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BROMOCRIPTINE MESYLATE- EFFERVESCENT FLOATING TABLETS

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ABSTARCT

In the present research work was carried out to formulate Bromocriptine Mesylate- Effervescent Floating Tablets by using various polymers. Among all the formulations the formulations prepared by using Methocel K15 were unable to produce desired drug release; they were unable to retard drug release up to 12 hours. The formulations prepared with Methocel K4 M retarded the drug release up to 12 hours in the concentration of 7.5 mg (BR3). The formulations prepared with Gellan gum were also retarded the drug release for more than 12 hours. Hence they were not considere. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed peppas mechanism of drug release.

KEYWORDS: Bromocriptine mesylate, Gellan gum, Methocel K4 M, Methocel K15 M and Floating tablets.

INTRODUCTION

Controlled release dosage forms is the part of modified drug release dosage form which covers a wide range of prolonged action which provide continuous release of their active ingredients at predetermined rate and predetermined time.[1,2] Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying

time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine) Out of various controlled drug delivery systems floating drug delivery system utilizes principle of gastric retention time of the dosage forms at the stomach and upper part of the small intestine and suitable for the drug having site-specific absorption from the above sites and control the delivery of active ingredients. Floating Drug Delivery System (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. While the system is floating on the gastric content, the drug is released slowly at the desired rate from the system.

AIM AND OBJECTIVE

Aim of the Work

Aim of the study is to formulate and evaluate Bromocryptine mesylate effervescent tablets using different polymers Methocel K 4M, Methocel K 15M, Gellan gum and Sod. Bicarbonate, Mag.stearate, Talc indifferent ratios.

METHODOLOGY

Analytical method development

Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.[1,3]

Preparation calibration curve

100mg of Bromocriptine mesylate pure drug was dissolved in 100ml of 0.1N HCl (stock solution) 10ml of solution was taken and make up with100ml of 0.1N HCl (100µg/ml).[5] From this 10ml was taken and make up with 100 ml of 0.1N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 1,2,3,4 and 5µg/ml of Bromocriptine mesylate per ml of solution. The absorbance of the above dilutions was measured at 266 nm 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.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends.[6,7] There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

Bulk density

Tapped density

Measures of powder compressibility

Formulation development of Tablets[8]

All the formulations were prepared by direct compression. The compression of different formulations are given in Table 6.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Bromocriptine mesylate. Total weight of the tablet was considered as 300mg.

Procedure

1) Bromocriptine mesylate 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.

Optimization of Sodium bicarbonate concentration

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on that, the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Table. 1: Optimization sodium bicarbonate concentration.

S. No	Excipient Name	EBR1	EBR2	EBR3
1	Bromocriptine mesylate	2.5	2.5	2.5
2	Methocel K15 M	5	5	5
4	$NaHCO_3$	5	10	15
5	Mg.Stearate	3	3	3
6	Talc	3	3	3
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	60	60	60

All the quantities were in mg.

Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.

Table. 2: Formulation composition for floating tablets.

Formulation No.	Bromocriptine mesylate	Methocel K 4 M	Methocel K 15 M	Gellan gum	$NaHCO_3$	Mag. Stearate	Talc	MCC pH 102
BR1	2.5	2.5	-----	-----	10	3	3	QS
BR2	2.5	5	-----	-----	10	3	3	QS
BR3	2.5	7.5	-----	-----	10	3	3	QS
BR4	2.5	-----	2.5	-----	10	3	3	QS
BR5	2.5	-----	5	-----	10	3	3	QS
BR6	2.5	-----	7.5	-----	10	3	3	QS
BR7	2.5	-----	-----	2.5	10	3	3	QS
BR8	2.5	-----	-----	5	10	3	3	QS
BR9	2.5	-----	-----	7.5	10	3	3	QS

All the quantities were in mg, Total weight is 60 mg.

Evaluation of post compression parameters for prepared Tablets

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

In vitro Buoyancy studies[9,10]

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* drug release studies**

Dissolution parameters

Apparatus -- USP-II, Paddle Method

Dissolution Medium	--	0.1 N HCl
RPM	--	75
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

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 the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm.[14] At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 266 nm using UV-spectrophotometer.

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.

