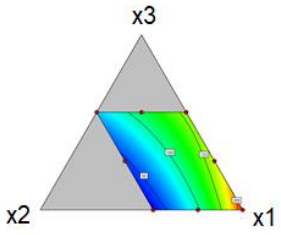
Tipos de Planejamentos



Planejamentos otimizados *(D-optimal I-optimal, A-optimal)*

✓ Limitações no domínio experimental;

✓ Ajustar um dado modelo com um numero específico de experimentos.



Exemplos:

Tipo de coluna cromatográfica;

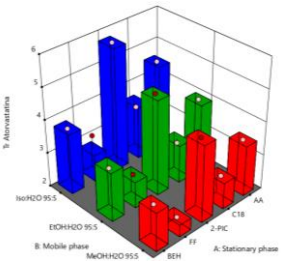
Tipo de diluente;

Tipo de aglutinante

etc...

Planejamentos somente para variáveis discretas

✓ Variáveis que não podem assumir qualquer valor dentro de uma determinada faixa



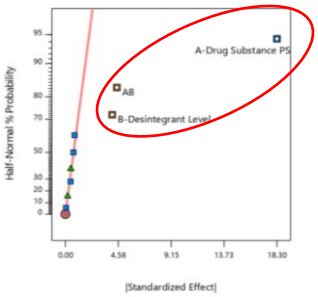
Tratamento de dados

➢ Etapa importante!

✓***Identificação dos efeitos significativos*** (incluindo efeitos de interação);

✓***Interpretação*** dos efeitos – Faz sentido?

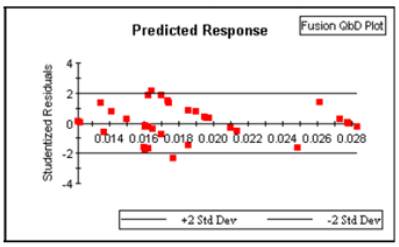
✓Construção e ***avaliação*** dos modelos matemáticos;



Regression ANOVA Statistics

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Regression	0.0010	11	<0.0001	16.2172	<0.0001
Residual	0.0002	34	<0.0001		
Lack-of-Fit	0.0002	29	<0.0001	0.7049	0.7529
Pure Error	<0.0001	5	<0.0001		
Total	0.0012	45			

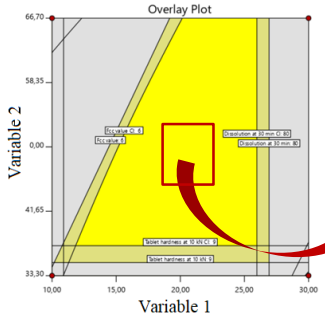
PRESS = 0.0003



Knowledge/Design/Control space

Knowledge space

Design Space



Control space

"***Design Space***: É a combinação ***multidimensional e de interações*** dos *inputs* (matéria-prima, formulação e processo) que *garantem a qualidade do produto*"

Região **robusta** de trabalho
= Flexibilidade regulatória

O Design Space deve ser construído com Planejamentos de resolução V ou superior

Exemplo – formulação

Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms

Exemplo:
Formulation Development Study #1

Table 21. Design of the 2^3 full factorial DOE to study intragranular excipients and drug substance PSD

Factors: Formulation Variables		Levels		
		-1	0	+1
A	Drug substance PSD (d_{90}, µm)	10	20	30
B	Disintegrant (%)	1	3	5
C	% MCC in MCC/Lactose combination	33.3	50.0	66.7

Responses		Goal	Acceptable Ranges
Y_1	Dissolution at 30 min (%) (with hardness of 12.0 kP)	Maximize	≥ 80%
Y_2	Disintegration time (min) (with hardness of 12.0 kP)	Minimize	< 5 min
Y_3	Tablet content uniformity (% RSD)	Minimize % RSD	< 5%
Y_4	Assay (% w/w)	Target at 100% w/w	95.0-105.0% w/w
Y_5	Powder blend flow function coefficient (ffc)	Maximize	> 6
Y_6	Tablet hardness@ 5 kN (kP)	Maximize	> 5.0 kP
Y_7	Tablet hardness @ 10 kN (kP)	Maximize	> 9.0 kP

(Fármaco pouco solúvel em água, pertencente à Classe II do BCS, processo de granulação a seco).

