HTTPS://DOI.ORG/10.33472/AFJBS.6.10.2024.5769-5779

African Journal of Biological Sciences

Validated Dissolution Method For Various Strengths Of Diltiazem Hydrochloride Tablet (Immediate Release) By UV Spectrophotometer.

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Article History

Volume 6,Issue 10, 2024

Received:24 May 2024

Accepted : 02 Jun 2024

doi: 10.48047/AFJBS.6.10.2024.5769-5779

ABSTRACT

The work defines the development of a dissolution method and validation of the method for Diltiazem Hydrochloride tablet immediate release and its various strengths (30, 60, 90, 120mg). The absorption maxima (λ_{max}) of Diltiazem HCl were found to be 237nm. The dissolution media used was water. Various Tablet batches were prepared and the dissolution test was carried out. The batch showing the highest accuracy towards the reference listed drug was finalized and then the method was validated using the finalized batch. The validation protocol was performed as per ICH guideline. The method was found to be cost effective, rugged, linear and precise.

1. Introduction

Diltiazem Hydrochloride belongs to the class of Calcium-Channel Blocker (CCB). It works by lowering the blood pressure by relaxing the blood vessel reducing the efforts of heart to pump blood thus preventing the high risk of coronary heart disease, heart attack and strokes. The studies have also shown that diltiazem HCl also help in reducing chest pain caused by angina and also increase the supply of blood and oxygen.[7]

1.1 Dissolution Process

Dissolution Testing has a very major importance in the pharma industry as a result of which the regulatory authorities have emphasized on dissolution as a quality control record for oral solid dosage forms. Dissolution testing is In-Vitro process which defines a way the drug product may behaves inside a human body. This helps in improving drug product before its final assessment or submission for its bioequivalence study as a result of which there is decrease in the cost of BE studies and increase in the quality of the product. The definition of dissolution is subtle simple. It is the process in which a solid substance goes into a solution. Obviously, there are numerous other factors, such as excipients, coatings, pH, the medium in which the drug is dissolving, the temperature of the

medium, and the affinity for the solid particles to dissolve in the medium, affect the rate of dissolution in most instances.[6]

1.2 Validation Process

Validation is one of the most widely used term in pharmaceuticals. The term validation or validation concept was brought up by FDA to improve quality of pharmaceutical products. According to FDA, "Validation is establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes".[1]

According to EU guidelines, "Validation means the action of proving, following GMP principles that any procedure, process, equipment, material, activity, or system leads to the expected results".[3]

Validation of a developed method is essential to provide substantial evidence to prove that the method/process produce the desired result consistently. Validation has a number of characteristics which are carried out and varies depending upon the test.

Validation Characteristics / Parameters	*TEST METHOD*				
	Identification	*Test for Impurities*		*Assay/ Dissolution*	*Specific Test*
		Quantitative	*Limits*		
Accuracy	×		×		
Precision					
Repeatability	×		×		
Intermediate Precision	×		×		
Specificity		×			
Detection Limit	×			×	×
Quantitation Limit	×		×	×	×
Linearity	×		×		×
Range	×		×		×
Robustness	×		×		

Fig 1. Various parameters of Analytical Validation according to US Pharmacopoeia

1.2.1 Accuracy[2]

According to ICH Q2(R1) guideline, "Accuracy is defined as the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found".

Sometimes the accuracy is also termed as Trueness.

Acceptance Criteria: 95.0%–105.0%.

1.2.2 Precision[2]

According to ICH Q2(R1) guideline, "Precision of an analytical method expresses the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed condition".

Precision is carried out on three different levels:

a. **Repeatability:** It expresses the precision under the same operating condition over a short interval of time.

It is also termed as intra-assay precision.

b. **Intermediate Precision:** It expresses precision under laboratory variation like different analyst, different days, and different equipment.

c. **Reproducibility:** It expresses precision between laboratories usually applied to standardization of methodology.

Acceptance Criteria: The RSD is NMT 5.0%.

1.2.3 Specificity[2]

According to ICH Q2(R1), "Specificity is defined as the ability to unequivocally assess each analyte element in presence of component that are expected to be present such as impurities, degradants, matrix, etc.

Acceptance Criteria: Demonstrated by meeting the accuracy requirement.

1.2.4 Detection limit[2]

According to ICH Q2(R1), "The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value".

