

Original Article

## Studies on Formulation of Doxazosin Mesylate Tablets Using Croscarmellose Sodium and Sodium Dodecyl Sulfate- Optimization by 2<sup>2</sup> Factorial Design

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### ABSTRACT

Doxazosin Mesilate, a widely prescribed anti hypertensive drug belongs to 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 Croscarmellose sodium (superdisintegrant) and Sodium dodecyl sulfate (anionic surfactant) were tried to enhance the dissolution rate of Doxazosin Mesilate in its tablet formulation development. The objective of the study is to optimize Doxazosin Mesilate tablet formulation by 2<sup>2</sup> factorial design to achieve NLT 85% dissolution in 15 minutes. For optimization of Doxazosin Mesilate tablets as per 2<sup>2</sup> factorial design the Croscarmellose sodium (superdisintegrant) and Sodium dodecyl sulfate (anionic surfactant) are considered as the two factors. The four levels of the factor A (Croscarmellose sodium) are ratio of drug: Croscarmellose sodium and the four levels of the factor B (Sodium dodecyl sulfate). Four Doxazosin Mesilate tablet formulations employing selected combinations of the two factors i.e. Croscarmellose sodium (superdisintegrant) and Sodium dodecyl sulfate (anionic surfactant) as per 2<sup>2</sup> factorial design were formulated. The tablets were prepared by direct compression method and were evaluated. The physical parameters of the Doxazosin Mesilate tablets evaluated and hardness of the tablets was in the range 89-117 N. Weight loss in the friability test was less than 0.02% in all the cases. Doxazosin Mesilate content of the tablets prepared was within 100±3 %. Much variations were observed in the disintegration and dissolution characteristics of the Doxazosin Mesilate tablets prepared. The disintegration times were in the range of 2 min 22 sec to 4 min 28 sec.

Dissolution rate of Doxazosin Mesilate tablets prepared was studied in 0.01N HCl. Dissolution of Doxazosin Mesilate from all the tablets prepared followed first order kinetics with coefficient of determination (R<sup>2</sup>) values above 0.985. The first order dissolution rate constant (K1) values were estimated from the slope of the first order linear plots. Much variations were observed in the dissolution rate (K1) and DE30 values of the tablets prepared due to formulation variables. ANOVA of K1 values indicated that the individual and combined effects of the two factors, Croscarmellose sodium and Sodium dodecyl sulphate except S010 (Combined effect of Croscarmellose sodium and Sodium dodecyl sulphate) in influencing the dissolution rate of Doxazosin Mesilate tablets are highly significant (P < 0.01). Doxazosin Mesilate tablets formulations S006 and S010 gave very rapid dissolution of Doxazosin Mesilate than others. These tablets (S006 and S010) gave above 90% dissolution in 15 min. Higher levels of Croscarmellose sodium and lower levels of Sodium dodecyl sulphate gave low dissolution of Doxazosin Mesilate tablets. The increasing order of dissolution rate (K1) observed with various formulations was S002 > S004 > S006 > S010. The optimized Diltiazem tablet formulation gave 91% dissolution in 15 min fulfilling the target dissolution set. Hence optimization by 2<sup>2</sup> factorial design could be used to formulate Doxazosin Mesilate tablets with the desired dissolution i.e., NLT 85% in 15 min.

## 1. INTRODUCTION

Doxazosin Mesilate, a widely prescribed anti hypertensive drug belongs to 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<sup>1-4</sup> in the dissolution rate in its formulation development to derive its maximum therapeutic efficacy. Among various techniques use of superdisintegrants<sup>5-6</sup> and surfactants<sup>7-9</sup> are widely accepted in industry for enhancing the dissolution rate of poorly soluble drugs from solid dosage forms. In the present study Croscarmellose sodium and sodium dodecyl sulphate were tried to enhance the dissolution rate of Doxazosin Mesilate in its tablet formulation development. The objective of the present study is to optimize Doxazosin Mesilate tablet formulation by 2<sup>2</sup> factorial design to achieve NLT 85% dissolution in 15 minutes.

Optimization<sup>10-11</sup> of Pharmaceutical formulations involves choosing and combining ingredients that will results 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 formulation 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

Doxazosin was obtained from Microlabs, Bangalore 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. Talc is from Imerys and Magnesium stearate had purchased from Petergrevens laboratory.