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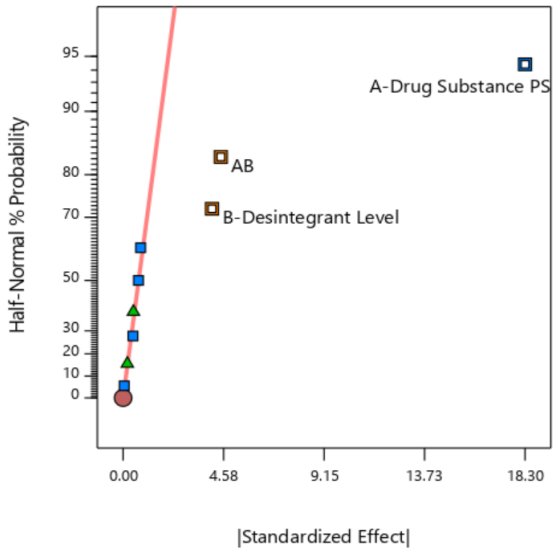
Tratando os resultados



Dissolution at 30 min

Error estimates

Shapiro-Wilk test
W-value = 0.926
p-value = 0.572

A: Drug Substance PS
B: Desintegrant Level
C: % MCC in MCC/Lactose

Positive Effects

Negative Effects

Modelo:

$$y = b_0 - b_1x_1 + b_2x_2 + b_{12}x_1x_2$$

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Análise de variância (ANOVA)

Modelo:

$$y = b_0 - b_1x_1 + b_2x_2 + b_{12}x_1x_2$$

Response 1: Dissolution at 30 min

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	742.19	3	247.40	219.84	< 0.0001	significant
A-Drug Substance PS	669.78	1	669.78	595.19	< 0.0001	
B-Desintegrant Level	32.81	1	32.81	29.15	0.0010	
AB	39.60	1	39.60	35.19	0.0006	
Residual	7.88	7	1.13			
Lack of Fit	4.44	5	0.8875	0.5160	0.7618	not significant
Pure Error	3.44	2	1.72			
Cor Total	750.07	10				

Resposta (variável dependente, CQA) é de fato uma função das variáveis independentes estudadas (inputs de alto risco)

Modelo linear postulado está OK

✓ **Ferramentas adicionais:** análise dos resíduos

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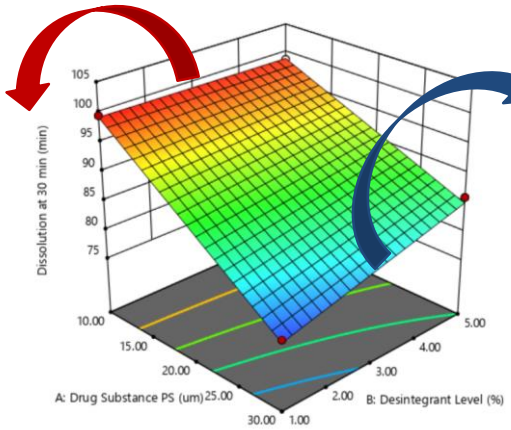
A importância das interações

➢ Superfície de resposta da dissolução em função de tamanho de partícula do fármaco e % de desintegrante:

Desintegrante não tem influência quando o tamanho de partícula do fármaco é 10 µm.



Mas aumenta dissolução em 30 minutos quando o tamanho de partícula do fármaco é 30 µm

Se o resultado obtido variando-se a variável A depende do nível da variável B então existe interação entre as variáveis A e B e elas não podem ser estudadas de forma separada (univariada)

Demais atributos críticos de qualidade

✓ **Tamanho de partícula tem um impacto significativo na dissolução, uniformidade de conteúdo e fluidez**. Partículas menores aumentam a dissolução, no entanto, impactam negativamente na uniformidade de conteúdo e na fluidez;

✓ **A porcentagem de MCC na mistura MCC/Lactose apresentou um impacto significativo na fluidez, uniformidade de conteúdo e dureza**. Aumentando a % MCC a dureza é aumentada mas a fluidez diminui, além de impactar negativamente na uniformidade de conteúdo, conforme evidenciado pelo aumento da % RSD.

