VOLUME-7, ISSUE-2, FEBRUARY-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper | Pharmaceutical

FORMULATION AND IN-VITRO EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF ANTI-PSYCHOTIC AGENT: A SEROTONIN ANTAGONIST-QUETIAPINE FUMERATE

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ABSTRACT

The objective of present work is to prepare and optimize extended release tablets of Quetiapine Fumarate which is an atypical antipsychotic agent used in the treatment of schizophrenia, bipolar disorder and major depressive disorder. The peaks of FTIR spectrum of API Quetiapine Fumarate was found to be compatible and no interference with the excipients used in present study. An attempt was made to prepare extended release tablets using Methocel E 50, Sodium Alginate and combination of both as release retarding agents of total 10 trials. Based on the blend characterization and in vitro evaluation parameters trials T-03 of Methocel E 50, T-07 of Methocel E-50 and Sodium alginate T-10 of Sodium Alginate were taken for optimizing and reproducible trials and based on comparative in-vitro drug release of these three trials, trial T-7 was taken for one month stability studies and determination of order of release rate kinetics. After one month accelerated stability studies, the drug release was found to be 96.33 % in 8 hrs. The order of release was found to be as 0.9954 for Koresmeyer Peppas release rate kinetics>0.9831 for Higuchi's model release rate kinetics>0.9823 for Zero order kinetics>0.8409 for First order kinetics. Based on the results obtained it was confirmed that release of drug from prepared in-house Quetiapine Fumarate extended release tablets fallows Koresmeyer Peppas with regression coefficient value 0.9954.

KEYWORDS : Quetiapine Fumarate, Methocel E 50, Sodium Alginate

INTRODUCTION:

The objective of present work is to prepare and optimize extended release tablets of Quetiapine Fumarate which is an atypical antipsychotic agent used in the treatment of schizophrenia, bipolar disorder and major depressive disorder. Quetiapine fumarate is a dibenzothiazepine and antipsychotic agent acts on serotonin 5-HT2 receptor along with dopamine D1 and D2 receptors.[1]

Tablets are solid dosage form within which fine particles, coarse or grainy form of medicine is packed in a compact or condensed form. Most often used way of directing a drug by the oral route.[2]

The expression modified-release is used to explain that they alter release and time of the drug itself. A dosage form where characteristics such as location time are predetermined to achieve the main objective that is the required beneficial effect in which is not offered by solutions ointments or immediate release tablets are primarily offered by modified release dosage forms.[3,4]

PRESENT TRENDS OF TABLETS [5,6]

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self medication, pain avoidance, versatility, leading to high levels of patient compliance. Tablets and capsules are the most powerful dosage forms. But one important drawback of such dosage forms is 'Dysphagia' or difficulty in swallowing. This is seen to afflict nearly 35%of the general population. This disorder is also associated with a number of conditions like:

Parkinsonism, Motion sickness, Unconsciousness, Elderly patients, Children, Mentally disabled people and Unavailability of water.

History, In Israel, Lipowsk patented the ER tablets in the year 1938. He covered small tablets that gave form to covering the particles. In the late 1940's and 1950's oral controlled and sustained release tablets were developed this gave way to the introduction of marine anti-foulants and fertilizers in the year 1970s. Liberation is frequently affected by disintegration, dissolution, or degradation of excipients in which the active compound is made.7

Materials and Methods:

API Quetiapine Fumarate was obtained as gift sample form aspen laboratories, whereas polymers and all other excipients were obtained from SD fine chemicals, HYDERABAD.

Analytical method:

Preparation of Standard solution in 6.8 phosphate buffer:

Procedure: 5mg of Quetiapine fumarate was weighed and dissolved to a volume of 100ml with 6.8 phosphate buffer i.e. 50µg/ml stock solution.

Dilutions: From the working standard solution 1ml was diluted to 10ml with 6.8 phosphate buffer, 5 µg/ml concentrated solution. From dilution 1, take 0.2, 0.4, 0.6, 0.8 and 1 ml and was dilute up to mark in 10ml flask to obtain 2, 4, 6, 8 and 10 µg/ml concentrated solutions. This solutions absorbance was noted at λmax=298µm.

