

Use of the Teledyne LABS CD14 for Dissolution Testing of an Extended Release Product—Diltiazem HCl CD Capsules, 180 mg

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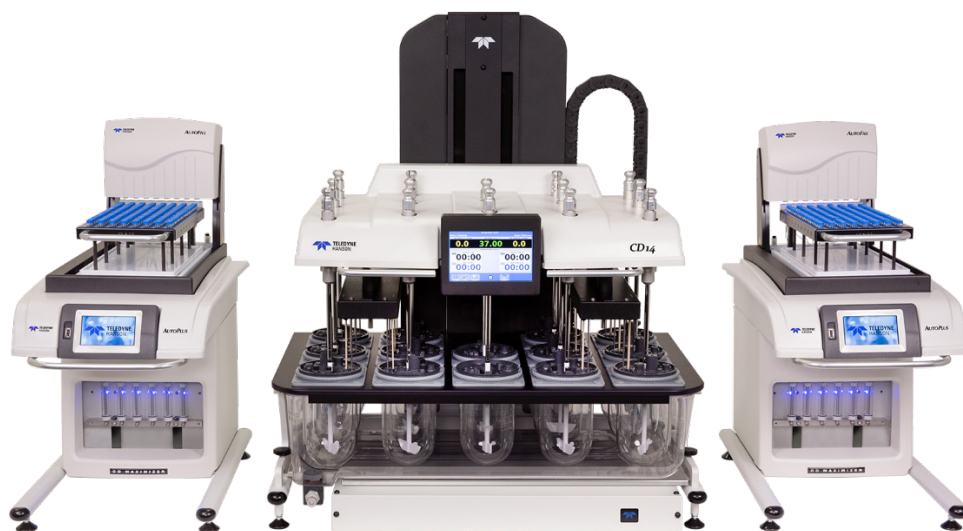


Figure 1. The CD14 Comparative Dissolution Tester flanked by two autosamplers.

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, using the world wide accepted concept of obtaining the similarity factor (f_2), which can be generated to prove the similarities between two products such as reference listed drug (RLD) and proposed generics. The same concept is also used for comparing two products after any changes are made per scale-up and post-approval change (SUPAC) guidance. The similarity factor is required for comparing dissolution profiles and to evaluate relative in vitro performance resulting from changes in raw materials, formulation, and/or manufacturing for both development and commercial products.

Background

It is very important to develop a discriminating, non-interfering, robust, accurate, and precise method for dissolution. The Teledyne LABS CD14 Comparative Dissolution Tester runs two methods simultaneously or independently, which is ideal to compare two products in same environment. This apparatus allows automated sampling in under 5 minutes if an CD Autoplus autosampler is used; otherwise, samples can be pulled at any interval if manual sampling is preferred. This tester is compatible with USP apparatus 1, 2, 5, and 6. Bioequivalence studies are required for all regulatory agencies to compare the dissolution profile between a reference listed drug and the generic drug product. After conducting this study on n=12 units, the similarity factor, f₂, and the difference factor, f₁, are calculated as recommended by the United States Food and Drug Administration (FDA). The 14 vessel system allows for 6+1 or 12+2 configurations to enhance the efficiency of any laboratory performing multiple dissolution tests on any given day.

Diltiazem is a well known and widely prescribed drug product to treat high blood pressure and prevent chest pain. By lowering high blood pressure, it helps prevent strokes, heart attacks, and kidney problems. When used regularly, it can decrease the number and severity of episodes of chest pain from angina. It is a calcium channel blocker. It relaxes the blood vessels to flow the blood easily and lowers the workload of heart.³ There are several brands of this product with multiple strengths available from multiple sources.