1.2.5 Quantitation Limit[2]

According to ICH Q2(R1), "The Quantitation Limit of an individual analytical procedure is defined as the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

Acceptance Criteria: The analytical procedure should be capable of determining the analyte precisely and accurately at a level equivalent to 50% of the specification.

1.2.6 Linearity[2]

According to ICH Q2(R1), "The linearity of an analytical procedure is its ability to obtain test results directly proportional to the concentration of analyte in the sample".

Acceptance Criteria: Correlation coefficient (R^2) NLT 0.995.

1.2.7 Range[2]

The range is normally derived from linearity studies and depends upon the intended application of the procedure. The analytical procedure provides an acceptable degree of linearity, accuracy and precision. For dissolution testing ± 20% over the specified range.

For example: if the specifications for a controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0-110% of the label claim.

1.2.8 Robustness[2]

It shows reliability of an analysis with respect to deliberate changes/variations in the procedure. The evaluation of robustness is considered during the development trials and depends upon the type of procedure.

Examples of typical variations are:

- stability of analytical solutions; extraction time.

In the case of liquid chromatography, examples of typical variations are,

- influence of variations of pH in a mobile phase; influence of variations in mobile phase composition; different columns (different lots and/or suppliers); temperature; flow rate.

In the case of gas-chromatography, examples of typical variations are,

- different columns (different lots and/or suppliers); temperature; flow rate.

2. Material Used

All the material used was of pharmaceutical grade. The Standard of Diltiazem HCl was obtained from MSN Pharmaceuticals. The tablets used for the validation and testing was obtained from Xenon laboratories. The Dissolution apparatus used for the dissolution process was a 6-unit apparatus of Electrolabs and the UV spectrophotometer was of Shimadzu i-1900 series. All the other chemicals and reagents used are of Analytical grade.

3. Methodology

3.1. Accuracy

The accuracy of the method was performed at three different levels i.e., at 25%, 100% and at 150%. In various levels the concentration of the API changes according to the labelled claim of the drug. For 25% the worst-case scenario is taken i.e., the concentration of the API depends upon the lowest labelled claim formulation.

For 25% Level: In a dried 1000ml volumetric flask about 7.5mg of API was added to the flask. It was carried out in three replicates. After addition of the API in each flask a placebo tablet was placed containing all the excipients. About 900ml of the media was filled in each of the following flask. A magnetic bead was placed inside each flask and was placed on a magnetic stirrer with hot plate. The speed was kept constant at 800rpm and the temperature was set up at 37.0^{o}C. The process was allowed to be performed for 3hrs. After the completion of the process the magnetic bead was taken out of the flask. The solution from each flask was filtered into three different test tubes using 0.45 µPVDF filter. Then further the dilution of the following filtered solution was done into its respective aliquots. The aliquots were then taken for measuring the absorbance and then the calculation was performed.

For 100% Level: In a dried 1000ml volumetric flask about 30mg of API was added to the flask. It was carried out in three replicates. After addition of the API in each flask a placebo tablet was placed containing all the excipients. About 900ml of the media was filled in each of the following flask. A magnetic bead was placed inside each flask and was placed on a magnetic stirrer with hot plate. The speed was kept constant at 800rpm and the temperature was set up at 37.0^{o}C. The process was allowed to be performed for 3hrs. After the completion of the process the magnetic bead was taken out of the flask. The solution from each flask was filtered into three different test tubes using 0.45 µPVDF filter. Then further the dilution of the following filtered solution was done into its respective aliquots. The aliquots were then taken for measuring the absorbance and then the calculation was performed.

For 150% Level: In a dried 1000ml volumetric flask about 180mg of API was added to the flask. It was carried out in three replicates. After addition of the API in each flask a placebo tablet was placed containing all the excipients. About 900ml of the media was filled in each of the following flask. A magnetic bead was placed inside each flask and was placed on a magnetic stirrer with hot plate. The

speed was kept constant at 800rpm and the temperature was set up at 37.0°C. The process was allowed to be performed for 3hrs. After the completion of the process the magnetic bead was taken out of the flask. The solution from each flask was filtered into three different test tubes using 0.45 µPVDF filter. Then further the dilution of the following filtered solution was done into its respective aliquots. The aliquots were then taken for measuring the absorbance and then the calculation was performed.
Results are shown in the table 4.1.

