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FORMULATION AND EVALUATION OF REGIOSELECTIVE CONTROLLED RELEASE DRUG DELIVERY OF QUETIAPINE FUMARATE

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ABSTRACT

The present study deals with the formulation and evaluation of Hydrodynamically Balanced Gastroretentive Systems which can retard the release of Quetiapine Fumarate for a prolonged period of time specifically in the upper part of the GIT i.e, stomach. Quetiapine Fumarate is an antipsychotic drug and it shows pH dependent solubility, since it is having high solubility at stomach pH, and as the pH increases its solubility decreases rapidly. Therefore gastro retentive floating drug delivery system has been selected with a view to improve its bioavailability. The purpose of this research is to increase the gastric residence time by preparing gastroretentive floating tablets whereby making it available at its site of absorption and to achieve an extended action for a time period of 24 hrs. Quetiapine Fumarate floating tablets were prepared by wet granulation method using various grades of METHOCEL, and POLYOX with three different concentrations. Preformulation studies were carried out and the compatibility of the drug with the excipients was confirmed through differential scanning calorimetry studies. The prepared gastroretentive floating tablets were evaluated for uniformity of weight, hardness, friability, density, drug content, floating lag time, floating time, swelling index and *in vitro* dissolution studies. The optimized formulations F5, F7, F14, F6 and F18 showed a floating time more than 20 hrs with matrix integrity in pH 1.2. The *in vitro* release studies revealed that the drug release was controlled upto 24hrs. Optimized formulations showed no significant change in physical appearance, pre and post compression parameters and drug dissolution studies after storage at 40° C ± 2° C and 75% ± 5% relative humidity in a humidity chamber for 3 months. Using Higuchi's Model and the Korsmeyer equation, the drug release mechanism from the floating controlled release tablets was found to be Anomalous (non-Fickian) diffusion.

KEYWORDS: Quetiapine Fumarate, Gastroretentive floating tablets, Floating lag time, Floating time, Swelling index.

INTRODUCTION

Oral drug delivery is the most widely used route of administration due to its ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. All controlled release drug delivery systems have limited applications if the systems cannot remain in the vicinity of the absorption site.[1,2] A gastric floating drug delivery system (GFDDS) can overcome some of these problems and is particularly useful for drugs that (i) are locally active in the stomach, (ii) have an absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, (iv) exhibit low solubility at high pH values.[3] Many approaches have been reported in literature for prolonging gastric retention time which include mucoadhesion[4], floatation[5], high-density systems[6], modified shape systems[7,8] or by the simultaneous administration of agents which delay gastric emptying.

The Quetiapine Fumarate is poorly water soluble Antipshycotic agent belonging to class 2 of biopharmaceutical classification system and is one of the most commonly prescribed drugs for the treatment of patients with Schizophrenia and Mojor depressive condition. It is practically water insoluble, but is highly lipophillic and its dissolution is considered to be a rate determining step (i.e., an effective factor) in its absorption from the gastrointestinal tract. The dose of the drug is 50 to 400 mg and the half life is 6 hrs making it a suitable candidate for a controlled release dosage form.[9.10,11]

Therefore present work is aimed towards enhancing the solubility by using micronized API, dissolution there by bioavailability of Quetiapine Fumarate using swellable polymers (HPMC and Polyox). Floating controlled release tablets are formulated to increase the gastric residence time by preparing gastroretentive floating tablets whereby making it available in the upper

gastrointestinal tract and to achieve an extended action for a time period of 24 hrs.

MATERIALS AND METHOD

Materials

Quetiapine Fumarate was obtained from Mylan Labs, Hyderabad. Hydroxy propyl methyl cellulose (HPMC K100LVCR, HPMC K4 MPCR, HPMC K15 MPCR), Polyox WSR 301, polyox coagulant, and polyox WSR 303 was obtained from Colorcon, Goa. Sodium bicarbonate and citric acid were obtained from SD Fine Chemicals, Mumbai. Avicel PH 101 (MCC) was obtained from FMC Bio Polymer, Mumbai and Magnesium stearate was obtained from Evonik, India.

