FORMULATION AND EVALUATION OF RISPERIDONE SUSTAINED RELEASE TABLETS

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ABSTRACT : Risperidone is characterized by its effectiveness againsts both positive and negative symptoms of schizophrenia. Furthermore, it produces fewer side effects, including extra pyramidal side effects, than conventional antipsychotic drugs.The present investigation concerns the formulation and evaluation of sustained release tablets of Risperidone which, after oral administration, are designed to prolong the gastric residence time and increase drug bioavailability. The aim of the present study was to develop extended release formulation of Risperidone to maintain constant therapeutic levels of the drug for over 12 hrs. Different grades of HPMC and Sodium CMC were employed as polymers. Risperidone dose was fixed as 4 mg. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Where as from the dissolution studies it was evident that the formulation (F5) showed better and desired drug release pattern i.e., 98.10 % in 12 hours. It contains the HPMC K15M polymer as extended release material.It followed peppas release kinetics mechanism (n=0.57 non fickian rule).
Keywords: Risperidone, HPMC and Sodium CMC, Extended release tablets.

I.INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counter part conventional forms that may have to take three or four times daily to achieve the same therapeutic effect.[1] 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.[2] 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.[3] Aim of the study is to formulate and evaluate Risperidone Sustained release tablets using different polymers such as Sodium CMC and various grades of HPMC Micro crystalline cellulose as diluents.[4] Risperidone (RSP) is one of presentative atypical antipsychotic drugs which have a potent antagonist effect on serotonin 5-HT2 and dopamineD2 receptors. This drug is characterized by its effectiveness against both positive and negative symptoms of schizophrenia. Furthermore, it produces fewer side effects, including extra pyramidal side effects, than conventional antipsychotic drugs[5]. Blockade of dopaminergic D2 receptors in the limbic system alleviates positive symptoms of schizophrenia such as hallucinations, delusions, and erratic behavior and speech. Blockade of serotonergic 5-HT_2 receptors in the mesocortical tract, causes an excess of dopamine and an increase in dopamine transmission, resulting in an increase in dopamine transmission and an elimination of core negative symptoms.[6] Dopamine receptors in the nigrostriatal pathway are not affected by risperidone and extrapyramidal effects are avoided. Like other 5-HT_2 antagonists, risperidone also binds at alpha(1)-adrenergic receptors and, to a lesser extent, at histamine H1 and alpha(2)-adrenergic receptors.[7]

II. MATERIALS AND METHODS

2.1MATERIALS

Risperidone was collected as a gift sample from sura Labs, and various polymers like HPMC k4M, HPMC K15M, Sodium CMC and other excipients were purchased from Merck Specialities Pvt Ltd, Mumbai, India.

2.2 METHODOLOGY

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes[8].

Formulation development of Tablets[9]:

All the formulations were prepared by direct compression. The compositions of different formulations.The tablets were prepared as per the procedure given below and aim is to prolong the release of Risperidone. Total weight of the tablet was considered as 150mg.

Procedure:

1) Risperidone and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table : 1 Formulation composition for tablets

Formulation No.	Risperidone	HPMC k15M	HPMC K100M	Sodium CMC	Mag. Stearate	Talc	MCC pH 102
F1	4	15	-	-	2	2	QS
F2	4	30	-	-	2	2	QS
F3	4	45	-	-	2	2	QS
F4	4	-	15	-	2	2	QS
F5	4	-	30	-	2	2	QS
F6	4	-	45	-	2	2	QS
F7	4	-	-	15	2	2	QS
F8	4	-	-	30	2	2	QS
F9	4	-	-	45	2	2	QS

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets[10,11,12]

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness', friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. the average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristics in reproducing appearance.Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask

containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium 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 and then the media 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from up to 12 hrs at 50 rpm. At definite time intervals with drawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 271 nm using UV-spectrophotometer.[13]

Application of Release Rate Kinetics to Dissolution Data[14,15]:

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, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the following equations.

$$F = K_o\, t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics:

The release rate data are fitted to the following equation

$$\text{Log}\,(100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\, t1/2$$

Where, 'k' is the Higuchi constant.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/\, M_\infty = K\, t^n$$

Where, $M_t/\, M_\infty$ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log ($M_t/\, M_\infty$) versus log (time) is linear.

