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Effect of polymers in the formulation of sustained release tablets of doxazosin mesylate using various hydrophilic polymers

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ABSTRACT

The aim of the present study was to develop sustained release formulation of Doxazosin mesylate to maintain constant therapeutic levels of the drug for over 12 hrs. HPMC-K 100 M, Ethyl cellulose, HPC and Eudragit RSPO were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (DM5) showed better and desired drug release pattern i.e., 99.21 % in 12 hours. It contains the HPMC-K 100 M 1:1 as sustained release material. It followed peppas release kinetics mechanism.

Keywords: Doxazosin mesylate, HPM HPMC-K 100 M, Ethyl cellulose, HPC, Eudragit RSPO, Sustained release system.

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body[1]. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action[2, 3]. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect[4]. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[5, 6].

The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[7, 8].

Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and

- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[9].

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

MATERIALS

Materials Used

Doxazosin mesylate provided by SURA LABS, Dilsukhnagar, Hyderabad. HPMC-K 100 M from Merck Specialities Pvt Ltd, Mumbai, India. Ethyl cellulose from Merck Specialities Pvt Ltd, Mumbai, India. HPC from Merck Specialities Pvt Ltd, Mumbai, India. Eudragit RSPO from Merck Specialities Pvt Ltd, Mumbai, India. MCC PH 102 from Merck Specialities Pvt Ltd, Mumbai, India. Sodium Stearyl Fumarate from Merck Specialities Pvt Ltd, Mumbai, India. Talc from Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development

a) Determination of absorption maxima

100mg of Doxazosin mesylate pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation calibration curve

100mg of Doxazosin mesylate pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 1, 2, 3, 4, and 5ml of solution and make up to 10ml with 0.1N HCl to obtain 10, 20, 30, 40 and 50 µg/ml of Doxazosin mesylate solution. The absorbance of the above dilutions was measured at 248nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

Formulation development of Sustained release Tablets

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Doxazosin mesylate.

Procedure

In the present work the Doxazosin mesylate tablets were prepared by direct compression method. The drug and the excipients were passed through 72# size mesh prior to the preparation of dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes in double cone blender to ensure uniform mixing in geometric ratio. The tablets were prepared by direct compression technique using 6mm punch.

Table 1: Formulation of Doxazosin mesylate release tablets

Ingredients(mg)	DM1	DM2	DM3	DM4	DM5	DM6	DM7	DM8	DM9	DM10	DM11	DM12
Doxazosin mesylate	1	1	1	1	1	1	1	1	1	1	1	1
HPMC-K 100 M	2.5	-	-	-	2.5	-	-	-	2.5	-	-	-
Ethyl cellulose	-	5	-	-	-	5	-	-	-	5	-	-
HPC	-	-	7.5	-	-	-	7.5	-	-	-	7.5	-
Eudragit RSPO	-	-	-	9.5	-	-	-	9.5	-	-	-	9.5
MCC PH 102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Sodium Stearyl Fumarate	4	4	4	4	4	4	4	4	4	4	4	4

Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total Wt	60	60	60	60	60	60	60	60	60	60	60	60

Post Compression parameters

Weight variation test: Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.

Friability test: Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss (F) was calculated by the following formula.

F =100 (W0-W)/W0

Where W0 = Initial weight, W = Final weight

Hardness test: The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test: The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.

Drug content: The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

In vitro drug release studies

Apparatus	--USP-II, Paddle Method
Dissolution Medium	-- p H 6.8 Phosphate buffer
RPM	--50
Sampling intervals (hrs)	--1, 2, 3, 4, 5, 6, 7, 8, 10, & 12.
Temperature	--37°c ± 0.5°c

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The media was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours. Then 0.1 N HCl was replaced with pH 6.8 phosphate buffer and process was continued up to 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at 248nm wavelength of drug using UV-spectrophotometer.

RESULTS AND DISCUSSION

Analytical Method

Standard graph of Doxazosin mesylate in 0.1N HCl

The scanning of the 10µg/ml solution of Doxazosin mesylate in the ultraviolet range (200-400nm) against 0.1 N HCl the maximum peak observed at λ_{max} as 248 nm. The standard concentrations of Doxazosin mesylate (10-50 µg/ml) was prepared in 0.1N HCl showed good linearity with R^2 value of 0.998, which suggests that it obeys the Beer-Lamberts law.

