AAPS 2013
Poster
T3376

Quality-by-Design: Differing Dissolution Philosophies

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Abstract

Purpose: To demonstrate how differing dissolution philosophies among Health Authorities can impact the approval and subsequently the supply chain of a product.

Method: An oral immediate release multiple strength tablet was developed using an enhanced Quality-by-Design (QbD) approach. Design of experiments (DOEs) along with suitable risk analysis was conducted to identify CMAs, CPPs, and CQAs. Dissolution methods with differing capabilities to discriminate formulation and process variables were developed. A human bioavailability study was conducted with tablets that contained both formulation and process variants.

Results: Using data from the human bioavailability study, in-vitro dissolution studies, formulation and process DOEs, a suitable design space was developed. Submissions were made in the US, EU and Canada. Health Authority assessment of the submission demonstrated the varying philosophical approaches to dissolution and their approach to the QbD paradigm. The US FDA determined that the proposed commercial dissolution method was over discriminatory versus the bioavailability data. FDA required a less discriminatory media with bio-relevance be adopted for use as the dissolution method for commercial release. However, they accepted that the discriminatory method was suitable for design space definition with limited cross validation. The EU accepted the more discriminatory dissolution method but required a tighten release specification even though they acknowledged that this was not required based on the human bioavailability data. The Canadian submission contained the revised US specification. Health Canada rejected this approach and required the more stringent EU approach.

Conclusion: Interpretation is an inevitable consequence of a science and risk based approach to development and has resulted in differences in review philosophies within ICH signatory countries and among rest of world countries. This has resulted in a more complicated supply chain for an oral immediate release tablet; the same product has different specifications for release and stability even though the clinical performance is guaranteed.

Submission Strategy

Common Technical CMC Document in ICH Markets – US, EU

Upon approval of US NDA and EU MAA, further submissions made in various markets taking supply chain considerations into account.

For example:

- ❑ Canada – use US NDA
- ❑ ROW - use EU MAA

Dissolution Development Strategy

For a QbD based development, a discriminatory dissolution method is key in developing product and process understanding, and is advantageous to product control strategy.

To facilitate continuous improvement, a control strategy which incorporates a discriminatory dissolution method enables informative monitoring of the manufacturing process and product quality in order to be able to make adjustments to the process and control strategy, as appropriate.

Dissolution method selection is a balance between bio-relevance of the dissolution media and the discriminatory power of the method.

The dissolution specification, when possible, should be based on the knowledge of in-vivo product performance.

Formulation & Manufacturing Process Development - QbD Approach

Development conducted according to the principles of QbD.

Utilized systematic approaches to:

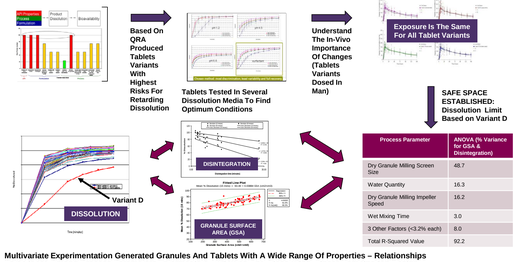
- ❑ Identify the material attributes and process parameters that can have an affect on the drug substance and product Critical Quality Attributes (CQAs).
- ❑ Establish the functional relationships among these material attributes and process parameters on the drug substance and product CQAs.
- ❑ This enhanced product and process understanding was linked to Quality Risk Management to define a Control Strategy.

Product Description

Small Molecule
pKa 5.2 & 9.4
BCS II Classification
Immediate Release Tablet – 2 Strengths from a Common Granulation
Conventional Wet Granulation Process with Pharmacopeia Excipients

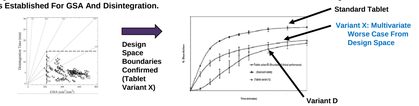
Dissolution – A Structured Development Program

Using In-Vivo Understanding To Set Meaningful Specifications

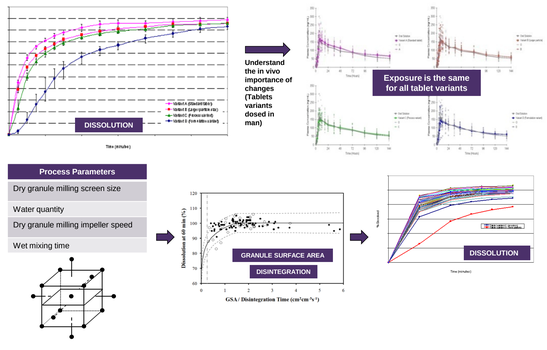


Process Parameter	ANOVA (% Variance for GSA & Disintegration)
Dry Granule Milling Screen Size	48.7
Water Quantity	16.3
Dry Granule Milling Impeller Speed	16.2
Wet Mixing Time	3.0
3 Other Factors (<3.2% each)	8.0
Total R-Squared Value	92.2

Multivariate Experimentation Generated Granules And Tablets With A Wide Range Of Properties – Relationships Established Among Process Parameters, Intermediate Attributes And Dissolution. Linear Combination Design Space Boundaries Established For GSA And Disintegration.