✓ **O nível do desintegrante intragranular mostrou um impacto significativo na dissolução** bem como a sua interação com o tamanho de partícula. O desintegrante apresentou maior impacto na dissolução se o tamanho de partícula é maior;

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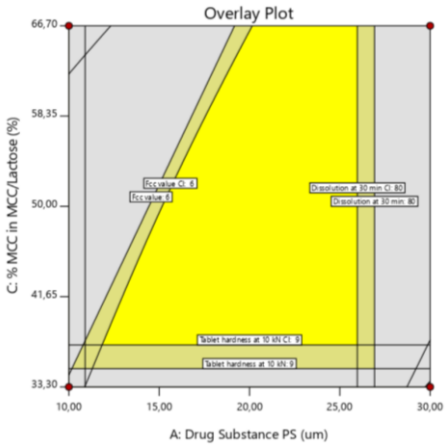
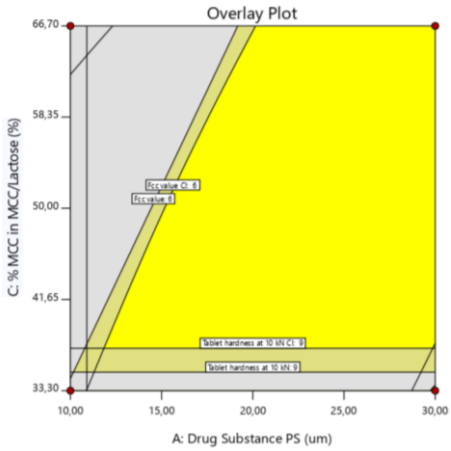
Design Space

Desintegrante = 1%



Desintegrante = 5%



PS = 15 – 25%
MCC in MCC/Lactose = 42 – 50 %
Desintegrante = 1 – 5%

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Exemplo - processo

Table 39. Design of the 2^{4-1} DOE to study roller compaction and integrated milling process variables

Defining Relation	I=ABCD			
Resolution	IV			
Factors: Process Variables		Levels		
		-1	0	+1
A	Roller pressure (bar)	20	50	80
B	Roller gap (mm)	1.2	1.8	2.4
C	Mill speed (rpm)	20	60	100
D	Mill screen orifice size (mm)	0.6	1.0	1.4

Responses		Goal	Acceptable Ranges
Y_1	Ribbon density (g/cc)	Target at 1.1	1.0-1.2
Y_2	d_{10} of milled granules (µm)	Target at 100 µm	50-150 µm
Y_3	d_{50} of milled granules (µm)	Target at 600 µm	400-800 µm
Y_4	d_{90} of milled granules (µm)	Target at 1000 µm	800-1200 µm
Y_5	Granule uniformity (% RSD)	Minimize % RSD	< 5%
Y_6	Granule flowability (ffc)	Maximize	> 6
Y_7	Assay of granule sieve cut (% w/w)	Target at 100% w/w	95.0-105.0% w/w
Y_8	Tablet hardness@ 5 kN (kP)	Maximize	> 5.0 kP
Y_9	Tablet hardness @ 10 kN (kP)	Maximize	> 9.0 kP
Y_{10}	Tablet hardness @ 15 kN (kP)	Maximize	> 12.0 kP
Y_{11}	Friability @ 5 kN (%)	Minimize	< 1.0%
Y_{12}	Friability @ 10 kN (%)	Minimize	< 1.0%
Y_{13}	Friability @ 15 kN (%)	Minimize	< 1.0%
Y_{14}	Tablet assay (% w/w)	Target at 100% w/w	95.0-105.0% w/w
Y_{15}	Tablet content uniformity (% RSD)	Minimize % RSD	< 5%

O que o um ponto central está fazendo em um planejamento 2^{4-1}???