### 2.2 Methods

#### 2.2.1 Estimation of Doxazosin Mesilate

UV-Spectrophotometric technique were used for involving the measurement of absorbance at 245 nm in distilled water for estimation of Doxazosin Mesilate. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 4-14 µg/ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.85% and 1.30% respectively. No interference by the excipients used in the study was observed.

#### 2.2.2 Formulation of Doxazosin Mesilate Tablets

For optimization of Doxazosin Mesilate tablets as per 2<sup>2</sup> factorial design the Croscarmellose sodium (superdisintegrant) and Sodium dodecyl sulfate (anionic surfactant) are considered as the three factors. Four Doxazosin Mesilate tablet formulations employing selected combinations of the two factors i.e. Croscarmellose sodium and Sodium dodecyl sulfate as per 2<sup>2</sup> factorial design were formulated and tablets were prepared by direct compression method.

#### 2.2.3 Preparation of Doxazosin Mesilate Tablets

Doxazosin Mesilate (8 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 Doxazosin Mesilate sifted through #20 mesh (1 mm) and cosifted 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 µm) Magnesium Stearate and Purified talc was added in to above pre lubricated blend and mixed for 5 minutes in 1L octagonal bender.

Lubricated blend was compressed using 12.1 × 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 Doxazosin Mesilate tablets prepared were tested for Assay, tablet hardness, determining friability, DT & drug dissolution as described below.

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

##### 2.2.4.1 Hardness

When the tablet is plaed in two portions, the tablet was tested using hardness tester (Monsanto) and measured as kg/cm<sup>2</sup>.

##### 2.2.4.2 Friability

The friability was determined by Roche of tablets was tested in friabilator (Roche). Friability was calculated as

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

##### 2.2.4.3 Assay

Doxazosin Mesilate Hydrochloride drug content of tablets prepared was determined by UV-Spectrophotometric method.

##### 2.2.4.4 Disintegration time (DT)

When the tablets are placed on Disintegration apparatus then the time of tablets were measured in disintegration apparatus using water as a dissolution medium.

##### 2.2.4.5 Determination of Dissolution Study

The dissolution of Doxazosin Mesilate Hydrochloride tablets manufactured were tested as per the following protocol.

Apparatus	: dissolution rate test apparatus
Stirrer	: Paddle stirrer

Speed	: 50 RPM
Temperature	: 37°C ± 1°C
Dissolution Fluid	: 0.01N HCl
Test Sample	: One tablet containing 8 mg of Doxazosin
Sampling	: 5 ml at 5, 10, 15, 20, 30, 45 and 60 minutes through filter
Assay	: UV at 245 nm
Replication	: n = 6

#### 2.2.4.6 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.

#### 2.2.4.7 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 Khan<sup>11</sup>. Dissolution rate ( $K_1$ ) values were analyzed as per ANOVA of 2<sup>2</sup> factorial experiments.

### 2.3 Stability Studies Evaluation

After the manufactured products the storage conditions for accelerated testing (as per ICH and WHO) are 40<sup>0</sup> ± 2<sup>0</sup> 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 40<sup>0</sup> ± 2<sup>0</sup> C and 75 ± 5 % RH for six months was used for short term accelerated testing analysis. Doxazosin Mesilate optimized tablet formulation employing  $\beta$ CD, Crospovidone and Croscarmellose complexation (S010) method.

## 3. RESULTS AND DISCUSSION

The objective of the present study is to optimize the Doxazosin Mesilate tablet formulation employing Croscarmellose sodium and Sodium dodecyl sulphate by 2<sup>2</sup> factorial design to achieve NLT 85% dissolution in 15 min. For optimization of Doxazosin Mesilate tablets as per 2<sup>2</sup> factorial design the Croscarmellose sodium (superdisintegrant) and Sodium dodecyl sulfate (Anionic surfactant) are considered as the two factors. The four levels of the factor A (Croscarmellose sodium) are ratio of drug:  $\beta$ CD, the four levels of the factor B (Sodium dodecyl sulfate). Four Doxazosin Mesilate tablet formulations employing selected combinations of the two factors i.e. Croscarmellose sodium and Sodium dodecyl sulphate as per 2<sup>2</sup> 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 2<sup>2</sup> factorial design to find out the significance of the individual and combined effects of the two

factors involved on the dissolution rate of Doxazosin Mesilate tablets formulated.

