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Formulation and invitro evaluation of tramadol extended release tablets.

Chaitanya K*, Dr D. Ramakrishna

Sushrut Institute of Pharmacy, Taddanapally village, Pulkal madal, Medak, Sangareddy.

***Corresponding author: Chaitanya K**

Email Id- chaitanyakaleru99@gmail.com

ABSTRACT

In the present work "Formulation and Evaluation of tramadol Extended Release Tablets" was undertaken. Wet granulation method was formulated. Granules were evaluated for tests such as bulk density, Tapped density, Compressibility Index and Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness and friability, in-vitro dissolution tests were performed and percentage drug release was calculated. Dissolution tests were performed and percentage drug release was calculated. Dissolution profile of Formulation – F6 was optimized based on evaluation parameters. In the dissolution modeling all the developed formulations followed Korsemeyer-peppas drug release. The optimized formulation F6 followed Korsemeyer-peppas drug release drug release and non-Fickian model. The developed formulation was tested for its stability for three months and found to be stable[1].

Keywords: Wet granulation method, Polymethacrylates and Hausner ratio

INTRODUCTION

The oral route of drug delivery is one of the most convenient means to administer drug to the human body to obtain the desired therapeutic effect. Though it is a convenient route it provides several challenges to the formulator to design a medication such that it provides the drug in an optimum concentration needed to attain a plasma level of the drug which will fall within the therapeutic window to obtain the desired effect.

Modified release drug delivery systems[3]

The *United States Pharmacopoeia* definition of an Modified Release system is that:

"The drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms[4]".

These may be divided conveniently in to four categories

1. Delayed release
2. Controlled release
   a) Sustained release
   b) Extended release
3. Site specific targeting
4. Receptor targeting

Controlled release systems

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be temporal or spatial nature, or both, of drug release in the body, or other words, the system is successful at

maintaining constant drug levels in the target tissue of cells[2].

Sustained release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time[3].

Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds[7].

AIM AND OBJECTIVE

Aim

The aim of the present study was to design and evaluate extended release tablets of Tramadol based on matrix tablets.

Objectives

Tramadol is used to treat moderate to moderately severe pain. It has two different mechanisms. First, it binds to the μ-opioid receptor. Second, it inhibits the reuptake of serotonin and norepinephrine[8].

1. To develop the extended release system over a period of time.
2. Increased patient compliance by reducing the dose frequency
3. To achieve this goal various trials are to be taken and evaluated with respect to the various quality parameters such as dissolution and related studies.
4. To design customized pre-formulation studies to predict the formulation and process variables for preparation of Tramadol extended release tablets.

METHODOLOGY

Formulation of extended release tablet

Extended release tablets of were prepared by direct compression method.

Manufacturing Procedure

Micro crystalline cellulose, osmotic agents, PVP K30 were weighed according to the given table and sifted through 40 mesh.To the above blend Tramadol was added and sifted through 18 mesh.The sifted materials were mixed for 10min.Magnesium Stearate and talc was weighed and sifted through 40 mesh.To the powdered blend, lubricated blend was added and mixed properly.Then the total blend was compressed using 8mm round punches.

Formulations

In the formulations prepared, the release retardants included were hydroxypropylmethylcellulose[5] (HPMC K15M, HPMC K100M CR), polyethylene oxide (PEO) and ethylcellulose (EC). Microcrystalline cellulose (MCC), lactose was used as diluents. Magnesium stearate (MS) 1% and talc 2 % were used as lubricants. 5% w/v solution of polyvinylpyrrolidone (PVP-K90) in isopropyl alcohol (IPA) was used as binder.

Table 1. Composition of Matrix Tablets Containing HPMC K15M*

F.Code	TM (mg)	HPMC K15M (%)	MCC (mg)	PVP- (mg)	K90	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F1	100	12.5	qs	6		qs	1.2	2.4	120
F2	100	25	qs	6		qs	1.2	2.4	120
F3	100	37.5	qs	6		qs	1.2	2.4	120
F4	100	50	qs	6		qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F1, F2, F3, and F4 respectively.

