

Development of a Discriminating Dissolution Test for an Immediate Release Tablet

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Introduction

It is clearly desirable to develop laboratory tests that provide an indication of the performance of tablets in man, the so-called *in vitro-in vivo* correlation (IVIVC) or relationship (IVIVR) (1-4). Many attempts have been made to establish these relationships for a variety of drugs and formulations (5) with

varying success. This article presents the development of a discriminating dissolution test that provides an IVIVC for an immediate release tablet undergoing clinical evaluation and describes how this test has been used to define the 'operating window' for critical processes in the manufacture of the tablets.

Solubility of the Drug Substance

The drug substance has poor aqueous solubility at low and moderate pH and needs to be modified to make it more soluble (figure 1).

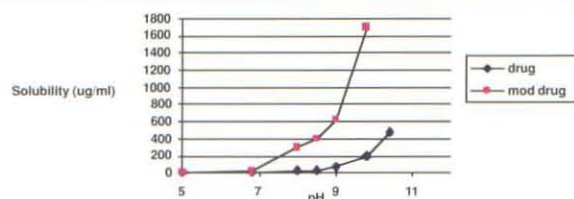


Figure 1. pH Solubility Profile for Drug and Modified Drug

This degree of solubility classifies the drug as having 'Low Solubility' as defined in the SUPAC guidelines recently produced by the FDA.

Development of a Discriminating Dissolution Test

For tablets containing 200 mg drug substance, a dissolution test was developed based on the USP Apparatus 2 paddle method with a weakly buffered

medium at pH 9.0. This test discriminated very well between tablets containing modified and unmodified drug substance, as shown in figure 2.

A release specification of >80% released after 20 minutes was set for clinical batches.

However, during early clinical evaluation of the compound, different batches of tablets gave different bioavailability (table 1) despite passing the dissolution test specification (figure 3).

Table 1. Relative Bioavailability of Early Clinical Batches

Tablet Batch Number	Relative Bioavailability
001 (Standard Batch of Tablets)	98
002	87
003	73
004	58

Clearly there was a need to develop a more discriminating dissolution test method. Simply reducing the pH in the USP Apparatus 2 paddle method did not work due to insufficient solubility

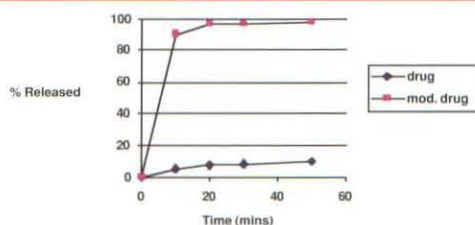


Figure 2. Discrimination Between Tablets Containing Drug and Modified Drug in the USP Apparatus 2 pH 9.0 Dissolution Test

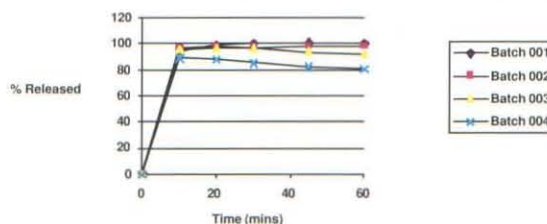


Figure 3. Dissolution Profiles of Early Clinical Batches in USP Apparatus 2/ pH 9 Test

Discriminating Dissolution Test...cont.

of the modified drug substance (figure 1). Instead, an alternative test method was developed using the USP 4 flow-through apparatus, which differs from the USP Apparatus 2 in having a much smaller dissolution cell (approx. 16 mL compared to 900 mL) and fresh dissolution medium constantly contacting the dosage form thus maintaining 'sink' conditions throughout the test.

The batch of standard tablets (batch 001) was used to assess the effects of several test variables on the dissolution rate, the most important one being pH (figure 4).

