WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 2634-2651. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF SUSTAINED RELEASE QUETIAPINE FUMARATE TABLET BY USING DIFFERENT POLYMERS

E.Esther Rani*, A.Swapna and Dr. H. Padmalatha

Gyana Jyothi College of Pharamacy.

Article Received on
16 March 2015,

Revised on 07 April 2015,
Accepted on 01 May 2015

***Correspondence for Author**
E.Esther Rani
Gyana Jyothi College of Pharamacy.

ABSTRACT

The main objective of the present work was to develop sustained release matrix tablets of Quetiapine fumarate by using different polymers viz., Hydroxy methyl propyl cellulose (HPMC) and Carbomer. Varying the ratios of drug and polymer like selected for the study. Quetiapine fumarate is prescribed for the treatment of Schizophrenia. It has a mean half life of 6hrs and administered at least thrice a day. The main objective of the study is to design once a day dosage form which can release the drug for 24hrs. The tablets were prepared by direct compression method. *In-vitro* dissolution studies showed that F7 has better release profiles when compared to other formulations. Though F4 showed release of 22hrs, the drug release was not constant. The experiment clearly stated that the usage of Carbomer has promoted the sustained release of QPF. Dissolution data was analyzed by Higuchi expression. Stability studies for 6 months indicated that Quetiapine fumarate was stable in the matrix tablets. The DSC and FTIR study revealed that there was no chemical interaction between drug and excipients.

KEYWORDS: Quetiapine fumarate, HPMC, Carbomer, Matrix tablets, Higuchi Model, Direct compression.

INTRODUCTION

SUSTAIN RLEASE DOSAGE FORM

Sustained release, sustained action, prolonged action, controlled action, extended action, timed release, depot and respiratory dosage form are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.

Sustained release dosage form are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for specific period of time with minimum side effects. This can be achieved through a variety of formulations, including liposomes's and drug polymer conjugates[an example being Hydrogels]. Sustained release's definition is more akin to a "controlled release" rather than "sustained".

The term "controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time.

Products of this have been formulated for oral, inject able, and topical use, include inserts for placement in body cavities as well.ss.

CLASSIFICATION OF ORAL SUSTAINED / CONTROLLED RELEASE SYSTEM

- ***DIFFUSION CONTROLLED SYSTEM***

1. Reservoir Device
2. Matrix Device

- ***DISSOLUTION CONTROLLED SYSTEM***

1. Matrix dissolution controlled system
2. Encapsulation dissolution controlled system
3. Diffusion and dissolution system
4. Sustain release matrix tablets

TABLET

Tablet is defined as compressed solid dosage form containing medicament with or without excipients. Tablets are solid unit dosage form meant for oral administration.

QUETIAPINE FUMARATE was used as ANTIPSYCHOTIC DRUG. Hence it was used in treatment SCHIZOPHERNIA. Anti psychotic drugs are also known as NEUROLEPTIC or TRANQUILIZERS. Psychiatric medication primarily used to manage psychosis, in particular in schizophrenia and bipolar disorder and are increasingly being used in the management of non-psychotic disorder.

First generation antipsychotic drugs, knows as TYPICAL ANTIPSYCHOTIC.

Second generation antipsychotic drugs, known as ATYPICAL ANTIPSYCHOTIC.

MATERIALS AND METHOD

Quetiapine fumarate (Shasun chemicals, pondy), Carbomer (Lyka Labs, Mumbai), HPMC(Griffon Laboratoies Pvt. Ltd, Mumbai), Lactose Monohydrate (Rolex Laboratoies, Mumbai), Micro crystalline cellulose (Himedia, Mumbai), Starch (S.D. Fine Chemicals Ltd, Hyderabad), Talc (Hetero Drugs, Hyderabad), Magnesium Stearate (Himedia, Mumbai).

METHOD

DIRECT COMPRESSION

FORMULATION OF MATRIX TABLETS: Quetiapine Fumarate matrix tablets were prepared by direct compression method. The drug and excipients except lubricants were sieved separately and mixed thoroughly. The dry blend was then lubricated and subjected to the compression using a tablet punching machine.

FORMULATION OF QUETIAPINE FUMARATE TABLETS

SUSTAINED RELEASE MATRIX TABLETS

COMPOSITION OF QUETIAPINE FUMARATE (300 mg) BY USING CARBOMER

S.No	Ingredients	Quantity in mg / Tablet								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Quetiapine Fumarate	200	200	200	200	200	200	200	200	200
2	Carbomer	20	20	20	40	40	40	60	60	60
3	Lactose monohydrate	74	-	-	54	-	-	34	-	-
4	Microcrystalline cellulose	-	74	-	-	54	-	-	34	-
5	Starch	-	-	74	-	-	54	-	-	34
6	Talc	3	3	3	3	3	3	3	3	3
7	Magnesium Sterate	3	3	3	3	3	3	3	3	3
	Total	300	300	300	300	300	300	300	300	300

COMPOSITION OF QUETIAPINE FUMARATE TABLETS (300 Mg) BY USING HPMC

S.No.	INGREDIENTS	QUANTITY IN mg / TABLET								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Quetiapine fumarate	200	200	200	200	200	200	200	200	200
2	HPMC	20	20	20	40	40	40	60	60	60
3	Lactose monohydrate	74	-	-	54			34	-	-
4	Microcrystalline cellulose	-	74	-	-	54	-	-	34	-
5	Starch	-	-	74	-	-	54	-	-	34
6	Talc	3	3	3	3	3	3	3	3	3
7	Magnesium Stearate	3	3	3	3	3	3	3	3	3
	Total	300	300	300	300	300	300	300	300	300

All the quantities are expressed as mg per tablet

BULK EVALUATION OF THE DRUG AND EXCIPIENTS USED IN THE FORMULATION

Drug and excipients were subjected to the physical evaluation tests such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio and the results have been discussed in the following table.

EVALUATION OF TABLETS: The post compression evaluation parameters such as weight variation, hardness, diameter, friability and dissolution as per USP were evaluated and the results were tabulated in the following table.

***In-Vitro* DISSOLUTION STUDIES:** Drug release profile was evaluated in-vitro using a dissolution test apparatus. One tablet containing 300mg of Quetiapine Fumarate was placed the 1000ml dissolution medium and speed of paddle was set at 50rpm. Samples(5ml) withdrawn at time interval of 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 & 24 hours and same value of fresh medium was replaced. The samples were analyzed for drug content against 0.1M HCL as blank at λ max 259.0 nm. The percentage drug release against time was determined. The values were tabulated in the following table.

DRUG RELEASE KINETICS: To analyze the mechanism of drug release from the prepared formulations, the data obtained from In- vitro release studies were subjected to

Zero-Order, First-Order, Higuchi's and Korsmeyer-peppas models as shown in the following tables.