RESULTS AND DISCUSSION

Analytical Method

Graphs of Bromocriptine mesylate was taken in Simulated Gastric fluid (pH 1.2) at 266 nm.

Table. 3: Observations for graph of Bromocriptine mesylate in 0.1N HCl (266 nm).

Conc [µg/l]	Abs
1	0.131
2	0.232
3	0.377
4	0.519
5	0.629
6	0.764

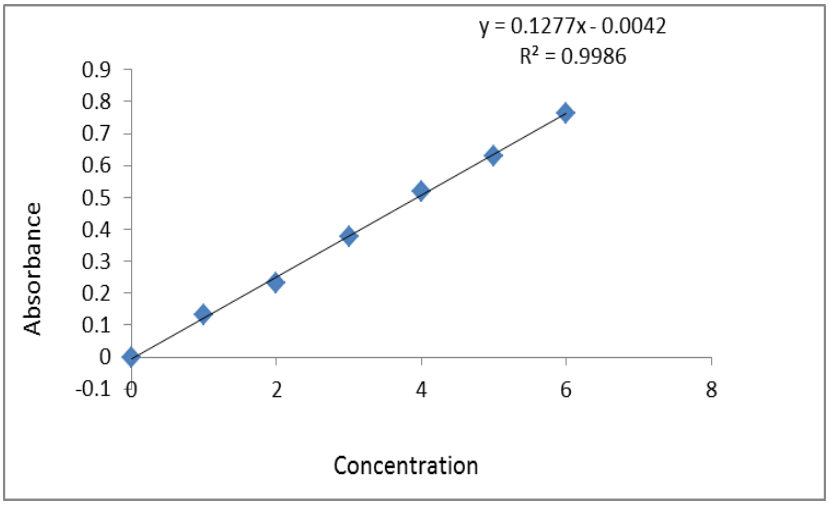

Fig. 1: Standard graph of Bromocriptine mesylate in 0.1N HCl.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy[11,12]

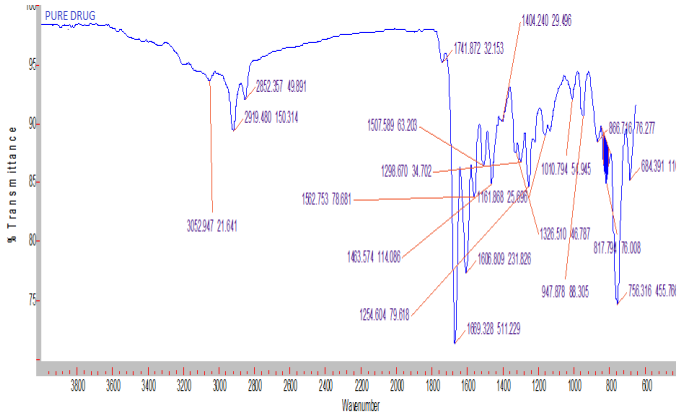

Fig. 2: FT-TR Spectrum of Bromocriptine mesylate pure drug.

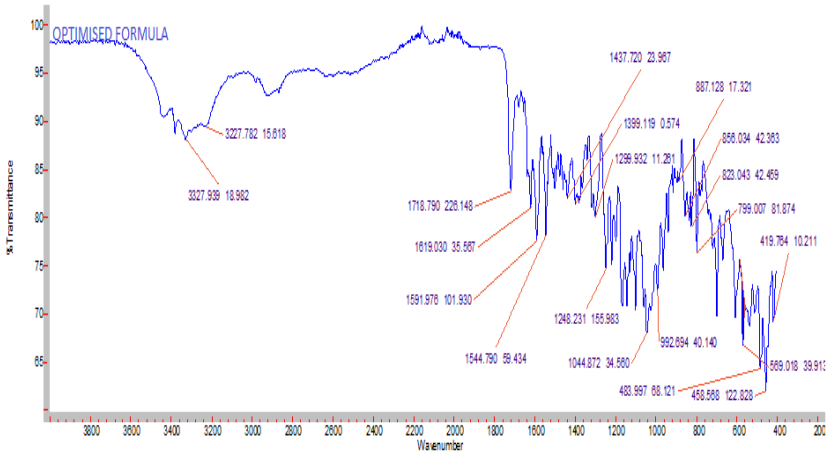

Fig. 3: FT-IR Spectrum of Optimized Formulation.

