TELEDYNE | Teledyne LABS

Dissolution Testing under Biowaiver Test Conditions for Metronidazole Tablets, USP 250 mg Using the CD14 Comparative Dissolution Tester

Ashvin Patel, PhD.

keywords: CD14, dissolution testing, metronidazole

Figure 1. The CD14 Comparative Dissolution Tester flanked by two autosamplers.

Introduction

Dissolution is a well known process in which a solid substance gets dissolved into solute and forms a solution. As described by the United States Pharmacopeia (USP), "Dissolution testing measures the extent and rate of solution formation from a dosage form, such as a tablet, a capsule, ointment, etc. The dissolution of a drug is important for its bioavailability and therapeutic effectiveness. Dissolution and drug release are terms used interchangeably."[1]

According to the United States Food and Drug Administration, "the objective of in vitro dissolution testing is to evaluate the variables that effect the rate and extent of release of a drug substance from the finished dosage form and, in turn, the in vivo performance of the drug product. When this objective is met, a comparison of product in vitro dissolution profiles or adherence to the product release specification ensures that the product or batch being evaluated will have consistent quality and performance."[2] Hence, the dissolution test is one of the most important product performance tests. In vitro bioequivalence and similarities between two products are evaluated by model-independent approaches using the similarity (f2) and the difference factor (f1). The same concept is also used for comparing two products when any allowable changes are made during the production or during any new product development and when formulation optimization steps are performed. This approach is useful for immediate release and for modified released products.[3] It is widely used in the pharmaceutical industry worldwide for oral solid drug development.

The Instrument

The 14 vessel CD14 Comparative Dissolution Tester allows users to run two methods simultaneously or independently. Also, users can choose to run the method for all 12 vessels at once and 6 vessels per product separately under test conditions. Such a setting is ideal for bioequivalence studies. The apparatus allows automated sampling under 5 minutes if an Autoplus autosampler is connected. This tester is compatible with USP apparatus 1, 2, 5, and 6. Bioequivalence studies can be performed to prove the similarity of two products by means of an in vitro dissolution test where dissolution test data is obtained from 12 doses of two products each. The CD14 tester provides the same environment to perform the dissolution test of two products—i.e., the innovator and the generic drug, or pre-change and post-change drug products.

About the Product Under Test

Metronidazole Tablets, USP, 250 mg were used to perform the dissolution test. Metronidazole belongs to a class of medications called nitroimidazole antimicrobials. Such antibiotics work by stopping the growth of bacteria. Consequently, they are ineffective against colds, flu, or other viral infections. Furthermore, using uneeded antibiotics increases the risk of antibiotic resistant infection. Instead, metronidazole is used to treat bacterial infections of the reproductive system, gastrointestinal (GI) tract, skin, heart, bone, joint, lung, blood, nervous system, and other areas of the body. It is also used to treat certain sexually transmitted diseases (STDs). Metronidazole is also used to treat bacterial vaginosis.[4]

Comparative Test Procedure

The dissolution test was performed using CD14. Two different products of Metronidazole Tablets 250 mg were obtained from a retail pharmacy in Toronto, Ontario, Canada. Both products were assigned unique product IDs—Product A and Product B—to mask their original identities. Per guidance provided by the US Food and Drug Administration (FDA), 12 tablets were tested for the percentaged dissolved from both products using three different dissolution mediums of pH 1.2 made from 0.1 N HCl, pH 4.5 of acetate buffer, and pH 6.8 of phosphate buffer. The dissolution test was performed at 37.0 ± 0.5°C, using USP Apparatus I (baskets) at 100 rpm. Samples were withdrawn by the autosampler at 10, 15, 30, 45, and 60 minute intervals; at each time point, replacement with fresh dissolution media was provided. The collected sample solutions were filtered using a 0.45 µ nylon syringe filters prior to measuring the absorbance at 278 nm on a UV visible spectrophotometer. Metronidazole reference standard solution was prepared from a certified reference material of metronidazole purchased from Sigma Aldrich, USA. All sample and standard solutions were diluted to bring the concentration of samples into the linearity range of the spectrophotometer. If required, a variety of other dissolution media can be used with a proper justification for this type of study.