RESULTS AND DISCUSSION

BULK EVALUATION OF THE DRUG AND EXICIPENTS USED IN THE FORMULATION

PRECOMPRESSED TESTS OF QUETIAPINE FUMARATE TABLETA BY USING CARBOMER

S.no	Ingredients	Angle of repose	Bulk density g/cc	Tapped density g/cc	Compressibility Index %	Hausner's Ratio
1	Quetiapine fumarate	27.80±1.06	0.689±0.003	0.857±0.004	19.87±0.34	1.26±0.006
2	Carbomer	27.70±0.81	0.699±0.003	0.820±0.007	16.02±1.04	1.19±0.016
3	Lactose monohydrate	25.57±0.43	0.705±0.002	0.805±0.002	12.21±0.21	1.20±0.004
4	Micro crystalline cellulose	27.27±1.25	0.683±0.003	0.795±0.004	13.67±0.08	1.22±0.019
5	Starch	30.05±0.77	0.715±0.005	0.855±0.006	16.45±1.15	1.20±0.017
6	Talc	29.48±0.45	0.754±0.002	0.872±0.04	15.56±0.73	1.15±0.003
7	Magnesium Stearate	28.27±1.23	0.765±0.003	0.861±0.004	12.0.7±0.36	1.18±0.005

PRECOMPRESSED TESTS OF QUETIAPINE FUMARATE TABLETS BY USING HPMC

S.NO	Ingredients	Angle of repose	Bulk density g /cc	Tapped density g /cc	Compressbility Index %	Hausner's Ratio
1	Quetiapine fumarate	28.82±1.07	0.686±0.003	0.856±0.003	19.86±0.32	1.30±0.004
2	HPMC	28.30 ±0.80	0.694±0.003	0.819±0.006	15.04±1.06	1.16±0.014
3	Lactose monohydrate	24.57±0.41	0.707±0.002	0.801±0.002	12.22±0.19	1.12±0.002
4	Microcrystalline cellulose	27.30±1.23	0.0684±0.003	0.790±0.004	14.65±0.07	1.15±0.001
5	Starch	29.07±0.74	0.714±0.005	0.858±0.005	16.40±1.14	1.24±0.015
6	Talc	29.45±0.42	0.730±0.004	0.870±0.004	15.90±0.74	1.18±0.012
7	Magnesium stearate	27.28±1.21	0.758±0.003	0.860±0.003	12.05±0.39	1.16±0.003

Evaluation of powders such as Angle of repose, Bulk density, Tapped density, Compressibility Index and Hausner's Ratio has been done , the results are as shown in the above table.

EVALUATION OF TABLETS

The post compression parameters such as weight variation, hardness, thickness, diameter, friability were evaluated and the results were as tabulated as follows.

EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF QUETIAPINE FUMARATE.

POST COMPRESSED TESTS OF QUETIAPINE FUMARATE TABLETS BY USING CARBOMER.

S.NO	Weight Uniformity (mg) n=20	Thickness (mm) n=03	Hardness (KG) n=03	Friability (%) n=10
F1	299.62±0.08	3.42±0.04	5.5±0.10	0.42±0.02
F2	298.22±0.30	3.54±0.02	5.2±0.10	0.50±0.02
F3	300.25±0.06	3.05±0.01	5.6±0.00	0.52±0.03
F4	299.54±0.10	3.49±0.03	5.3±0.11	0.41±0.02
F5	299.58±0.23	3.52±0.02	5.4±0.12	0.59±0.02
F6	300.29±0.08	3.5±0.01	5.4±0.00	0.49±0.03
F7	299.75±0.25	3.58±0.02	5.83±0.12	0.34±0.03
F8	299.85±0.09	3.52±0.03	5.7±0.17	0.48±0.02
F9	299. 90±0.30	3.56±0.02	5.6±0.00	0.36±0.02

POST COMPRESSED TESTS OF QUETIAPINE FUMARATE TABLETS BY USING HPMC

S.NO	Weight Uniformity(mg) n=20	Thickness (mm) n=03	Hardness (KG) n=03	Friability (%) n=10
F1	299.65±0.09	3.45±0.03	5.3±0.11	0.45±0.02
F2	299.43±0.31	3.7±0.01	5.43±0.10	0.49±0.02
F3	300.75±0.20	3.50±0.03	5.2±0.10	0.56±0.03
F4	298.06±1.12	3.46±0.02	5.4±0.00	0.39±0.02
F5	299.54±0.25	3.56±0.01	5.50±0.12	0.41±0.02
F6	299.05±0.08	3.52±0.01	5.51±0.10	0.58±0.03
F7	300.28±0.21	3.5±0.02	5.80±0.12	0.38±0.02
F8	299.05±0.30	3.58±0.03	5.9±0.20	0.40±0.03
F9	299.83±0.24	3.52±0.02	5.8±0.00	0.37±0.02

IN- VITRO DISSOLUTION STUDIES

Drug release profile was evaluated in – vitro using a dissolution test apparatus. One tablet containing 200 mg of Quetiapine fumarate was placed in the 1000 ml dissolution medium and speed of paddle was set at 50 rpm . Samples (5ml) withdrawn at a time interval of 0, 0.5 , 1 , 2,4 , 6 , 8 , 10 , 12 , 14 , 16 , 18 , 20, 22 & 24 hrs and same value of fresh medium was replaced . The samples were analyzed for drug content against 0.1 M HCL as blank at ƛ max 259.0 nm .The percentage drug release against time was determined . The value were tabulated as follows.

COMPARITIVE STUDY OF THE DRUG RELEASE PROFILE OF ALL THE FORMULATIONS.

COMPARITIVE STUDY OF THE DRUG RELEASE PROFILE OF ALL THE FORMULATIONS BY USING CARBOMER.