Hixson-Crowell release model:

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

III. RESULTS AND DISCUSSION

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

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 0.48±0.05 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57±0.02 to 0.69±0.04 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

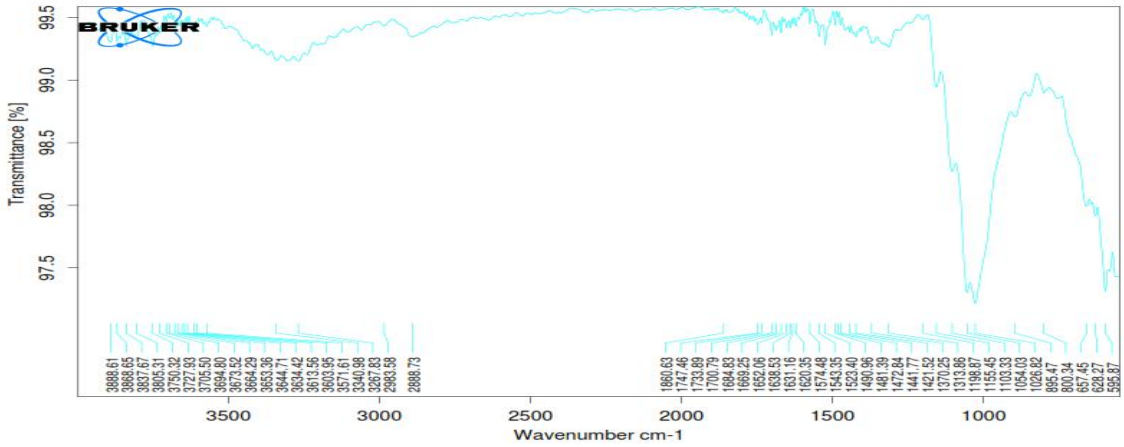

Figure :1 FT-IR Spectrum of Risperidone pure drug.