METHODS

Drug Analysis

- Simple High performance liquid chromatography method was developed for the determination of Quetiapine Fumarate. Chromatography was performed on Alliance high performance liquid chromatography equipped with Alliance chromatograph pump with 20 µl loop and Alliance Photo Diode Array detector. Column is kromasil100, C-8, 150*4.6mm, particle size: 5um /equivalent at a column temperature of 40ºc and Sample tray temparature 10+2c. Detection was performed at wavelength of 210 nm having flow rate 2ml/min. Mobile phase used is mixture of 600ml of HPLC buffer + 400ml of acetonitrile(degas).

Standard stock solution

- Transfer 100.0 mg of Quetiapine Fumarate accurately weighed, to a 100-mL volumetric flask and make up the volume with mobile phase and mix well.
- Filter the solution through 0.45µm membrane filter.

Chromatographic System

The liquid Chromatographic system is equipped with a 210-nm PDA detector.

- HPLC buffer: 3.48gm of potassium dihydrigen phosphate in 1000 ml of water & pH 7.2+0.05 ortho phosphoric acid.
- Mobile phase: 600 HPLC buffer + 400 acetonitrile (degas)
- Column: kromasil100,C-8,150*4.6mm, particle size:5um /equivalent
- Flow rate: 2ml/min
- Colum temparature: 40+2 c
- Sample tray temp:10+2c
- Wave length:210nm
- Inject vol: 10ul
- Run time: 15minutes
- RT: 8.96 minutes

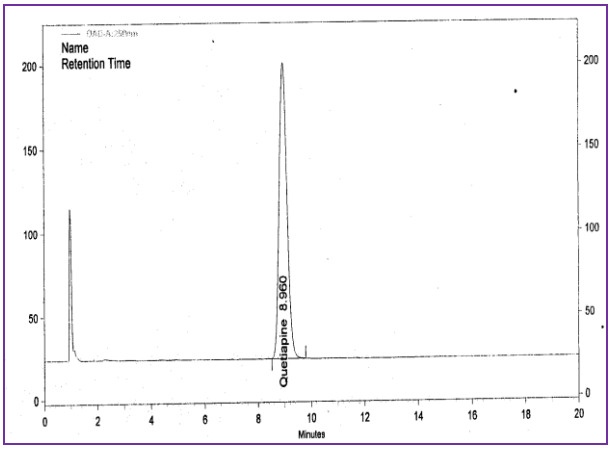


Figure 1: HPLC Chromatogram of Quetiapine Fumarate Standard.

Solubility studies[12,13]

An excess amount of drug was added to 250 mL of respective buffer in a conical flask and subjected to mechanical shaking at 200 rpm for 24hrs. The resultant solutions were collected and filtered through 0.45 µ membrane filters and the concentration of drug was determined from absorbance at respective wave lengths for different media. Solubility studies were done for model drug by the above procedure in different media like 1.2 SGF, Milliq water, acetate buffer pH 4, Phosphate buffer ph 6.8, Phosphate buffer ph 7.2.

Drug-Excipient Compatibility studies

Differential Scanning Calorimetry

Differential scanning calorimetry is used to determine drug excipient compatibility studies and also used to observe more phase changes, such as glass transitions, crystallization, amorphous forms of drugs and polymers. DXM, Physical mixtures of drug and excipients were analysed by differential scanning calorimeter(Mettler Toledo, USA).The thermo grams of DXM, physical mixture of DXM with excipients were obtained at scanning rate of 20^0C/min conducted over 25-250^0C.

Preparation of Quetiapine Fumarate floating tablets

Floating tablets of Quetiapine Fumaratewere prepared by wet granulation method. API and diluent were passed through 40# mesh, and blended for 10min. Prepare HPMC 5cps solution by dissolving hpmc 5cps with water, and added to step 1 for granulation. And dry the granules for 1hour at 60° C. after that the dried granules were sieved though 30#. Remaining excipients other than magnesium stearate were passed through 30#mesh. And added to step 2 and blended for 10min. magnesium stearate was weighed and passed through 60# and added to step 3, and blended for 5min. the final blend was individually weighed and compressed into tablets using 16station compression machine using 12mm punches.