Table 2. Composition of Matrix Tablets Containing Polyethylene Oxide

F.Code	TM (mg)	PEO (%)	MCC (mg)	PVP-	K90 (mg)	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F5	100	12.5	qs	6		qs	1.2	2.4	400
F6	100	25	qs	6		qs	1.2	2.4	400
F7	100	37.5	qs	6		qs	1.2	2.4	400
F8	100	50	qs	6		qs	1.2	2.4	400

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F5, F6, F7, and F8 respectively.

Table 3. Composition of Matrix Tablets Containing HPMC K100M CR*

F.Code	TM (mg)	HPMC K 100M (%)	MCC (mg)	PVP- (mg)	K90	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F9	100	12.5	qs	6		qs	1.2	2.4	400
F10	100	25	qs	6		qs	1.2	2.4	400
F11	100	37.5	qs	6		qs	1.2	2.4	400
F12	100	50	qs	6		qs	1.2	2.4	400

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F9, F10, F11, and F12 respectively.

RESULTS AND DISCUSSION

Drug and excipient compatibility studies

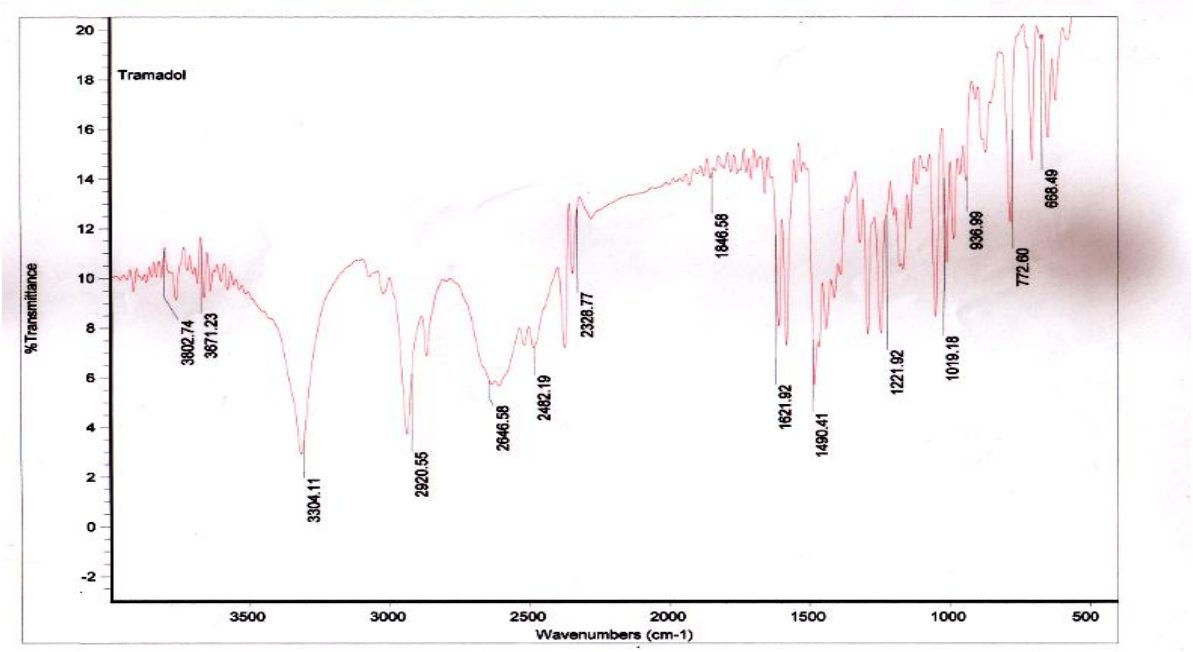

FIG No: 1 FTIR Spectra of Tramadol pure drug

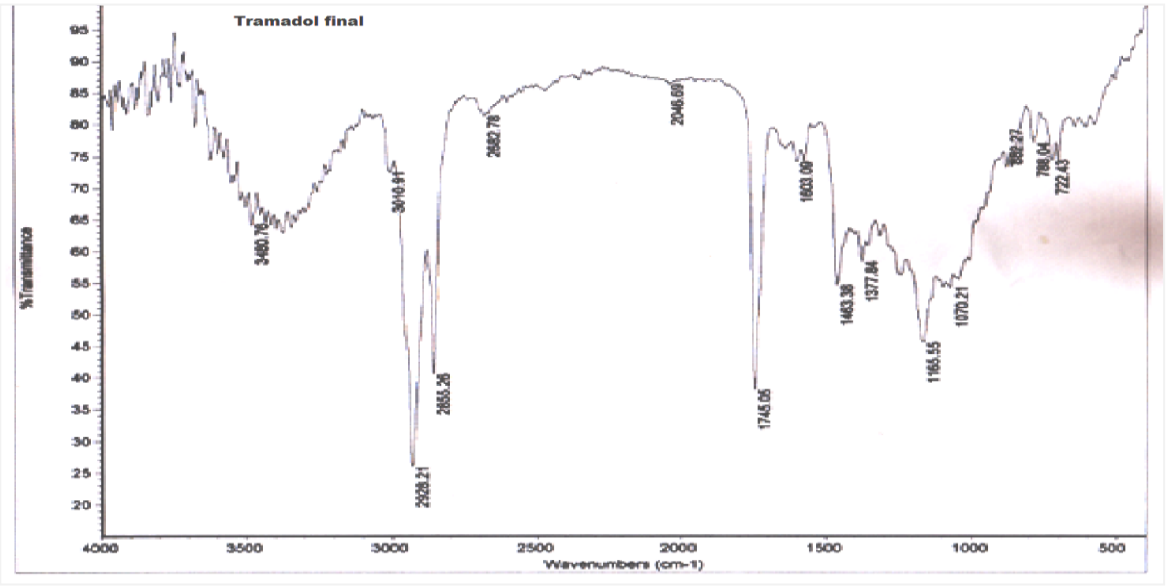

FIG No: 2 FTIR Spectra of Tramadol optimized formulation

Preformulation parameters

Table: 4 Preformulation parameters of Tramadol tablets

S.no	Formulations	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Angle of repose θ	Haunser ratio
1	**F1**	0.43	0.49	12.24	22.7	1.14
2	**F2**	0.41	0.47	12.77	25.7	1.15
3	**F3**	0.46	0.53	13.21	26.1	1.15
4	**F4**	0.44	0.51	13.73	25.9	1.16
5	**F5**	0.40	0.47	14.89	24.3	1.18
6	**F6**	0.37	0.43	13.95	26.6	1.16
7	**F7**	0.41	0.48	14.58	25.5	1.17