Understanding the Impact on In-Vivo Performance



Dissolution Method – FDA Comments

Based on the submitted information, the proposed dissolution method and specification were not acceptable, for the following reasons:

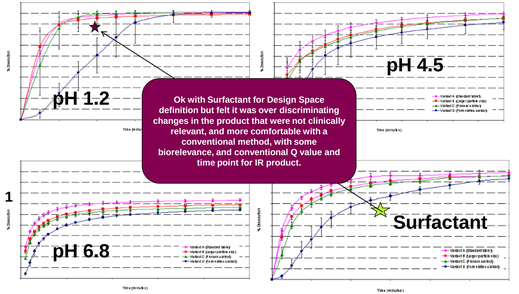
- ❑ The pH range at which the drug substance is soluble (pH 1.2 to 6) was not selected, instead a medium with surfactant and a very high paddle speed was selected.
- ❑ The data from the in vivo study show that absorption across the gut-wall is the rate-limiting step rather than dissolution. It appears that pH 1.2 might be a more adequate dissolution medium.
- ❑ The proposed dissolution method does not provide in vivo relevance.

Follow-up TC:

- ❑ FDA felt that the surfactant dissolution method is relevant from a development perspective, but the Sponsor has unnecessarily constrained itself with this methodology from a specification perspective which may result in failure of clinically acceptable batches.
- ❑ From a dissolution method and specification perspective, the FDA had issue from a policy and philosophical viewpoint with the surfactant dissolution method. The method is considered overly discriminatory and FDA is looking for clinically meaningful discrimination. This was supported by the Biopharmaceutics and Chemistry Reviewers and Division Director.

Where we ended up with a Release Test/QC Method & Specification

Dissolution profiles in aqueous buffers and surfactant:
Sponsor (Surfactant, Q=75% in 60 min)
FDA (pH 1.2, Q=80% in 30 min)

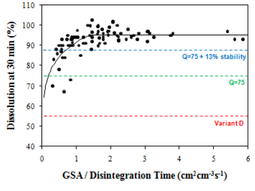


Dissolution Method – EMA Comments

In order to ensure the consistency of the quality of the product in terms of dissolution, a meaningful dissolution limit, which reflects what is readily and routinely achievable, should be set. For these immediate release products a suitable limit (Q = 75%) should be defined at 30 minutes rather than 60 minutes.

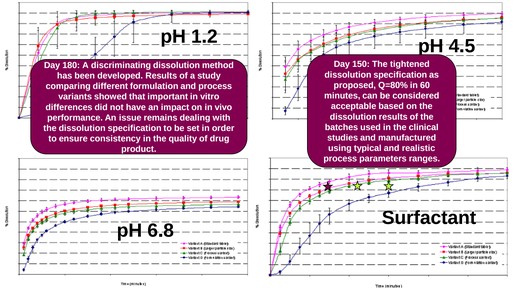
A specification of Q = 75% at 45 minutes was agreed

Comments in Day 180 report:
Indeed, a percentage of Q=75% in 45 min remains far from the worst case scenario (Variant D, which had the slowest dissolution of the batches tested in vivo), while leaving an acceptable margin of normal operating variability. Besides, the applicant has restricted the original design space for drug product. The settings associated with material and process parameters subsequently provide a constraint to the overall potential dissolution profile variability. The overall updated manufacturing process settings and control strategy for the drug product are considered satisfactory to ensure product quality consistency.



Where we ended up with a Release Test/QC Method & Specification

Dissolution profiles in aqueous buffers and surfactant:
Sponsor (Surfactant, Q=75% in 60 min)
EMA (Surfactant, Q=75% in 45 min)



Dissolution Method – Health Canada Comments

The initial submission contained the US NDA Dissolution Method (pH 1.2, Q = 80% in 30 minutes) to keep consistent with the North America supply strategy.

Health Canada Comment:

It is noted that you are proposing a dissolution method (pH 1.2) that is different than the one used in pharmaceutical development (surfactant). As stated throughout pharmaceutical development, the surfactant method was considered to be the most discriminating method. As well, the method was used for the establishment of the design space boundaries. Hence, proposed pH 1.2 dissolution method is not considered as routine QC method. In addition, the acceptance criteria (Q = 80% in 60 minutes) used throughout the development and control of clinical batches should be revised to Q = 75% in 30 minutes as the clinical formulation (Variant A) has met that criteria when tested using the method.

Sponsor Response:

The Sponsor agree to the request to switch to the surfactant dissolution method used throughout pharmaceutical development for routine QC testing.

The Sponsor believes that a revised proposed specification of Q = 75% in 45 minutes, in combination with the constraints provided by the design space and control strategy, is suitable to assure complete release from the tablets and to provide verification of manufacturing process consistency. The technical data generated do not support further tightening of the specification, or indeed provide any greater level of quality assurance of the in-vivo product performance.

Outcomes & Conclusions

Differing interpretations and philosophies towards QbD and dissolution within the ICH Health Authority community have resulted in different outcomes in the review and approval of the same CMC dossier.

This has complicated the supply chain for this product due to the need for different quality control dissolution methods and specifications being required for release testing and change control.

Initial Submissions: Surfactant; Q = 75% in 60 minutes

Approved Dossiers:

US	pH 1.2; Q = 80% in 30 minutes
EU	Surfactant; Q = 75% in 45 minutes
Canada	Surfactant; Q = 75% in 45 minutes