Formulation:

Table no: 01 Ingredients used in T1-T3

Ingredients	T-1	T-2	T-3
Quetiapine fumerate	40	40	40
Methocel E50	200	250	300
Sodium alginate	-	-	-
Lactose	239	189	139
MCC	-	-	-
Binder solution	Q.S.	Q.S.	Q.S.
Magnesium stearate	10	10	10
Talc	11	11	11
Total Weight-Mg	500	500	500

Table no: 02 Ingredients used in T4-T7

Ingredients	T-4	T-5	T-6	T-7
Quetiapine fumerate	40	40	40	40
Methocel E50	75	100	125	-
Sodium alginate	25	50	75	150
Lactose	60	50	25	25

MCC	279	239	214	264
Binder solution	-	-	-	-
Magnesium stearate	10	10	10	10
Talc	11	11	11	11
TOTAL WEIGHT-MG	500	500	500	500

RESULTS AND DISCUSSIONS:

The absorption maxima was determined by using the pure drug that is Quetiapine fumarate and the resultant wavelength was found to be 298nm

Table no: 03 Ingredients used in T8-T10

Ingredients	Trial 8	Trail 9	Trial 10
Quetiapine fumerate	40	40	40
Methocel E50	-	-	-
Sodium alginate	200	275	350
Lactose	35	35	35
MCC	204	129	54
Binder solution	-	-	-
Magnesium stearate	10	10	10
Talc	11	11	11
TOTAL WEIGHT-MG	500	500	500

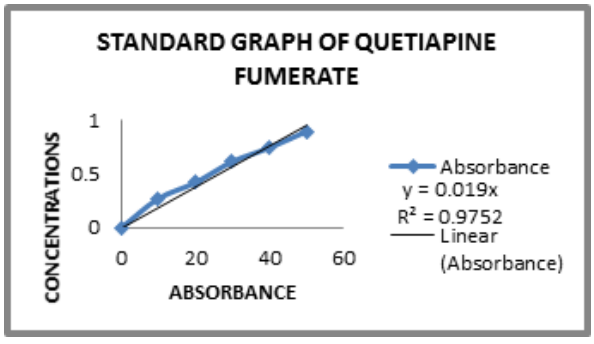


FIGURE NO: 01 STANDARD GRAPH OF QUETIAPINE FUMERATE

The slope was found to be 0.019 and R2=0.9752

FTIR STUDIES:

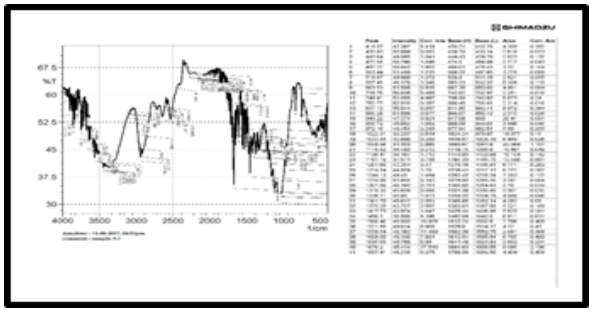


Fig no. 02 FTIR spectra of Methocel E50

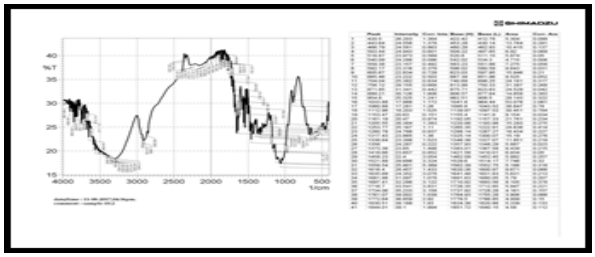


Fig no.03: FTIR spectra of sodium alginate

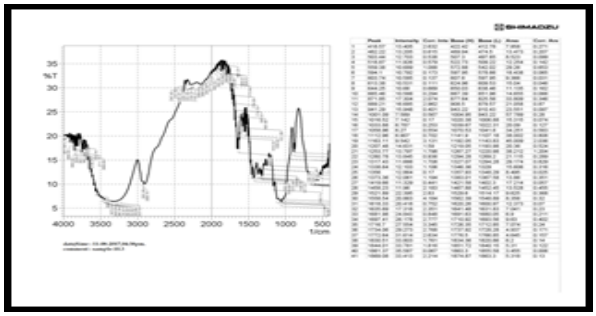


Fig. No 04: FTIR spectra of pure drug

Table no 04: FTIR functional groups peaks

S. NO.	QUETIAPINE FUMERATE	HPMC-E50	Na. Alginate	T-7
1	503.44	482.22	502.44	472.64
2	665.46	738.76	594.1	484.35
3	812.06	943.22	644.25	584.45
4	898.96	1008.22	889.21	665.46
5	954.76	1201.68	1016.52	1034.6

**No compatibility was found between the drug and polymer and they do not react with each other

RESULTS OF IN-VITRO EVALUATION PARAMETERS OF FORMULATED TRIALS FROM T1 TO T10

Physical characterization of powder blend of trials T-01 to T-10

Table no: 05: Blend Characterization T-01 to T-10

Trials	Bulk density	Tapped density	Angle of repose	Carr's index
T-1	0.44	0.62	35.21	29.032
T -2	0.42	0.67	34.15	37.31
T -3	0.42	0.58	33.28	27.58
T -4	0.41	0.6	37.21	31.66
T -5	0.42	0.68	38.25	38.23
T -6	0.41	0.64	39.35	35.93
T -7	0.42	0.67	36.75	37.31
T -8	0.44	0.62	34.38	29.03
T -9	0.43	0.68	35.02	36.76
T -10	0.42	0.64	35.08	34.37

The powder characterization properties like bulk density, tapped density, angle of repose, compressibility index were established to be within the limits.

Post formulation studies In-vitro evaluation parameters

Hardness: hardness the prepared tablets from T01 toT10 was established to be in between 8-9.5 kg/cm2, of which hardness of 8.4 kg/cm2 for trial 10 was optimized, based on friability and drug release studies

Thickness and diameter: the uniformity of the thickness and diameter was maintained in all the trials from T-01 to T-10 in between the narrow range of 0.4 to 0.6mm for thickness and 0.9 to 1.0 for diameter.

Weight variation: variation in the weights of prepared tablets of all the trials T-01 to T-10 was in the range between 490-502mg i.e. not more than 2% in weight variation.

Friability: The percent of friability for the prepared tablets was established to be in the range of 0.40 – 1.35 % and the trial 10 with 0.62 % of friability was optimised

Disintegration studies: After 4 hours the tablets were found to be intact without losing their physical structure.

Content uniformity: the content uniformity of all the trials was conducted and were found to be as follows

Table no.06: Content uniformity studies

S no.	Trial	content uniformity in mg
1	T-01	38.74
2	T-02	39.04
3	T-03	39.26
4	T-04	39.55
5	T-05	39.84
6	T-06	40.14
7	T-07	40.27
8	T-08	40.65
9	T-09	41.48
10	T-10	41.82

Table no. 07: Post compression parameters from T-01 to T - 10

Trials	Hardness	Thickness	Diameter	Weight variation	Friability
T-1	9	0.4	0.9	498	1.06
T-2	8.7	0.5	0.9	501	1.35
T -3	8.2	0.6	1	499	1.26
T-4	9.1	0.4	0.9	501	0.49
T-5	8	0.4	0.9	500	0.5
T-6	8.6	0.4	0.9	502	0.75
T-7	9.5	0.4	0.9	498	0.52
T-8	8	0.4	0.9	496	0.52
T-9	9	0.4	0.9	501	0.4
T-10	8.4	0.4	0.9	502	0.62