3.2. Precision

The precision of the method was carried out in two ways:

In the first step the %RSD of the standard was calculated which was to be < 2%
(*Repeatability*)

For performing this process six different samples (at 100% concentration) of the standard were prepared. For preparation, about 56mg of the API was weighed in a 100ml volumetric flask. To this about 70% of media was added (Water). The flask was kept for sonication so as the API gets dissolved properly. The volume was made up to the mark and the flask were shaken left and right so that the API gets properly dissolved. Further dilution of the standard was done to prepare a sample of defined pp. Six different aliquots were prepared in the same manner.
Results are shown in the table 4.2.1.

(Reproducibility)

In the second method the dissolution data of the tablet was matched. It is also known as Reproducibility. It is considered in the cases of standardization of Analytical procedures and for inclusion of procedures in pharmacopoeia.
Results are shown in the table 4.2.2.

3.3. Robustness

For performing robustness various parameters were taken into consideration. As we are performing the dissolution study the parameters involved are not only for UV spectroscopy but also for the dissolution apparatus.
The robustness is divided into the following category for this process:

1. For UV spectrophotometer
a. Change in wavelength (±5nm)
b. Use of different UV instrument
c. Change of analyst
2. For Dissolution Apparatus
a. Change in RPM (±3)

Since the media used for dissolution activity is water therefore there is no need to vary the pH of the media for robustness.
Results are shown in the table 4.3.1., 4.3.2.,4.3.3., 4.3.4.

3.4. Linearity

For performing the linearity study a minimum of five preparation was used to obtained a concentration curve. The concentration of the preparation was determined according to ICH Q2 R1 Guideline. The aliquots were prepared by making a standard preparation. The standard was prepared

by weighing about 56mg of standard in a 100ml volumetric flask. Further addition of 75ml of water in the flask and vigorous shaking done in left and right was done making sure that the standard gets dissolved. The flask was kept in the Ultra Sonicator for 10mins with shaking at regular intervals. For preparation of aliquots the dilutions were prepared from the stock prepared above. The aliquots prepared were of the following concentration 2ppm, 6ppm, 10ppm, 14ppm and 18ppm respectively. The prepared dilution was taken for measuring the absorbance at 237nm. The graph was plot between Absorbance v/s Concentration and the correlation values was observed.
Results are shown in table 4.4.

3.5. Specificity

For performing the specificity, the excipients used for manufacturing of tablets same excipients were used. A batch of placebo tablet was prepared. The placebo tablet was taken and placed in the dissolution apparatus. The placebo tablets were allowed to run for the specified time of dissolution of the formulation. Two Q-time point samples were taken and further the dilution was performed in the same manner as performed for the formulation. The dilutions were taken for measuring the absorbance and also the spectrum was observed to check whether the excipients were having any interference or not.

4. Result and Discussion

The pronounced method has been validated for rejoinder function, accuracy, repeatability, specificity and precision. The results of UV analysis have been shown in Tables 4.1-4.5. The proposed method was found to be linear between concentration 2.8-18 µg/ml with a linear correlation coefficient (R^2) of 0.9998 and the linear regression equation, y =0.0407X+0.197. The linearity of concentration levels at which Diltiazem HCl can be reliably 2.8-18µg/ml (Table 4.4) (Fig. 2). The mean recoveries at different level were found to be 99.9, 99.2, 99.1 respectively and substantiated the method as accurate (Table 4.1). The method was found to be precise at 100% level of concentration and showed reproducibility (Table 4.2.1-4.2.2). Robustness was performed was by changing the wavelength as well as the RPM and the changes in the result were found to be within the acceptable limit (Table 4.3.1-4.3.4). Specificity is the ability of the reported method provides data on specificity for their estimation in the presence of formulation excipients. The absorbance obtained with the mixture of the excipients showed no interference with the absorbance of standard (Table 4.5). The repeatability, linearity, specificity, and accuracy, (RSD) was less than 2% which met the criteria set by the International Council of Harmonization (ICH). The product met the standard criteria with the new analytical method.

