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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF DOXAZOSIN MESYLATE

Ruchir R. Kadia

Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Ahmedabad - 382421, Gujarat, India.

Keywords:

Sustained Release, Doxazosin Mesylate, Eudragit RS-100, Eudragit RL-100, 3^2 full factorial design

Correspondence to Author:
Ruchir R. Kadia

Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Ahmedabad - 382421, Gujarat, India.

E-mail: Kadiaruchir2424@gmail.com

ABSTRACT: The objective of the present investigation was to develop a sustained release (SR) tablets of Doxazosin Mesylate by wet granulation technique using a combination of synthetic polymers (Eudragit RS-100 and Eudragit RL-100). Different batches of Doxazosin Mesylate sustained release tablets were prepared by using microcrystalline cellulose as diluents by wet granulation technique. The compatibility of the drug and excipients was ruled out by FT-IR studies and found to be compatible. Granules of prepared batches were evaluated for their physical properties and found to be good and satisfactory. Tablets were evaluated for various physicochemical parameters like hardness, thickness, friability, weight variation test, drug content, and *in-vitro* drug release. To study the effect of concentration of polymers on drug release from SR tablets, 3^2 full factorial design was applied. The concentration of Eudragit RS-100 and Eudragit RL-100 were used as independent variables, while percentage drug release at 2 h and 22 h were selected as the dependent variable. Contour as well as response surface plots were constructed to show the effect of variables on % CDR and predicted that batch R1 containing Eudragit RS-100 (10 mg) and Eudragit RL-100 (10 mg) shows a maximum response. The kinetic release study showed that Korsmeyer equation had shown r^2 = 0.9984 which was close to one indicating that the dissolution profile fits in Korsmeyer-Peppas model and the mechanism of drug release from these tablets was by a non-fickian diffusion mechanism. The results of the accelerated stability study of final formulation for 1 month revealed that storage conditions were not found to have made any significant changes in final formulation.

INTRODUCTION: Sustained release, sustained action, prolonged action controlled release, extended release, depot release is the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period after administration of single dose of the drug.

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These are the type of controlled drug delivery systems, which continuously release the drug by both dissolutions controlled as well as diffusion controlled mechanisms [1]. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials [2].

The basic rationale of a sustained drug delivery system is to optimize the Pharmacodynamics and Pharmacokinetic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using the smallest amount

of drug which is administered by the most effective route [3]. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which is characteristic of the conventional intermittent dosage regimen [4]. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug [5]. Doxazosin mesylate is a selective inhibitor of α1-adrenergic receptors and is shown that it is effective for treatment of hypertension and benign prostatic hyperplasia (BPH). Doxazosin mesylate lowers the blood pressure of hypertensive patients by blocking postjunctional α1-adrenergic receptors, and then systemic vascular resistance decreases. Taking a doxazosin mesylate can cause first-dose side effects like hypotension because of the rapid increase of drug concentration in the blood. so a formulation of sustained release of doxazosin mesylate it is an ideal candidate to be designed as sustain release dosage form, which would result in prolonged clinical efficacy, reduced frequency of dosage and lesser side effects, could avoid this first dose effect [6].

The present invention relates to a sustained release tablet containing doxazosin mesylate, and more particularly to a sustained release tablet showing a constant release rate of the drug for more than 8 h.

MATERIALS AND METHODS: Doxazosin mesylate was obtained as gift sample from West-coast Pharmaceutical Works Ltd, Ahmedabad, Gujarat. Microcrystalline cellulose (Avicel pH-102) was procured from Accent Microcell Pvt. Ltd, Ahmedabad, Gujarat. Eudragit RS-100 and Eudragit RL-100 were acquired from Evonik Industries, Mumbai, Maharashtra. PVP K-30, Magnesium Stearate, and Talc were purchased from S. D. Fine Chemicals. Mumbai, Maharashtra. All other chemicals were of analytical reagent grade.

Drug- Excipients Compatibility Study by Fourier Transform Infra-Red (FT-IR): [7] The Fourier transform infrared spectrum of moisture-free powdered sample of 1:1 ratio of Doxazosin Mesylate with excipients will be recorded on IR spectrophotometer by potassium bromide (KBr) pellet method.

Formulation of Doxazosin Mesylate Sustain Release Tablets: [9] Doxazosin Mesylate and other excipients are weighed accurately, passed through a 40# sieve, transferred in mortar-pestle and thoroughly mixed for 15 min. The powder mixture was granulated with PVP K30 as a binder. The wet mass was passed through 10# sieve and granules were dried at 60 °C for 30 min. in a tray dryer. The dried granules were passed through a 20# sieve and lubricated with talc and magnesium stearate which was previously passed through an 80# sieve. Tablets were compressed using a 9.5 mm punch on 10 stations rotary tablet punching machine (Karnavati Engineering).

