ANVISA's current practice and challenges in the evaluation of dissolution profile comparisons in support of minor/moderate product quality changes– Case Studies

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Outline

1) Short overview of Anvisa's Dissolution regulation – Actual scenario, gaps and goals

- RDC 31/2010
- Anvisa's Dissolution Guide

2) Main problems in dissolution profiles assessment

- Lack of development (Use of compendial methods)
- Brazilian requirements for the realization of the dissolution test
- Utilization of the model independent method (F2)
- Inadequate treatment of data (exclusion of points...)

3) Case Study
4) Summary
5) Conclusion

Anvisa's Dissolution Regulation

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Legislation for Dissolution Profile Comparison

Resolution 31/2010

→Development of dissolution methods
→ Determination of specification
→ Aplicable just to generic products
→ Statistical method for dissolution profile comparison;

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RESOLUÇÃO-RDC Nº 31, DE 11 DE AGOSTO DE 2010

Dispõe sobre a realização dos Estudos de Equivalência Farmacêutica e de Perfil de Dissolução Comparativo.

A Diretoria Colegiada da Agência Nacional de Vigilância Sanitária (Anvisa), no uso da atribuição que lhe confere o inciso IV do art. 11 do Regulamento aprovado pelo Decreto Nº 3.029, de 16 de abril de 1999, e tendo em vista o disposto no inciso II e nos §§ 1º e 3º do art. 54 do Regimento Interno aprovado nos termos do Anexo I da Portaria Nº 354 da Anvisa, de 11 de agosto de 2006, republicada no DOU de 21 de agosto de 2006, em reunião realizada em 5 de agosto de 2010, adota a seguinte Resolução e eu Diretor-Presidente determino a sua publicação:

Anvisa's Dissolution Guidance

→ Focused on development of methods
→ Stablishment of clinically relevant specifications

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GUIA DE DISSOLUÇÃO APLICÁVEL A MEDICAMENTOS GENÉRICOS, NOVOS E SIMILARES

VIGENTE A PARTIR DE 09/05/2018

Início do período de contribuições: 16/05/2018
Fim do período de contribuições: 15/05/2019

2018

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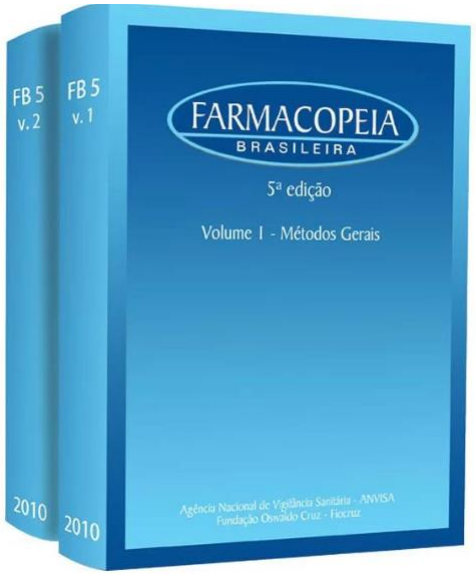
Discriminative methods
x
Compendial methods

Use of Compendial methods – RDC 31/2010

"In post-approval solicitations the study of Dissolution profile must be realized using the method described in the Brazilian Pharmacopeia"



→ Compendial methods disvantage: Low number of products described; Last edition 2010, old methods,

→ Lack of a definition for discriminative methods (changes in formulation, how relevant changes?);

→ Generic products x Inovator products (products with distinct excipients)

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Brazilian Requirements for the realization of the test

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RDC 31/2010 - Center of Pharmaceutical Equivalence (Eqfar)

" The study of Dissolution Profile must be realized by a Center of Pharmaceutical Equivalence"

Eqfar

Physicochemical Laboratory certified by Anvisa and responsible for physochemical

Initial idea

→ Labs of public universities;
→ Idependent organizations;
→ Spread across the whole country;
→ Confidence of the results.

