

Original Article

Studies on Formulation of Diltiazem Tablets Using β CD, Croscarmellose Sodium and Sodium Dodecyl Sulfate-Optimization By 2^3 Factorial Design

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ARTICLE INFO

Received 13 July 2019

Revised 18 August 2019

Accepted 24 September 2019

Keywords:

- Optimization
- Diltiazem tablets
- Factorial design
- β -Cyclodextrin
- Croscarmellose sodium
- Sodium dodecyl sulphate

ABSTRACT

Diltiazem, a widely prescribed anti-hypertensive drug belongs to the class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It needs enhancement in the dissolution rate in its formulation development to derive its maximum therapeutic efficacy. In the present study β -cyclodextrin (β CD), Croscarmellose sodium and Sodium dodecyl sulphate were tried to enhance the dissolution rate of Diltiazem in its tablet formulation development. The objective of the study is to optimize Diltiazem tablet formulation by 2^3 factorial design to achieve NLT 85% dissolution in 15 minutes. For optimization of Diltiazem tablets as per 2^3 factorial design the Cyclodextrin (β CD), Croscarmellose sodium and Sodium dodecyl sulphate are considered as the three factors. The six levels of the factor A (β CD) are ratio of drug: β CD, the eight levels of the factor B (Croscarmellose sodium) and the eight levels of factor C (Sodium dodecyl sulfate). Eight Diltiazem tablet formulations employing selected combinations of the three factors i.e. β -CD, Croscarmellose sodium and Sodium dodecyl sulphate as per 2^3 factorial design were formulated. The tablets were prepared by direct compression method and were evaluated. The physical parameters of the Diltiazem tablets evaluated and hardness of the tablets was in the range 96-132 N. Weight loss in the friability test was less than 0.04% in all the cases. Diltiazem content of the tablets prepared was within $100 \pm 3\%$. Much variations were observed in the disintegration and dissolution characteristics of the Diltiazem tablets prepared. The disintegration times were in the range 3 min 02 sec to 4 min 12 sec. Dissolution rate of Diltiazem tablets prepared were studied in phosphate buffer pH 5.8. Dissolution of Diltiazem from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.942. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K_1) and DE30 values of the tablets prepared due to formulation variables. ANOVA of K_1 values indicated that the individual and combined effects of the three factors, β CD, Croscarmellose sodium and Sodium dodecyl sulphate except F020 (Combined effect of Croscarmellose sodium and Sodium dodecyl sulphate) and F020 (Combined effect of β CD, Croscarmellose sodium and Sodium dodecyl sulphate) in influencing the dissolution rate of Diltiazem tablets are highly significant ($P < 0.01$). Diltiazem tablet formulations F018 and F020 gave very rapid dissolution of Diltiazem than others. These tablets (F018 and F020) gave above 90% dissolution in 15min. Higher levels of β CD and lower levels of Croscarmellose sodium gave low dissolution of Diltiazem tablets. The increasing order of dissolution rate (K_1) observed with various formulations was $F014 > F008 > F011 > F016 > F017 > F018 > F020$. The optimized Diltiazem tablet formulation gave 91% dissolution in 15 min fulfilling the target dissolution set. Hence optimization by 2^3 factorial design could be used to formulate Diltiazem tablets with the desired dissolution i.e., NLT 85% in 15 min.

1. INTRODUCTION

Diltiazem, a widely prescribed anti-hypertensive drug belongs to the class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development to derive its maximum therapeutic efficacy. Among various techniques Cyclodextrin complexation¹⁻⁴, use of superdisintegrants⁵⁻⁶ and surfactants⁷⁻⁹ are widely accepted in industry for enhancing the dissolution rate of poorly soluble drugs from solid dosage forms. In the present study β -cyclodextrin (β CD), Croscarmellose sodium and Sodium dodecyl sulphate were tried to enhance the dissolution rate of Diltiazem in its tablet formulation development. The objective of the present study is to optimize Diltiazem tablet formulation by 2^3 factorial design to achieve NLT 85% dissolution in 15 minutes.