Comparative Testing Procedure

To evaluate the comparison of dissolution profiles, Diltiazem Hydrochloride Controlled Delivery 180 mg capsules, manufactured by two drug manufacturing companies in Canada, were obtained from a retail pharmacy in Toronto, Ontario, Canada. The dissolution test was performed on a CD14 Tester, equipped with an autosampler, using 12 capsules each from both lots per the method described in the current United States Pharmacopeia (USP) at 37.0 ± 0.5 °C, using 900 mL of pH 6.8 Phosphate buffer as dissolution medium. Apparatus I (Basket) was used at 100 rpm. During the 24-hour test, 10 mL sample was collected at 1, 4, 8, 12, 16, and 24-hour time points from all 12 vessels. At each timepoint, 10 mL of fresh dissolution medium was replaced and was maintained at 37 °C. After collection, a sample was filtered using 0.45 µ nylon syringe filters, and NLT 3 mL was discarded prior to collecting sample solution for UV Analysis. The samples were then diluted for measurement of absorbance at 237 nm. The results were calculated against the absorbance of same concentration of known standard solution prepared from Diltiazem HCl certified reference standard obtained from Sigma Aldrich, USA. The % dissolved data were also used to calculate f₁ and f₂ to understand the similarity between two dissolution profiles. The equation below is obtained from the FDA's guidance document.⁴ FDA has set a general standard of f₂ values between 50 and 100, which shows the similarity between two profiles:

$$f_1 = \{ [\sum_{t=1}^n |R_t - T_t|] / [\sum_{t=1}^n R_t] \} \cdot 100$$

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

Results

Results obtained in this study using CD14 systems with Apparatus I (Baskets) are summarized in Table 1 and graphically presented in Figure 2.