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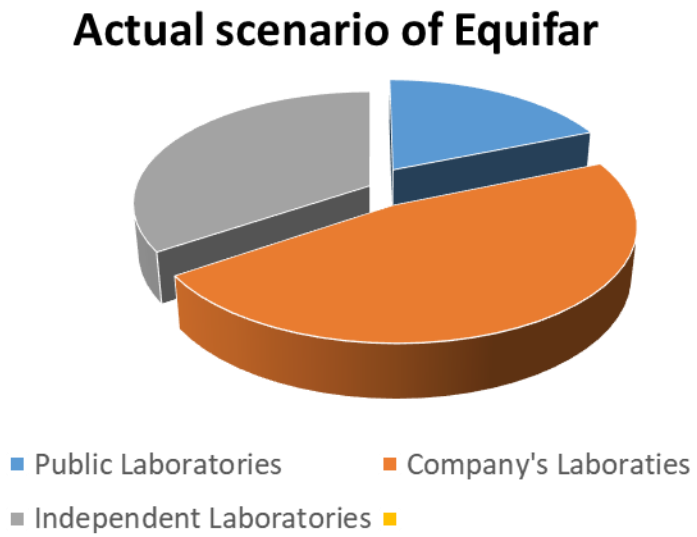
RDC 31/2010 - Center of Pharmaceutical Equivalence (Eqfar)



Eqfar – Reality

→ Low capability of the public University (low Budget)

→ Rigid norms

→ No interaction with the R&D

→ No differenciation between Eqfar x CQ

→ Harmonization with other Agencies.

Utilization of the Model independent Method (F2)

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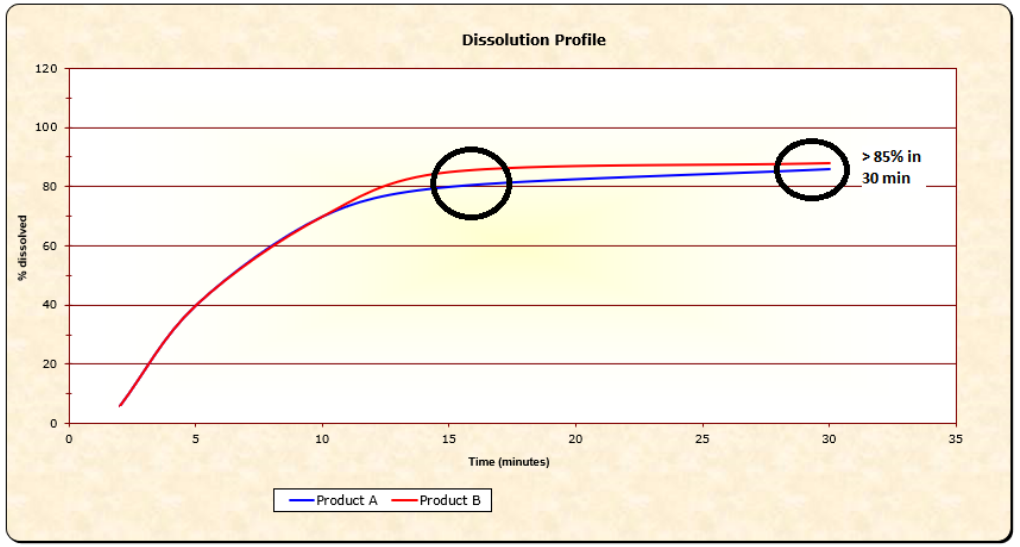
RDC 31/2010 – Different dissolution performances

"The test units and the standard approved product must present correspondent kinds of dissolution. For instance, if the approved product has an average dissolution of 85% in 30 min (rapid dissolution) the changed product must have the same performance".

F1 =
F2 = 83,74



F1 = 2,48
F2 = 79,19

Sanitária

RDC 31/2010 - Alternative statatistical methods for comparison (f2)

"The comparison of the dissolution profiles must be done (...) calculating the F2 fator".

→ What should be done when the test doesn't comply with the parameters of the method?

→ What are the acceptable alternative methods?

→ What are the parameters that should be used for the alternative methods?

→ Is there a preference among the different tests described in the literature?

RDC 31/2010 - Use of the Model Independent Approach Using a Similarity Factor (f2)

FDA

To allow the use of mean data, the coefficient of variation should not be more than 20 percent at the earlier time points (e.g., 15 minutes), and should not be more than 10 percent at other time points

X

Anvisa

It's considered earlier points the amount correspondent to 40% of the total number of points. For example, in a dissolution profile with 5 time points (5, 10 , 15, 20 and 30 min) the percent coefficient of variation of the two ealier points (5 and 10 min) should no be more than 20%.