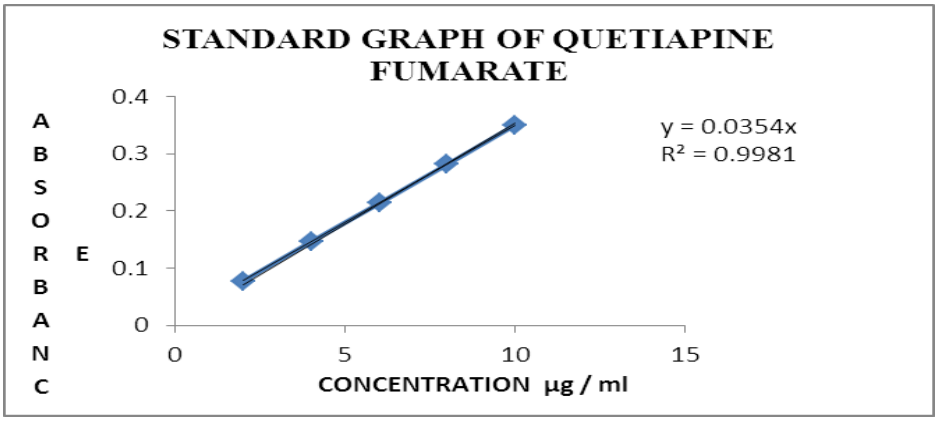
S.NO	Time(hr)	% Drug release of formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.5	2.60	2.61	10.32	2.98	1.58	5.13	1.69	1.53	2.08
3	1	11.18	11.19	23.14	4.99	11.68	12.57	2.78	11.68	13.00
4	2	22.93	22.94	32.55	12.34	22.59	23.62	9.28	22.57	23.45
5	4	30.05	30.05	43.42	27.15	30.03	31.45	21.99	30.03	30.29
6	6	40.45	41.46	52.82	32.94	39.74	40.09	26.98	39.73	40.08
7	8	48.92	48.93	64.12	42.75	48.35	50.17	36.00	48.38	48.54
8	10	55.89	56.89	72.08	50.25	55.86	57.84	45.66	55.85	56.28
9	12	63.23	63.24	84.45	57.40	63.10	69.29	52.69	63.09	64.45
10	14	77.68	78.70	91.19	62.68	76.72	79.40	63.89	76.72	78.54
11	16	85.62	86.62	100.10	77.82	85.30	89.00	71.49	86.30	88.28
12	18	93.34	93.35		87.08	95.16	100.08	79.36	95.15	96.38
13	20	100.40	100.41		93.20	100.04		89.50	100.03	99.94
14	22				100.11			93.31		
15	24							99.95		

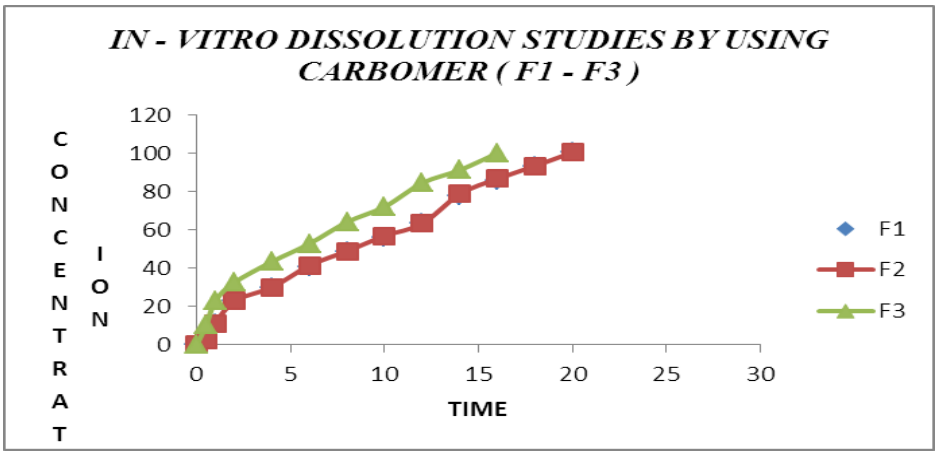
COMPARITIVE STUDY OF THE DRUG RELEASE PROFILE OF ALL THE FORMULATIONS BY USING HPMC

S.NO	Time(hr)	% Drug release of formulation								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	0.5	2.60	2.60	10.31	1.98	1.52	4.12	1.68	1.52	2.06
3	1	11.16	11.16	22.12	3.98	10.67	11.55	2.78	10.67	12.00
4	2	20.92	20.92	31.55	11.33	21.57	22.61	8.28	21.57	22.44
5	4	29.05	29.05	43.41	27.12	29.02	30.44	21.98	29.02	29.29
6	6	38.44	38.44	51.81	32.92	38.72	40.07	35.00	38.72	40.06
7	8	46.90	46.90	62.10	42.72	47.33	49.15	45.67	47.33	47.53
8	10	53.87	53.87	71.07	49.21	54.84	56.82	51.70	51.84	55.27
9	12	61.20	61.20	83.43	55.40	62.09	67.28	62.88	62.09	63.44
10	14	74.67	74.67	90.91	61.65	75.71	78.49	70.50	75.71	77.53
11	16	84.62	84.62	100.11	75.81	85.29	88.00	78.36	85.15	87.27
12	18	92.33	92.33		86.07	94.15	100.09	85.41	94.15	94.38
13	20	100.38	100.38		92.18	100.02		93.33	100.02	99.92
14	22				100.10			99.96		

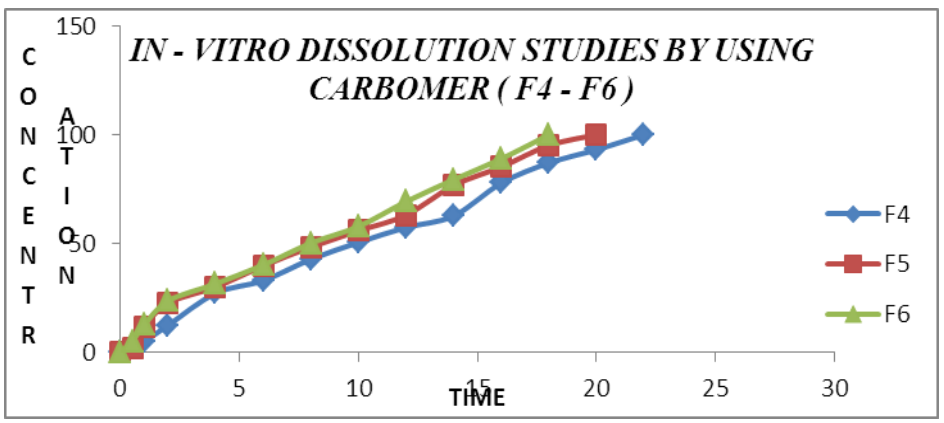
MEAN ABSORBANCE VALUES & STATISTICAL DATA OF THE CALIBRATION CURVE FOR THE ESTIMATION OF QUETIAPINE FUMARATE

CONCENTRATION	MEAN ABSORBANCE ± S.D
2	0.0776 ± 0.00046
4	0.1466 ±0.0004
6	0.2136 ±0.00013
8	0.2816 ± 0.00026
10	0.3506 ± 0.00029