Optimization of Formulation: [10] A 3^2 full factorial design was adopted and the number of polymers, Eudragit RS100 (X_1) and Eudragit RL100 (X_2), were taken as independent variables and % CDR at 2 h (Y_1) and % CDR at 22 h (Y_2) was taken as dependent variables as shown in **Table 1**. The factors were studied at three levels (−1, 0, +1) indicating low, medium and high, respectively, as represented in **Table 2**. A statistical model incorporating interactive and polynomial term was used to evaluate the responses of formulations.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is dependent variable, b_0 is the arithmetic mean response of the 9 runs and bi (b_1, b_2, b_{12}, b_{11}, and b_{22} is the estimated coefficient for the factor X_1). The main effect (X_1 and X_2) represents the average results of changing one factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when 2 factors are changed simultaneously. The polynomial terms (X_{12} and X_{22}) are included to investigate nonlinearity. The statistical optimization procedure was performed with the help of optimization software like Design Expert 11.0.4 (Stat‑Ease Inc.). The software performs the multiple regression analysis (MRA), analysis of variance (ANOVA) and statistical optimization.

TABLE 1: SELECTION OF INDEPENDENT VARIABLES AND DEPENDENT VARIABLES

Independent variables		Dependent variables	
X_1	X_2	Y_1	Y_2
Concentration of Eudragit RS100 (mg)	Concentration of Eudragit RL 100 (mg)	% CDR at 2 h	% CDR at 22 h

TABLE 2: SELECTION OF LEVELS FOR INDEPENDENT VARIABLES AND CODING OF VARIABLE

Levels	Coded value	Independent variables	
		Concentration of Eudragit RS 100 (mg) X_1	Concentration of Eudragit RL 100 (mg) X_2
Low	-1	80	80
Intermediate	0	90	90
High	+1	100	100

TABLE 3: COMPOSITION OF FACTORIAL DESIGN BATCHES

Ingredients (mg)	R1	R2	R3	R4	R5	R6	R7	R8	R9
Doxazosin mesyalte	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose	75	65	55	65	55	45	55	45	35
Eudragit RS 100	80	90	100	80	90	100	80	90	100
Eudragit RL 100	80	80	80	90	90	90	100	100	100
PVP K-30	4	4	4	4	4	4	4	4	4
IPA	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total Weight (mg)	250	250	250	250	250	250	250	250	250

Evaluation Parameters: [11, 12]

Pre Compressional Parameters:

Bulk Density: It is the ratio of the total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder, and the volume was noted. It is expressed in gm/ml

$$\text{Bulk density} = \text{Weight of powder} / \text{Bulk volume}$$

Tapped Density: It is the ratio of the total mass of powder to the tapped volume of powder. It is determined by placing a graduated cylinder containing the known weight of powder; mechanical tapper apparatus operated for a fixed number of taps until the powder bed volume has reached a minimum volume.

$$\text{Tapped density} = \text{Weight of powder} / \text{Tapped volume}$$

Carr's Index (I): It is measured by using values of bulk density and tapped density.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio: Hausner's ratio is the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

The angle of Repose: The angle of repose can measure the frictional forces in a loose powder, θ.

$$\Theta = \tan^{-1} h/r$$

Where the h= height of the heap; the r= radius of the heap.

It is determined by pouring the powder a conical on a level, flat surface, measured the included angle with the horizontal.

Post-Compressional Studies:

Thickness: The thickness of the three tablets was measured using vernier caliper. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

Weight Variation: Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. The following % deviation in weight variation is allowed.

$$\text{Percentage deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Individual weight}}$$

TABLE 4: WEIGHT VARIATION AS PER IP/BP

Weight in mg (IP/BP)	Limit
80 mg or less	± 10%
More than 80 mg and less than 250 mg	± 7.5%
250 mg or more	± 5%

Hardness: The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm^2 is considered adequate for mechanical stability.

Friability: The friability of the tablets was measured in a Roche friabilator. Tablets of known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in the equation as below. The weight loss should not be more than 1%.

$$F = \frac{\text{W initial } (W_0) - \text{W final } (W)}{\text{W initial } (W_0)} \times 100$$

Drug Content: Content of drug was carried out by weighing on ten tablets from each batch and calculated average weight. Then tablets triturated to receive fine powder. From the received triturate powder was weighed precisely that is equivalent to 5 mg of the Doxazosin Mesylate and dissolved in 100 ml to the measured flask containing 100 ml of Phosphate buffer pH 6.8 and volume was made to 100 ml with solvent. The volumetric flask was shaken using sonicate for 1 h and after suitable dilution with Phosphate buffer pH 6.8, the drug content was determined using UV-Visible Spectrophotometer at 247 nm.