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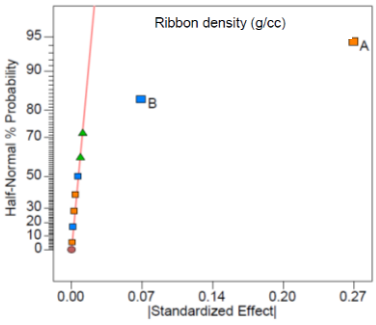
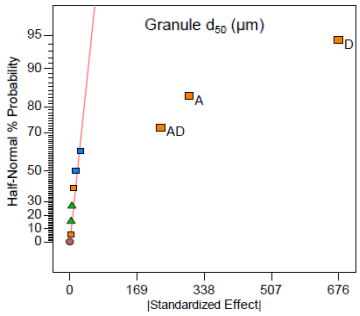
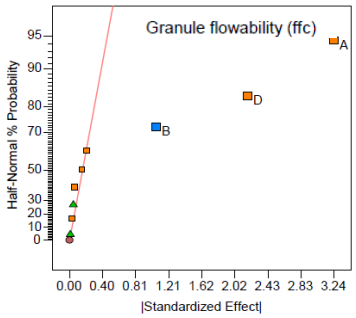
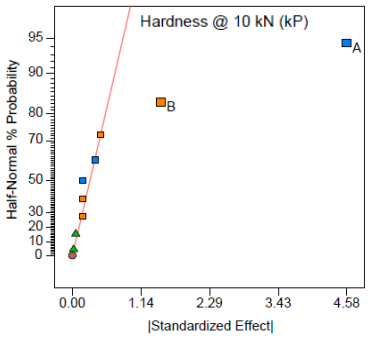
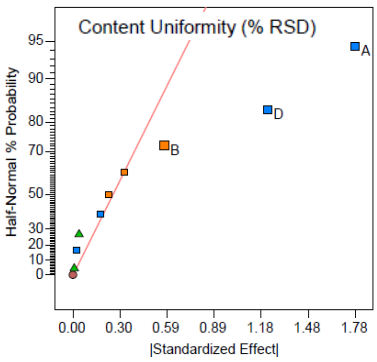










Fator C é um fator inerte!!

Planejamento fracionário

↓

Planejamento completo!
PC permite avaliar curvatura!!

Design Space

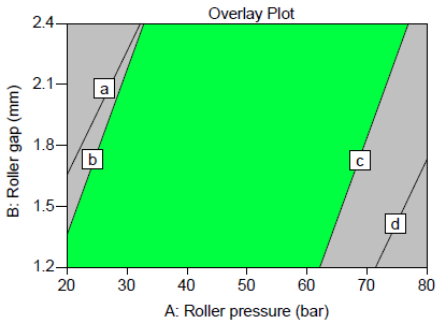
LabFarQui
Laboratório de Pesquisas Farmacêuticas e Químiometria

➢ É possível construir o *Design Space*!

A: Roller pressure (bar)
B: Roller gap (mm)

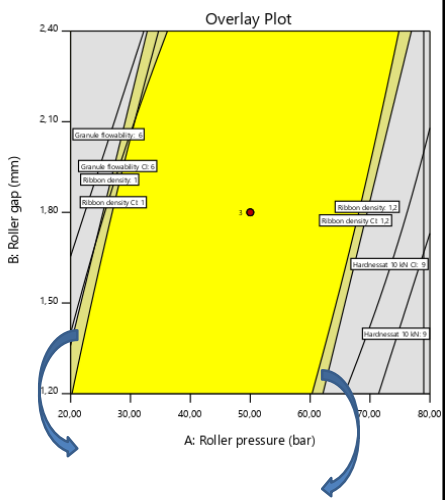
Actual Factors:
C: Mill speed (rpm) = 60
D: Mill screen orifice size (mm) = 1.0

a) Granule flowability (ffc): 6.00
b) Ribbon density (g/cc): 1.000
c) Ribbon density (g/cc): 1.200
d) Hardness (kP): 9.0



Green Zone:	All responses met the predefined criteria.
Gray Zone:	One or more responses failed to meet the predefined criteria.