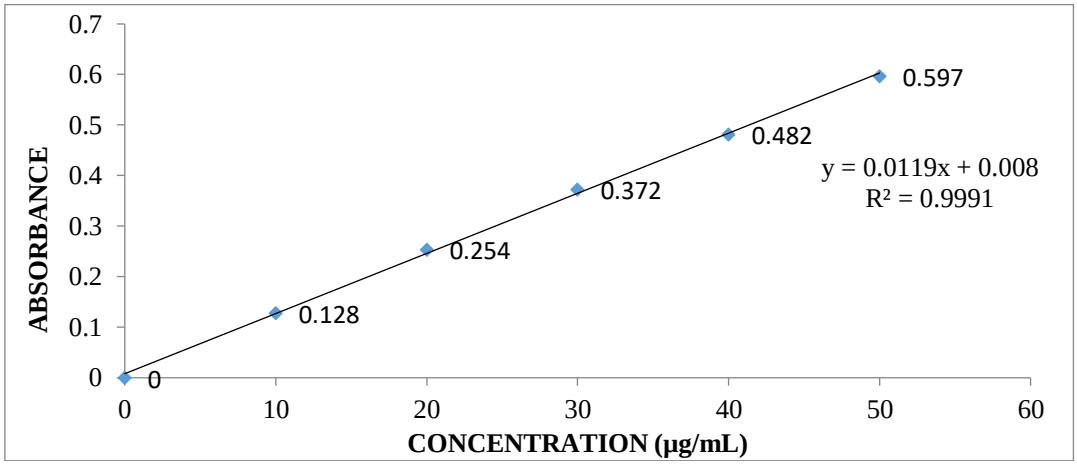

Fig 1: Calibration curve of Doxazosin mesylate in 0.1 N HCl at 248nm

Standard Curve of Doxazosin mesylate in Phosphate buffer pH 6.8

The scanning of the 10µg/ml solution of Doxazosin mesylate in the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the λ_{max} as 250 nm.

The standard concentrations of Doxazosin mesylate (10-50µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