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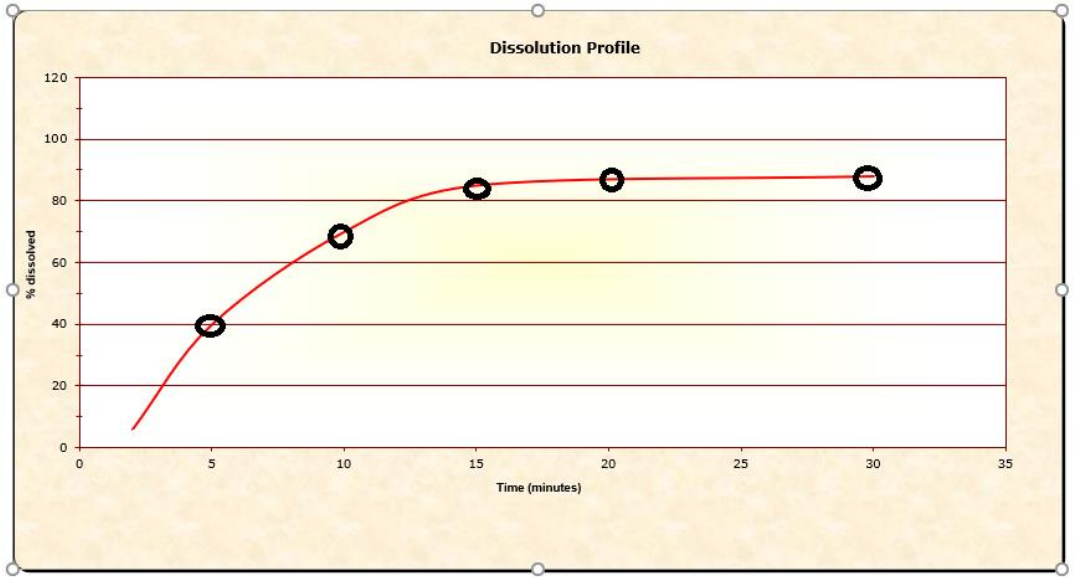
RDC 31/2010 - Use of the Model Independent Approach Using a Similarity Factor (f2)

"For the F2 calculation it must be used at least the 3 ealier points"

"The number of points must be representative of the dissolution profile"



RSD

5 min : 23%
10 min: 17%
15 min: 9%
20 min: 5 %
30 min: 2%

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RDC 31/2010 - Use of the Model Independent Approach Using a Similarity Factor (f2)

→ Representativity of the dissolution profile

→ F2 x Alternative methods

→ Differences in the begining of the profile

Inadequate treatment of data

Inadequate treatment of data

→ Exclusion of points (aberrant values, problems during the analysis)

→ Inappropriate selection of points

→ Datasheets x raw data

Case Study

Complex formulations

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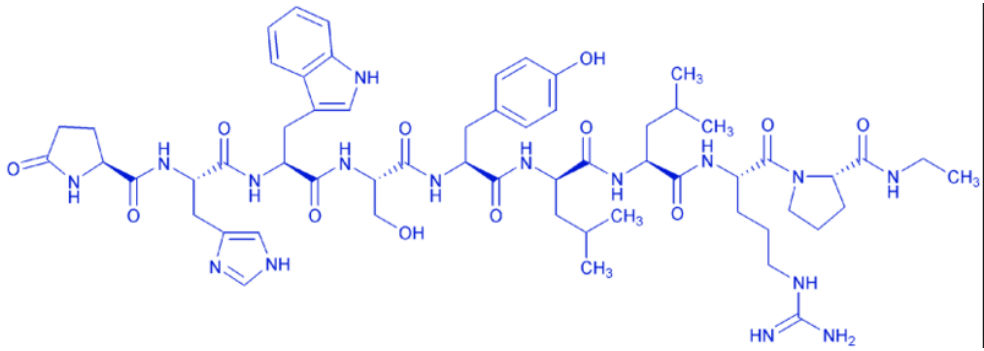
Presentation of the product

Active: Leuprorelin Acetate

Dosage form: Suspension for injection

Pharmacology: Superactive luteinizing hormone-releasing hormone(LH-RH) agonist

Pharmaceutical Technology: system of PLGA/PLA microparticles encapsulating a hydrophobic drug