8	**F8**	0.34	0.39	12.82	24.9	1.15
9	**F9**	0.38	0.44	13.64	26.6	1.16
10	**F10**	0.33	0.38	13.16	28.5	1.15
11	**F11**	0.40	0.47	14.89	24.3	1.18
12	**F12**	0.37	0.43	13.95	26.6	1.16

The entire formulations blend was evaluated. The results were shown in the Table No 4, All these are within the limit.

Post formulation parameters

Table: 5 Post formulation parameters of tablets

Formula code	Hardness (Kg/cm^2)	AvgWeight mg)	Thickness (mm)	Friability (%)	Drug content (%)
F1	6.0	401	2.22	0.35	99.7
F2	6.6	402	2.12	0.32	98.8
F3	6.1	400	2.20	0.34	99.4

F4	6.2	398	2.19	0.37	99.1
F5	6.4	401	2.15	0.33	98.6
F6	6.3	400	2.17	0.42	98.3
F7	6.5	399	2.14	0.39	99.5
F8	6.7	401	2.11	0.34	98.2
F9	6.4	400	2.16	0.42	99.0
F10	6.5	399	2.13	0.38	99.3
F11	6.5	399	2.14	0.39	99.5
F12	6.2	398	2.19	0.37	99.1

In vitro dissolution studies

Table: 6Dissolution data of formulation F1-F12

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	36.1	17.5	21.0	35.7	19.8	20.6	14.3	18.4	38.7	25.0	28.2	20.0
2	42.4	21.8	29.4	44.0	27.3	29.3	26.4	34.8	41.0	34.1	35.6	30.4
3	63.7	25.6	48.9	56.1	38.4	36.8	98.2	56.1	79.5	46.9	48.2	49.9
4	78.9	59.4	54.8	68.8	45.9	44.2	--	103.4	99.2	57.2	55.6	56.8
6	86.3	78.4	74.5	76.3	56.4	59.1	--	--	--	63.3	62.4	79.5
8	98.5	89.6	86.8	82.5	68.1	64.1	--	--	--	66.1	79.3	89.8
12	--	99.2	97.2	89.5	77.3	76.5	--	--	--	74.6	86.2	99.2
16	--	--	--	99.6	89.4	92.4	--	--	--	99.4	99.5	--
20	--	--	--	--	99.8	97.1	--	--	--	--	--	--
24	--	--	--	--	--	100.2	--	--	--	--	--	--