The physical parameters of the Doxazosin Mesilate tablets prepared are given in Table 2. The hardness of the tablets was in the range 89-117 N. Weight loss in the friability test was less than 0.02% in all the cases. Doxazosin Mesilate content of the tablets prepared was within 100±3 %. Much variations were observed in the disintegration and dissolution characteristics of the Doxazosin Mesilate tablets prepared. The disintegration times were in the range 2 min 22 sec to 4 min 28 sec. However, all the Doxazosin Mesilate 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 Doxazosin Mesilate tablets prepared was studied in 0.01N HCl. The dissolution profiles of the tablets are shown in Fig.1 and the dissolution parameters are given in Table 3. Dissolution of Doxazosin Mesilate from all the tablets prepared followed first order kinetics with coefficient of determination ( $R^2$ ) values above 0.985. 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 two factors, Croscarmellose sodium and Sodium dodecyl sulphate except S010 (Combined effect of Croscarmellose sodium and Sodium dodecyl sulphate) in influencing the dissolution rate of Doxazosin Mesilate tablets are highly significant ( $P < 0.02$ ).

Doxazosin Mesilate tablet formulations S006 and S010 gave very rapid dissolution of Doxazosin Mesilate than others. These tablets (S006 and S010) gave above 90% dissolution in 15 min. Higher levels of Croscarmellose sodium and lower levels of Sodium dodecyl sulphate gave low dissolution of Doxazosin Mesilate tablets. The increasing order of dissolution rate ( $K_1$ ) observed with various formulations was S002 > S004 > S006 > S010. The optimized Diltiazem tablet formulation gave 91% dissolution in 15 min fulfilling the target dissolution set. Hence optimization by 2<sup>2</sup> factorial design could be used to formulate Doxazosin Mesilate tablets with the desired dissolution i.e., NLT 85% in 15 min.

### 3.1 Optimization

For optimization, percent drug dissolved in 5 min was taken as response (Y) and level of Croscarmellose sodium as ( $X_1$ ) and level of Sodium dodecyl sulphate as ( $X_2$ ). The polynomial equation describing the relationship between the response, Y and the variables,  $X_1$  and  $X_2$  based on the observed data. Based on the polynomial equation, the optimized Doxazosin Mesilate tablet formulation with NLT 85% dissolution in 15 min. To verify Doxazosin Mesilate, tablets were formulated employing the optimized levels of Croscarmellose sodium and Sodium dodecyl sulphate. The formula of the optimized Doxazosin Mesilate tablets is given in Table 1. The optimized Doxazosin Mesilate tablet formulation was prepared by 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 tablets was in the range 89-117 N. Weight loss in the friability test was less than 0.02% in all the cases. The disintegration times were in the range of 2 min 22 sec to 4 min 28 sec. The optimized Doxazosin Mesilate tablet formulation gave 91% dissolution in 15 min fulfilling the target dissolution set.

### 3.2 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<sup>0</sup> ± 2<sup>0</sup> 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.

### 4. CONCLUSIONS

- (i) Doxazosin Mesilate tablet formulations S006 and S010 disintegrated rapidly within 5 min and gave very rapid dissolution of Doxazosin Mesilate, above 90% in 15 min.
- (ii) Higher levels of Croscarmellose sodium and lower levels of Sodium dodecyl sulphate gave low dissolution rates of Doxazosin Mesilate tablets.
- (iii) The increasing order of dissolution rate (K1) observed with various formulations was S002 > S004 > S006 > S010.
- (iv) The polynomial equation describing the relationship between the response i.e. percent drug dissolved in 10min (Y) and the levels of Croscarmellose sodium as (X1) and level of Sodium dodecyl sulphate as (X2) based on the observed results. The optimized Doxazosin Mesilate tablet formulation with NLT 85% dissolution in 15 min could be formulated.
- (v) The optimized Doxazosin Mesilate tablet formulation gave 90% dissolution in 15 min fulfilling the target dissolution set.
- (vi) Hence optimization by 2<sup>2</sup> factorial design could be used to formulate Doxazosin Mesilate tablets with the desired dissolution i.e., NLT 85% in 15 min.
- (vii) Comparative dissolution profile of Doxazosin 8 mg Tablets (Reference Product) Vs Doxazosin Mesilate 8 mg Tablets (Test Product) were evaluated for the following medium 0.01N HCl, pH 4.5 acetate buffer, pH 7.2 phosphate buffer and pH 5.8 phosphate buffer.
- (viii) Doxazosin Mesilate 8 mg Tablets (Test Product - B.No: S010) dissolution profiles were similar to Doxazosin 8 mg Tablets (Reference Product) in media studied i.e. PH 0.01N HCl, PH 4.5 Acetate buffer, pH 7.2 phosphate buffer and pH 5.8 phosphate buffer.
- (ix) The dissolution profile for Doxazosin Mesilate 8 mg tablets (S010) was comparable with reference product Doxazosin 8 mg Tablets in 0.01N HCL and S010 was selected as final formula.
- (x) The stability parameters of Doxazosin Mesilate 8 mg tab-