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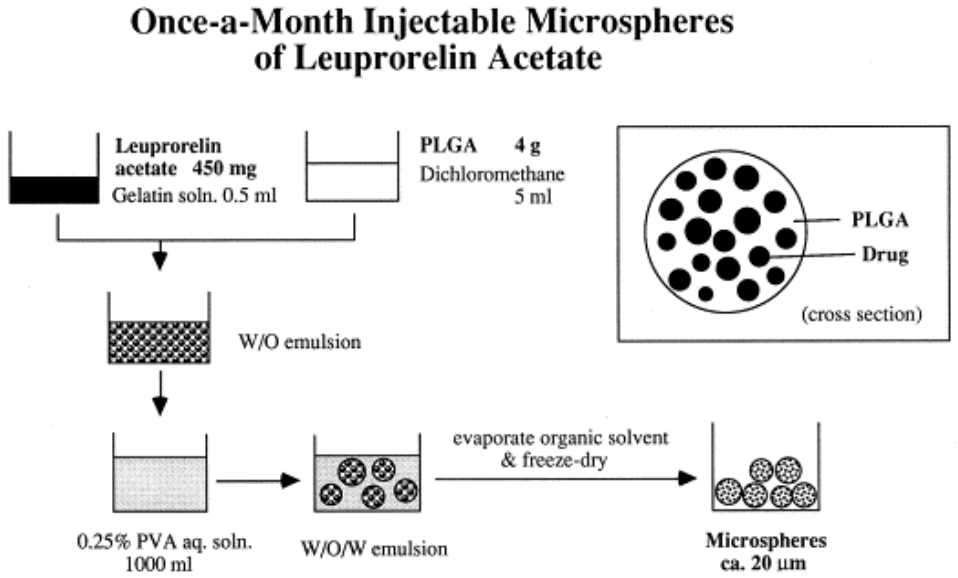
PLGA/PLA microparticles

"They normally contain substantial amounts of potent therapeutic agents and therefore, any unanticipated changes in their in vivo drug release characteristics may lead to severe side effects and impaired in vivo efficacy"



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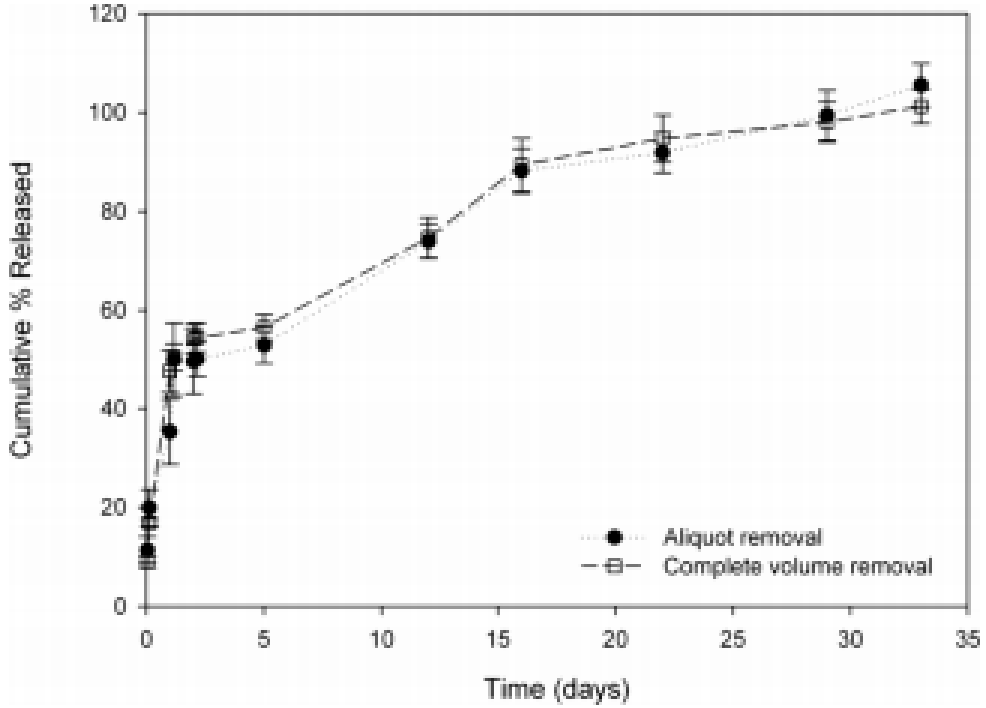
Dissolution Characteristics