Optimization¹⁰⁻¹¹ of Pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is relatively new to the practice of Pharmacy. In general the procedure consists of preparing a series of formulations, varying the concentrations of the formulations ingredients in some systematic manner. These formulations are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, stability, taste and so on. Based on the results of these tests, a particular formulation (or series of formulations) may be predicted to be optimal. The optimization procedure is facilitated by applying factorial designs and by the fitting of an empirical polynomial equation to the experimental results. The predicted optimal formulation has to be prepared and evaluated to confirm its quality.

2. MATERIALS AND METHODS

2.1 Materials

Diltiazem Hydrochloride was obtained from Macleods Pharmaceuticals Limited Mumbai as gift sample. Crospovidone is from Ashland, Croscarmellose sodium, MCC PH 102 & MCC PH 200 is from FMC Biopolymer, Sodium dodecyl sulphate from Sigma labs and β -CD were obtained from Hetero labs.

2.2 Methods

2.2.1 Estimation of Diltiazem

UV-Spectrophotometric techniques were used for involving the measurement of absorbance at 236 nm in distilled water were used for estimation of Diltiazem. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 6-16 μ g/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be

0.75% and 1.20% respectively. No interference by the excipients used in the study were observed.

2.2.2 Formulation of Diltiazem Tablets

For optimization of Diltiazem tablets as per 2^3 factorial design the β -cyclodextrin (β CD), Croscarmellose sodium (superdisintegrant) and Sodium dodecyl sulfate (Anionic surfactant) are considered as the three factors. Eight Diltiazem tablets formulations employing selected combinations of the three factors i.e. β -cyclodextrin (β CD), Croscarmellose sodium and Sodium dodecyl sulfate as per 2^3 factorial design were formulated and tablets were prepared by direct compression method.

2.2.3 Preparation of Diltiazem Tablets

Diltiazem (120 mg) tablets were prepared by direct compression method as per the formula given in Table 1. Brief description of the manufacturing process is sifting of Diltiazem through #20 mesh (1 mm) and cosited β -Cyclodextrin, MCC PH 102, Crospovidone and Croscarmellose sodium is through #40 mesh. These cosifted materials of above is combined and sifted through #40 mesh. Further the Sodium dodecyl sulphate (SDS) and Microcrystalline cellulose PH 200 are sifted using #40 mesh and Pre-lubricate the materials in 1L octagonal blender for 10 minutes. Finally the sifted #60 mesh (250 μ m) Magnesium stearate and Purified talc was added in to the above pre lubricated blend and mixed for 5 minutes in 1L octagonal bender.

The lubricated blend was compressed using 12.1 X 5.5 mm embossed with oval double concave, upper punch and lower punch was plain with lip line.

2.2.4 Evaluation of Tablets

In quality analysis of Diltiazem tablets prepared were tested for assay, tablet hardness, determining friability, DT & drug dissolution as described below.

2.2.4.1 Description

White, oval shaped slightly biconvex, uncoated tablets with a score line on each side.

2.2.4.2 Hardness

When the tablet is placed in two portions, the tablet was tested using hardness tester (Monsanto) and measured as kg/cm².

2.2.4.3 Friability

The friability was determined by Roche friabilator (Roche). Friability was calculated as

$$\text{Friability (\%)} = \frac{[(\text{Init wt} - \text{Fin wt}) / (\text{Init wt})] \times 100}$$

2.2.4.4 Assay

Diltiazem Hydrochloride drug content of tablets prepared were determined by UV-Spectrophotometric method described in Chapter III.

2.2.4.5 Disintegration time (DT)

When the tablets were placed on the Disintegration apparatus then their disintegration time was measured using water as dissolution medium.

2.2.4.6 Determination of Dissolution Study

The dissolution of Diltiazem Hydrochloride tablets manufactured were tested as per following protocol.