The difference factor is f1. It is proportional to the average difference between the two profiles; that is, the percent (%) difference between two curves at each time point. It is the measurement of the relevant error between two of them. Normally, f1 values should be below 15. The simililarity factor f2 measures the closeness between two profiles; it is inversely proportional to the average squared difference between the two profiles. It assures the similarity in product performance. The formulas for f1 and f2 are shown below.[5]

$$f_1 = \{[\,\Sigma_{t=1}^{n} \mid R_t - T_t \mid\,]/[\Sigma_{t=1}^{n} \mid R_t \mid]\} \cdot 100$$

$$f_2 = 50 \cdot \log\{[1+(1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2\,]^{-0.5} \cdot 100\}$$

If the f2 value is 100, the two profiles are identical. An average difference of 10% at all measured time points results in an f2 value of 50. To indicate similarity, the FDA standard requires an f2 value above 50 between two dissolution profiles and an f1 value below 15.

Results

The % Metronidazole dissolved for an average of 12 tablets using a pH 1.2 dissolution medium prepared from 0.1 N HCl is presented in Table 1.

% Dissolved in pH 1.2, 0.1 N HC		
Time, Minutes	Product A	Product B
0	0	0.00
10	74.73	71.07
15	82.71	76.22
30	90.35	83.99
45	94.17	91.57
60	94.99	99.10

Table 1. % Dissolved of Metronidazole Tablets UPS in 0.1 N HCl.

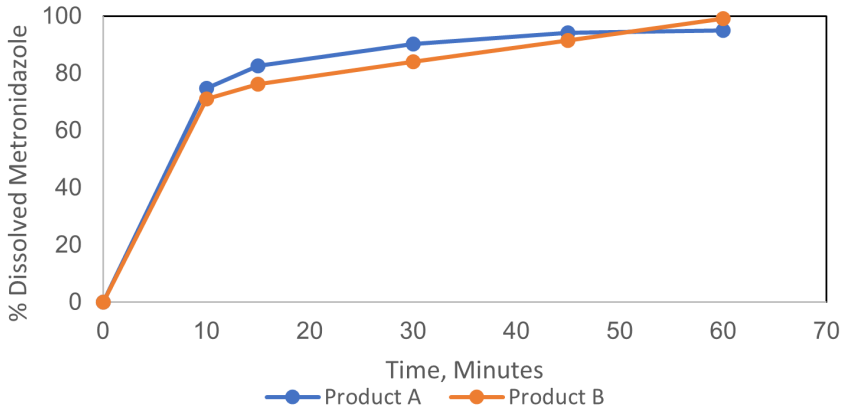

Figure 1. Dissolution profile graph for % Dissolved Metronidazole in 0.1 N HCl.

The % Metronidazole dissolved for an average of 12 tablets using Acetate Buffer, pH 4.5 dissolution medium is presented in Table 2.

% Dissolved in Acetate Buffer pH 4.5		
Time, Minutes	Product A	Product B
0	0	0.00
10	61.89	70.25
15	74.01	81.13
30	81.13	88.85
45	86.90	93.50
60	92.54	95.71

Table 2. % Dissolved of Metronidazole in Acetate Buffer, pH 4.5.

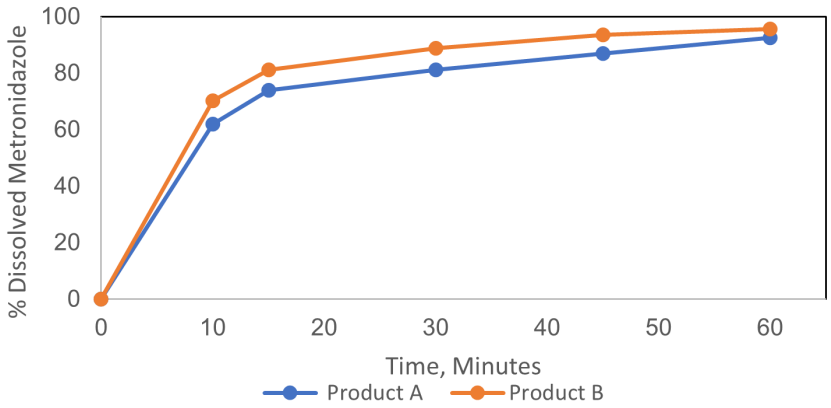

Figure 2. Dissolution profile graph for % Dissolved of Metronidazole in Acetate Buffer, pH 4.5

The % Metronidazole dissolved for an average of 12 tablets using Acetate Buffer, pH 4.5 dissolution medium is presented below in Table 3.