Table 4.1: Results showing the Accuracy Study

Level	Sets	Absorbance Obtained	mg of API Added	mg of API Recovered	% Recovery	Mean Recovery
25%	1	0.173	8.25	8.11	98.3	99.9%
25%	2	0.181	8.30	8.29	99.9	
25%	3	0.181	8.30	8.44	101.7	
100%	1	0.685	33.15	32.10	96.8	99.2%
100%	2	0.722	33.32	33.84	101.6	
100%	3	0.738	34.83	34.59	99.3	
150%	1	1.054	200.21	196.58	98.2	99.1%
150%	2	1.068	200.18	199.19	99.5	
150%	3	1.069	200.32	199.38	99.5	

Table 4.2.1: Results Showing Precision Study (Data for Repeatability)

S.No.	Level	Absorbance
1	100%	0.750
2	100%	0.752
3	100%	0.750
4	100%	0.752
5	100%	0.750
6	100%	0.751
Mean		0.751
SD		0.001
RSD		0.131

Table 4.2.2: Results Showing Precision Study (Data for Reproducibility)

Time Point	Tablet No.						Average Dissolution With correction factor
	1	2	3	4	5	6	
15min	0.085	0.095	0.079	0.086	0.074	0.081	12
% Dissolved	12.0	13.4	11.1	12.1	10.4	11.4	
30min	0.149	0.169	0.145	0.160	0.140	0.147	22
% Dissolved	21.2	24.0	20.6	22.7	19.9	20.9	
60min	0.279	0.307	0.263	0.288	0.254	0.265	39
% Dissolved	39.8	43.7	37.5	41.1	36.3	37.8	
90min	0.385	0.423	0.364	0.405	0.356	0.366	55
% Dissolved	55.3	60.7	52.3	58.1	51.1	52.5	
120min	0.471	0.521	0.449	0.503	0.430	0.443	68
% Dissolved	68.2	75.4	64.9	72.7	62.2	64.1	
180min	0.600	0.650	0.565	0.640	0.555	0.560	87
% Dissolved	87.4	94.6	82.2	93.0	80.7	81.4	
240min	0.650	0.660	0.637	0.670	0.622	0.624	95
% Dissolved	95.6	97.3	93.4	98.5	91.3	91.6	
300min	0.667	0.655	0.666	0.658	0.657	0.648	98
% Dissolved	99.3	97.6	98.8	98.2	97.5	96.2	
Recovery	0.659	0.648	0.658	0.653	0.653	0.647	99
% Dissolved	99.6	98.2	99.0	98.8	98.2	97.4	

Table 4.3.1: Results showing Robustness studies (For RPM±3) (72RPM)

Time Point	Tablet No.						Average Dissolution With correction factor
	1	2	3	4	5	6	
15min	0.080	0.091	0.074	0.081	0.070	0.076	11
% Dissolved	11.2	13.2	11.0	12.0	10.2	11.4	
30min	0.147	0.150	0.139	0.156	0.135	0.140	21
% Dissolved	21.2	22.0	20.6	22.7	19.9	20.9	
60min	0.274	0.297	0.260	0.288	0.250	0.260	38

% Dissolved	**38.8**	**40.7**	**37.1**	**40.1**	**36.3**	**36.8**	
90min	0.380	0.421	0.360	0.400	0.350	0.360	54
% Dissolved	**54.3**	**58.7**	**52.1**	**57.5**	**51.1**	**51.5**	
120min	0.466	0.516	0.445	0.500	0.425	0.440	67
% Dissolved	**67.2**	**74.4**	**63.9**	**71.7**	**61.2**	**62.1**	
180min	0.595	0.645	0.560	0.635	0.550	0.555	86
% Dissolved	**86.4**	**93.6**	**81.2**	**92.0**	**79.7**	**80.4**	
240min	0.650	0.660	0.637	0.670	0.622	0.624	94
% Dissolved	**94.6**	**96.3**	**92.4**	**97.5**	**90.3**	**90.6**	
300min	0.667	0.655	0.666	0.658	0.657	0.648	97
% Dissolved	**98.3**	**96.6**	**97.8**	**97.2**	**96.5**	**95.2**	
Recovery	0.659	0.648	0.658	0.653	0.653	0.647	98
% Dissolved	**98.6**	**98.2**	**99.0**	**98.8**	**98.2**	**97.4**	

Table 4.3.2: Results showing Robustness studies (For RPM±3) (78RPM)