***In-vitro* Drug Release Study:** [13] Release of the prepared tablets was determined using U.S.P type II paddle type dissolution rate test apparatus (TDT-06P, Electrolab) using 900 ml of 6.8 pH phosphate buffer as dissolution medium. The temperature of 37 ± 1 ºC was maintained, and the paddle was adjusted at 50 rpm throughout the experiment. Withdrawn not less than 5 ml of the dissolution solution at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h time interval up to 24 h and were replaced with 5 ml of fresh dissolution media after each withdrawal and filtered each sample through a membrane filter with a pore size of not more than 0.45 mm. The samples were analyzed after appropriate dilution by UV spectrophotometer at λ_{max} 247 nm.

Drug Release Kinetics: [14] Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Korsmeyer-Peppas release model, and Hixson-Crowell equation.

Stability Study: [15] Stability studies of the optimized formulation was carried out to determine the effect of the presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40 ± 2 ºC/ 75 ± 5 % Rh for a period of 1 month.

RESULTS AND DISCUSSION:

Drug-Excipient Compatibility Studies Fourier Transform Infrared (FTIR) Spectroscopy: FTIR spectrum of a mixture of drug and excipients are shown in **Fig. 1**. The characteristic peaks of the drug were observed in the spectra of drug and excipients mixture, indicates that there is no interaction between the drug and excipients.

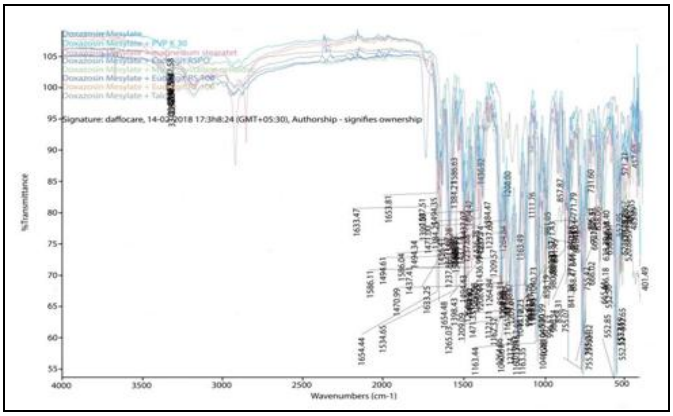

FIG. 1: COMPARISONS OF FT-IR SPECTRA OF DRUG AND MIXTURE OF DRUG AND OTHER EXCIPIENTS

Pre-compression Evaluation of Powder Blend of Batches R1 to R9: The present study focused on sustained release matrix formulation for Doxazosin Mesylate was designed and developed to achieve a 24 h release profile. Using Eudragit RS 100 and Eudragit RL 100 as matrix forming agent to control the release of Doxazosin Mesylate. The matrix tablets for these formulations were prepared by wet granulation. The values of Bulk density, Tapped density, Carr's index, Hausner's ratio, Angle of repose were determined, and results are shown in **Table 5**. All the formulations showed good flow property.

TABLE 5: PRE-COMPRESSION EVALUATIONS OF BATCHES R1 TO R9

Batch code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (Θ)
R1	0.547 ± 0.031	0.609 ± 0. 026	10.18 ± 1.17	1.11 ± 0.25	24.69º ± 0.52
R2	0.568 ± 0.042	0.634 ± 0.038	10.41 ± 1.10	1.11 ± 0.35	25.25º ± 0.15
R3	0.558 ± 0.025	0.624 ± 0.041	10.57 ± 1.12	1.11 ± 0.57	25.20º ± 0.15
R4	0.567 ± 0.054	0.637 ± 0.049	10.98 ± 1.26	1.12 ± 0.15	26.68º ± 0.25
R5	0.557 ± 0.035	0.619 ± 0.032	10.01 ± 1.15	1.11 ± 0.27	25.84º ± 0.45
R6	0.564 ± 0.041	0.629 ± 0.028	10.33 ± 1.34	1.11 ± 0.51	25.50º ± 0.78
R7	0.578 ± 0.039	0.645 ± 0.021	10.38 ± 1.32	1.11 ± 0.45	26.73º ± 0.43
R8	0.598 ± 0.038	0.678 ± 0.038	11.79 ± 1.28	1.13 ± 0.25	27.20º ± 0.31
R9	0.588 ± 0.046	0.662 ± 0.048	11.17 ± 1.11	1.12 ± 0.41	26.34º ± 0.27

All values are expressed as mean ± standard deviation, n=3

Post Compression Evaluation of Batches R1 to R9: All the formulations were evaluated for various post-compression evaluation parameters as shown in **Table 6**. The % deviation in weights of tablets was ± 5% which is within the range according to IP. This shows uniform die fill during tablet compression. As there was no much variation in thickness of tablets in each formulation, it shows that granules and powder blends were consistent in particle size and uniform behavior during the compression process. The hardness of the tablet was measured; the hardness was in the range of 5.11 ± 0.63 to 5.94 ± 0.26 kg/cm^2. The two factors, *i.e.* the high value of hardness and absence of disintegrant in the formulation, indicate that tablet will not disintegrate in the gastrointestinal tract and release the drug slowly by a diffusion process. Friability was found to be 0.50 ± 0.15 to 0.72 ± 0.18%. As friability was below 0.8% in each formulation can withstand the mechanical shocks. Drug content of all batches was in the range of 98.13 ± 2.23 to 99.86 ± 1.52% complies the limit given in the pharmacopeia.