IN-VITRO DRUG RELEASE FROM TRIAL T – 01 TO T – 03

TABLE NO 08: DRUG RELEASE FROM TRIAL T-01 TO T-03

Time in min	T-1	T-2	T-3
0	0	0.0	0.00
30	4.51	7.7	10.34
60	34.81	19.9	21.43
90	45.00	25.2	35.23
120	56.98	36.5	49.19
180	68.74	57.0	57.78
240	76.59	69.5	68.77
300	95.87	88.4	74.23
360	99.78	97.3	89.54
480	97.87	99.6	97.28

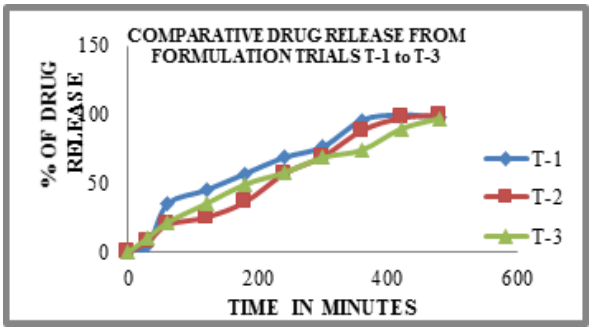


FIGURE NO: 05 DRUG RELEASE PROFILE FROM TRIAL 01 TO 03

Comparative IN-VITRO DRUG RELEASE OF T4-T7 HAVING METHOCEL –E-50 and SODIUM ALGINATE combination:

Table no: 09 DRUG RELEASE FROM TRIAL T-04 TO T-07

TIME	T-4	T-5	T-6	T-7
0	0	0	0	0
30	15.24	10.34	10.14	17.23
60	55.43	27.93	30.34	28.45
120	64.56	45.93	55.33	38.03
180	68.94	70.76	71.54	47.34
240	76.23	73.23	73.54	57.93
300	84.56	88.32	83.53	69.45
360	89.34	95.20	97.23	78.94
420	98.34	98.45	100.32	90.15
480	99.23	100.21	98.23	99.23

Comparative graphical representation of trial t-4 to t-7

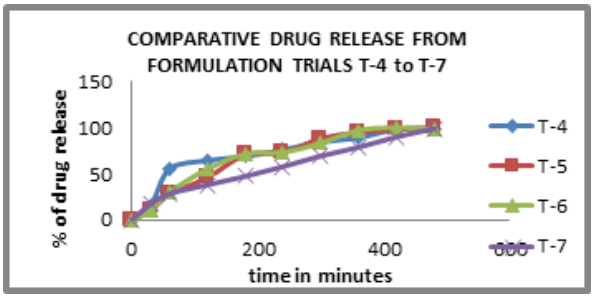


Figure no: 06 Comparative drug release profile from trial 04-07

Comparative drug release of T8-T10 having sodium alginate

Table no: 10 Drug release profile from trial t-8 to t-10

Time in min	T-8	T-9	T-10
0	0	0	0
30	15.23	10.93	12.39
60	34.76	28.28	21.82
120	46.94	41.38	34.98
180	59.34	54.27	41.34
240	69.94	71.73	58.93
300	79.39	82.37	63.37
360	95.93	95.82	76.37
420	100.23	98.28	86.34
480	99.65	99.84	97.38

Sampling interval (minutes)	% drug release from optimized trial T-07
0	0
30	15.34
60	24.84
120	34.25
180	45.98
240	58.35
300	63.93
360	76.49
420	84.39
480	96.33

COMPARITIVE GRAPHICAL REPRESENTATION OF T-8 TO T - 10

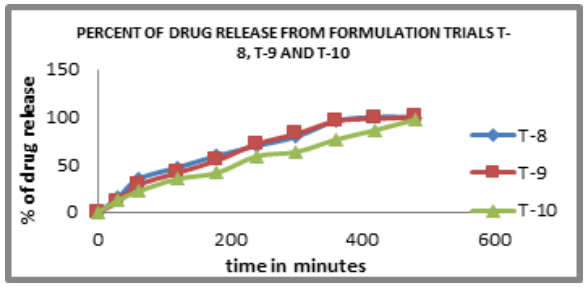
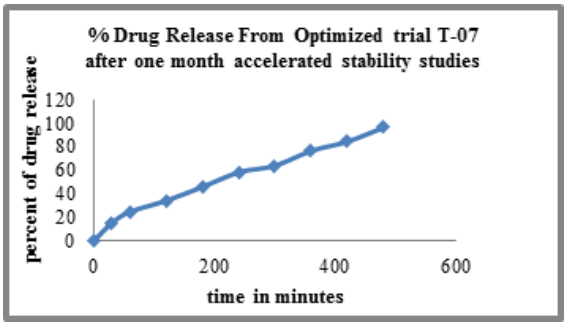