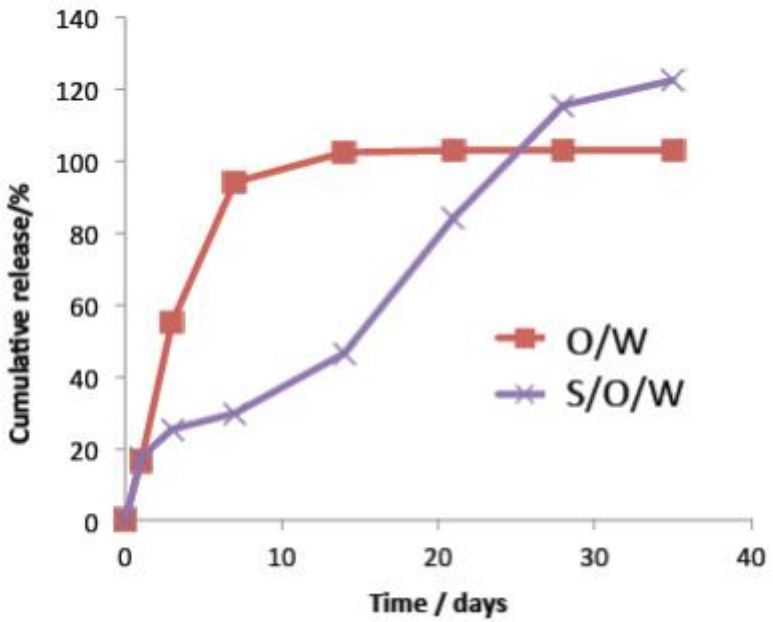


Fast initial release (burst) – Caused by the amount of active substance in the surface of the microspheres

Gradual release – Caused by the gradual hydrolysis of the polymer and diffusion of the substance

Final release – Occurs when the microsphere achieve the minimum size due to the degradation;

Manufacturing process x Dissolution kinetics



The dissolution profile may be very sensitive to the manufacturing process

The same formulation may present huge differences related to the dissolution

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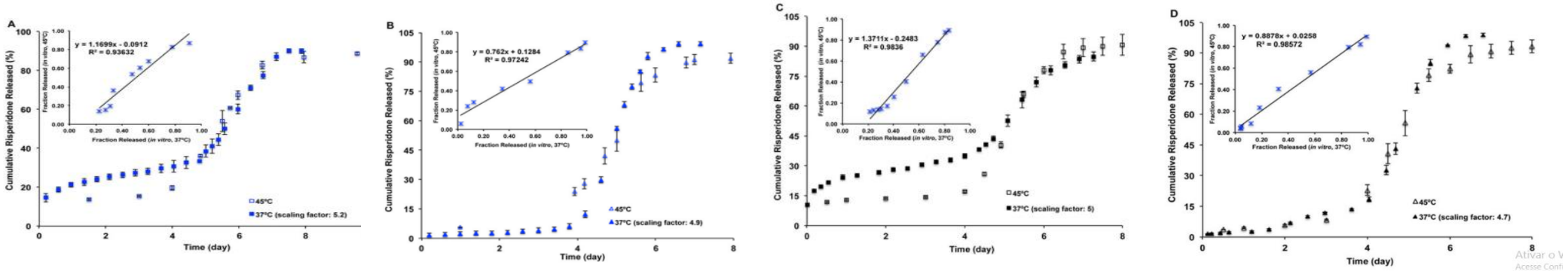
Utilization of accelerated methods

_ **Real-time release testing x accelerated methods –** short time for batch release, degradation of the polymer

_ **How to develop accelerated methods?-** extreme conditions of temperature, pH, surfactants, and the presence of enzymes

_ **Correlation between methods** - accelerated in vitro release methods of PLGA microspheres which can correlate with realtime in vitro release are essential

Correlation between accelerated method x real time method



In vitro release profiles of the prepared risperidone microspheres in 10 mM PBS (pH 7.4) at 37°C (time-scaled) and at 45°C using different release testing methods (n=3). (A) Formulation 1 and (B) Formulation 2 using the sample-and-separate method. (C) Formulation 1 and (D) Formulation 2 using the USP apparatus 4 method. Insert figures show linear correlations between real-time (time-scaled) (37°C) and accelerated (45°C) fraction risperidone released