Time Point	**Tablet No.**						**Average Dissolution With correction factor**
	1	2	3	4	5	6	
15min	0.080	0.091	0.074	0.081	0.070	0.076	11
% Dissolved	**11.2**	**13.2**	**11.0**	**12.0**	**10.2**	**11.4**	
30min	0.147	0.150	0.139	0.156	0.135	0.140	21
% Dissolved	**21.2**	**22.0**	**20.6**	**22.7**	**19.9**	**20.9**	
60min	0.274	0.297	0.260	0.288	0.250	0.260	38
% Dissolved	**38.8**	**40.7**	**37.1**	**40.1**	**36.3**	**36.8**	
90min	0.380	0.421	0.360	0.400	0.350	0.360	54
% Dissolved	**54.3**	**58.7**	**52.1**	**57.5**	**51.1**	**51.5**	
120min	0.466	0.516	0.445	0.500	0.425	0.440	67
% Dissolved	**67.2**	**74.4**	**63.9**	**71.7**	**61.2**	**62.1**	
180min	0.595	0.645	0.560	0.635	0.550	0.555	86
% Dissolved	**86.4**	**93.6**	**81.2**	**92.0**	**79.7**	**80.4**	
240min	0.650	0.660	0.637	0.670	0.622	0.624	94
% Dissolved	**94.6**	**96.3**	**92.4**	**97.5**	**90.3**	**90.6**	
300min	0.667	0.655	0.666	0.658	0.657	0.648	97
% Dissolved	**98.3**	**96.6**	**97.8**	**97.2**	**96.5**	**95.2**	
Recovery	0.659	0.648	0.658	0.653	0.653	0.647	98
% Dissolved	**98.6**	**98.2**	**99.0**	**98.8**	**98.2**	**97.4**	

Table 4.3.3: Results showing Robustness studies (For Wavelength±5nm) (232nm)

Time Point	**Tablet No.**						**Average Dissolution With correction factor**
	1	2	3	4	5	6	
15min	0.085	0.095	0.079	0.086	0.074	0.081	12
% Dissolved	**12.0**	**13.4**	**11.1**	**12.1**	**10.4**	**11.4**	
30min	0.149	0.169	0.145	0.160	0.140	0.147	22
% Dissolved	**21.2**	**24.0**	**20.6**	**22.7**	**19.9**	**20.9**	

60min	0.279	0.307	0.263	0.288	0.254	0.265	39
% Dissolved	**39.8**	**43.7**	**37.5**	**41.1**	**36.3**	**37.8**	
90min	0.385	0.423	0.364	0.405	0.356	0.366	55
% Dissolved	**55.3**	**60.7**	**52.3**	**58.1**	**51.1**	**52.5**	
120min	0.471	0.521	0.449	0.503	0.430	0.443	68
% Dissolved	**68.2**	**75.4**	**64.9**	**72.7**	**62.2**	**64.1**	
180min	0.600	0.650	0.565	0.640	0.555	0.560	87
% Dissolved	**87.4**	**94.6**	**82.2**	**93.0**	**80.7**	**81.4**	
240min	0.650	0.660	0.637	0.670	0.622	0.624	95
% Dissolved	**95.6**	**97.3**	**93.4**	**98.5**	**91.3**	**91.6**	
300min	0.667	0.655	0.666	0.658	0.657	0.648	98
% Dissolved	**99.3**	**97.6**	**98.8**	**98.2**	**97.5**	**96.2**	
Recovery	0.659	0.648	0.658	0.653	0.653	0.647	99
% Dissolved	**99.6**	**98.2**	**99.0**	**98.8**	**98.2**	**97.4**	

Table 4.3.4: Results showing Robustness studies (For wavelength ±5) (242nm)