Figure 38. Overlay plot – effect of roller compaction and integrated milling process variables on responses



Intervalos de confiança para valores previstos

O que apresentar no relatório

10 December 2014
EMA/59240/2014

Questions and answers on level of detail in the regulatory submissions

What level of detail should be considered for design of experiments (DOEs) in a regulatory submission?

The level of detail should be commensurate with the significance of the outcome of the DOE to the selection of the product design, commercial manufacturing process and control strategy. For example, a DOE to define operating ranges for an important unit operation would normally be considered of high significance. The information to be provided in such cases could include:

- Type of experimental design and parameter ranges studied. Justification for choice of design could be useful, in particular if the design is not fully balanced.
- Tables summarizing inputs and outputs, including batch size.
- Summary of parameters that were kept constant during the DOE.
- Delineation of factors as scale dependent or independent, with justification (for example experimental results, scientific rationale, prior knowledge).
- Description of main effects and interactions on response variables, including statistical significance of parameters (p-value).
- Discussion of regression model validation parameters (e.g. table of coefficients, output from ANOVA regression analysis, residual plots, goodness of fit (R2), goodness of prediction, table of predicted response values with confidence intervals), if applicable.

Algumas referências

Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms

Introduction to the Example

This is an example pharmaceutical development report illustrating how ANDA applicants can move toward implementation of Quality by Design (QbD). The purpose of the example is to illustrate the types of pharmaceutical development studies ANDA applicants may use as they implement QbD in their generic product development and to promote discussion on how OGD would use this information in review.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step 4* version
dated August 2009

Quality by Design for ANDAs: An Example for Modified Release Dosage Forms

Introduction to the Example

INSTRUÇÃO NORMATIVA - IN Nº 47, DE 21 DE AGOSTO DE 2019

Dispõe sobre as Boas Práticas de Fabricação complementares às atividades de qualificação e validação.

A Diretoria Colegiada da Agência Nacional de Vigilância Sanitária, no uso das atribuições que lhe confere o art. 15, III e IV, aliado ao art. 7º, III e IV da Lei nº 9.782, de 26 de janeiro de 1999, e ao art. 53, VI, §§ 1º e 3º do Regimento Interno aprovado pela Resolução da Diretoria Colegiada - RDC nº 255, de 10 de dezembro de 2018, em reunião

Algumas referências

Drug Development and Industrial Pharmacy

ISSN: 0363-9045 (Print) 1520-5762 (Online) Journal homepage: http://www.tandfonline.com/loi/iddi20

Design of experiments (DoE) in pharmaceutical development

BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902018000001006

Review

Design of Experiments (DoE) applied to Pharmaceutical and Analytical Quality by Design (QbD)

Isa Martins Fukuda[1], Camila Francini Fidelis Pinto[1], Camila dos Santos Moreira[1], Alessandro Morais Saviano[1], Felipe Rebello Lourenço[1,*]

[1]Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of São Paulo, São Paulo, Brazil

BioProcess TECHNICAL

Practical Considerations for DoE Implementation in Quality By Design

Mahesh Shivhare and Graham McCreath

It is generally accepted that quality cannot be tested or inspected into a finished product, but rather that quality, safety, and effectiveness must be "designed" and built into a product and its manufacturing process. To encourage new initiatives and provide guidance to pharmaceutical process developers, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use introduced the quality by design (QbD) concept. ICH-Q8 defines it as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (1).

A typical bioprocess for influenced by a complicated matrix of input and output parameters, including critical process parameters (CPPs) critical quality attributes (CQAs), as illustrated in Figure 1. quality (2). Application of a DoE strategy provides scientific understanding of the effects of multiple process parameters and raw material attributes on product CQAs