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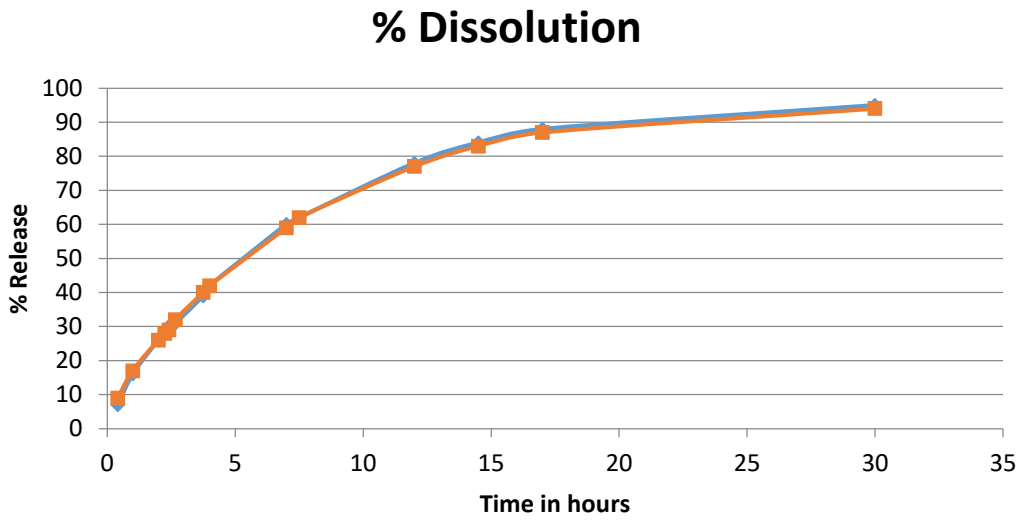
Accelerated dissolution profile



__ 3,75 mg x __ 7,5 mg

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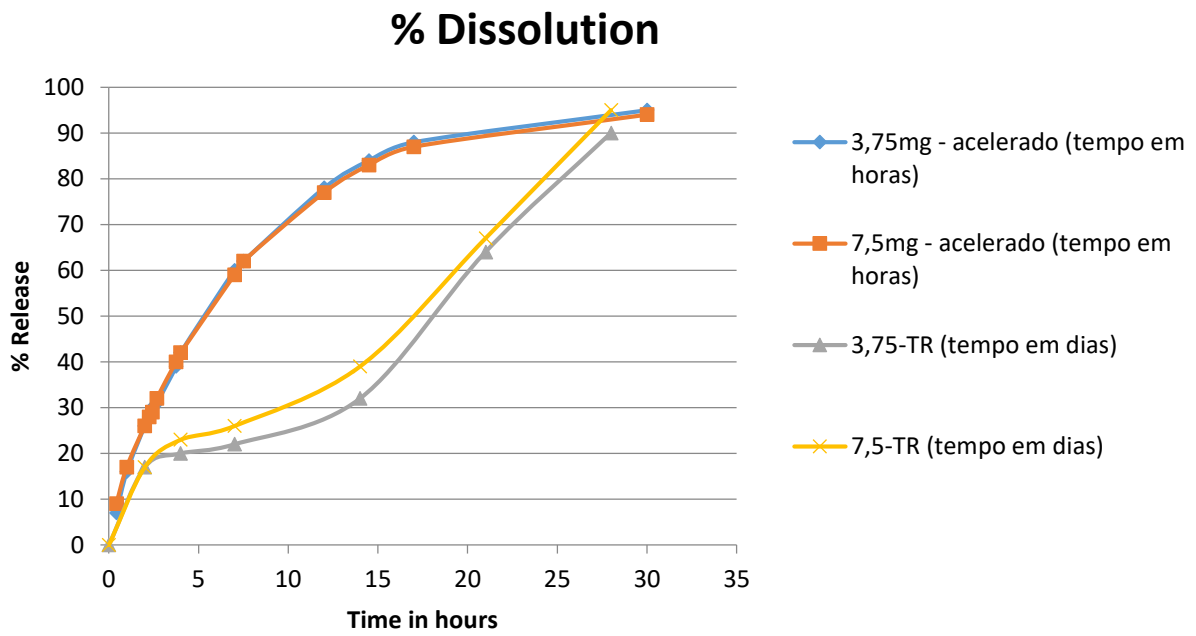
Accelerated method x real time method