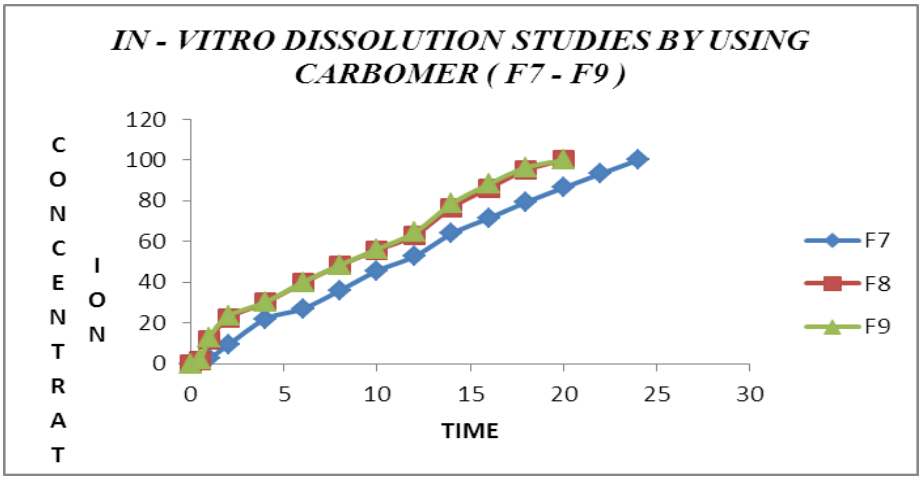




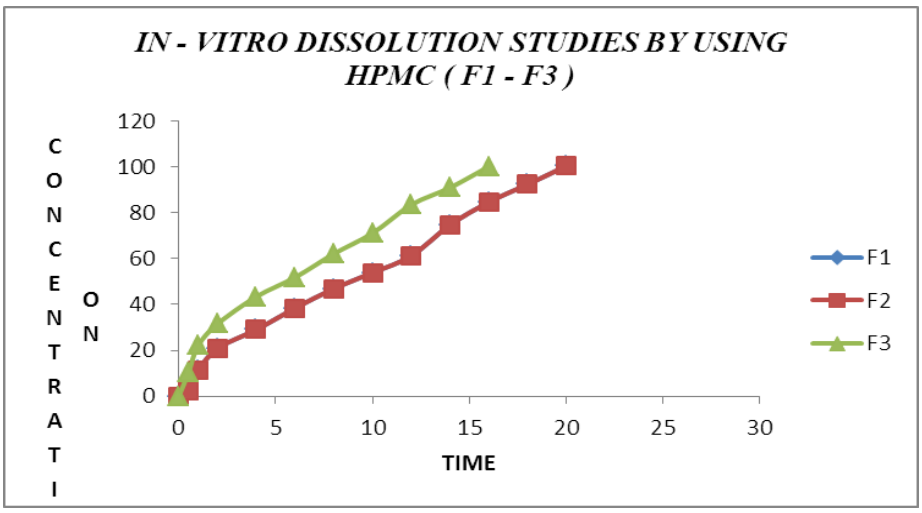
IN- VITRO DISSOLUTION STUDIES BY USING CARBOMER (F1 – F3)



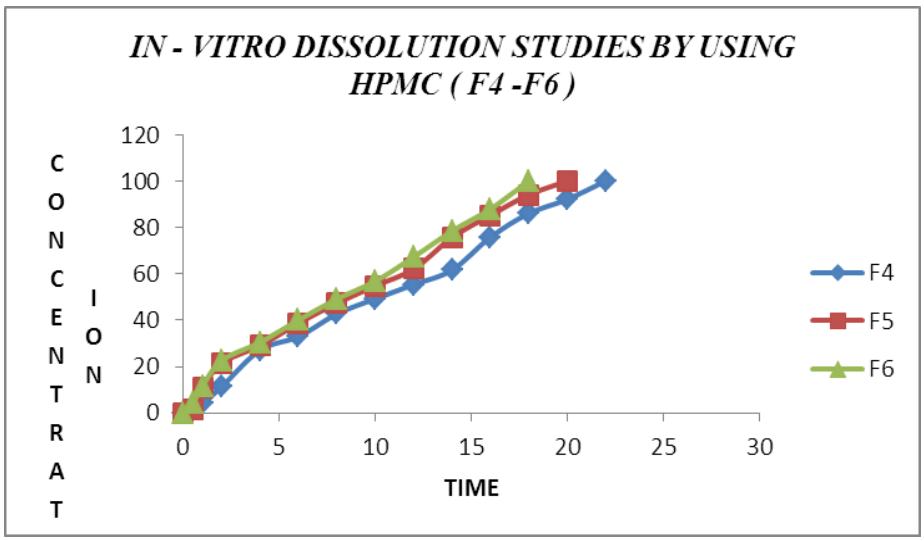
IN – VITRO DISSOLUTION STUDIES : (F4 –F6)



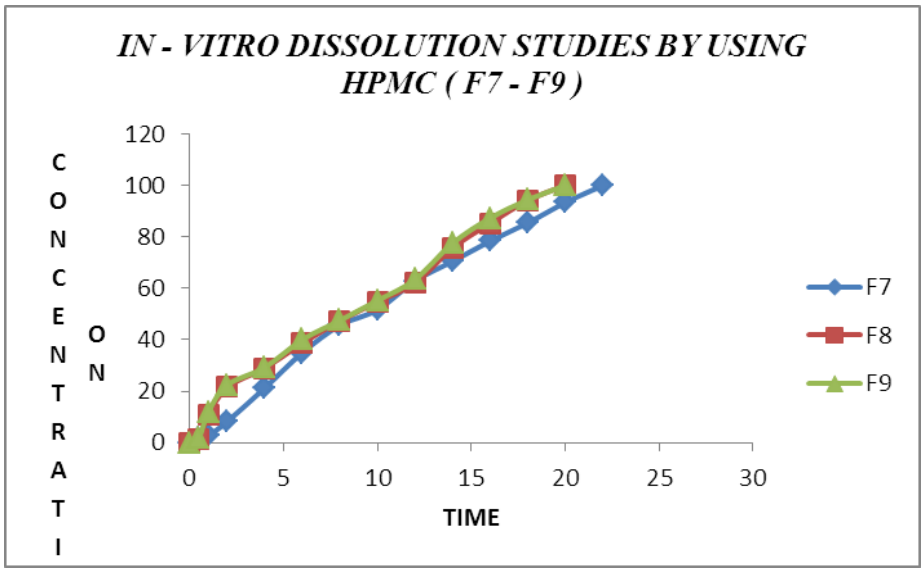
IN – VITRO DISSOLUTION STUDIES : (F7 – F9)