Figure no: 07 Comparative drug release profile from trial 08-10

STABILITY STUDIES

Based on the comparative release studies of optimized trials T-3, T-7 and T-10, trial T-7 containing METHOCEL-K-100 was taken for one month stability studies at accelerated stability conditions 60 ± 2

TABLE NO: 11 DRUG RELEASE FROM OPTIMIZED TRIAL T07 AFTER ONE MONTH ACCELERATED STUDIES



The results of drug release after 1 month of T- 07 are given in below table and represented graphically in above figure 10

RELEASE RATE KINETICS

Graphical Representation of Release Rate Kinetics from Optimized Formula-T-07

ZERO ORDER RATE KINETICS:

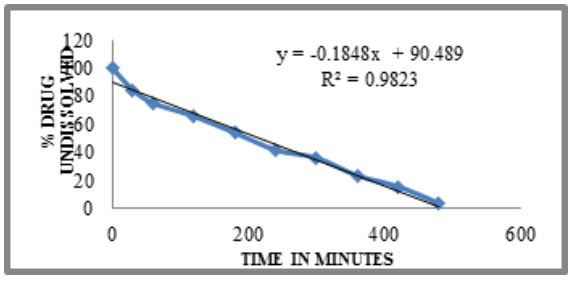


Fig no 08: zero order rate kinetics of optimized trial T 07

HIGUCHI'S MODEL RELEASE RATE KINETICS:
FIRST ORDER RELEASE RATE KINETICS:

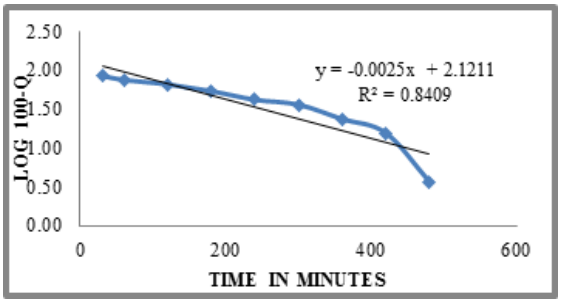


Fig no. 9: First order rate kinetics of optimized trial T- 07

Fig no 12: Koresmeyer Peppas release rate kinetics of optimized Formula T - 07

Determination of Released rate kinetics from Optimized T7 formula: The drug release from T-7 was determined for Zero order kinetics, First order kinetics, Higuchi's model release rate kinetics and Koresmeyer Peppas release rate kinetics of which regression coefficient, R2 was found to be as 0.9823 for Zero order kinetics, 0.8409 for First order kinetics, 0.9831 for Higuchi's model, 0.9954 for Koresmeyer Peppas release.

Swelling behaviour and water uptake studies: As discussed in methodology these studies are particularly done for hydrogels – which show swelling property as well as water absorbing property. This study was done for T-07 tablets. The results of percentage axial swelling and percentage weight gain were described graphical representation shown in figure no 13

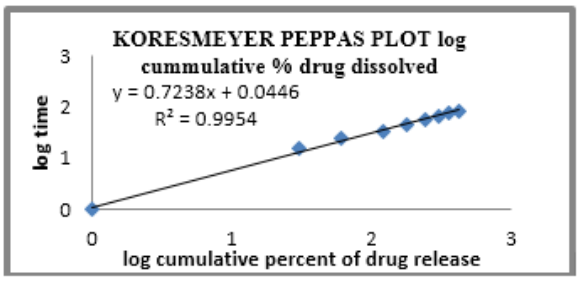


Figure no 13: The percent swelling and water uptake.