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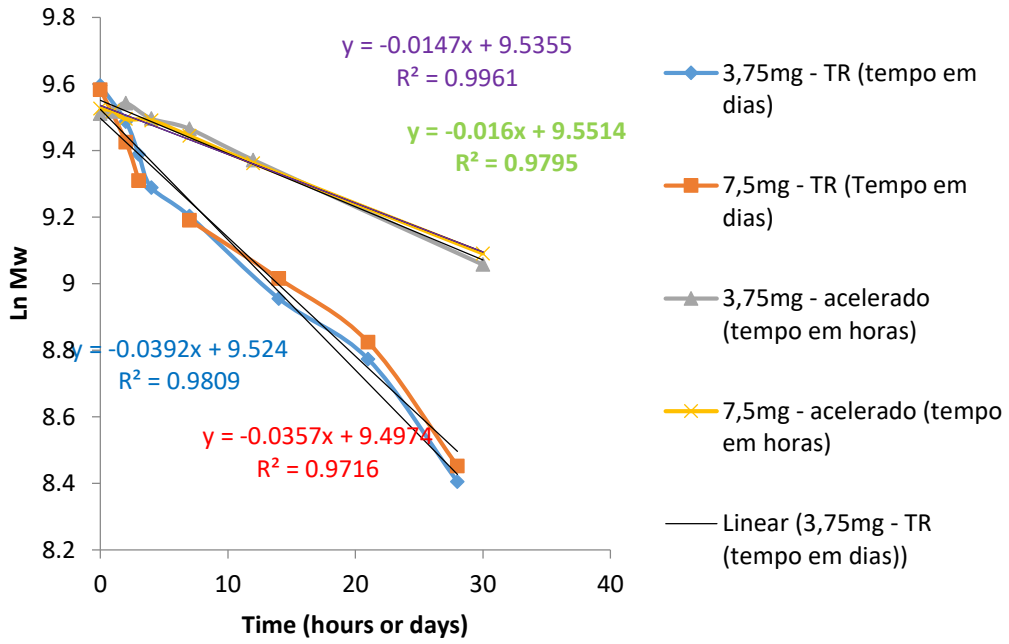
Studies of degradation

Size of the spheres



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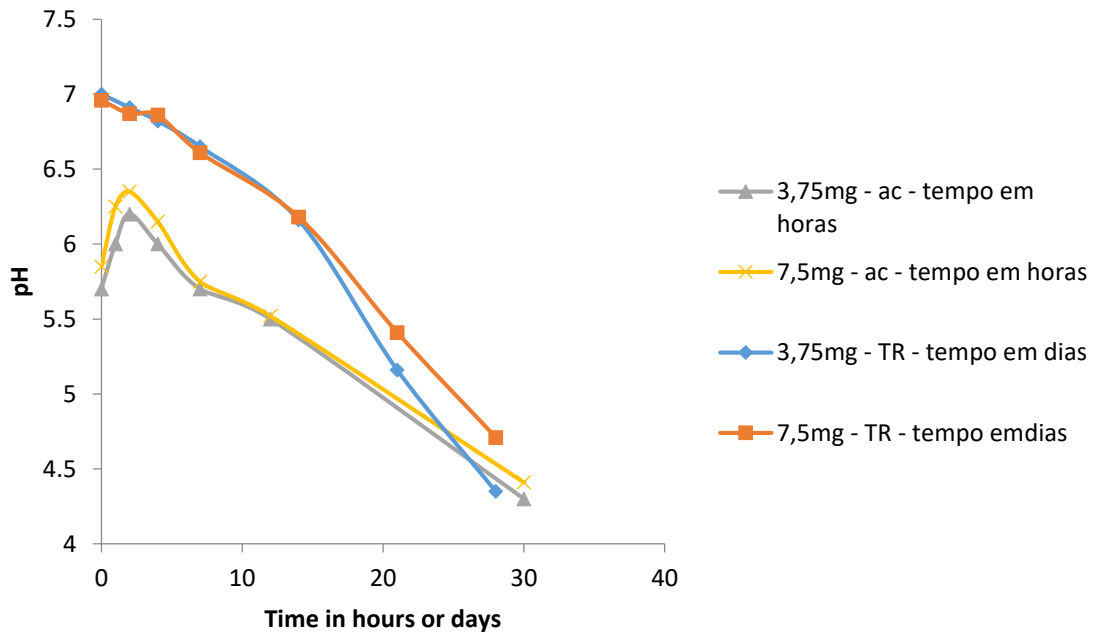
Studies of degradation