Table No 1: Formulation of Quetiapine Fumarate gastroretentive floating tablets. (Weight in mg).

INGREDIENTS	FORMULATION CODE QTY: mg/tab																			
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
Intra granular																				
API	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7	172.7
Avicel 101	223.3	148.8	73.3	223.3	148.8	73.3	223.3	148.8	73.3	223.3	148.8	223.3	148.8	73.3	223.3	148.8	73.3	223.3	148.8	73.3
HPMC 5cps	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5	19.5
Extra granular																				
HPMC K100LVCR	150	225	300	-	-	-	-	-	-	-	-									
HPMC K4MPCR	-	-	-	150	225	300	-	-	-	-	-									
HPMC K15MPCR	-	-	-	-	-	-	150	225	300	-	-									
HPMCK100MPCR	-	-	-	-	-	-	-	-	-	150	225									
PEO WSR 301												150	225	300	-	-	-	-	-	-
PEO WSR COAGULANT												-	-	-	150	225	300	-	-	-
PEO WSR 303												-	-	-	-	-	-	150	225	300
SODIUM BICARBONATE	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65	65
CITRIC ACID	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
MAGNESIUM STEARATE	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
P. WATER	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL WEIGHT	650	650	650	650	650	650	650	650	650	650	650	650	650	650	650	650	650	650	650	650

Charecterisation of Floating tablet[14]

Hardness of the tablets: Ten tablets were measured in the hardness examination. The hardness was examined using a Schleuniger hardness tester, Switzerland

Friability of the tablets: Twenty tablets of the formulation were weighed and measured in a Roche type friabilator (Electrolab, Mumbai). The tablets were rotated at 25rpm for 4min, and the samples were then reweighed. The percentage friability was calculated using the equation:

$$\%\text{Friability} = [(W_1-W_2)/W_1] \times 100$$

Tablet density: Tablet density is an important parameter for floating tablets .the tablet will float if density is less than that of gastric fluid (1.004 g/cc).Density was determined using the relationship**.**

$$D=m/v$$

$$V=\pi r^2 h$$

Weight variation: 20 tablets were taken and weighed individually on a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{2}$$

Assay of Drug Content: Ten tablets from each formulation were powdered. The powdered sample equivalent to 150mg of drug was transferred to a 100ml volumetric flask. Required amount of media was added, mixed and filtered; the filtrate was suitably diluted with media and analyzed against blank by using HPLC.

In vitro buoyancy studies[15]

Floating lag time and floating time: The floating lag time and the floating time were determined in dissolution apparatus II (Electrolab, Mumbai) in an acid environment (i.e. 0.1N Hydrochloric acid). The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating time and the duration for which the system was floating was observed visually.[12]

Matrix integrity: The swollen mass of the tablets remained intact or not was checked.[13] Matrix integrity was observed throughout *in vitro* dissolution studies.

Swelling index: The swelling behavior of dosage forms can be measured by studying its dimensional changes, weight gain, or water uptake. The swelling property of the formulation was determined by various techniques. The study is performed by immersing the tablets in 0.1 N HCl at 37±5°C and determining these factors at regular interval.[14] Water uptake (Q) is measured in terms of percent weight gain and it calculated using the formula given below,

$$Q = \frac{100(W_w - W_i)}{W_i}$$

In vitro Drug release: The in vitro drug release was studied by performing dissolution test for the tablets. The dissolution studies for the prepared formulation were conducted for a period of 24 hrs using an Electro lab model dissolution tester USP Type-2 apparatus (rotating paddle) set at 50 rpm and a temperature of 37± 0.5°C formulation was placed in the 900ml of the medium. At specified intervals 8ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed using HPLC. Three replicates for each experiment were obtained.