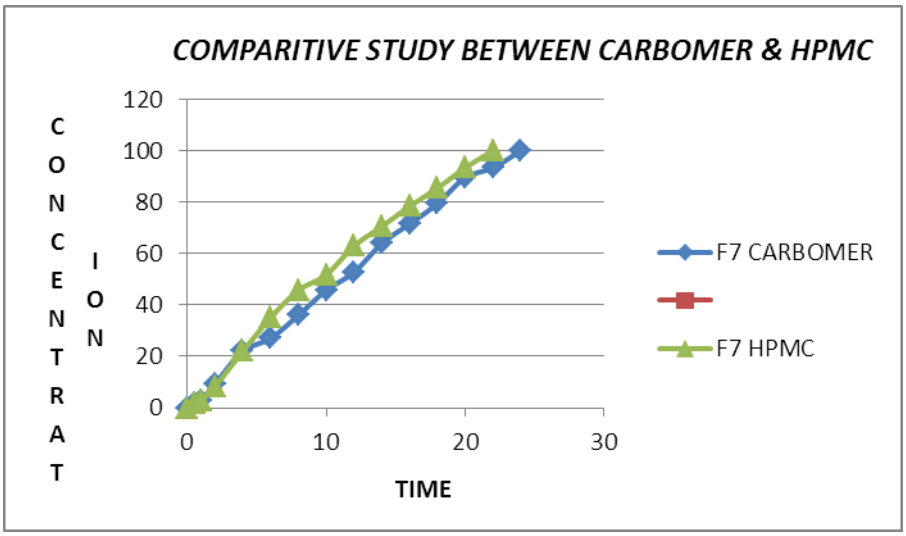
IN – VITRO DISSOLUTION STUDIES BY USING HPMC : (F1 – F3)



IN – VITRO DISSOLUTION STUDIES : (F4- F6)



IN – VITRO DISSOLUTION STUDIES : (F7- F9)

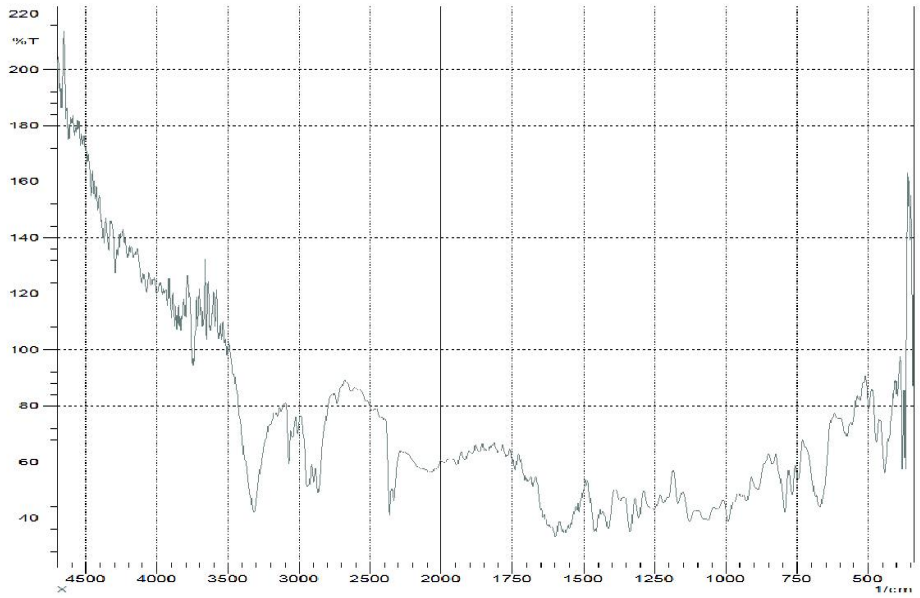


COMPARITIVE STUDY BETWEEN CARBOMER AND HPMC.

FTIR STUDY

I R Spectrum of Quetiapine fumarate shows a broad peak at 3750 cm^{-1} may be due to O – H stretching, 3080 cm^{-1} Ar – H stretching and 2880 cm^{-1} C- H stretching, 2380 cm^{-1} may be due to aromatic C = C stretching, 1600 cm^{-1} may be due to C- N , 1340 cm^{-1}may be due to C – H bending. 1030 cm^{-1} may be due to C –O – C group. 791 cm^{-1} may be due to substituted benzene ring. The I R spectrum of the best formulation obtained during from the results, it is clear that, there is no appreciable change in the positions of the characteristics bands of the drug along with the I R spectrum of the best formulation derived during the present investigation. Since there is no change in the nature and position of the bands in the

formulation, it can be concluded that the drug maintains it's identity without going any chemical interaction with the polymers used.



DSC STUDY

The DSC thermographs of pure drug and formulations obtained by DSC studies , revealed that melting point of pure drug is 234^0C and that of the drug in the formulation is 233^0C as there is no much difference in the melting point of the drug in the thermographs of drug and that of in the formulation . It may be concluded that , the drug is in the same pure state even in the formulation without interacting with the polymers