% Dissolved in Phosphate Buffer pH 6.8		
Time, Minutes	Product A	Product B
0	0	0.00
10	67.96	71.49
15	74.50	73.60
30	80.60	78.47
45	89.63	84.45
60	96.13	91.73

Table 3. % Dissolved of Metronidazole in Phosphate Buffer, pH 6.8.

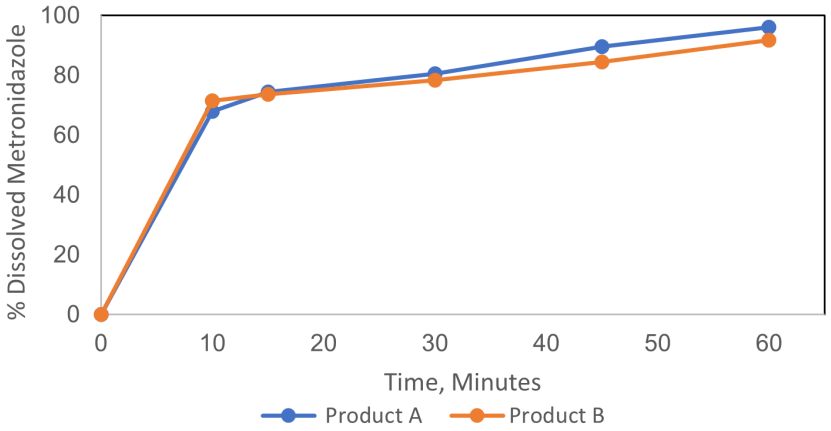

Figure 3. Dissolution profile graph for % Dissolved of Metronidazole in Phosphate Buffer, pH 6.8.

f1 and f2 calculated based on Product A as a Reference and Product B as a Test					
0.1 N HCl		Acetate Buffer pH 4.5		Phosphate Buffer pH 6.8	
f1	f2	f1	f2	f1	f2
5.3	65.2	3.5	75.1	3.9	71.5

Table 4. The summary of the difference factor (f1) and the similarity factor (f2) between two products.

Conclusion

The purpose of this study was only to compare two dissolution profiles using various dissolution media, and not to perform quality tests or check them against set specifications of the marketed products used in this study. Regardless of the purpose of the study, the product conforms to the specification of "NLT 85% (Q) of the labelled amount of $C_6H_9N_3O_3$" as mentioned in the USP Monograph.[6] The dissolution data obtained in this study are comparable for both products. If this approach is used for bio-waiver application along with other require data for an abbreviated new drug application (ANDA), this data would be accepted without any question. Using the optional autosampler with the CD14 Tester will allow users to perform comparative dissolution tests in most compliant and time efficient manner. The CD14 has all the tools for meeting compliance with 21 CFR Part 11 and for maintaining the robust data integrity required by most regulatory agencies. The CD14 is relatively compact, occupying less space on a lab bench compared to other dissolution testers in its class.

References

1. USP. Dissolution Testing and Drug Release Tests [Internet]. www.usp.org. Available from: https://www.usp.org/small-molecules/dissolution
2. FDA. Compilation of FDA Guidance and Resources for in vitro Dissolution Testing of Immediate Release Solid Oral Dosage Forms. FDA [Internet]. Available from: https://www.fda.gov/animal-veterinary/new-animal-drug-applications/compilation-fda-guidance-and-resources-in-vitro-dissolution-testing-immediate-release-solid-oral-dosage
3. FDA. Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances Guidance for Industry; August 2018
4. MedlinePlus. Metronidazole [Internet]. Available from: https://medlineplus.gov/druginfo/meds/a689011.html#why
5. Shah VP, Tsong Y, Sathe P, Williams RL. Dissolution profile comparison using similarity factor, f2. Dissolution Technol. 1999;6(3):15. Available from: dx.doi.org/10.14227/DT060399P15
6. The United States Pharmacopeia. Metronidazole Tablets [Internet]. Available from: https://online.uspnf.com/uspnf/document/1_guid-6fa17848-0236-4133-B908-A7D20D5AEE69_3en-US doi:10.31003/USPNF_M53700_03_01