From the results of FTIR studies it was evident that the drug and excipients does not have any interactions.

Table. 4: Preformulation parameters of powder blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
BR1	24.02	0.51	0.55	16.34	1.11
BR2	25.82	0.53	0.61	16.18	0.99
BR3	23.24	0.51	0.67	17.32	0.68
BR4	24.23	0.56	0.62	17.61	1.04
BR5	25.21	0.52	0.65	16.88	1.22
BR6	24.11	0.55	0.62	17.26	1.07
BR7	26.06	0.57	0.67	16.33	0.85
BR8	26.52	0.42	0.58	17.91	1.14
BR9	25.49	0.52	0.61	17.64	1.18

Pre-formulation parameters of blend

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 0.42 to 0.57 (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 0.55 to 0.67 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging" between 16 to 18 which show 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.

Optimization of sodium bicarbonate concentration

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 75mg concentration "showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

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 tablets.

Table. 5: Invitro quality control "parameters for tablets.

Formulation code	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)
BR1	62.5	3.5	0.53	4.8	98.34	4.1
BR2	65.4	3.2	0.52	3.9	99.67	4.4
BR3	58.6	3.4	0.53	3.9	98.42	4.2
BR4	60.6	3.5	0.54	3.9	99.74	4.0
BR5	69.4	3.4	0.55	3.7	98.16	4.2
BR6	60.7	3.2	0.48	3.5	99.54	4.4
BR7	62.3	3.1	0.50	3.4	98.23	4.4
BR8	61.2	3.3	0.48	3.7	98.58	4.6
BR9	58.3	3.5	0.52	3.6	98.72	4.5

Invitro quality control parameters for tablets: 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. 6: Dissolution Data of Bromocriptine mesylate Tablets Prepared With Methocel K4M In Different Concentrations.

TIME (hr)	Cumulative Percent Drug Released		
	BR1	BR2	BR3
0.5	9.77	12.14	9.21
1	17.51	23.16	21.8
2	23.4	28.77	29.21
3	28.14	32.47	35.11
4	32.11	38.64	39.45
5	36.97	42.97	48.21
6	41.97	46.12	53.77
7	48.79	50.77	59.34
8	52.77	52.74	65.77
9	55.94	58.44	72.64
10	61.87	75.32	89.54
11	69.77	85.11	93.11
12	85.22	95.21	97.45

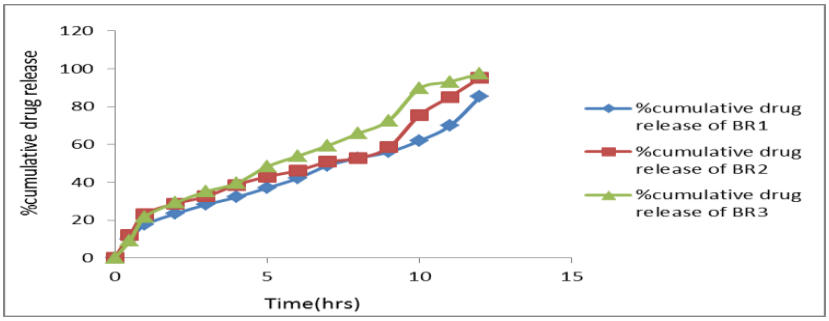

Fig. 4: Dissolution profile of Bromocriptine mesylate floating tablets (BR1, BR2, BR3 formulations).

Table. 7: Dissolution Data of Bromocriptine mesylate Tablets Prepared With Methocel K15M In Different Concentrations.