TABLE 6: POST-COMPRESSION EVALUATION PARAMETERS OF FULL FACTORIAL DESIGN BATCHES

Batch code	Weight variation (n=20)	Diameter (n=10)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	% Friability (n=5)	% Drug content (n=10)
R1	Pass	9.58 ± 0.003	3.59 ± 0.037	5.48 ± 0.16	0.71 ± 0.03	99.40 ± 0.36
R2	Pass	9.66 ± 0.001	3.55 ± 0.047	5.61 ± 0.59	0.70 ± 0.03	99.45 ± 1.18
R3	Pass	9.59 ± 0.002	3.75 ± 0.041	5.48 ± 0.05	0.70 ± 0.03	99.86 ± 1.52
R4	Pass	9.57 ± 0.005	3.43 ± 0.050	5.68 ± 0.14	0.50 ± 0.15	99.33 ± 1.52
R5	Pass	9.52 ± 0.001	3.78 ± 0.075	5.83 ± 0.45	0.70 ± 0.12	98.13 ± 2.23
R6	Pass	9.68 ± 0.002	3.51 ± 0.095	5.94 ± 0.26	0.70 ± 0.03	99.26 ± 1.32
R7	Pass	9.56 ± 0.004	3.62 ± 0.022	5.69 ± 0.15	0.71 ± 0.47	98.60 ± 1.87
R8	Pass	9.59 ± 0.003	3.97 ± 0.015	5.11 ± 0.63	0.54 ± 0.03	99.00 ± 0.71
R9	Pass	9.59 ± 0.005	3.53 ± 0.032	5.73 ± 0.28	0.72 ± 0.18	99.50 ± 1.47

All values are expressed as mean ± standard deviation

In-vitro Drug Release Study of Batches R1-R9:

TABLE 7: % CDR OF FULL FACTORIAL DESIGN BATCHES

Time (h)	R1	R2	R3	R4	R5	R6	R7	R8	R9
0	0	0	0	0	0	0	0	0	0
1	6.92 ±2.42	5.82 ±3.15	4.52 ±2.42	5.22 ±2.72	6.02 ±2.25	5.98 ±2.42	2.00 ±2.92	1.87 ±2.21	1.02 ±3.32
2	8.24 ±3.11	7.52 ±2.65	5.89 ±3.81	7.98 ±3.22	8.85 ±1.92	6.23 ±3.11	4.99 ±3.17	4.06 ±2.98	2.99 ±3.43
4	18.66 ±3.46	17.92 ±2.65	16.38 ±2.92	17.02 ±2.53	15.82 ±3.40	13.98 ±2.91	14.82 ±2.62	12.85 ±3.93	8.26 ±2.64
6	29.92 ±2.88	28.82 ±2.92	27.92 ±2.42	27.54 ±2.92	25.65 ±3.09	24.42 ±2.47	23.56 ±2.82	20.82 ±3.32	14.93 ±2.42
8	38.42 ±2.75	37.42 ±3.01	36.66 ±3.82	36.45 ±2.84	34.25 ±2.14	33.53 ±2.92	32.65 ±2.73	30.95 ±3.21	22.64 ±2.88
10	47.52 ±2.42	46.54 ±2.51	45.54 ±2.92	44.77 ±3.42	42.21 ±3.43	40.99 ±2.13	39.53 ±2.93	35.68 ±2.56	32.44 ±3.62
12	56.12 ±2.85	55.45 ±2.43	54.32 ±3.21	52.22 ±3.92	50.26 ±2.43	48.82 ±2.82	46.79 ±3.62	44.98 ±2.82	40.93 ±2.72
14	63.72 ±3.88	62.65 ±2.98	61.65 ±2.47	60.66 ±2.92	58.47 ±2.22	56.32 ±2.95	55.52 ±3.72	52.68 ±2.88	48.14 ±2.82

16	70.33 ±3.12	69.43 ±2.86	68.66 ±2.92	67.98 ±3.05	65.32 ±2.18	63.98 ±3.12	62.23 ±2.11	60.46 ±2.52	59.36 ±3.23
18	76.21 ±2.49	74.42 ±2.18	72.43 ±2.49	70.88 ±1.60	69.35 ±1.89	67.45 ±3.74	66.26 ±2.65	64.39 ±3.42	63.99 ±2.42
20	85.42 ±2.76	83.43 ±3.94	81.76 ±2.81	82.81 ±3.10	78.35 ±2.16	74.26 ±3.64	71.93 ±2.45	70.65 ±2.82	67.77 ±2.88
22	92.02 ±3.33	91.55 ±2.65	89.88 ±3.42	89.12 ±3.16	87.02 ±3.10	86.44 ±3.73	78.29 ±2.47	76.36 ±2.56	74.22 ±2.63
24	99.97 ±2.92	97.43 ±3.22	95.76 ±2.46	96.05 ±3.82	94.44 ±1.16	92.36 ±3.21	93.82 ±3.82	90.58 ±3.92	88.56 ±3.42