Apparatus	: Dissolution rate test apparatus
Stirrer	: Paddle stirrer
Speed	: 50 RPM
Temperature	: 37°C ± 1°C
Dissolution Fluid	: Phosphate buffer of PH 5.8 (900 ml)
Test Sample	: One tablet containing 120 mg of Diltiazem
Sampling	: 5 ml at 5, 10, 15, 20, 30, 45 and 60 minutes through filter
Assay	: UV at 272 nm
Replication	: n = 6

3. DATA ANALYSIS

The dissolution data were analyzed to estimate dissolution rate (K_1), Dissolution efficiency (DE_{30}), T_{50} (Time for 50% total amount of drug in dissolution), T_{90} (Time for total amount of 90% drug dissolved) and percent drug dissolved in 15 min in each case.

3.1 Analysis of Data

The dissolution data were analyzed as per zero order and first order kinetic models. Dissolution efficiency (DE_{30}) values were estimated as suggested by Khan¹¹. Dissolution rate (K_1) values were analyzed as per ANOVA of 2³ factorial experiments.

3.2 Stability Studies Evaluation

The storage conditions of the manufactured products for accelerated testing (as per ICH and WHO) are 40⁰ ± 2⁰ C and 75 ± 5 % RH for solid tablet dosage forms for six months. World health organization recommended testing at 0, 1, 2, 3, and 6 months during storage. ICH has not given testing time frequency.

In the present study, the product storage condition of 40⁰ ± 2⁰ C and 75 ± 5 % RH for six months were used for short term accelerated testing analysis. Diltiazem optimized tablet formulation employing β CD, Croscarmellose sodium and Sodium dodecyl sulphate (F020) method.

4. RESULTS AND DISCUSSION

The objective of the present study was to optimize the Diltiazem tablets formulation employing β CD, Croscarmellose sodium and Sodium dodecyl sulphate by 2³ factorial design to achieve NLT 85% dissolution in 15 min. For optimization of Diltiazem tablets as per 2³ factorial design the β -cyclodextrin (β CD), Croscarmellose sodium (superdisintegrant) and Sodium dodecyl sulfate (anionic surfactant) are considered as the three factors. The six levels of the factor A (β CD) are ratio of drug: β CD, the eight levels of the factor B (croscarmellose sodium) and the eight levels of factor C (Sodium dodecyl sulfate). Eight Diltiazem tablet formulations employing selected combinations of the three factors i.e. β CD, Croscarmellose sodium and Sodium

dodecyl sulphate as per 2³ factorial design were formulated and tablets were prepared by direct compression method as per the formulae given in Table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The dissolution rate (K_1) values were analyzed as per ANOVA of 2³ factorial design to find out the significance of the individual and combined effects of the three factors involved on the dissolution rate of Diltiazem tablets formulated.

The physical parameters of the Diltiazem tablets prepared are given in Table 2. The hardness of the tablets was in the range of 96-132 N. Weight loss in the friability test was less than 0.04% in all the cases. Diltiazem content of the tablets prepared was within 100±3 %. Much variations were observed in the disintegration and dissolution characteristics of the Diltiazem tablets prepared. The disintegration times were in the range of 3 min 02 sec to 4 min 12 sec. However, all the Diltiazem tablets prepared fulfilled the official (IP 2010) requirements with regard to drug content, hardness, friability and disintegration time specified for uncoated tablets.

Dissolution rate of Diltiazem tablets prepared were studied in phosphate buffer pH 5.8. The dissolution profiles of the tablets are shown in Fig.1 and the dissolution parameters are given in Table 3. Dissolution of Diltiazem from all the tablets prepared followed first order kinetics with coefficient of determination (R^2) values above 0.942. The first order dissolution rate constant (K_1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K_1) and DE_{30} values of the tablets prepared due to formulation variables. ANOVA of K_1 values indicated that the individual and combined effects of the three factors, β CD, Croscarmellose sodium and Sodium dodecyl sulphate except F020 (Combined effect of Croscarmellose sodium and Sodium dodecyl sulphate) and F020 (Combined effect of β CD, Croscarmellose sodium and Sodium dodecyl sulphate) in influencing the dissolution rate of Diltiazem tablets are highly significant ($P < 0.01$).