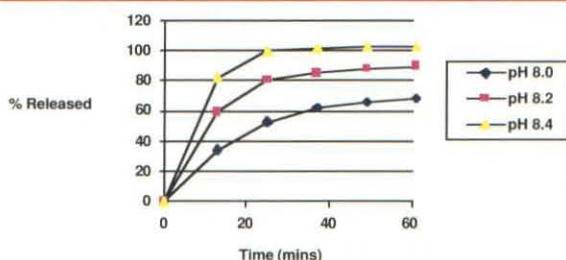


Figure 4. The Effect of pH on the Dissolution of Standard Tablet Batch 001 in the USP 4 Flow-through Dissolution Test

pH 8.2 was chosen to provide high release for standard tablets after 30 minutes and a discriminating test that would indicate tablet batches that released drug substance faster as well as slower than standard.

This USP Apparatus 4 test provided excellent discrimination between tablets containing modified and unmodified drug substance (figure 5) and also discriminated well between the clinical batches that had low bioavailability (figure 6).

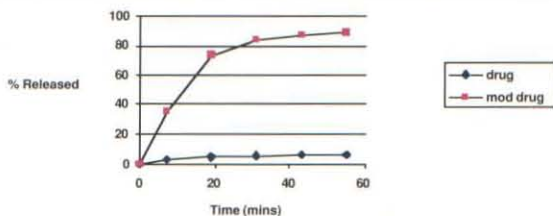


Figure 5. Discrimination Between Tablets Containing Drug and Modified Drug in the USP Apparatus 4 Dissolution Test

These data can be transformed into a graph showing the correlation between relative bioavailability and dissolution rate (figure 7).

Although not linear, there is a clear relationship between % released after 30 minutes and bioavailability, all four batches showing the correct rank order. From figure 7, a specification limit of > 55% released after 30 minutes was set for acceptable release of drug from the tablets. This corresponded to tablets that gave 90% relative bioavailability in man.

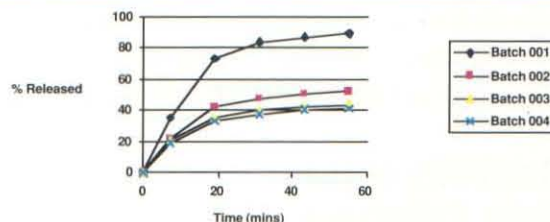


Figure 6. Dissolution Profiles of Early Clinical Batches in USP Apparatus 4 Test

The relationship shown in figure 7 was confirmed by more recent clinical batches shown to have a relative bioavailability of 94 to 101% in man and a release of 70 to 80% after 30 minutes in the USP Apparatus 4 test.

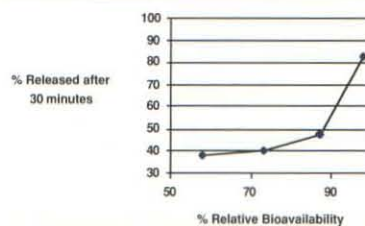


Figure 7. Correlation Between % Released After 30 minutes in the USP Apparatus 4 Dissolution Test and Relative Bioavailability in Man

Use of Discriminating Test to Define Process 'Operating Window'

Having developed a discriminating dissolution test that demonstrated a good in vitro-in vivo relationship, it was used to look at critical parameters for the tablet manufacturing process, such as mill speed and compression force. Figure 8 shows the effect of mill speed on dissolution rate, indicating that a mill speed

of at least 4500 is required to produce tablets with an acceptable dissolution rate of > 55% after 30 minutes.

From such studies, the 'operating window' for the entire process at the manufacturing scale is being defined.

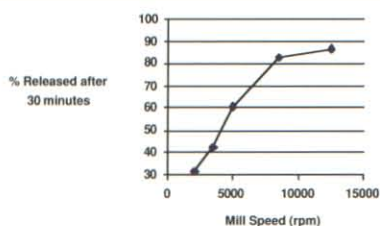


Figure 8. Effect of Mill Speed on Dissolution Rate in The USP Apparatus 4 Test

Conclusion

A dissolution test that shows an in vitro-in vivo correlation has been developed using the USP Apparatus 4 flow-through dissolution test. This discriminating test has been a powerful tool in defining the 'operating window' for the process and has obviated the need to conduct expensive and time consuming bioequivalence studies every time a process change has been conducted.

References:

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