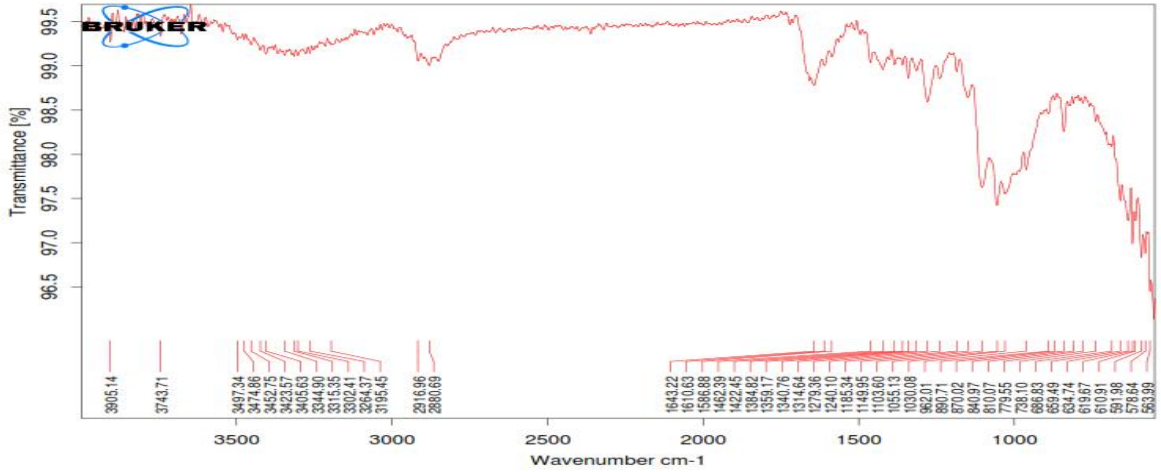

Figure : 2 FT-IR Spectrum of Optimized Formulation

Preformulation parameters of powder blend

Table : 2 Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.07	0.57±0.01	16.21±0.06	1.16±0.06
F2	25.67	0.56±0.06	0.62±0.05	16.87±0.05	1.07±0.05
F3	25.54	0.52±0.03	0.68±0.07	17.11±0.01	1.20±0.03
F4	25.43	0.54±0.04	0.64±0.08	17.67±0.08	1.18±0.04
F5	25.34	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.56±0.05	0.66±0.06	17.65±0.09	1.17±0.09
F7	25.18	0.58±0.06	0.69±0.04	16.43±0.05	1.18±0.03
F8	24.22	0.48±0.05	0.57±0.02	17.97±0.02	1.18±0.09
F9	25.05	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	148.6±1.13	4.5±0.02	0.57±0.05	3.48±0.07	98.69±0.15
F2	150.6±1.53	4.5±0.04	0.61±0.05	3.39±0.02	99.45±0.24
F3	149.6±2.15	4.4±0.05	0.67±0.04	3.62±0.02	98.34±0.042
F4	150.6±0.35	4.5±0.02	0.75±0.06	3.42±0.04	99.87±0.25
F5	152.4±1.52	4.4±0.05	0.66±0.07	3.65±0.05	99.74±0.31
F6	149.7±1.31	4.5±0.021	0.55±0.08	3.47±0.01	101.56±0.41
F7	148.3±1.24	4.5±0.36	0.61±0.02	3.34±0.06	99.42±0.52
F8	151.2±2.03	4.4±0.04	0.59±0.08	3.67±0.08	99.89±0.36
F9	150.3±1.95	4.5±0.06	0.65±0.06	3.56±0.05	100.94±0.16

Table : 3 Invitro quality control parameters for tablets

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 7.4. The average weight of the tablet is approximately in range of 148.3±1.24 to 152.4± 1.52 mg, so the permissible limit is ±7.5% (<250 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 7.4. The results showed that the hardness of the tablets is in range of 4 to 4.5 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper. The result showed that thickness of the tablet is from 3.34 ±0.06 to 3.67±0.08 mm.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 7.4. The average friability of all the formulations lies in the range of 0.55±0.08 to 0.65±0.06% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 98.34±0.042 -101.56±0.41 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In-Vitro Drug Release Studies

Table : 4 Dissolution Data of Risperidone Tablets Prepared With HPMC K 4M In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F1	F2	F3
0	0	0	0
0.5	26.5	23.1	17.4
1	48.7	34.4	25.7
2	7645	48.3	33.6
3	99.4	55.3	42.4
4		67.3	51.4

5		80.4	58.4
6		98.34	66.4
7			72.5
8			83.3
9			90.45
10			100.21
11			
12			

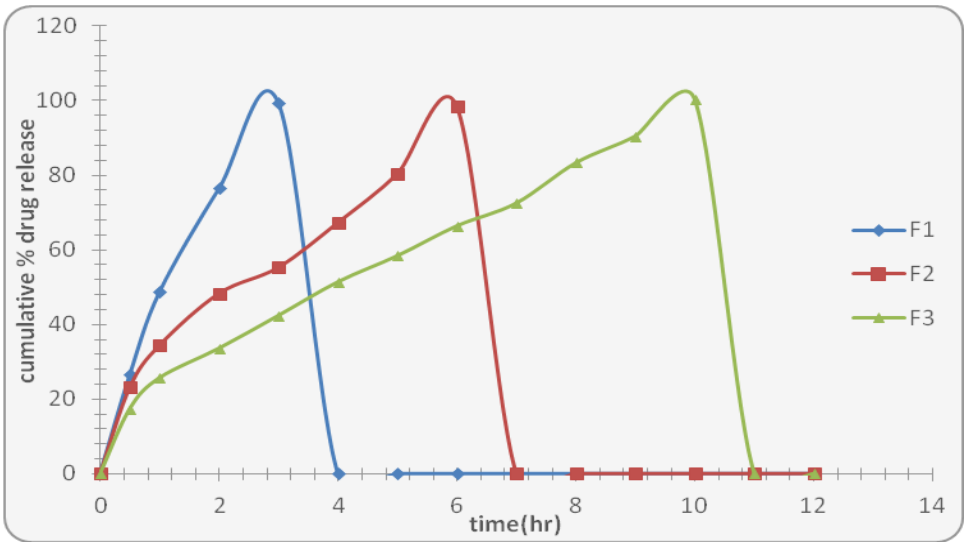

Fig :3 Dissolution profile of Risperidone (F1, F2, F3 formulations).