All values are expressed as mean ± standard deviation, n=3

In-vitro drug release study of Doxazosin Mesylate expandable tablets was indicated sustained release for 24 h. It was observed that all the tablets achieved good expansion within 1st h and remained swelled, until the completion of release studies. The release was affected by the swelling behavior of the tablet. The drug release study was carried out up to 24 h, and results are shown in **Fig. 2**. The cumulative percentage drug release of batches R1-R9 was in the range of 88.56 ± 3.42-99.97 ± 2.92% for 24 h. The percentage release of the optimized batch (R1) was found to be 6.92 ± 2.42 at 1 h and 99.97 ± 2.92 at 24 h. *In-vitro* release study results revealed that the release of drug was retarded with the proportional increase of the polymer concentration. Large concentrations of hydrophilic polymers swell in the presence of water. These polymers form porous structures on the surface of the tablet matrix and form a strong viscous gel layer, which slows down the water diffusion. The phenomenon of swelling resulted in the slow the drug release. Batch R1 was considered as optimized batch comparative all formulated batches on depending on drug release. All the formulations showed the initial burst in release rate. This may be due to the drug release from the surface and the time needed for the formation of an active gel layer capable of controlling water penetration and drug diffusion.

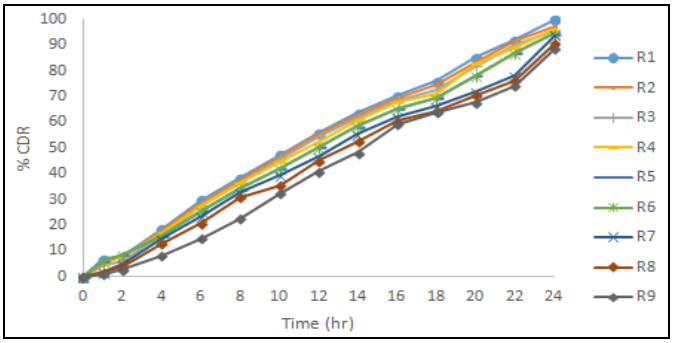

FIG. 2: CUMULATIVE % DRUG RELEASE STUDY OF R1 TO R9 BATCHES

The result of Full Factorial Design: The coefficients of the polynomial equations for responses % CDR at 2 h and % CDR at 22 h along with their values of R2. Coefficients (R1) were calculated with B_0 as the intercept using the polynomial equation.

TABLE 8: ANOVA RESPONSE SURFACE QUADRATIC MODEL FOR (Y_1)

Source	Sum of squares	Df	Mean square	F-value	p-value	
Model	31.35	5	6.27	17.32	0.0202	
X_1	6.2	1	6.2	17.13	0.0256	
X_2	15.39	1	15.39	42.5	0.0073	
X_1X_2	0.0306	1	0.0306	0.0846	0.7901	Significant
X_1^2	1.15	1	1.15	3.16	0.1734	
X_2^2	8.58	1	8.58	23.7	0.0166	
Residual	1.09	3	0.3621	-	-	
Cor Total	32.44	8	-	-	-	

TABLE 9: ANOVA RESPONSE SURFACE QUADRATIC MODEL FOR (Y2)

Source	Sum of squares	Df	Mean square	F-value	p-value	
Model	374.31	5	74.86	324.57	0.0003	
X_1	13.17	1	13.17	57.11	0.0048	
X_2	331.23	1	331.23	1436.06	< 0.0001	
X_1X_2	0.9312	1	0.9312	4.04	0.1381	Significant
X_1^2	0.0007	1	0.0007	0.0029	0.9603	
X_2^2	28.98	1	28.98	125.65	0.0015	
Residual	0.6920	3	0.2307	-	-	
Cor Total	375.01	8	-	-	-	

A mathematical relationship in the form of the polynomial equation for % CDR at 2 h (Y_1) and % CDR at 22 h (Y_2) are as follows:

$Y_1 = 8.19 - 1.02X_1 - 1.60X_2 + 0.0875X_1X_2 - 0.7567X_1^2 - 2.07X_2^2$, $R^2 = 0.9665$

$Y_2 = 87.51 - 1.48X_1 - 7.43X_2 - 0.4825X_1X_2 + 0.0183X_1^2 - 3.81X_2^2$, $R^2 = 0.9981$

The coefficient of the above equation was calculated by regression using the transformed data taken for Factor Concentration of Eudragit RS100 (X_1) and Eudragit RL100 (X_2) as shown in **Table 2**. The value of R2 is quite high for % CDR at 2 h and % CDR at 22 h so for these responses; the polynomial equations form excellent fits to all the experimental data and statistically valid.