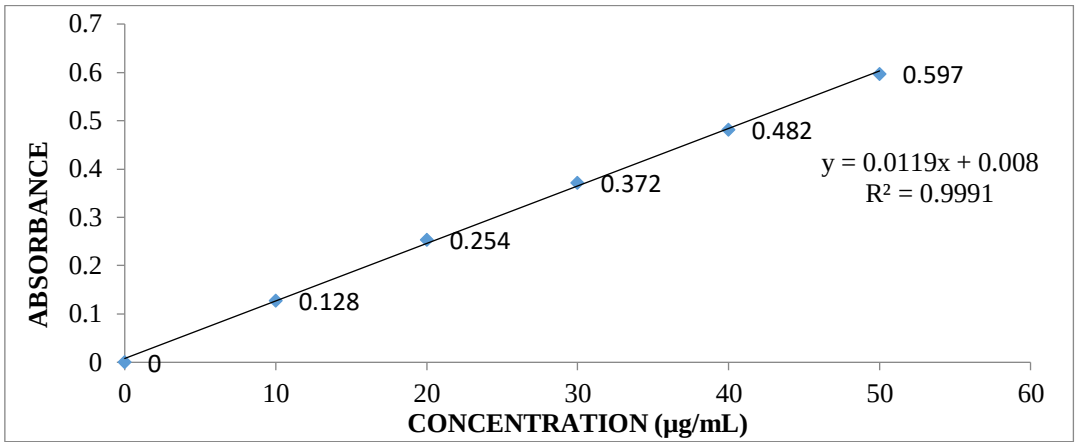

Fig 2: Calibration of Doxazosin mesylate in Phosphate buffer pH 6.8

Drug and Excipient Compatibility Studies

FTIR study

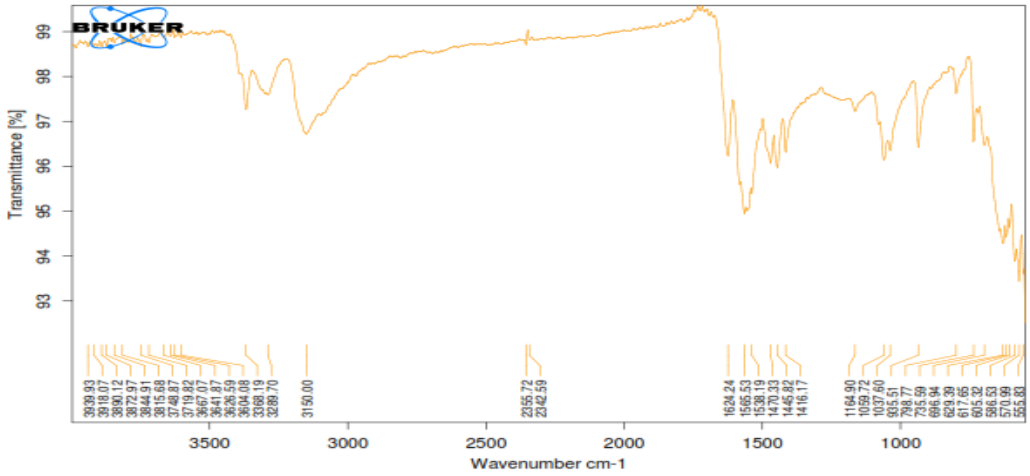

Fig 3: FTIR GRAPH OF PURE DRUG

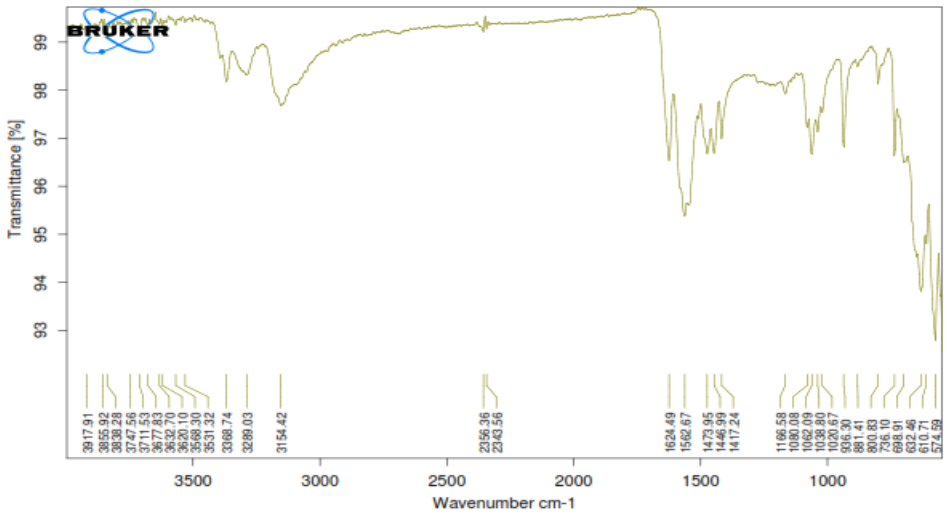

Fig 4: FTIR GRAPH OF OPTIMISED FORMULATION

From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

EVALUATION PARAMETERS

Pre-compression parameters

Table 2: Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
DM1	35.24±0.07	0.525±0.11	0.619±0.02	15.32±0.09	1.197±0.07
DM2	36.27±0.06	0.522±0.34	0.621±0.04	14.87±0.35	1.185±0.06
DM3	34.65±0.08	0.526±0.65	0.614±0.01	15.62±0.72	1.187±0.13
DM4	33.54±0.04	0.522±0.25	0.615±0.04	15.64±0.26	1.175±0.02
DM5	32.21±0.01	0.516±0.24	0.622±0.05	14.96±0.15	1.186±0.03
DM6	39.23±0.01	0.527±0.45	0.618±0.01	16.53±1.6	1.198±0.21
DM7	31.10±0.02	0.522±0.36	0.623±0.02	14.56±0.20	1.170±0.01
DM8	32.19±0.02	0.525±0.99	0.611±0.01	14.91±0.33	1.175±0.03
DM9	33.28±0.01	0.517±1.05	0.617±0.03	15.66±0.10	1.185±0.15
DM10	30.86±0.03	0.518±0.25	0.613±0.02	15.35±0.3	1.18±0.01
DM11	31.24±0.04	0.523±0.45	0.612±0.01	14.95±0.66	1.17±0.02
DM12	30.48±0.02	0.515±1.47	0.610±0.01	15.57±1.4	1.18±0.01

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.515±1.47 to 0.527±0.45 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.610±0.01 to 0.623±0.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 16.53 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.198 indicating the powder has good flow properties.