Table 5 : Dissolution Data of Risperidone Tablets Prepared With HPMC K15 M In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F4	**F5**	**F6**
0	0	0	0
0.5	20.25	15.42	10.62
1	37.26	19.86	15.86
2	52.16	25.35	21.35
3	68.01	30.45	25.45
4	88.26	39.8	30.8
5	97.1	47.25	36.25
6		58.24	43.24
7		65.73	48.73
8		71.34	54.34
9		77.52	58.52
10		80.17	65.17
11		89.1	69.1
12		98.4	78.4

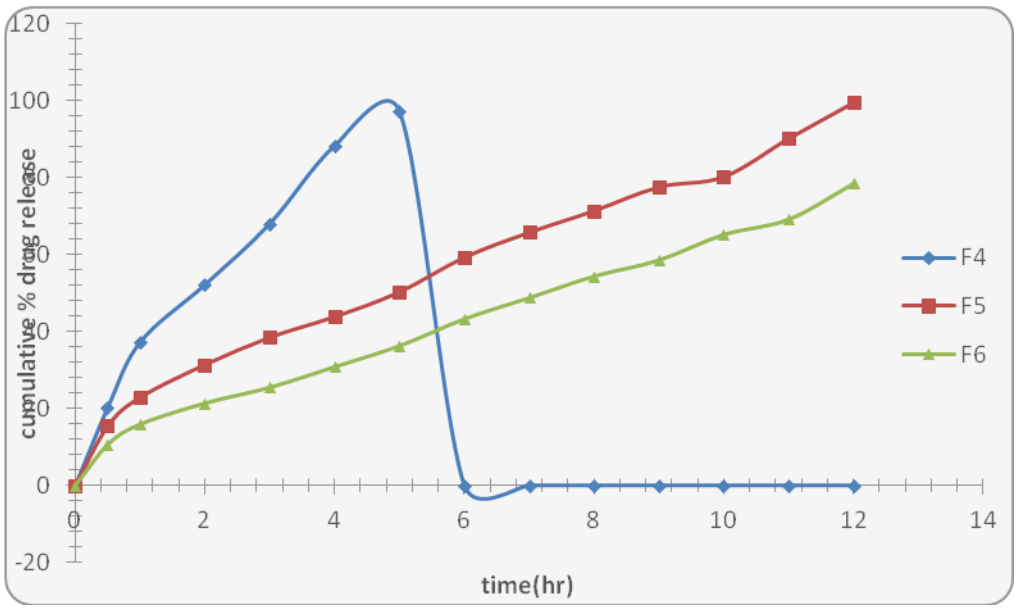

Fig:4 Dissolution profile of Risperidone (F4, F5, F6 formulations)

Table :6 Dissolution Data of Risperidone Tablets Prepared With Sodium CMC In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED		
	F7	F8	F9
0	0	0	0
0.5	30.4	27.4	24.5
1	46.5	35.6	32.5
2	68.6	41.4	38.4
3	79.5	56.7	43.4
4	88.5	62.4	48.2
5		79.6	54.8
6		85.3	60.2
7		97.3	68.8
8			75.4
9			83.34
10			98.27
11			
12			