Diltiazem tablets formulations F018 and F020 gave very rapid dissolution of Diltiazem than others. These tablets (F018 and F020) gave above 90% dissolution in 15min. Higher levels of β CD, and lower levels of Croscarmellose sodium gave low dissolution of Diltiazem tablets. The increasing order of dissolution rate (K_1) observed with various formulations was F014 > F008 > F011 > F016 > F017 > F018 > F020

4.1 Optimization

For optimization, percent drug dissolved in 5 min was taken as response (Y) and level of β CD as (X_1), level of Croscarmellose sodium as (X_2) and level of Sodium dodecyl sulphate as (X_3). The polynomial equation describing the relationship between the response, Y and the variables, X_1 , X_2 and X_3 based on the observed data. Based on the polynomial equation, the optimized diltiazem tablet formulation with NLT 85% dissolution in 15 min. Diltiazem tablets were formulated employing the optimized levels of β CD, Croscarmellose sodium and Sodium dodecyl sulphate for verifying. The formula of the optimized Diltiazem tablets is given in Table 1. The optimized Diltiazem tablet formulation

was prepared by employing direct compression method and the tablets were evaluated. The physical parameters of the optimized formulation are given in Table 2 and dissolution parameters are given in Table 3. The hardness of the optimized Diltiazem tablets were found to be 96 - 132 N. The Friability (percent weight loss) was less than 0.01%. Disintegration time of the tablets was 4 min 12 sec. The optimized Diltiazem tablet formulation gave 91% dissolution in 15 min fulfilling the target dissolution set.

4.2 Stability Results

In each case, tablets were taken in PVC/PVDC Clear 90 GSM-Alu Blister Pack (1 x 10's) and were stored at 40^o ± 2^o C and 75 % RH for 1, 2, 3 and 6 months. After storage for 6 months, products were tested for assay and drug dissolution rate as per methods described earlier. Results are given in Tables 5 & 6 and shown in Figure 2.

5. CONCLUSION

The stability parameters of Diltiazem 120 mg Tablets Physical and chemical parameters of Batch Number: F020 packed in PVC/PVDC clear 90 GSM - Alu Blister Pack Pack are passed and found with in the limits.

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Table 1 Formula of Diltiazem Tablets Prepared Employing βCD, Croscarmellose sodium and sodium dodecyl sulphate as per 2³ Factorial Design

Ingredient (mg/Tab)	F008	F011	F014	F015	F016	F017	F018	F020
Diltiazem	120.00	120.00	120.00	120.00	120.00	120.00	120.00	120.00
B-CD	1.00	2.00	4.00	6.00	7.00	7.00	8.00	10.00
MCC PH 102	75.00	62.00	62.00	57.00	51.00	43.00	43.00	45.00
Crospovidone	20.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
Croscarmellose sodium	5.00	10.00	15.00	20.00	25.00	27.00	30.00	35.00
Sodium dodecyl sulphate	5.00	7.00	10.00	12.00	15.00	18.00	20.00	25.00
MCC PH200	64.00	64.00	54.00	50.00	47.00	50.00	44.00	30.00
Talc	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Mg.st	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Total Weight	300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00

Table 2 Physical parameters of Diltiazem Tablets Prepared Employing βCD, Croscarmellose sodium and sodium dodecyl sulphate as per 2³ Factorial Design

Batch Number	F008	F011	F014	F015
Tablet weight (mg)	293.2 - 307.4	296.4 - 305.4	296.2 - 305.4	298.4 - 307.4
Thickness (mm)	5.24 – 5.33	5.18 - 5.29	5.23 – 5.35	5.21 - 5.32