Post Compression Parameters For tablets

Table 3: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
DM1	50.5 ± 0.25	4.8±0.04	0.51±0.04	2.6±0.03	102.3 ± 0.21
DM2	50.53 ± 0.34	4.5 ± 0.02	0.561±0.03	2.2 ±0.02	99.50 ± 0.22
DM3	49.25± 1.15	4.7±0.01	0.45±0.02	2.3 ±0.05	97.2 ± 0.19
DM4	50.15 ± 1.31	4.7±0.05	0.54±0.07	2.6±0.04	99.3 ± 0.13
DM5	49. 23±0.25	4.6±0.09	0.48±0.08	2.6 ±0.09	104.3 ± 012
DM6	50.26 ± 1.25	4.7±0.01	0.45±0.02	2.4±0.05	98.2 ± 0.19
DM7	49.5 ± 0.95	4.8±0.07	0.51±0.04	2.3 ±0.03	102.3 ± 0.28
DM8	50.5 ± 0.86	4.7±0.04	0.55±0.07	2.3 ±0.05	98.3 ± 0.20
DM9	50.36 ± 1.17	4.7±0.04	0.56±0.04	2.7±0.08	100.8 ± 0.17
DM10	49.95 ± 1.72	4.8±0.01	0.45±0.05	2.4 ±0.05	98.8 ± 0.14
DM11	50.26 ± 0.81	4.5±0.01	0.55±0.02	2.6±0.06	98.2 ± 0.15
DM12	50.25 ± 2.02	4.8±0.03	0.52±0.03	2.7±0.04	103.5 ± 0.14

In Vitro Drug Release Studies

The formulations prepared with different polymers by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 4: Dissolution Data of Doxazosin mesylate Tablets Prepared with (Drug: polymer) Ratios of polymers like HPMC-K 100 M (DM1), Ethyl cellulose (DM2), HPC (DM3), Eudragit RSPO (DM4)

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED			
	DM1	DM2	DM3	DM4
0	0	0	0	0
1	25.41	30.21	33.04	25.62
2	32.39	40.56	47.21	30.80
3	43.62	48.60	61.09	37.61
4	55.05	61.36	69.63	56.39
5	62.26	68.21	81.83	70.83
6	74.93	79.66	93.03	78.66
7	82.02	91.90	99.56	86.81
8	93.77	99.43		97.40
10	99.08			100.13

12				

The % drug release of formulations (DM1 to DM4) containing polymers like HPMC-K 100 M (DM1), Ethyl cellulose (DM2), HPC (DM3), Eudragit RSPO (DM4). Depends on the concentration of polymer. The concentration of was 1:3 ratios was able to retard the drug release up to desired time. In DM1 and DM4 formulation was showed maximum % drug release up to 10 hours i.e., 99.08 and 100.13%.

Table 5: Dissolution Data of Doxazosin mesylate Tablets Prepared with (Drug: polymer) Ratios of polymers like HPMC-K 100 M (DM5), Ethyl cellulose (DM6), HPC (DM7), Eudragit RSPO (DM8)

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED			
	DM5	**DM6**	**DM7**	**DM8**
0	0	0	0	0
1	21.07	26.28	20.90	16.82
2	31.29	35.39	40.62	32.70
3	44.01	44.61	48.26	43.53
4	55.49	57.35	60.43	59.16
5	63.56	63.82	66.85	61.79
6	71.81	75.64	73.69	68.81
7	75.92	82.89	77.32	73.45
8	84.60	90.23	84.74	78.17
10	96.03	93.10	91.46	88.22
12	99.21	96.27	93.11	90.33

The % drug release of DM5 to DM6 formulations depends on ratio of polymer in the solution and retard the drug release up to 12h. The concentration of polymer was unable to retard the drug release up to desired time DM7 to DM8 Formulations.

Table 6: Dissolution Data of Doxazosin mesylate Tablets Prepared with (Drug: polymer) Ratios of polymers like HPMC-K 100 M (DM9), Ethyl cellulose (DM10), HPC (DM11), Eudragit RSPO (DM12)

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED			
	DM9	**DM10**	**DM11**	**DM12**
0	0	0	0	0
1	21.24	18.76	15.06	11.79
2	30.66	22.63	26.98	17.86
3	42.82	38.69	33.69	26.33
4	52.30	40.21	49.98	33.13
5	60.81	57.84	52.15	41.98
6	66.90	61.60	62.13	58.72
7	73.39	67.82	70.66	68.23
8	79.73	72.85	79.75	78.98
10	80.54	86.98	88.06	81.09
12	97.17	92.19	90.33	88.19

The % drug release of DM9 to DM12 formulations depends on polymer ratio 1:1. DM10 and DM12 were unable to retard the drug release up to desired time. In DM9 formulations, HPMC-K 100 M **1:1 ratio** showed 97.17 % drug release at 12 hours.