Time (hr)	Cumulative Percent Drug Released		
	BR4	BR5	BR6
0.5	14.21	8.11	5.12
1	21.55	17.5	10.22
2	22.47	22.85	18.21
3	35.11	28.14	28.77
4	40.94	33.14	34.57
5	45.71	36.47	36.11
6	55.87	42.64	39.14
7	59.44	49.66	42.15
8	61.47	52.77	46.78
9	69.14	56.52	49.14
10	73.41	62.99	59.14
11	79.41	68.14	69.14
12	83.41	88.34	76.12

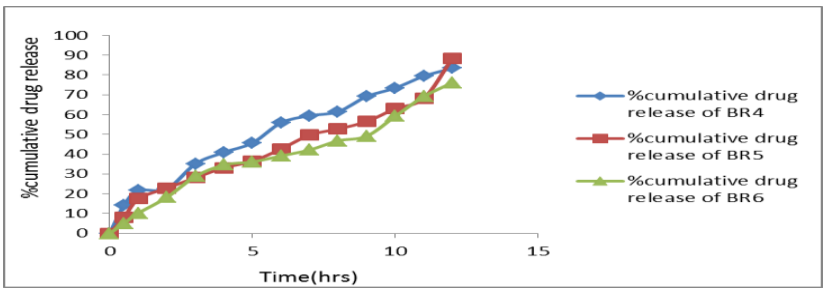

Fig. 5: Dissolution profile of Bromocriptine mesylate floating tablets (BR4, BR5, BR6 formulations).

Table. 8: Dissolution Data of Bromocriptine mesylate Tablets Prepared With Gellan gum In Different Concentrations.

Time (hr)	Cumulative Percent Drug Released		
	BR7	BR8	BR9
0.5	2.11	6.12	18.51
1	8.15	15.45	22.15
2	15.21	20.47	28.55
3	29.54	25.44	32.14
4	33.47	30.14	38.74
5	37.64	35.79	42.44
6	42.55	40.78	48.71
7	48.31	45.88	58.64
8	53.11	60.22	66.54
9	56.47	63.48	71.24
10	62.44	69.47	82.14
11	68.21	73.44	86.14
12	88.54	92.14	90.14

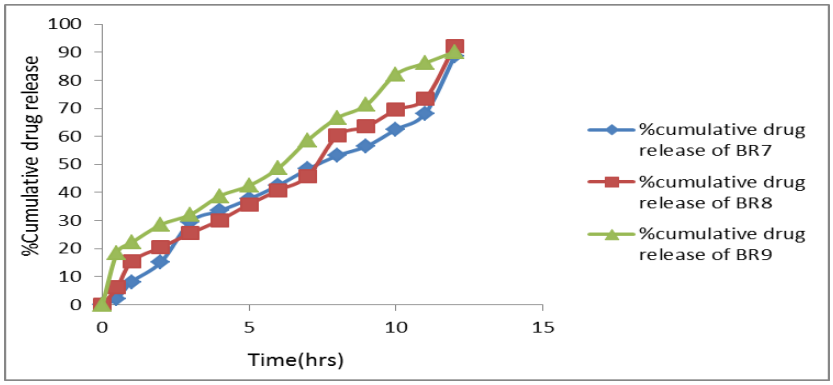

Fig. 6: Dissolution profile of Bromocriptine mesylate floating tablets (BR7, BR8, BR9 formulations).

From the dissolution data it was evident that the formulations prepared with Methocel K4M retarded the drug release in the concentration of 7.5 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 97.45% in 12 hours (Formulation BR3) with good floating lag time and floating buoyancy time. The formulations prepared with Guar gum showed more retardation even after 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.

Table. 9: Release kinetics data for optimised formulation (BR6).

Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	LOG (T)	Log (%) Remain
0	**0**	0			2.000
9.21	0.5	0.000	0.964	0.000	1.958
21.8	1	1.000	1.338	0.000	1.893
29.21	2	1.414	1.466	0.301	1.850
35.11	3	1.732	1.545	0.477	1.812
39.45	4	2.000	1.596	0.602	1.782
48.21	5	2.236	1.683	0.699	1.714
53.77	6	2.449	1.731	0.778	1.665
59.34	7	2.646	1.773	0.845	1.609
65.77	8	2.828	1.818	0.903	1.534
72.64	9	3.000	1.861	0.954	1.437
89.54	10	3.162	1.952	1.000	1.020
93.11	11	3.317	1.969	1.041	0.838
97.45	12	3.464	1.989	1.079	0.407