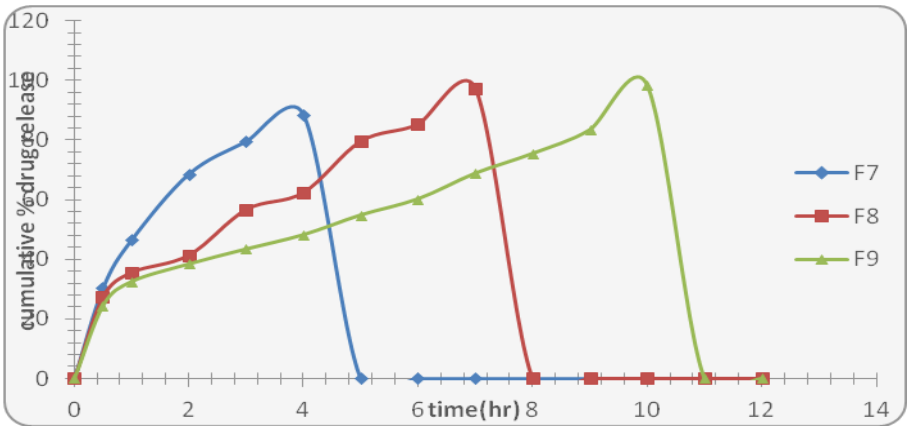

Fig :5 Dissolution profile of Risperidone (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with HPMC K 4M as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Where as the formulations prepared with HPMC K15 M retarded the drug release in the concentration of 30 mg (F5 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.4% in 12 hours with good retardation. The formulations prepared with Sodium CMC were un able to retard up to 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data:

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, and Korsmeyer-Peppas release model.