lets physical and chemical parameters of Batch Number: S010 packed in PVC/PVDC clear 90 GSM - Alu Blister Pack are passed and found within the limits.

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**Table 1** Formulae of Doxazosin Mesilate Tablets Prepared Employing Croscarmellose sodium and sodium dodecyl sulphate as per 2<sup>2</sup> Factorial Design

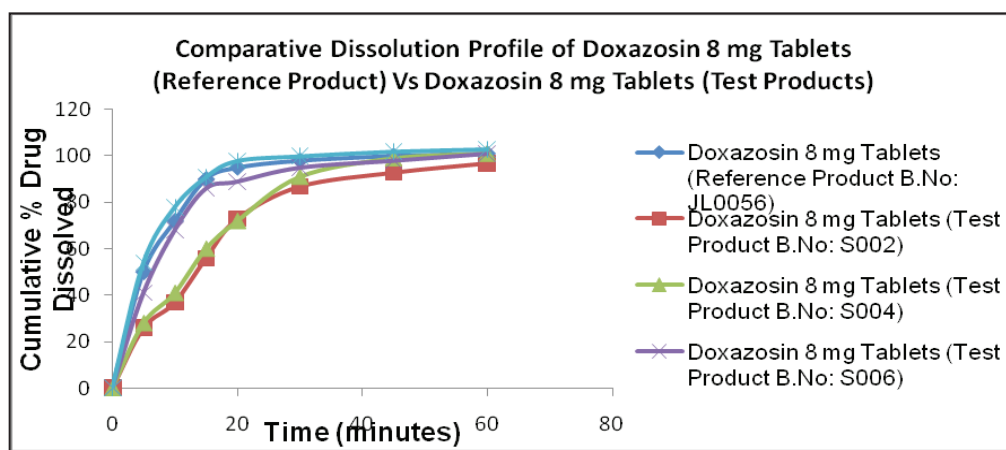
Ingredient (mg/Tab)	S002	S004	S006	S010
<b>Doxazosin Mesilate</b>	8.00	8.00	8.00	8.00
<b>Microcrystalline cellulose sodium PH 102</b>	85.00	75.00	72.00	67.00
<b>Crospovidone</b>	20.00	25.00	25.00	25.00
<b>Croscarmellose sodium</b>	5.00	10.00	15.00	20.00
<b>Sodium dodecyl Sulphate</b>	5.00	7.00	10.00	12.00
<b>Microcrystalline cellulose sodium PH 200</b>	67.00	65.00	60.00	58.00
<b>Purified talc</b>	5.00	5.00	5.00	5.00
<b>Magnesium stearate</b>	5.00	5.00	5.00	5.00
<b>Total Weight</b>	<b>200.00</b>	<b>200.00</b>	<b>200.00</b>	<b>200.00</b>

**Table 2** Physical Parameters of Doxazosin Mesilate Tablets Prepared Employing Croscarmellose sodium and sodium dodecyl sulphate as per 2<sup>2</sup> Factorial Design

Batch Number	S002	S004	S006	S010
Tablet weight (mg)	194.2 - 204.4	196.4 - 203.4	198.2 - 203.4	198.4 - 206.2
Thickness (mm)	4.22 - 4.23	4.12 - 4.27	4.25 - 4.32	4.22 - 4.45
Hardness (N)	89 - 112	95 - 117	95 - 102	89 - 94
Friability (%)	0.02	0.01	0.02	0.01
Disintegration time (min' sec'')	3'12'' to 3'38''	3'24'' to 4'28''	2'22'' to 2'58''	2'24'' to 3'15''