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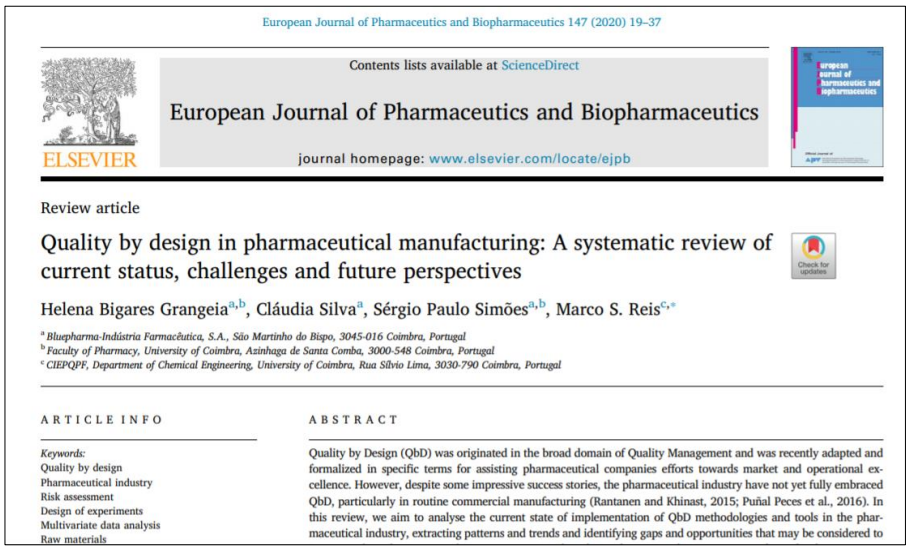
Algumas referências

✓ Revisão da literatura e analise do cenário atual:



European Journal of Pharmaceutics and Biopharmaceutics 147 (2020) 19–37

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

ELSEVIER

Review article

Quality by design in pharmaceutical manufacturing: A systematic review of current status, challenges and future perspectives

Helena Bigares Grangeia[a,b], Cláudia Silva[a], Sérgio Paulo Simões[a,b], Marco S. Reis[c,*]

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[c] CIEPQPF, Department of Chemical Engineering, University of Coimbra, Rua Sílvio Lima, 3030-790 Coimbra, Portugal

ARTICLE INFO

Keywords:
Quality by design
Pharmaceutical industry
Risk assessment
Design of experiments
Multivariate data analysis
Raw materials

ABSTRACT

Quality by Design (QbD) was originated in the broad domain of Quality Management and was recently adapted and formalized in specific terms for assisting pharmaceutical companies efforts towards market and operational excellence. However, despite some impressive success stories, the pharmaceutical industry have not yet fully embraced QbD, particularly in routine commercial manufacturing (Rantanen and Khinast, 2015; Puñal Peces et al., 2016). In this review, we aim to analyse the current state of implementation of QbD methodologies and tools in the pharmaceutical industry, extracting patterns and trends and identifying gaps and opportunities that may be considered to

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Conclusões

- ✓ QbD: Método sistemático para o desenvolvimento farmacêutico baseado em metodologia científica e análise de risco (racional!);
- ✓ DOE: Papel fundamental para a compreensão de causa e efeito (CQAs são **modelados** em função dos CMAs e CPPs) e para a identificação das **interações** entre as variáveis. OBSERVAÇÕES: 1) DOE vem após a análise de risco. 2) Existem planejamentos econômicos quando as variáveis são muitas. MUDANÇA DE PARADIGMA!!
- ✓ Design Space: **conhecimento do produto/processo/método -** Identificação dos limites de falha do processo e problemas de matéria-prima. A robustez é trazida ao desenvolvimento!
- ✓ Agências regulatórias do mundo todo estão estimulando o uso da metodologia;
- ✓ Já foi provado que a metodologia funciona e seus benefícios. Agora estamos em um momento de **treinamento** !

Onde aprender DOE de forma aplicada

- ✓ **Curso QUI 0043 na Extensão da UNICAMP (online)**:

www.extecamp.unicamp.br (somente quando as inscrições estiverem abertas)

Confira a ementa em nosso site: www.labfarqui.com.br

- ✓ Também no modo *in-company* (online).
- ✓ Aguarde: "*Estatística aplicada à validação de métodos analíticos na área farmacêutica e os princípios de Analytical Quality by Design* (AQbD)"

OBRIGADA PELA ATENÇÃO!

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