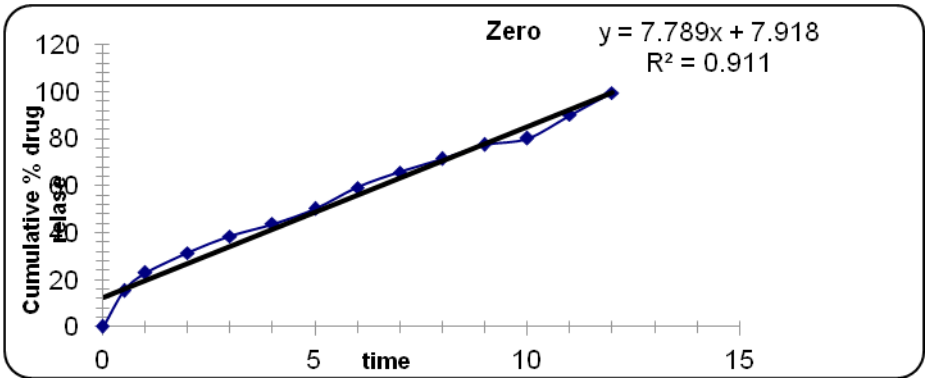

Fig : 6 Zero order release kinetics graph

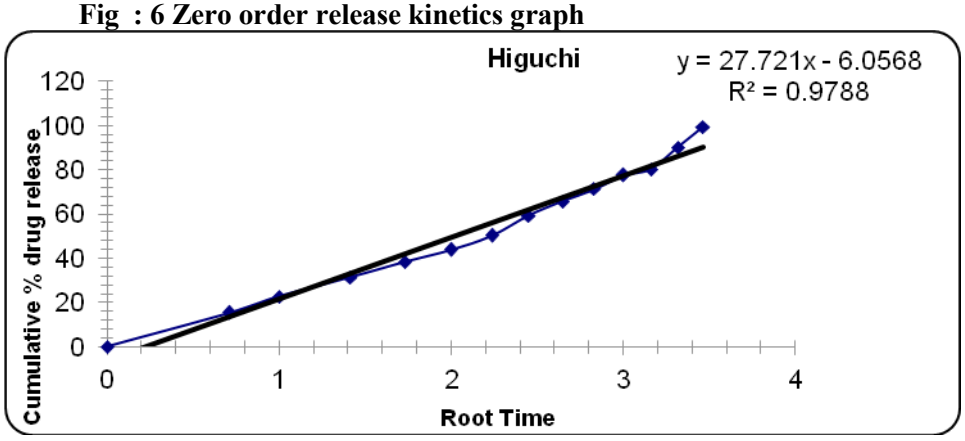

Fig :7 Higuchi release kinetics graph

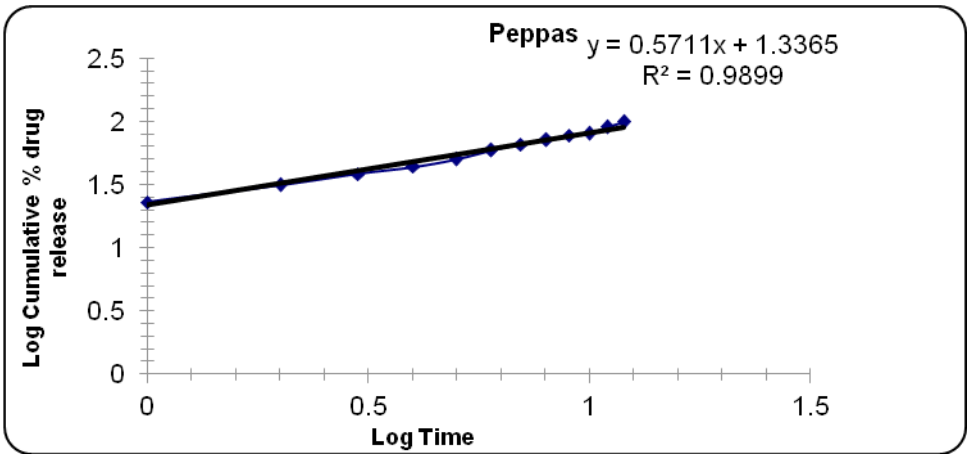

Fig : 8 Kars mayer peppas graph

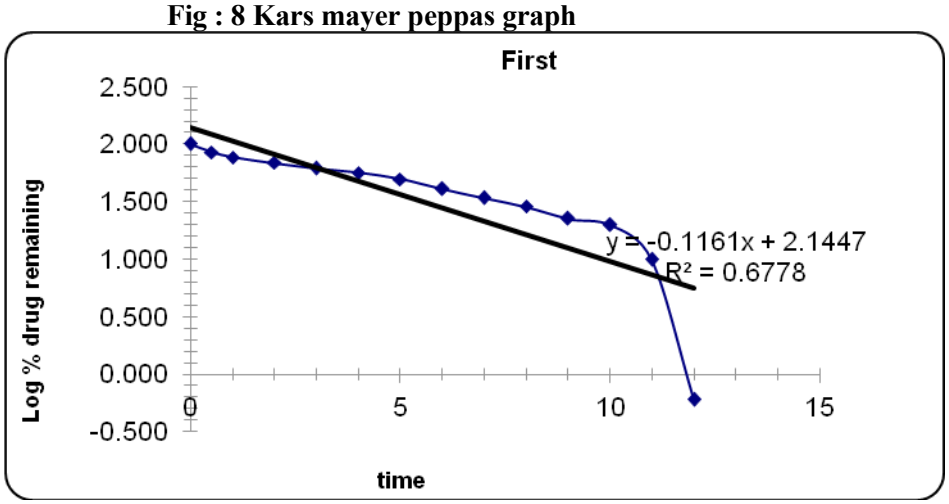

Fig : 9 First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed peppas order release kinetics.

IV.CONCLUSION

The aim of the present study was to develop extended release formulation of Risperidone to maintain constant therapeutic levels of the drug for over 12 hrs. Different grades of HPMC and Sodium CMC were employed as polymers. Risperidone dose was fixed as 4 mg. 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 (F5) showed better and desired drug release pattern i.e., 98.10 % in 12 hours. It contains the HPMC K15M polymer as extended release material. It followed peppas release kinetics mechanism (n=0.57 non fickian rule).

Sustained release tablet formulation was needed for Risperidone because there is a less risk of dose dumping, less inter and intra subject variability ,high degree of dispersion in the digestive tract minimizing the risk of high local drug interactions. The basic approach was to select rate controlling polymers and formulate Sustained release tablets.

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