**Table 3** Dissolution Profiles of Doxazosin Mesilate Tablets Prepared Employing Croscarmellose sodium and sodium dodecyl sulphate as per 2<sup>2</sup> Factorial Design

Time (min)	Amount (Percent) of drug dissolved (%)				
	Innovator	S002	S004	S006	S010
5	50 ± 6.4	26 ± 6.0	28 ± 1.4	41 ± 12.3	54 ± 3.3
10	72 ± 3.8	37 ± 3.8	41 ± 4.1	68 ± 0.9	78 ± 2.7
15	90 ± 1.6	56 ± 5.6	60 ± 2.2	86 ± 1.9	91 ± 3.0
20	95 ± 0.7	73 ± 2.	72 ± 3.1	89 ± 0.6	98 ± 0.5
30	98 ± 0.9	87 ± 2.5	91 ± 1.3	95 ± 0.6	100 ± 0.6
45	100 ± 0.8	93 ± 1.3	99 ± 1.9	98 ± 0.8	102 ± 0.4
60	101 ± 0.9	97 ± 2.5	101 ± 1.5	101 ± 1.5	103 ± 1.2



**Fig. 1** Dissolution Profiles of Doxazosin Mesilate Tablets Prepared Employing Croscarmellose sodium and sodium dodecyl sulphate as per 2<sup>2</sup> Factorial Design

**Table 4** Dissolution Parameters of Doxazosin Mesilate Tablets Prepared Employing Croscarmellose sodium and sodium dodecyl sulphate as per 2<sup>2</sup> Factorial Design

Formulation	PD <sub>10</sub> (%)	T <sub>50</sub> (min)	T <sub>90</sub> (min)	DE <sub>30</sub> (%) ( $\bar{X} \pm s.d$ )	K <sub>1</sub> X 10 (min <sup>-1</sup> ) ( $\bar{X} \pm s.d$ )
S002	16.04	35	>60	22.75±0.83	1.64±0.06
S004	100	0.5	2.5	91.66±0	78.2±0
S006	50.69	10	35.5	57.45±1.92	7.44±1.06
S010	91.04	2	4	87.19±1.89	26.8±1.91

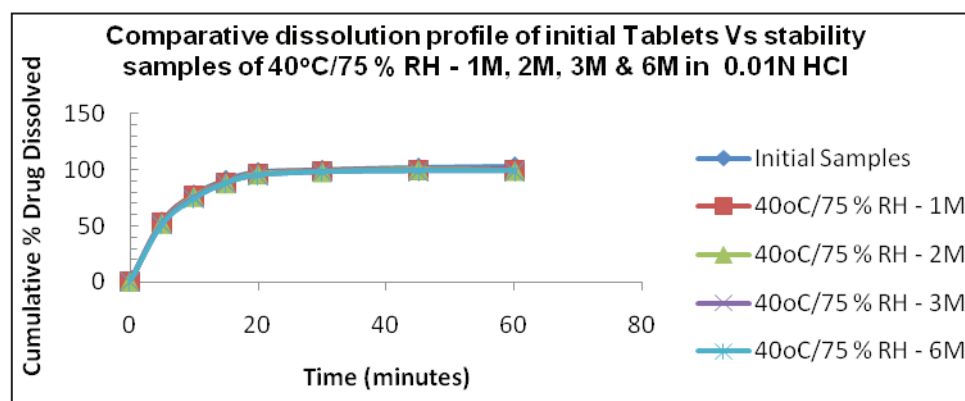
**Table 5** Stability Characterization of Tablets (S010)