Hardness (N)	105 - 128	110 - 132	97 - 112	102 - 122
Friability (%)	0.02	0.01	0.04	0.02
Disintegration time (min sec⁰⁰)	3'02" to 3'58"	3'14" to 4'18"	3'12" to 3'38"	3'16" to 4'22"

Batch Number	F016	F017	F018	F020
Tablet weight (mg)	298.3 - 306.3	297.2 - 306.4	297.3 - 305.3	296.2 - 305.4
Thickness (mm)	5.24 – 5.37	5.19 - 5.28	5.12 – 5.27	5.18 - 5.24
Hardness (N)	96 - 114	104 - 124	99 - 124	101 - 122
Friability (%)	0.03	0.02	0.02	0.01
Disintegration time (min sec⁰⁰)	3'22" to 3'48"	3'08" to 4'32"	3'05" to 3'38"	3'02" to 4'12"

Table 3 Dissolution Profiles of Diltiazem Tablets Prepared Employing βCD, Croscarmellose sodium and sodium dodecyl sulphate as per 2³ Factorial Design

Time (min)	Amount (Percent) of drug dissolved (%)								
	Innovator	F008	F011	F014	F016	F015	F017	F018	F020
5	36 ± 8.8	17 ± 20.0	17 ± 21.0	14 ± 14.0	19 ± 22.4	16 ± 12.5	20 ± 14.4	55 ± 5.9	50 ± 8.6
10	57 ± 8.9	26 ± 9.0	24 ± 10.2	21 ± 11.0	43 ± 12.5	42 ± 10.1	43 ± 11.4	70 ± 4.4	68 ± 5.2
15	91 ± 4.7	39 ± 9.2	43 ± 9.7	25 ± 8.8	56 ± 8.7	65 ± 7.5	69 ± 9.7	90 ± 3.5	91 ± 4.6
20	95 ± 2.0	51 ± 6.7	53 ± 8.5	42 ± 11.7	70 ± 6.2	71 ± 5.5	77 ± 6.6	94 ± 3.6	95 ± 2.4
30	98 ± 0.8	65 ± 4.6	67 ± 6.8	54 ± 6.2	77 ± 4.0	78 ± 3.8	79 ± 7.3	97 ± 1.7	99 ± 1.5
45	99 ± 1.2	76 ± 2.5	74 ± 3.5	65 ± 3.6	89 ± 4.0	85 ± 3.6	89 ± 3.3	100 ± 0.8	100 ± 1.5
60	101 ± 1.5	78 ± 2.4	80 ± 5.9	79 ± 4.5	101 ± 2.2	99 ± 1.8	100 ± 2.6	102 ± 1.3	101 ± 3.3