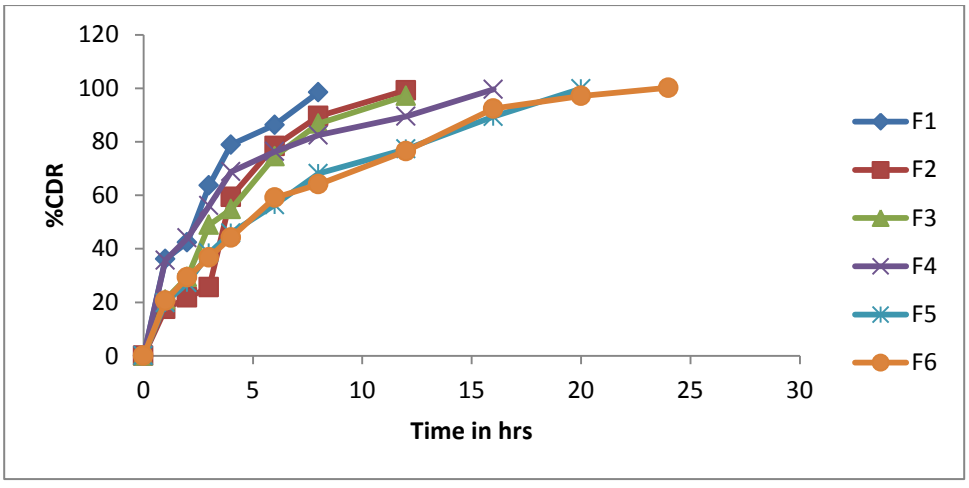

Fig No.3 Dissolution profile of Formulations F1 and F6

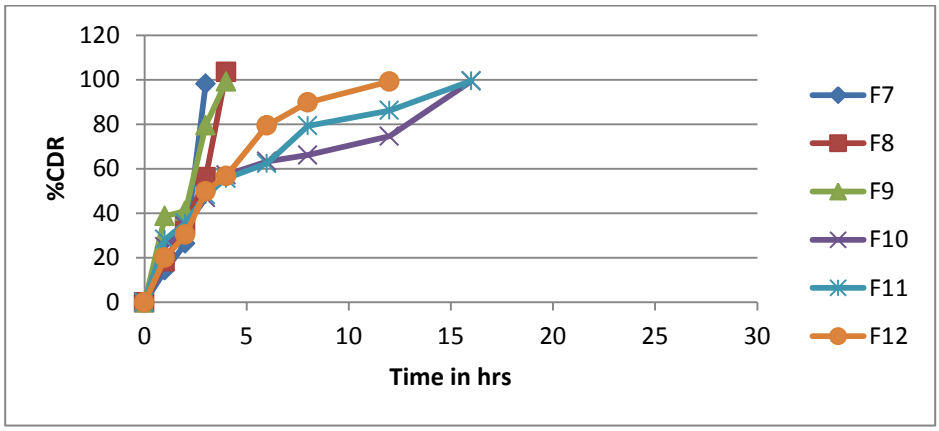

Fig No.4 Dissolution profile of Formulations F7and F12

DISCUSSION

All the formulations evaluated for preformulations, all the formulations are within the limits. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 6.0 to 6.7 kg/sq cm. Friability values below 1% were an indication of good mechanical resistance of the tablets.

All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight variation in all theNine formulations was found to be 398 to 402 mg, which was in pharmacopoeial limits of ±5% of the average weight.

The percentage drug content of all the tablets was found to be between 98.2 to 99.7 % of Tramadol which was within the acceptable limits.