Time Point	**Tablet No.**						**Average Dissolution With correction factor**
	1	2	3	4	5	6	
15min	0.080	0.091	0.074	0.081	0.070	0.076	11
% Dissolved	**11.2**	**13.2**	**11.0**	**12.0**	**10.2**	**11.4**	
30min	0.147	0.150	0.139	0.156	0.135	0.140	21
% Dissolved	**21.2**	**22.0**	**20.6**	**22.7**	**19.9**	**20.9**	
60min	0.274	0.297	0.260	0.288	0.250	0.260	38
% Dissolved	**38.8**	**40.7**	**37.1**	**40.1**	**36.3**	**36.8**	
90min	0.380	0.421	0.360	0.400	0.350	0.360	54
% Dissolved	**54.3**	**58.7**	**52.1**	**57.5**	**51.1**	**51.5**	
120min	0.466	0.516	0.445	0.500	0.425	0.440	67
% Dissolved	**67.2**	**74.4**	**63.9**	**71.7**	**61.2**	**62.1**	
180min	0.595	0.645	0.560	0.635	0.550	0.555	86
% Dissolved	**86.4**	**93.6**	**81.2**	**92.0**	**79.7**	**80.4**	
240min	0.650	0.660	0.637	0.670	0.622	0.624	94
% Dissolved	**94.6**	**96.3**	**92.4**	**97.5**	**90.3**	**90.6**	
300min	0.667	0.655	0.666	0.658	0.657	0.648	97
% Dissolved	**98.3**	**96.6**	**97.8**	**97.2**	**96.5**	**95.2**	
Recovery	0.659	0.648	0.658	0.653	0.653	0.647	98
% Dissolved	**98.6**	**98.2**	**99.0**	**98.8**	**98.2**	**97.4**	

Table 4.4: Results showing Linearity Study

S.No.	*Concentration(ppm)*	*Absorbance(nm)*
1	2.8	0.310
2	6	0.445
3	10	0.604
4	14	0.762
5	18	0.934

	Co-relation Coefficient (R^2)	**0.9998**
	Equation	**y = 0.0407x + 0.197**
	Slope	**0.0407**

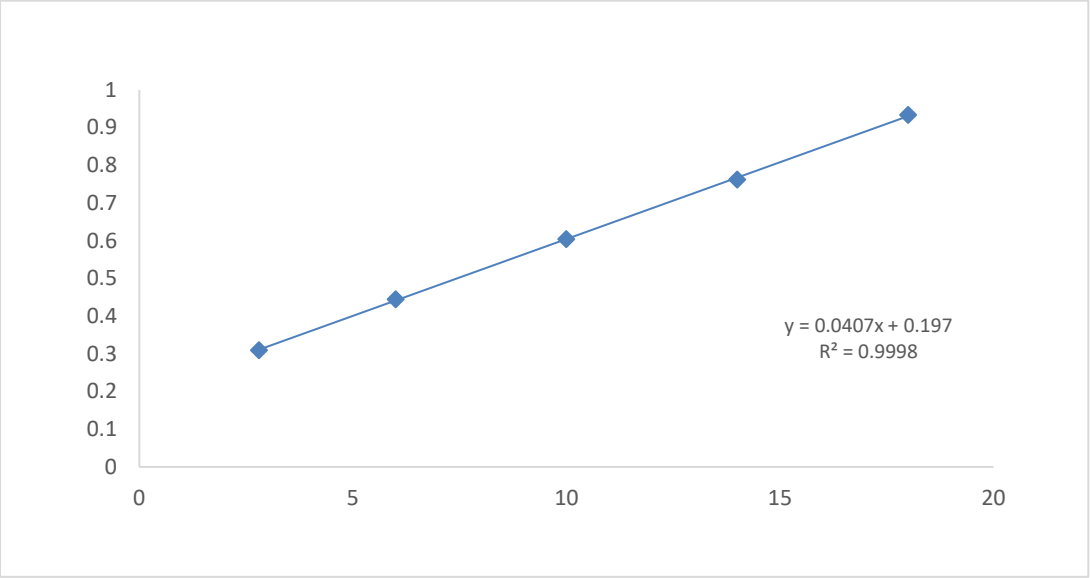

Fig. 2: Linearity graph

Table 4.5: Results Showing Specificity Study

S.No.	*Tablet Strength(mg)*	*Time point*	*Absorbance*
1	30mg	30min	0.000
2.	30mg	180min	0.000
3.	180mg	30min	0.000
4.	180mg	180min	0.001

5. *CONCLUSION*

The dissolution method for different strength of Diltiazem Hydrochloride was developed and validated as per the ICH guideline. Validation shows that the developed method for dissolution test is appropriate for quantification of Diltiazem Hydrochloride in tablet pharmaceutical form for in vitro studies, presenting linearity, range, specificity, precision (repeatability and reproducibility), accuracy, and robustness. The method is adequate for use in quality control testing of various strengths of Diltiazem Hydrochloride tablets.

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