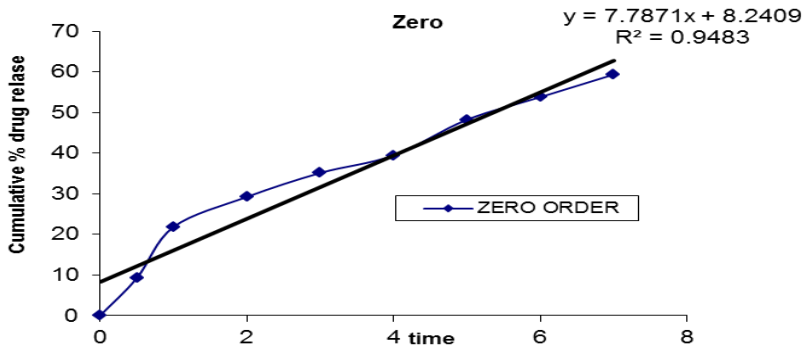

Fig. 7: Zero order release kinetics graph.

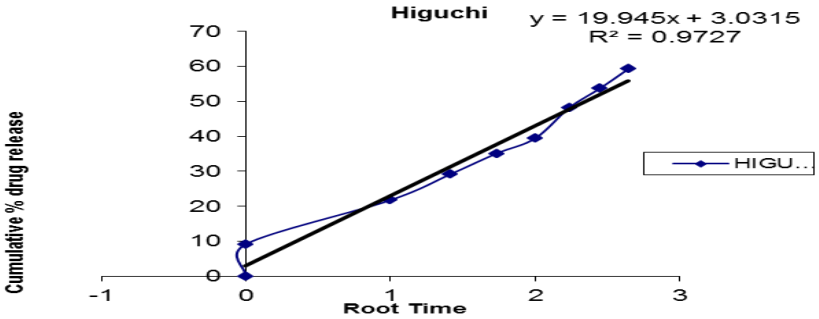

Fig. 8: Higuchi release kinetics graph.

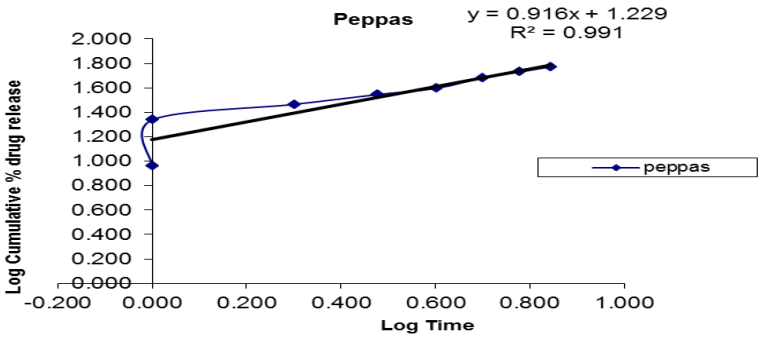

Fig. 9: Kars mayer peppas graph.

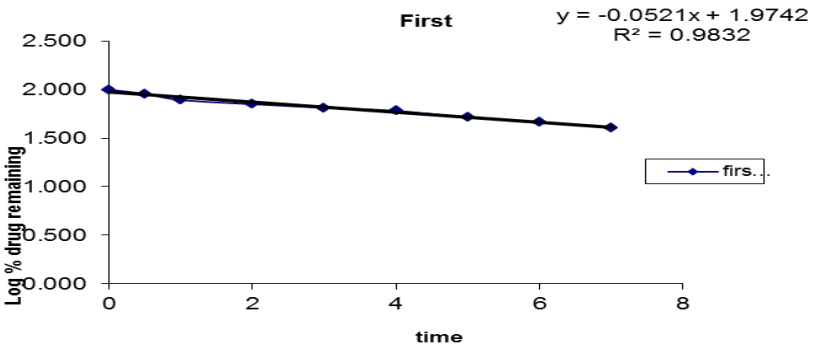

Fig. 10: First order release kinetics graph.

From the above graphs it was evident that the formulation BR3 was followed peppas mechanism.

5. CONCLUSION

In the present research work was carried out to formulate Bromocriptine Mesylate-Effervescent Floating Tablets by using various polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared with Methocel K4 M retarded the drug release up to 12 hours in the concentration of 7.5 mg (BR3) The formulations prepared by using Gellan gum were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Methocel K 15M were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed peppas mechanism of drug release.

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