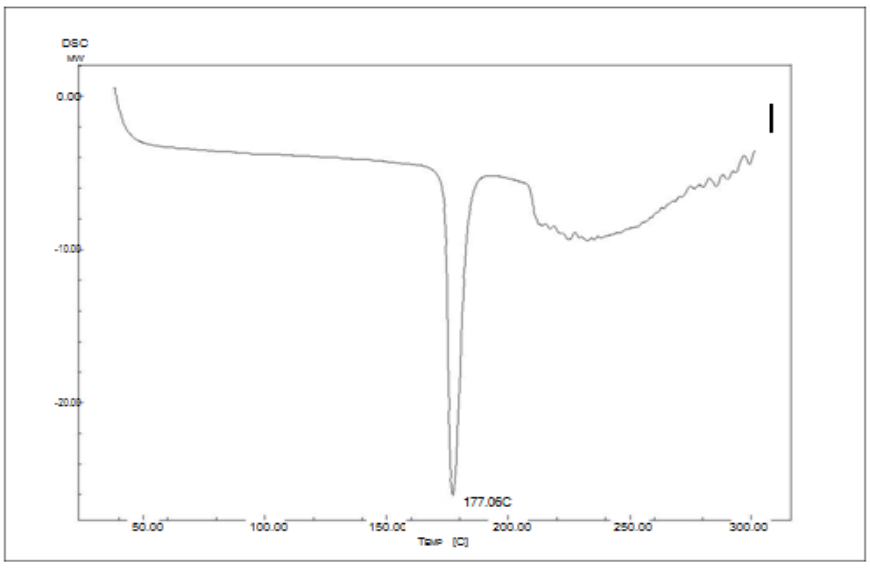


Figure 6: DSC thermographs of pure drug

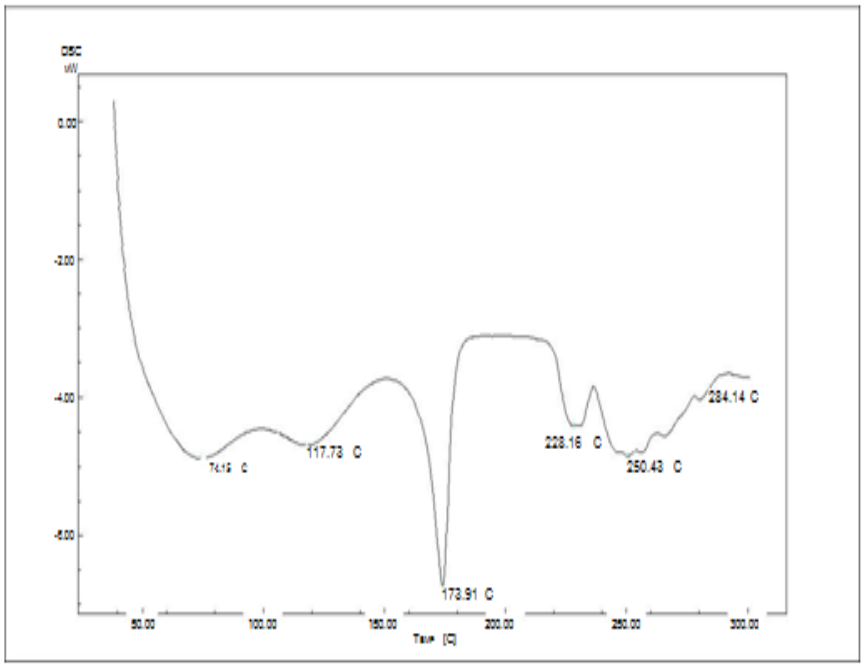
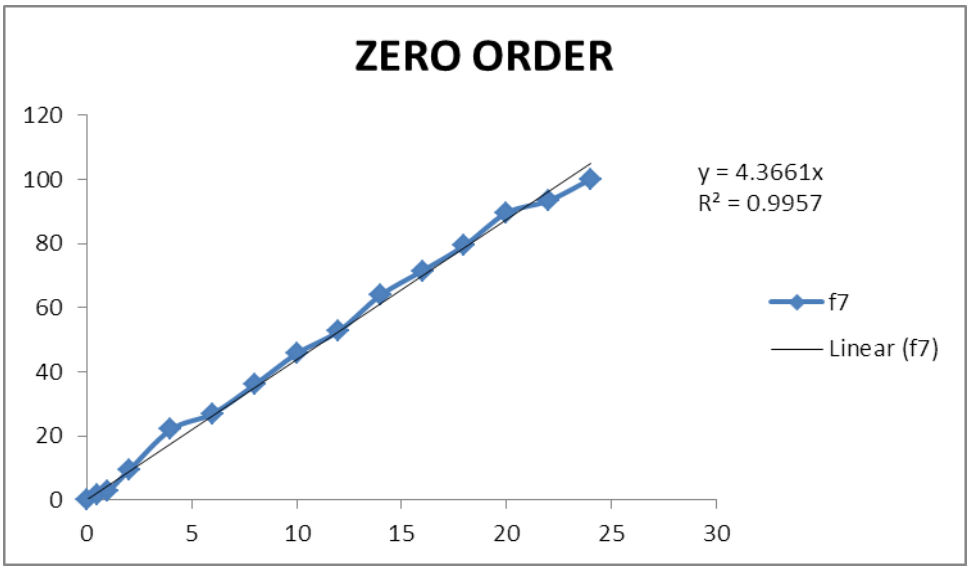


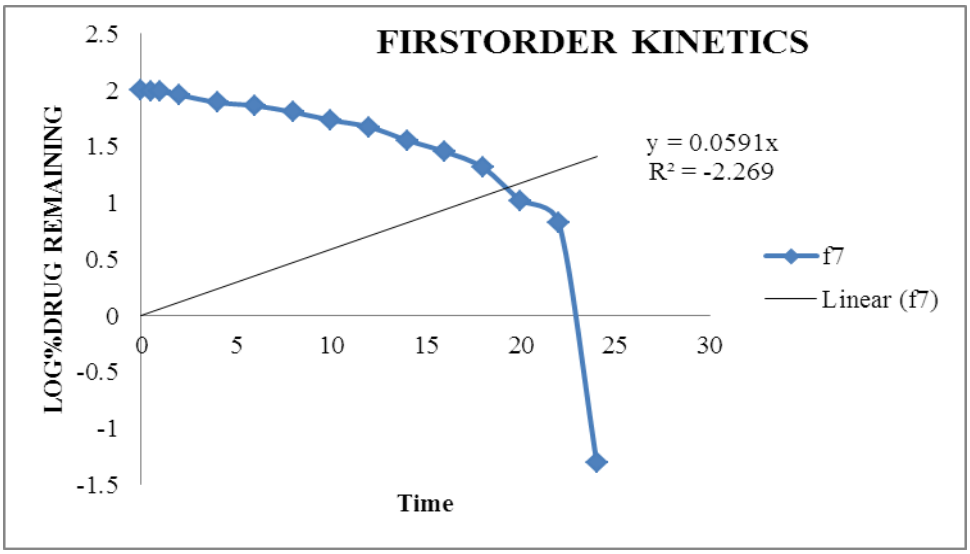
Figure 7: DSC thermographs of quetiapine fumarate SR tablet