pH variation



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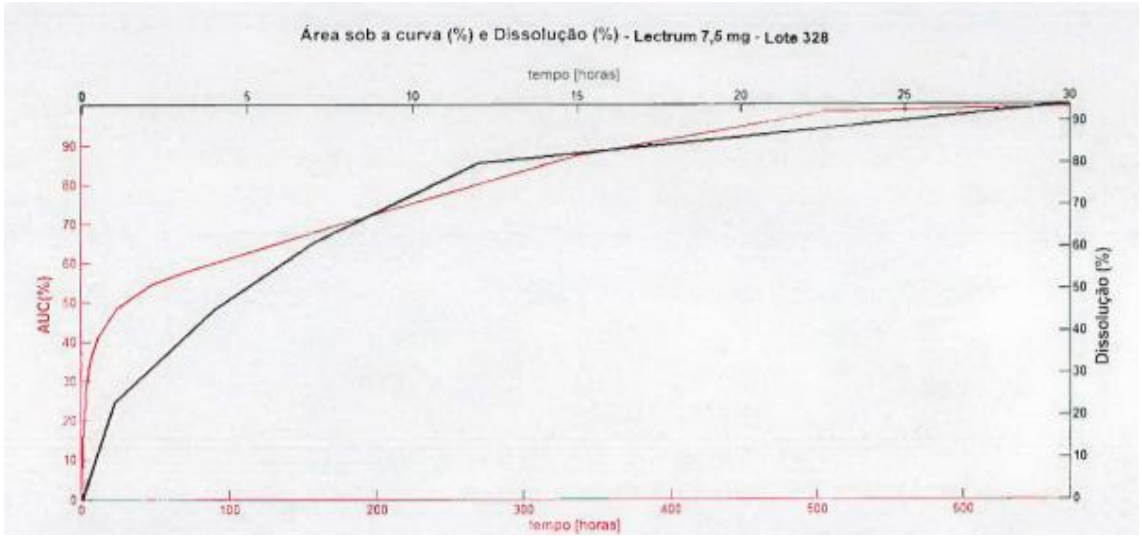
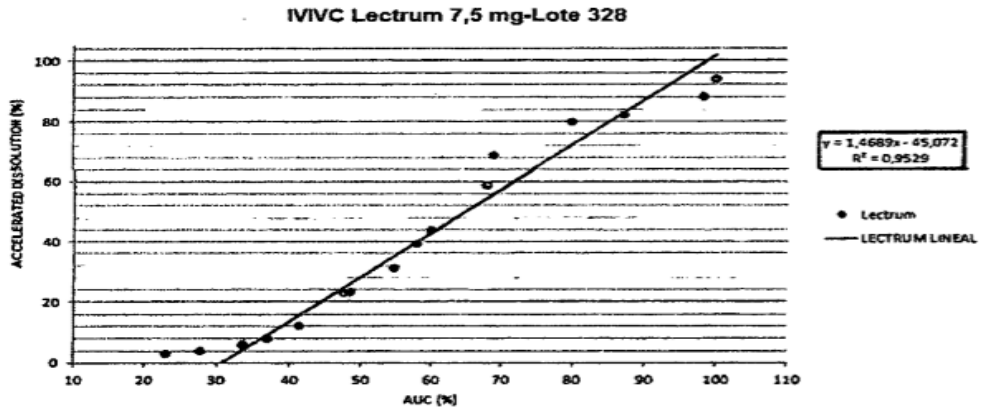
IVIV Correlation – New accelerated method



Tiempo en disolución in vitro	0	1	4	7	12	30
Correspondencia con tiempo in vivo (horas)	0	22,4	89,6	156,8	268,8	672



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Conclusion of the Case

→ Development of a new accelerated method

→ The discriminative power of the new method has been prooved (Buffer concentration, temperature and pH)

→ Comparison between accelerated and real time methods ((r=0,99 for 7,5mg and 0,96 for 3,75mg)

→ Batycky Model x Weibull

Summary

Brazilian Legislation

→ Problems originated by Old legislation (Norms x Guidances)

→ Lack of harmonization with international requirements (specific requirements, non scientific justified)

→ Poor description of the alternative models

Conclusion

→ Update of the brazilian dissolution legislation

→ Harmonization with international guidances

→ Stablishment of recommendations for the utilization of statistical models

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