Kinetic studies for optimized formulation

Table no: 7 Release kinetics for the optimized formulation F6

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	4.227962963	-0.063258255	21.3693521	1.207730615
Intercept	0.833641975	2.166610516	-16.87673946	0.419307821
Correlation	0.996837882	-0.923901295	0.963694821	0.956451967
R 2	0.993685763	0.853593602	0.928707708	0.914800364

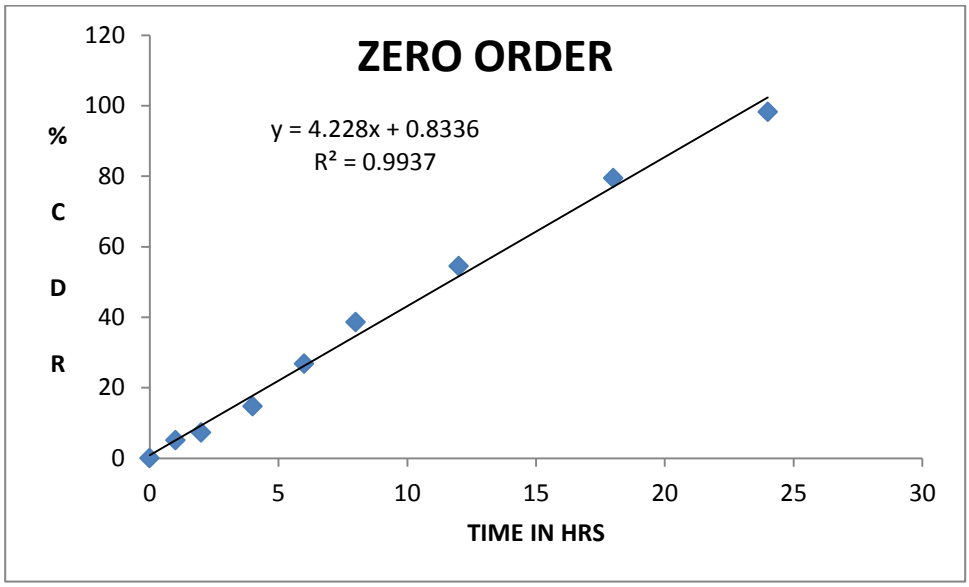

Fig no: 5 Zero order plot for optimized formulation F6

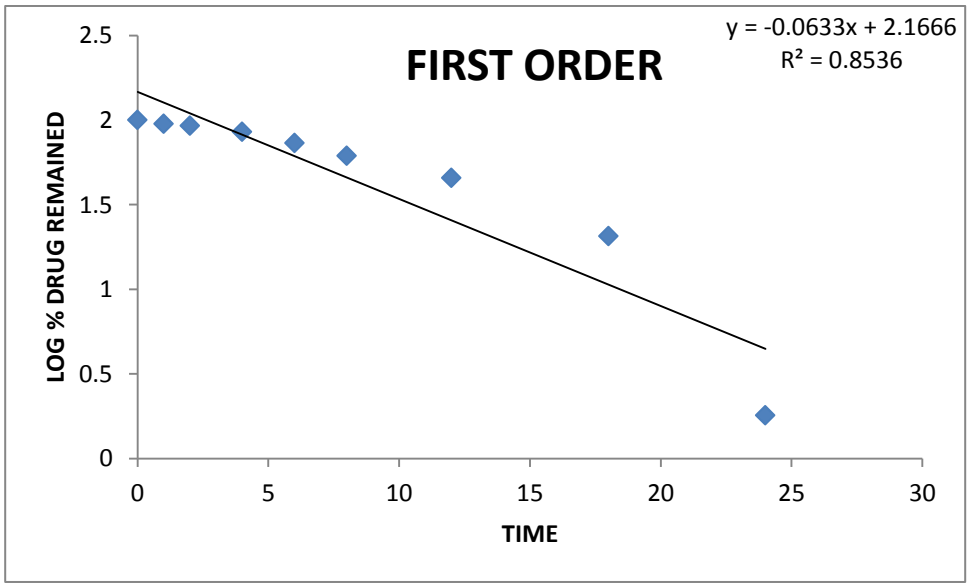

Fig no: 6 first order plot for optimized formulation F6

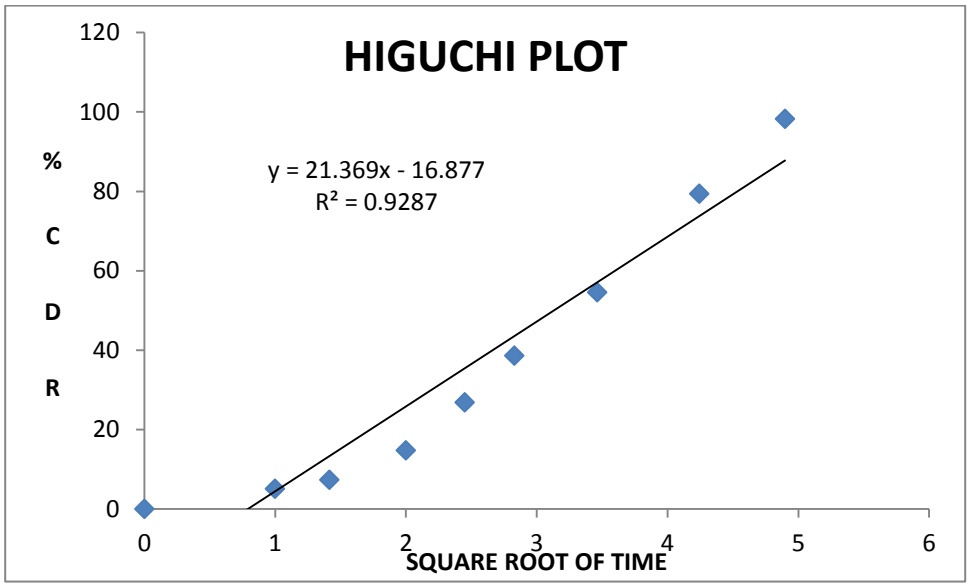

Fig no: 7 Higuchi plot for optimized formulation F6

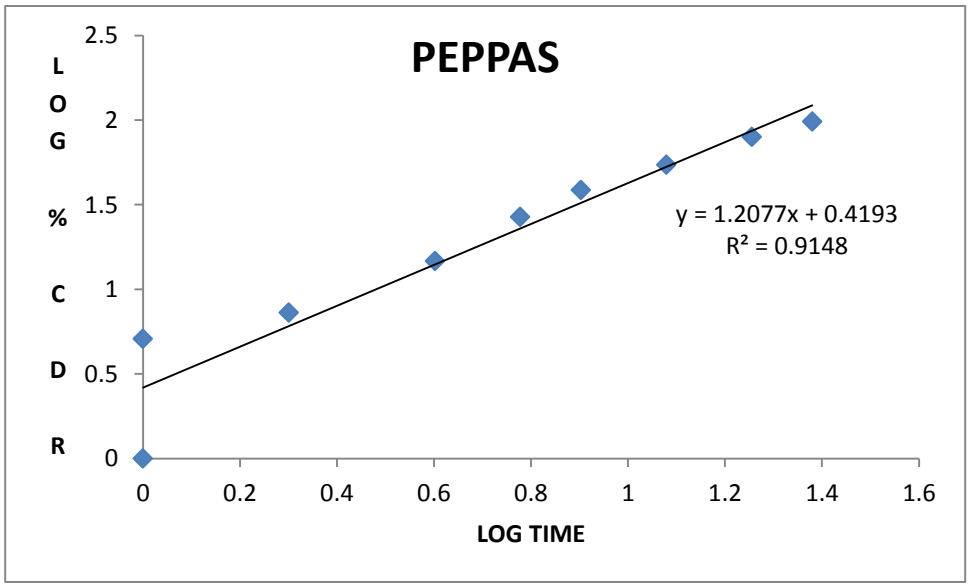

Fig no: 8 Peppas plot for optimized formulation F6

CONCLUSION

The following conclusion could be drawn from the research work carried out from the project:Extended release tablets for Tramadol could be successfully prepared with different polymers in different concentration.In vitro release studies were carried out for all formulations to quantify percentage cumulative release of drug. Based on the drug release profile suitable formulation was selected. The Formulationno-6 containing drug and polymer concentration has shown 100.2% of drug release in 24 hours and the drug release followed in zero order kinetics.Formulations of extended tablets shown increased drug release rate with an increase in polymer concentration.There is a good scope for the development of extended release tablets for this drug.

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