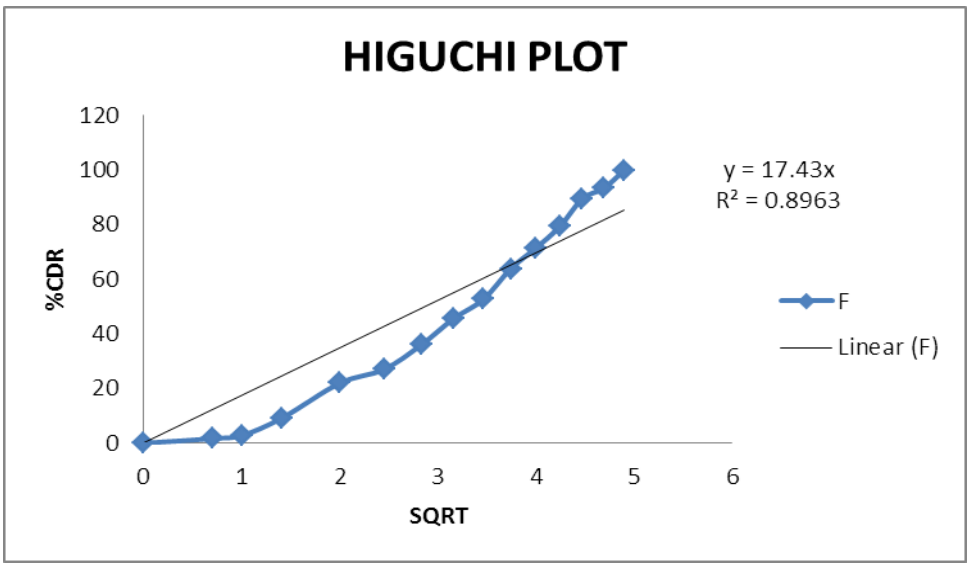
RELEASE KINETICS

F7 FORMULATION

SNO	TIME(hr)	%CDR	LOG%CDR	SQRT	LOG TIME	LOG DRUG REMAINING
1	0	0	2	0	NUM	NUM
2	0.5	1.69	1.992598	0.707107	-0.30103	0.227887
3	1	2.78	1.987756	1	0	0.444045
4	2	9.28	1.957703	1.414214	0.30103	0.967548
5	4	21.99	1.89215	2	0.60206	1.342225
6	6	26.98	1.863442	2.44949	0.778151	1.431042
7	8	36	1.80618	2.828427	0.90309	1.556303
8	10	45.66	1.73512	3.162278	1	1.659536
9	12	52.69	1.674953	3.464102	1.079181	1.721728
10	14	63.89	1.557627	3.741657	1.146128	1.805433
11	16	71.49	1.454997	4	1.20412	1.854245
12	18	79.36	1.31471	4.242641	1.255273	1.899602
13	20	89.5	1.021189	4.472136	1.30103	1.951823
14	22	93.31	0.825456	4.690416	1.342423	1.969928
15	24	99.95	-1.30103	4.898979	1.380211	1.999783


ZERO ORDER
120
100
80
60
40
20
0
0
5
10
15
20
25
30
y = 4.3661x
R² = 0.9957
f7
Linear (f7)


FIRSTORDER KINETICS
LOG%DRUG REMAINING
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
0
5
10
15
20
25
30
Time
y = 0.0591x
R² = -2.269
f7
Linear (f7)


HIGUCHI PLOT
%CDR
120
100
80
60
40
20
0
0
1
2
3
4
5
6
SQRT
y = 17.43x
R² = 0.8963
F
Linear (F)

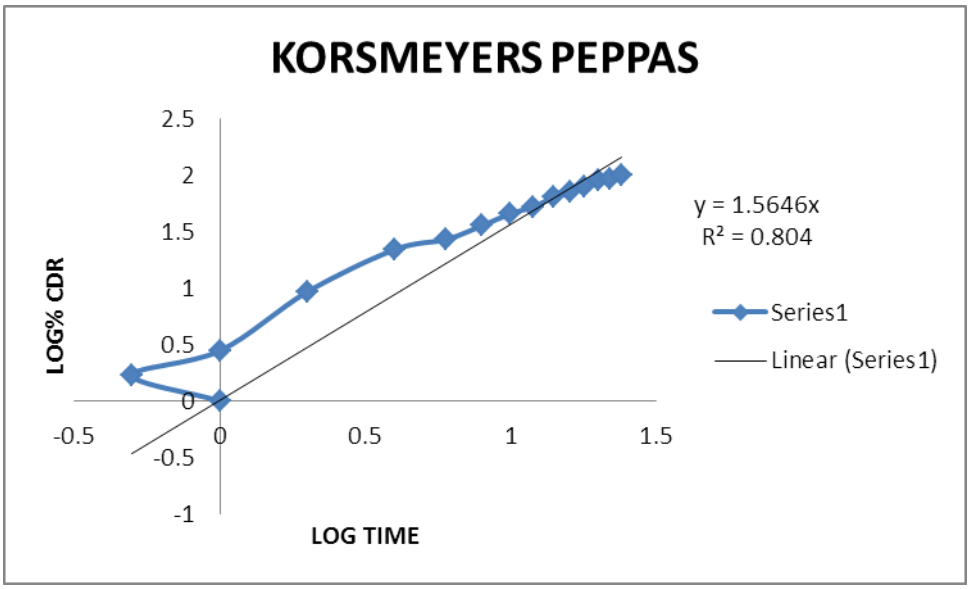


TABLE NO: RELEASE KINETICS PARAMETERS FOR QUETIAPINE FUMARATE SR FORMULATIONS

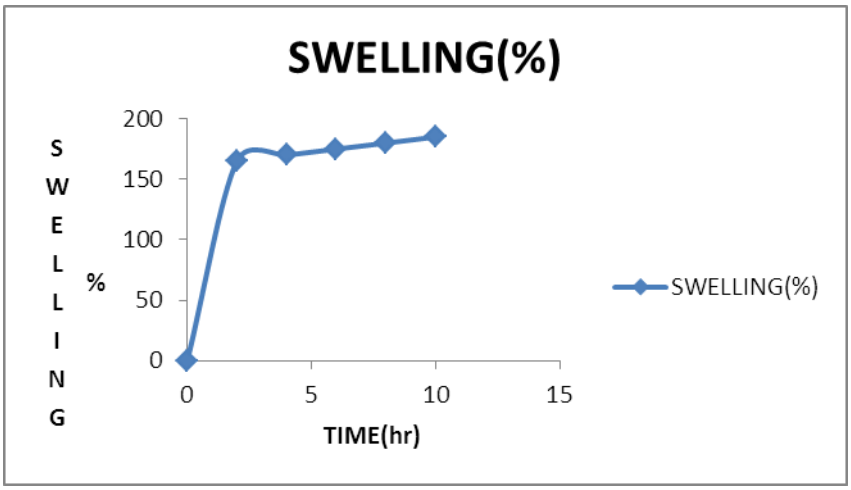
FORMULATIONS	ZERO ORDER		FIRST ORDER		HIGUCHI MODEL		KOSYMER-PEPPAS MODEL	
	m	r^2	m	r^2	m	r^2	m	r^2
F1	5.267	0.977	-0.051	0.906	35.220	0.995	0.520	0.983
F2	5.519	0.976	-0.044	0.930	36.140	0.987	0.393	0.979
F3	6.923	0.897	-0.064	0.953	37.620	0.998	0.589	0.997
F4	4.692	o.989	-0,046	0.899	31.820	0.986	0.530	0.981
F5	5.317	0.976	-0.055	0.884	29.370	0.994	0.493	0.957
F6	5.694	0.976	-0.049	0.937	27.610	0.968	0.329	0.987
F7	4.298	0.996	-0.043	0.92	28.640	0.994	0.504	0.961
F8	5.317	0.976	-0.055	0.884	29.530	0.961	0.399	0.959
F9	5.377	0.972	-0.057	0.89	30.510	0.992	0.346	0.970