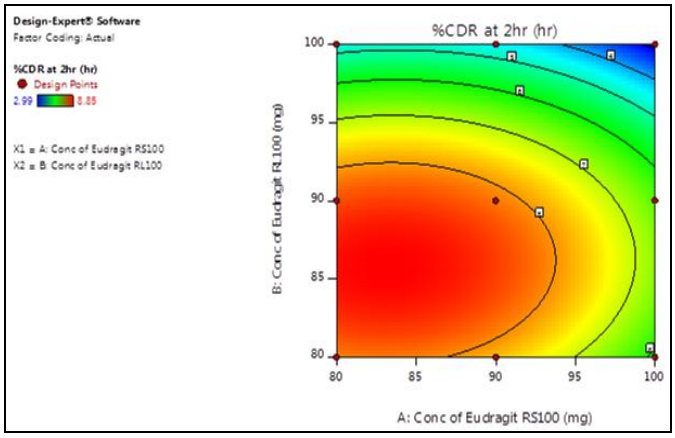

FIG. 3: TWO-DIMENSIONAL CONTOUR CURVE OF CONCENTRATION OF EUDRAGIT RS100 (X_1) & CONCENTRATION OF EUDRAGIT RL100 (X_2) FOR % CDR AT 2 h (Y_1)

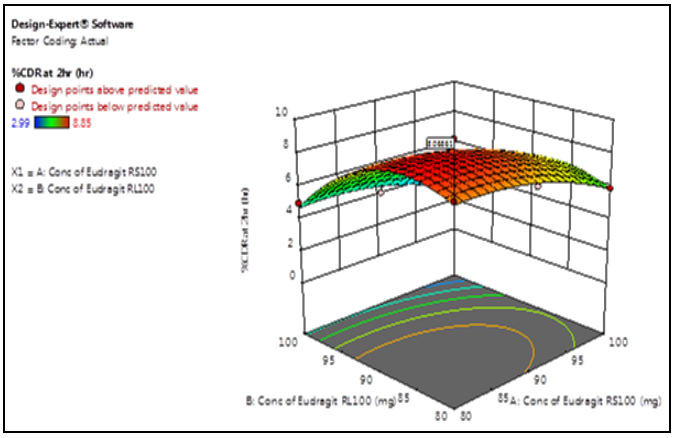

FIG. 4: 3-D GRAPH SHOWING EFFECT OF CONCENTRATION OF EUDRAGIT RS100 (X1) & CONCENTRATION OF EUDRAGIT RL100 (X2) FOR % CDR AT 2 H (Y1)

Contour Plots of Response using the Graphical Method for % CDR at 22 h:

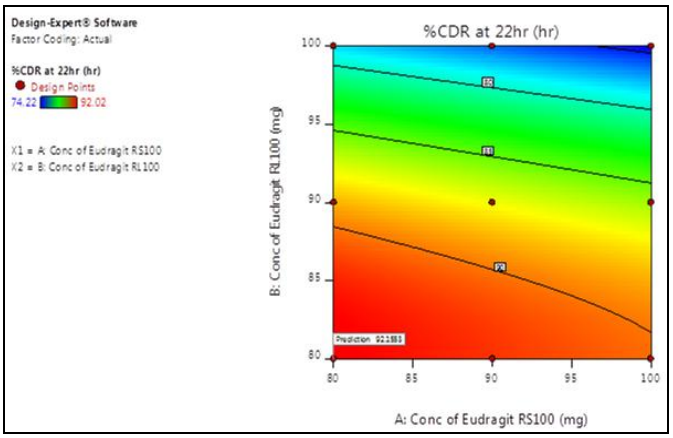

FIG. 5: TWO-DIMENSIONAL CONTOUR CURVE OF CONCENTRATION OF EUDRAGIT RS100 (X1) & CONCENTRATION OF EUDRAGIT RL100 (X2) FOR % CDR AT 22 h (Y2)

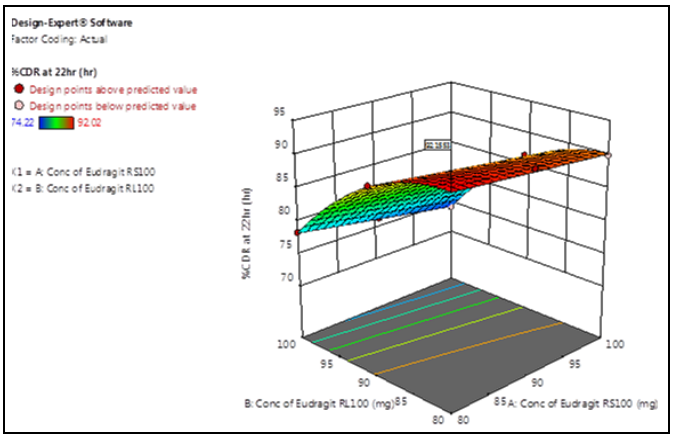

FIG. 6: 3-D GRAPH SHOWING EFFECT OF CONCENTRATION OF EUDRAGIT RS100 (X_1) & CONCENTRATION OF EUDRAGIT RL100 (X_2) FOR % CDR AT 2 h (Y_2)

Check Point Analysis: Three checkpoint batches were prepared & evaluated for % CDR at 2 h & % CDR at 22 h, as shown in **Table 10**. When measured % CDR values were compared with predicted % CDR, the differences were found to be not significant. Thus, it can be concluded that the obtained mathematical equation is valid for predicted values.