Parameters	Specification	Initial	1 month	2 month	3 month	6 months
<b>Physical Characteristics</b>						
<b>Description</b>	*	*	Complies	Complies	Complies	Complies
Tablet weight (mg)	200.0 mg	198.2 - 203.4	195.4 - 204.5	196.7 - 202.8	198.5 - 205.2	194.5 - 203.8
Thickness (mm)	3.90 - 4.50	4.25 - 4.32	4.26 - 4.31	4.29 - 4.34	4.29 - 4.32	4.28 - 4.32
Hardness (N)	70 – 130	95 - 102	98 - 104	97 -105	96 - 112	99 - 114
Disintegration time (min' sec'')	NMT 15 MInutes	2'22'' to 2'58''	3'05'' to 3'35''	3'12'' to 3'58''	3'14'' to 3'55''	3'15'' to 3'49''
Loss on Drying (5 mins @ 105°C)	4.0 %	1.84	1.85	1.89	1.92	1.95
<b>Chemical Characteristics</b>						
Assay	95.0 - 105.0 %	95.6	98.2	98.8	99.4	99.2
Dissolution (0.01N HCl / 50 rpm / Paddle)	NLT 85 % in 15 minutes	88 - 94 %	89 %	90 %	91 %	88%
<b>Related Substances</b>						
Impurity - A	NMT 0.2%	0.001	0.001	0.001	0.002	0.003
Impurity - B	NMT 0.2%	ND	ND	ND	ND	ND
Maximum individual other impurity	NMT 0.5%	0.009	0.012	0.013	0.015	0.017
Total Imputrities	NMT 1.0%	0.018	0.019	0.022	0.025	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 (S010) Vs stability samples of 40°C/75 % RH - 1M, 2M, 3M & 6M in 0.01N HCl

Time (Minutes)	% Doxazosin Mesilate dissolved in 900 ml /0.01N HCl / 50 rpm /Paddle				
	Doxazosin Mesilate (Test product) Batch No: S010				
	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	54	53	52	52	51
10	78	77	76	75	74
15	91	89	88	88	88
20	98	96	96	95	95
30	100	99	98	98	98
45	102	100	100	99	99
60	103	100	99	99	99



**Fig. 2** Comparative dissolution profile of initial Tablets Vs stability samples of 40°C/75 % RH - 1M, 2M, 3M & 6M in 0.01N HCL.

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Drawing Settings:	
Chain angle	120°
Bond spacing	18% of width
Fixed length	14.4 pt (0.500 cm, 0.2 in)
Bold width	2.0 pt (0.071 cm, 0.0278 in)
Line width	0.6 pt (0.021 cm, 0.0084 in)
Margin width	1.6 pt (0.096 cm)
Hash spacing	2.5 pt (0.088 cm, 0.0347 in)
Text settings:	
Font	Times New Roman
Size	8 pt

**Figures :** Should be on separate pages but not inserted within the text. Figures should be numbered consecutively in Arabic numerals and bear a brief title (Figure caption) in lower case bold face letters below the figure. Graphs and bar graphs should preferably be prepared using Microsoft Excel and submitted as Excel graph pasted in Word. These graphs and illustrations should be drawn to approximately twice the printed size to obtain satisfactory reproduction. Photographs and photomicrographs can be submitted as jpeg images.

**Figure captions:** Ensure that each illustration has a caption. A caption should comprise a brief title of the illustration. Keep text in the illustrations to a minimum.

**Tables :** Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article. Every table should contain a suitable caption.

**References :** Ensure that every reference cited in the text is also present in the reference list (and vice versa). If these references are included in the reference list they should follow the standard **Vancouver style** of referencing. Citation of a reference as ‘in press’ implies that the item has been accepted for publication and a copy of the title page of the relevant article must be submitted. Use of the DOI is encouraged. For Web references as a minimum, the full URL should be given and the date when the reference was last accessed.

*Examples:*

**Reference to a journal publication:**

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med.* 2002; 347(7): 284-7.

**Reference to a book:**

Murray PR, Rosenthal KS, Kobyashi GS, Pfaller MA. *Medical microbiology.* 4th ed. St Louis: Mosby; 2002.

**Reference to a chapter in an edited book:**

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. *The genetic basis of human cancer.* New York: McGraw-Hill; 2002. p. 93-113.

**Web references:**

Barton CA, McKenzie DP, Walters EH, et al. Interactions between psychosocial problems and management of asthma: who is at risk of dying? *J Asthma* [serial on the Internet]. 2005 [cited 2005 Jun 30];42(4):249-56. Available from: <http://www.tandf.co.uk/journals>.

The manuscript of a review article should be arranged as described for research articles but according to the following sections: title page, abstract and keywords, Introduction, Specific sections determined by the author, Conclusions, Acknowledgements, References, Figure legends, Figures and Tables.

The submitted manuscript may be subjected to substantial editing so that the paper conforms to our style. Only electronic submission via email will be accepted for publication. **All the manuscripts should be submitted to** [mitijps@gmail.com](mailto:mitijps@gmail.com) or [fop@mitpublications.org](mailto:fop@mitpublications.org).