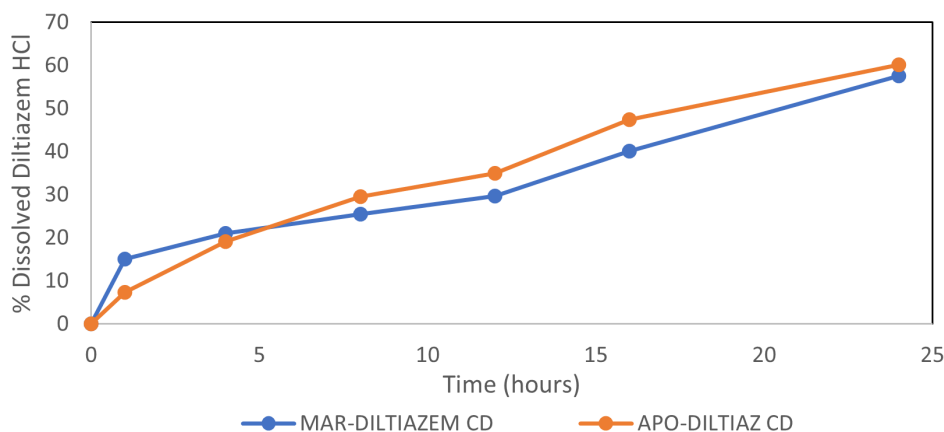


Figure 2. % Dissolved comparison

Time Hours	Apotex Diltiazem CD Lot # TG8718, Exp: Sep 2023 % Dissolved												Average
	V-1	V-2	V-3	V-4	V-5	V-6	V-7	V-8	V-9	V-10	V-11	V-12	
0	0	0	0	0	0	0	0	0	0	0	0	0	0.00
1	16.8	16.7	16.5	14.5	13.6	17.0	14.1	13.9	14.9	14.6	14.5	13.9	15.09
4	21.6	20.4	20.2	21.4	20.0	20.2	21.8	21.0	21.0	21.6	21.4	21.3	20.99
8	26.0	24.5	25.8	26.7	24.8	26.1	23.4	26.3	23.9	27.9	24.7	26.2	25.52
12	30.2	28.9	26.8	27.3	28.6	32.2	29.9	28.9	30.6	29.9	31.3	32.0	29.72
16	42.4	36.5	41.6	39.5	40.3	44.3	37.3	41.5	40.3	38.4	39.9	38.4	40.03
24	54.2	59.4	62.3	60.1	56.1	57.3	55.6	56.1	58.1	53.2	56.3	61.3	57.50
Time Hours	MarCan Diltiazem CD Lot # H220012, Exp: Sep 2023 % Dissolved												Average
	V-1	V-2	V-3	V-4	V-5	V-6	V-7	V-8	V-9	V-10	V-11	V-12	
0	0	0	0	0	0	0	0	0	0	0	0	0	0.0
1	7.2	7.3	6.8	6.7	7.4	7.2	8.1	8.1	7.1	7.7	7.2	7.3	7.35
4	19.3	18.2	17.7	17.4	18.2	17.3	21.0	19.8	20.4	19.6	20.1	20.3	19.10
8	30.1	28.5	30.1	30.2	31.9	28.9	29.4	28.7	29.6	29.1	29.0	28.5	29.50
12	34.4	38.9	36.6	34.7	35.5	33.6	34.2	32.1	35.2	33.1	35.8	34.6	34.91
16	46.0	47.5	46.4	46.9	45.7	46.6	48.7	48.0	49.0	47.9	47.9	48.1	47.41
24	58.9	57.6	61.2	60.3	58.9	55.1	65.3	62.3	60.2	59.1	64.35	57.9	60.10

Table 1. % Data for dissolved Diltiazem HCl obtained with CD14 automated sampling.

Product Name: Diltiazem HCl Capsules, 180 mg						
Apparatus: I Baskets, USP 40 mesh				rpm:100		
Dissolution Medium, pH 6.80 Phosphate Buffer				Volume (mL): 900 mL		
Time Point: 1,4, 8,12,16,24 Hours			Sample Volume: 10 mL			
Time in hours	MarCan Diltiazem- CD [R]*	Apotex Diltiazem-CD [T]**	R-T	R-t	(R-T) ²	No. of time points
1	7.35	15.09	-7.74	7.74	59.85	1
4	19.10	20.99	-1.89	1.89	3.57	1
8	29.50	25.52	3.98	3.98	15.82	1
12	34.91	29.72	5.19	5.19	26.89	1
16	47.41	40.03	7.38	7.38	54.45	1
24	60.10	57.50	2.60	2.6	6.76	1
Sigma R	198.4	188.9	9.52	28.77	167.35	6
Difference Factor		f1= 14.5				
Similarity Factor		f2= 63.5				
If the f1 value is below 15 and f2 is above 50, the dissolution profiles of two products are comparable.						

Table 2 % Data for the difference factor (f1) and similarity factor (f2).

* Diltiazem HCl Controlled Delivery capsules from MarCan Pharmaceuticals Inc.

** Diltiazem HCl Controlled Delivery capsules from Apotex Inc.

Conclusion

The study results are comparable for both products. In this study, there was no intention to test the product quality or its specification limits set forth by manufacturers or by the USP monographs. The purpose of this study is only to evaluate two products being tested under the same environment using the CD14 Tester. In this study, both products behaved like each other. Regardless of their overall dissolved amount, the products are similar in terms of their data and dissolution profile characteristics. The difference factor, f_1 , and similarity factor, f_2 , are both well within the standard specification generally accepted by the regulatory agency for which two dissolution profiles can be said to be similar. The CD14 can be used for extended-release drug product dissolution where longer test times are required. It is a very useful apparatus for obtaining robust data for abbreviated new drug application (ANDA) submission, where the comparison study is performed between the reference listed drugs and the proposed generic drug product or during SUPAC process of manufacturing drug products. Because 14 vessels are available under one temperature controlling bath, the CD14 can also be used in formulation development labs during the early development phase, where $n=3$ tablets or capsules are tested for optimization steps to evaluate the effectiveness of various parameters or impact of ingredients. For R&D purposes, 4 parameters can be evaluated simultaneously if $n=3$ samples are tested in one run.

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