TABLE 10: CHECKPOINT BATCHES WITH PREDICTED AND MEASURED VALUE OF % CDR AT 2 h (Y_1) AND AT 22 h (Y_2)

Batch code	X_1	X_2	% CDR at 2 h (Y_1)		% CDR at 22 h (Y_2)	
			Measured	Predicted	Measured	Predicted
R10	0	0.5	6.32	6.87	84.54	84.70
R11	0.5	1	3.22	3.86	75.02	75.29
R12	1	0.5	5.32	5.53	80.11	80.18

Optimization of Formulation: The overlying plot of responses generates an optimized area as per the desired criteria. This was the most essential part of the response surface methodology. The formulation of the drug which released the drug in a controlled and complete manner was selected for optimum formulation.

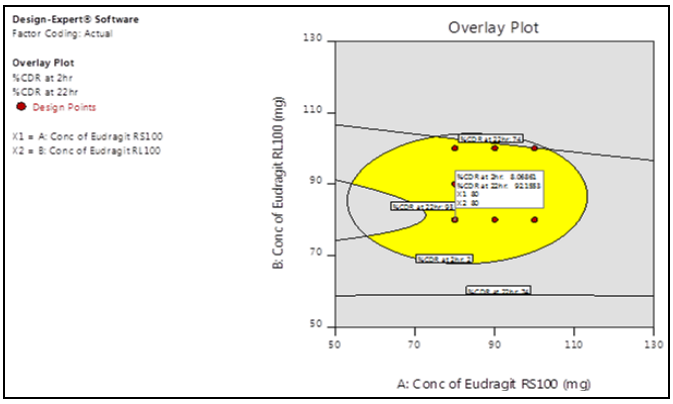

FIG. 7: RELEASE ORDER OVERLAY PLOT OF BATCH R1

After studying the effect of the independent variables on the responses, the levels of these variables that give the optimum response were determined. The optimum formulation was selected based on the criteria of attaining complete and controlled drug release. Batch R1 is having 80 mg of Eudragit RS100 and 80 mg of Eudragit RL100 fulfilled maximum requisites of an optimum formulation because of better regulation of release rate. The said formulation released 8.06% of the drug in 2 h and 92.15% in 22 h, however, the drug completely got released, *i.e.* 99.97% in 24 h, which were in close agreement with the theoretical values.

Drug Release Kinetic Study: The release data were fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of R1 could be best expressed by Korsmeyer-Peppas; it was confirming the desired release profile. The calculated R^2 value for Korsemeyer-Peppas was 0.9884. According to Korsmeyer-Peppas equation, the release exponent "n" value is between $0.45 < n < 0.89$, which indicates that drug release is non-fickian diffusion type and states that release followed the diffusion controlled mechanism. The criteria for the selection of the most suitable model were the value of regression coefficient (R2) nearer to 1, the smallest values of SSR and AIC. **Table 11** shows the data obtained.

TABLE 11: FITTING OF RELEASE PROFILE OF OPTIMIZED FORMULATION TO KINETIC MODELS

Batch	Model	Parameters Used				
		R^2	R	K	SSR	AIC
R1	Zero-order	0.9921	0.9976	4.327	114.7823	68.4025
	First-order	0.9537	0.9847	0.076	669.0474	93.0820
	Higuchi	0.9045	0.9768	17.382	1380.7767	103.2256
	Korsemeyer - Peppas	0.9984	0.9992	6.135 n=0.879	23.2940	48.0747
	Hixson Crowell	0.9791	0.9928	0.021	301.8092	81.9371