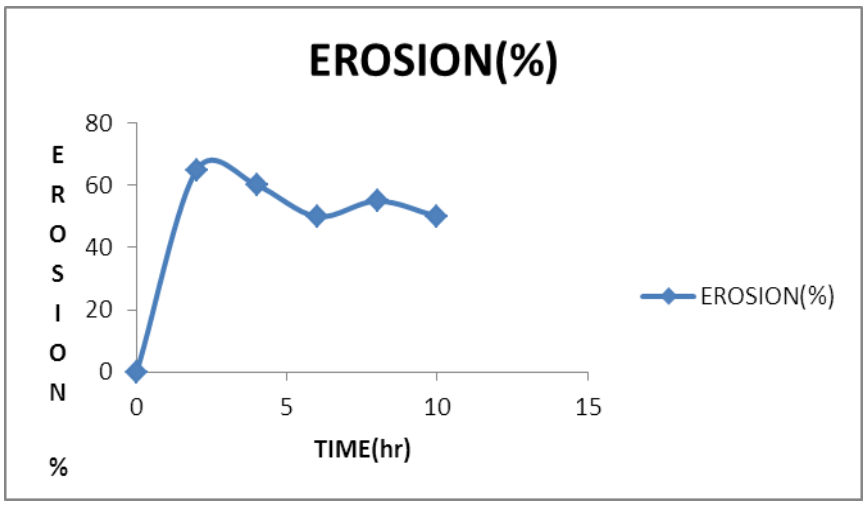
SWELLING INDEX AND EROSION.

SWELLING INDEX AND EROSION OF CARBOMER FORMULATIONSSWELLING INDEX AND EROSION OF F7 FORMULATION

TABLE NO: 1: SWELLING INDEX AND EROSION OF F7 FORMULATION

SNO	TIME (hr)	INITIAL WEIGHT(g)	FINAL WEIGHT(g)	SWELLING (%)	WEIGHT AFTER DRYING(g)	EROSION (%)
1	0	0	0	0	0	0
2	2	0.3	0.30	165	0.18	65
3	4	0.3	0.60	170	0.15	60
4	6	0.3	0.5	175	0.1	50
5	8	0.3	0.55	180	0.6	55
6	10	0.3	0.52	185	0.5	50



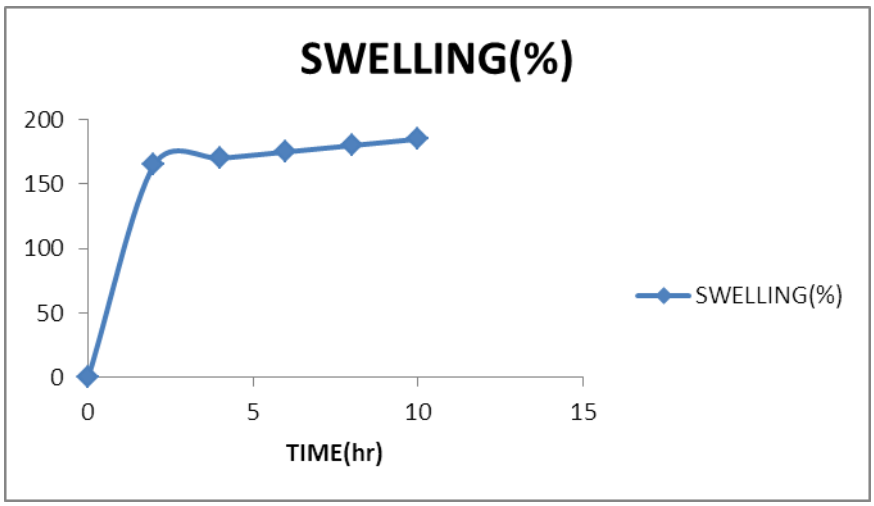


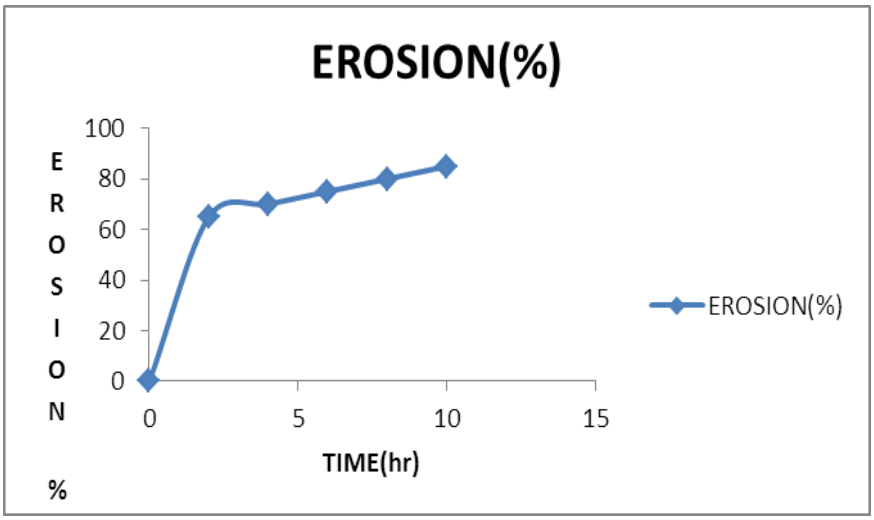
SWELLING INDEX AND EROSION FOR HPMC FORMULATIONS.

SWELLING AND EROSION OF F7 FORMULATION.

TABLE NO: 1: SWELLING AND EROSION OF F7 FORMULATION

SNO	TIME(hr)	INITIAL WEIGHT(g)	FINAL WEIGHT(g)	SWELLING(%)	WEIGHT AFTER DRYING(g)	EROSION(%)
1	0	0	0	0	0	0
2	2	0.3	0.30	165	0.18	65
3	4	0.3	0.60	170	0.15	70
4	6	0.3	0.5	175	0.1	75
5	8	0.3	0.55	180	0.6	80
6	10	0.3	0.52	185	0.5	85





STABILITY STUDY

After storage the formulation was analyzed for various physical parameters , results are shown in table. Stability studies of optimized formulation of Quetiapine fumarate sustained release tablets are shown in the following table.

STABILITY STUDY OF QUETIAPINE FUMARATE SUSTAIN RELEASE TABLET

Formulation code	Duration of period (Months)	Assay (%)	Hardness (kg / cm^2)	Friability (%)
F7	1	98.460	5.84	0.481
	2	98.458	5.83	0.524
	3	98.120	5.83	0.524

CONCLUSION

The formulations prepared with carbomer & HPMC polymers. In which Carbomer shows 100 % drug release in 24 hrs, where as HPMC shows 99.96 % drug release in 22 hrs and formulations could retard the drug release up to desired time period. The formulations F7

showed desired drug release profile. The controlled release drug delivery system of Quetiapine fumarate was able to shown sustain release of drug for 24 hrs. Release profile kinetics follows zero order kinetics and follows Higuchi kinetics.

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