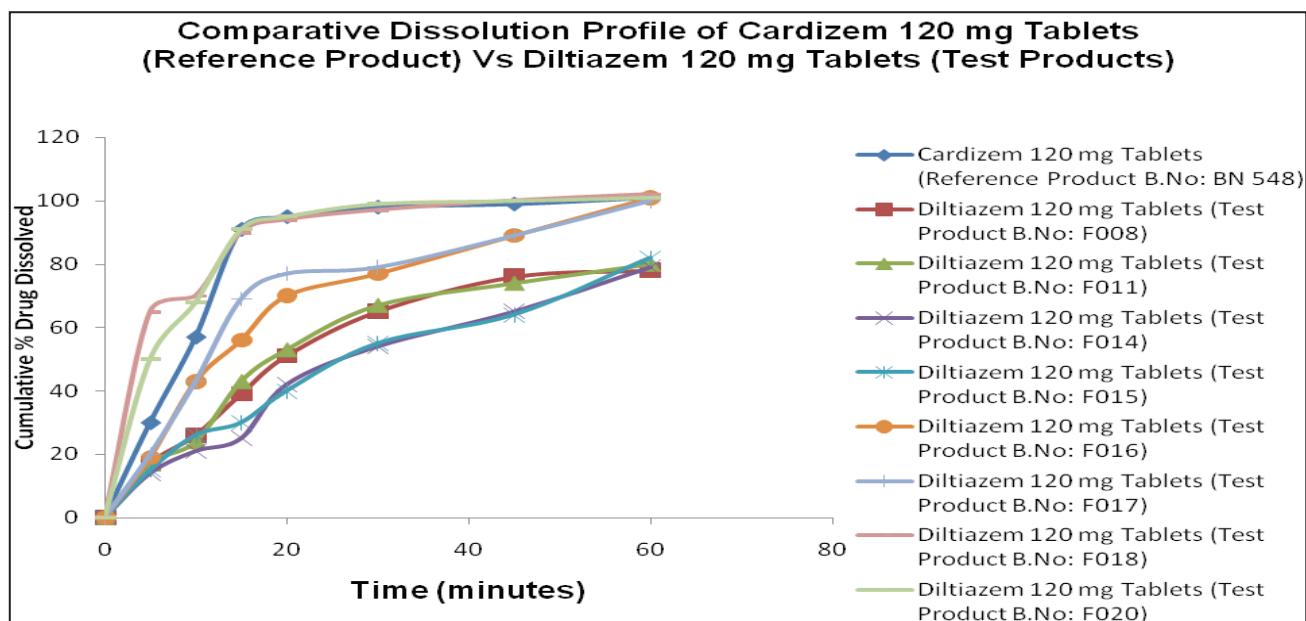


Fig. 1 Dissolution Profiles of Diltiazem Tablets Prepared Employing βCD, Croscarmellose sodium and sodium dodecyl sulphate as per 2³ Factorial Design

Table 4 Dissolution Parameters of Diltiazem Tablets Prepared Employing β CD, Croscarmellose sodium and sodium dodecyl sulphate as per 2^3 Factorial Design

Formulation	PD ₁₀ (%)	T ₅₀ (min)	T ₉₀ (min)	DE ₃₀ (%)	K ₁ × 10 (min ⁻¹) (± s d)
F008	14.12	36.5	84.0	13.65	0.2216±0.039
F011	46.53	9.5	38.5	33.53	0.7436±0.579
F014	98.30	1.5	5.0	74.52	5.2267±0.271
F015	94.15	2.0	7.5	69.22	3.0721±0.022
F016	9.53	46.0	89.0	9.66	0.1341±0.000
F017	26.13	2.0	2.5	28.73	0.4243±0.201
F018	98.76	16.5	54.0	73.23	5.2659±0.079
F020	87.56	2.5	12.5	64.25	1.7805±0.007

Table 5 Stability Characterization of Tablets (F020)

Parameters	Specification	Initial	1 month	2 month	3 month	6 months
Physical Characteristics						
Description	*	*	Complies	Complies	Complies	Complies
Tablet weight (mg)	300.0 mg	296.2 - 305.4	297.4 - 306.2	295.2 - 302.4	297.8 - 306.8	296.2 -305.4
Thickness (mm)	5.00 - 5.60	5.18 - 5.24	5.17 - 5.25	5.18 - 5.25	5.17 - 5.29	5.17 - 5.30
Hardness (N)	80 - 140	101 - 122	108 - 128	106- 127	105 - 125	104- 127
Disintegration time (min' sec'')	NMT 15 Minutes	3'02'' to 4'12''	3'15'' to 4'20''	3'20'' to 4'18''	3'25'' to 4'24''	3'10'' to 4'15''
Loss on Drying (5 mins @ 105°C)	4.0 %	1.82	1.85	1.94	2.05	2.08
Chemical Characteristics						
Assay	95.0 - 105.0 %	99.4	98.5	98.9	98.6	98.2
Dissolution (pH 5.8 Phosphate buffer/ 50 rpm / Paddle)	NLT 85 % in 15 minutes	85 - 96%	94 %	96 %	94%	91%
Related Substances						
DTZ-I Impurity	NMT 0.2%	0.001	0.001	0.001	0.002	0.003
DTZ - II Impurity	NMT 0.2%	ND	ND	ND	ND	ND
Maximun individual other impurity	NMT 0.5%	0.006	0.012	0.014	0.016	0.022
Total Impurities	NMT 1.0%	0.014	0.016	0.018	0.022	0.026