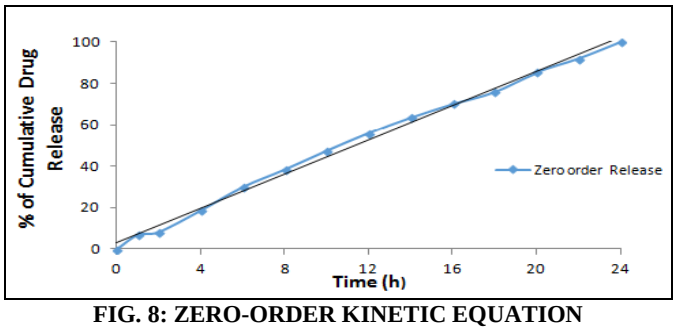

FIG. 8: ZERO-ORDER KINETIC EQUATION

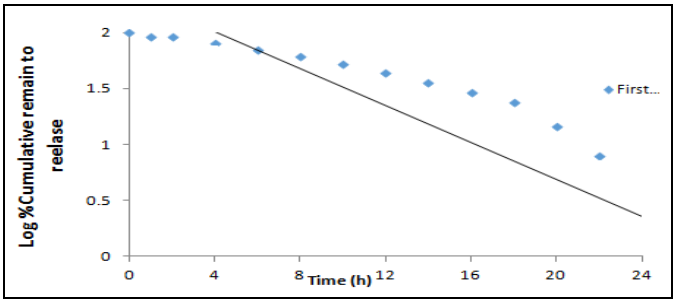

FIG. 9: FIRST-ORDER KINETIC EQUATION

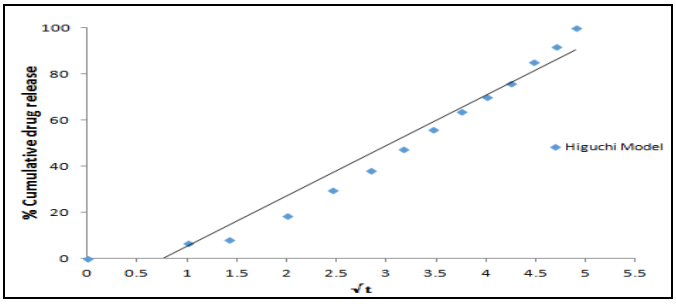

FIG. 10: HIGUCHI KINETIC EQUATION

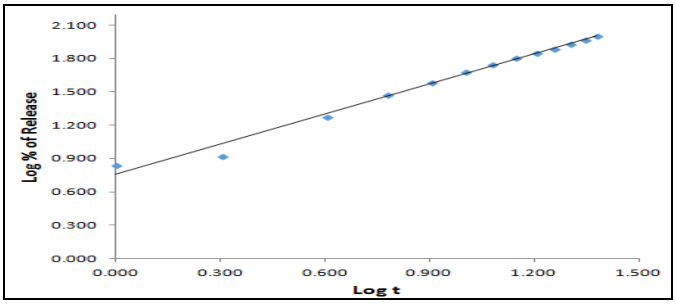

FIG. 11: KORSMEYER-PEPPAS KINETIC EQUATION

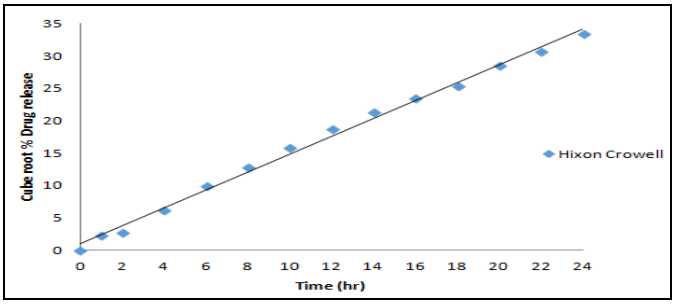

FIG. 12: HIXSON CROWELL KINETIC EQUATION

Stability Study: Stability study of sustained release matrix tablet of Doxazosin Mesylate was carried out for 1 month at the specified condition. All data are mentioned in table 12. The stability studies of the optimized formulation (R1) shown no significant changes in the physical parameters, %drug content, and % drug release in 24 h when stored at 40 ± 2 ºC/ 75 ± 5 % Rh.

TABLE 12: STABILITY STUDY OF OPTIMIZED FORMULATION (R1) CARRIED OUT AT 40 ± 2 ºC/ 75 ± 5 % RH

No. of months	% Drug content (n=3)	% Drug release at 24 h (n=3)
0	99.40 ± 0.76	99.97 ± 3.19
1	99.55 ± 0.71	99.59 ± 2.72

All values are expressed as mean ± standard deviation, n=3

CONCLUSION: The matrix type of tablets is the potential to be an effective sustained release drug delivery system over a prolonged period. The type and level of polymer used are important factors that can affect the drug release and also the physicochemical properties of this sustained release matrix tablets. 3^2 full factorial design was applied to achieve controlled drug release up to 24 h Among all the developed formulations, R1 formulation which contains the mixture of two polymers Eudragit RS-100 and Eudragit RL-100 sustained drug release for 24 h when compared with other formulations. So, R1 was selected as the best formulation containing Eudragit RS-100 and Eudragit RL-100 in a proportion of 80 mg and 80 mg formulation providing desired sustained release.

The drug release kinetics follows Korsemeyer-peppers. So, the mechanism was found to be non Fickian and shows continuous and uniform drug release for an extended period, an attribute highly desirable for any sustained release formulation. The stability study was carried out according to ICH guideline which indicates that the selected formulation was stable.

From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of sustained release product.

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CONFLICT OF INTEREST: Nil

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