Matrix erosion study: As discussed in methodology chapter these revision were completed for T-07 tablets. The speed of matrix erosion of T-07 tablets was found to 0.062 /min. the speed of matrix erosion is shown in figure no- 5.25

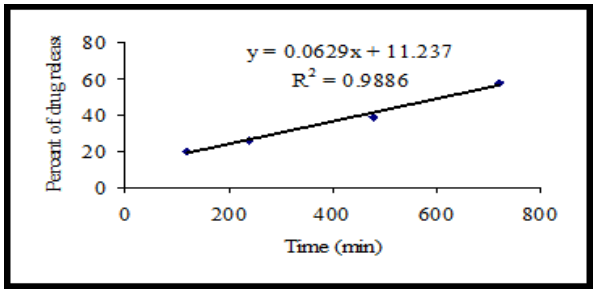


Figure no 14: percent polymer erosion of matrix tablet

CONCLUSION

The aim of the present study was to develop extended release formulation of Quetiapine Fumarate to maintain constant therapeutic levels of the drug for over 12 hours. Methocel E-50 and sodium alginate were employed as polymers. All the formulations were assessed for various parameters such as pre compression parameters:

Bulk density: the bulk density of all the trials was found to be in the range of 0.41 - 0.44

Tapped density: the tapped density for all the trials was found to be in the range of 0.58 - 0.68

Angle of repose: the angle of repose for all the formulations were conducted and were found to be in the range of 33.28 - 39.35

Compressibility index: the compressibility index of all the trials was found to be in the range of 27.58 - 38.23

Post compression parameters:

Hardness: the hardness of all the tab lets in each trial were measured using Monsanto hardness tester and it was to be in the range of 8-9.5kg/cm2

Thickness: the thickness of all the tablets in every trials was measured using Vernier calibres and it was found to be in the range of 0.4 – 0.6 mm

Diameter: the diameter of all the tablets were found to be in the range of 0.9 – 1.0 cm

Weight variation: the weight variation of all the trials was found to be in the range of 496 - 502mg Percent friability: the percent friability of all the trials was found to be in the range of 0.4 – 1.35%

Based on the powder characterisation and in vitro evaluation of all 10 trials, trials T-3 , T-7 and T-10 were taken for optimisation and the drug release of these trials were found to be as follows, for T-3 it is 99.27%, for T-7 it is 97.67%, and for T-10 it is 99.78% The result of percent drug release after 1 month of T- 07 was found to be 96.3% The order of release was found to be as 0.9954 for Koresmeyer Peppas release rate kinetics>0.9831 for Higuchi's model release rate kinetics>0.9823 for Zero order kinetics>0.8409 for First order kinetics. Based on the results obtained it was confirmed that release of drug from prepared in-house Quetiapine Fumarate extended release tablets fallows Koresmeyer Peppas with regression coefficient value 0.9954.

Based on above all in-vitro evaluation parameters it was concluded that the aim and objectives of present research work entitled "FORMULATION AND IN-VITRO EVALUATION OF EXTENDED RELEASE TABLETS OF QUETIAPINE FUMARATE TABLETS" are achieved and further the work can be taken to in-vivo studies in animals."

References:

1. https://pubchem.ncbi.nlm.nih.gov/compound/Quetiapine_fumarate
2. https://en.wikipedia.org/wiki/Tablet_(pharmacy)
3. Applied Biopharmaceutics & Pharmacokinetics, 6e,Leon Shargel, Susanna Wu-Pong, Andrew B.C. Yu
4. Opie LH, Messerli FH. Nifedipine and mortality: grave defects in the dossier. Circulation 1995; 92:1068-73.
5. Schall R, Müller FR, Müller FO, Luus HG. Bioequivalence of controlled-release calcium antagonists. Clinical Pharmacokinetics 1997; 32:75-89.
6. DiMatteo MR, DiNicola DD. Achieving patient compliance:the psychology of the medical practitioner's role. New York: Pergamon Press; 1982.
7. Gupta PK and Robinson JR. Oral controlled release delivery. Treatise on controlled drug delivery. 1992;93(2):545-555.