***Description:** White, oval shaped slightly biconvex, uncoated tablets with a score line on each side.

ND: Not Detected

Table 6 Drug Release Comparison of initial Tablets (F020) Vs stability samples of 40°C/75 % RH - 1M, 2M, 3M & 6M in pH 5.8 phosphate Buffer

Time (Minutes)	% Diltiazem dissolved in 900 ml /pH 5.8 phosphate buffer/ 50 rpm /Paddle				
	Diltiazem Tablets (Test product) Batch No: F020				
	Initial samples	40°C/75 % RH - 1M	40°C/75 % RH - 2M	40°C/75 % RH - 3M	40°C/75 % RH - 6M
0	0	0	0	0	0
5	50	48	49	49	50
10	68	67	68	68	69
15	91	90	91	92	90
20	95	97	94	94	95
30	99	98	98	98	98
45	100	99	98	99	99
60	101	100	99	100	100

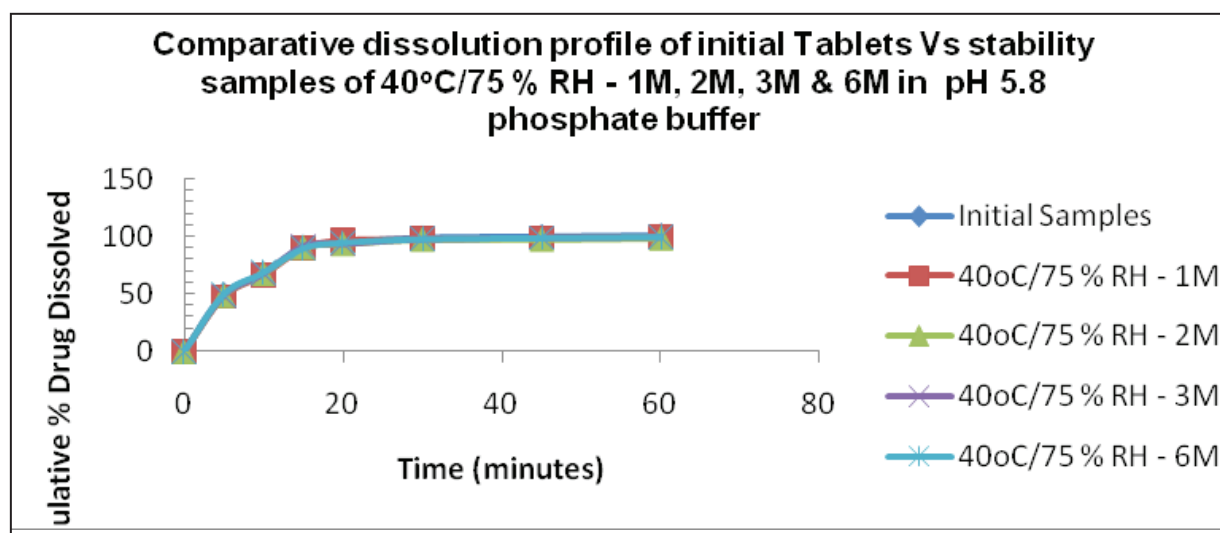


Fig. 2 Comparative dissolution profile of initial Tablets Vs stability samples of 40°C/75 % RH - 1M, 2M, 3M & 6M in pH 5.8 phosphate buffer.