Hence based on dissolution data of 12 formulations, DM5 (HPMC-K 100 M) Polymer formulation showed better release up to 12 hours. Among these 12 formulations DM5 shows better within the specified limits. So DM5 formulation is optimised formulation.

Application of Release Rate Kinetics to Dissolution Data

Table 7: Release kinetics data for optimized formulation (DM5)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
21.07	1	1.000	1.324	0.000	1.897	21.070	0.0475	-0.676	78.93	4.642	4.290	0.352
31.29	2	1.414	1.495	0.301	1.837	15.645	0.0320	-0.505	68.71	4.642	4.096	0.546
44.01	3	1.732	1.644	0.477	1.748	14.670	0.0227	-0.356	55.99	4.642	3.826	0.816
55.49	4	2.000	1.744	0.602	1.648	13.873	0.0180	-0.256	44.51	4.642	3.544	1.098
63.56	5	2.236	1.803	0.699	1.562	12.712	0.0157	-0.197	36.44	4.642	3.315	1.326
71.81	6	2.449	1.856	0.778	1.450	11.968	0.0139	-0.144	28.19	4.642	3.043	1.598
75.92	7	2.646	1.880	0.845	1.382	10.846	0.0132	-0.120	24.08	4.642	2.888	1.754
84.6	8	2.828	1.927	0.903	1.188	10.575	0.0118	-0.073	15.4	4.642	2.488	2.154
96.03	10	3.162	1.982	1.000	0.599	9.603	0.0104	-0.018	3.97	4.642	1.583	3.058
99.21	12	3.464	1.997	1.079	-0.102	8.268	0.0101	-0.003	0.79	4.642	0.924	3.717

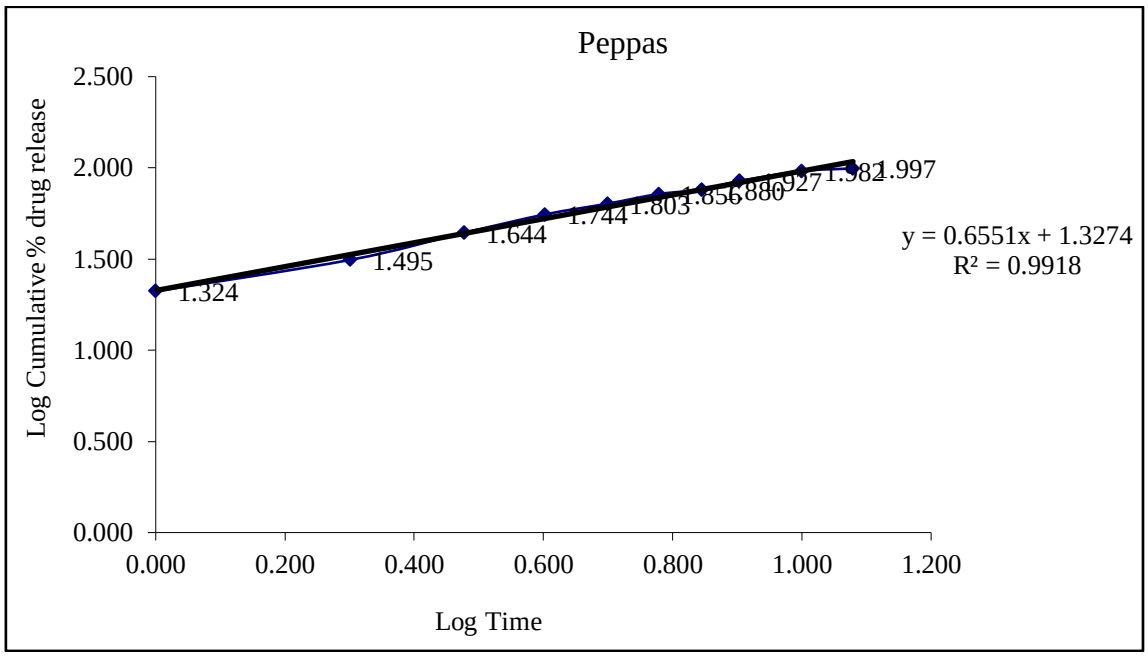

Fig 5: Graph of peppas release kinetics

CONCLUSION

Results of the present study demonstrated that SR matrix of Doxazosin mesylate prepared with polymers like Hydrophilic polymer HPMC K100 M proved to control the drug release for 12hr. The formulations contain same concentration polymers like HPC and Eudragit RSPO are not retard the drug release up to 12Hrs. The optimized formulation kinetic parameters were evaluated it follows the peppas release kinetics.

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