Kinetic modeling of drug release: The dissolution of all the batches of floating tablets of Quetiapine Fumarate was carried out. Kinetic model has described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer-Pappas model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of test.[16,17,18]

Stability Studies: To assess the physical and chemical stability of the floating tablets, stability studies were conducted for 3 month under different storage conditions mentioned in ICH guidelines. The sample containing optimized formulation were placed in vials and stored at 40^0C/75%RH. After 90 days the formulations was checked for physical appearance and drug content.[19]

Fourier Transform Infrared Spectroscopy (FTIR) studies: Quetiapine Fumarate, physical mixtures and optimized formulations were subjected for FTIR analysis. The samples were prepared on KBr-press (Startech Lab, India). The samples were scanned over a range of 4000-400 cm-1 using fourier transformer infrared spectrophotometer. Spectra were analysed for drug polymer interactions.[20]

RESULTS AND DISCUSSION

Solubility studies of Quetiapine Fumarate

The solubility study of model drug was carried out at different pH conditions; it was observed that the solubility of model drug was dependent on pH.

Table 2: solubility data of Quetiapine Fumarate.

Solubility of Model drug (API)		
S.No	**Medium**	**Solubility (mg/ml) at 25°C**
1	0.1N Hydrochloric acid pH 1.2	26.56
2	Acetate buffer pH 4.5	6.1
3	Milli Q water	4.32
4	Phosphate buffer pH 6.8	2.8
5	Phosphate buffer pH 7.2	1.86

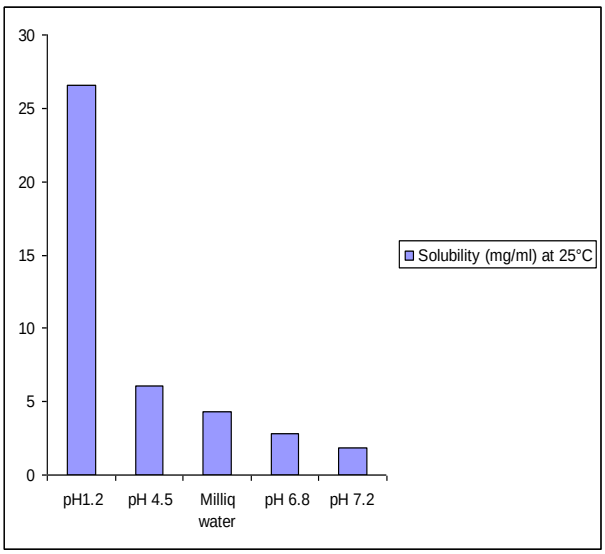


Figure 2: solubility data of Quetiapine Fumarate.

Drug-Excipient Compatibility studies

The DSC endotherms of drug with various excipients showed no change in melting point of the drug and no additional peaks were observed indicating compatibility of drug with the excipients.

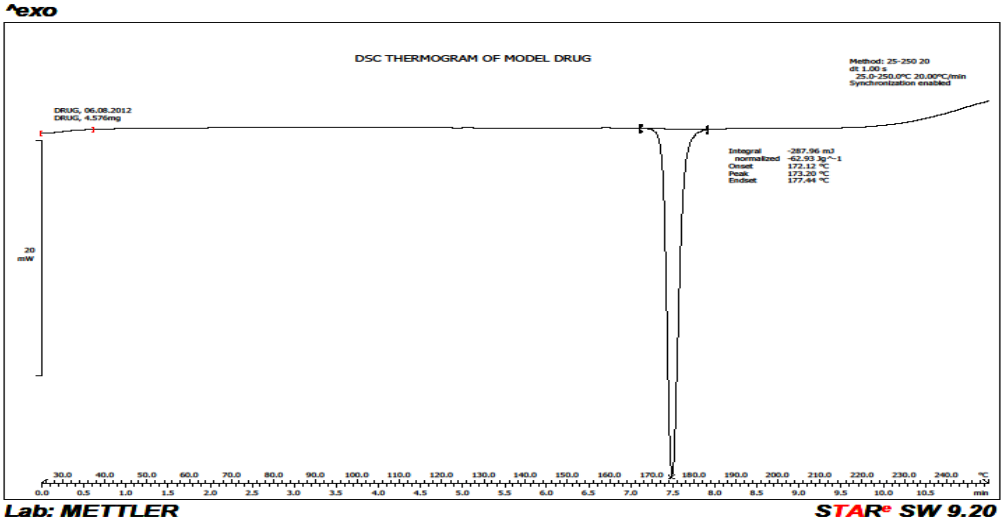


Figure 3: DSC Thermogram of Quetiapine Fumarate.

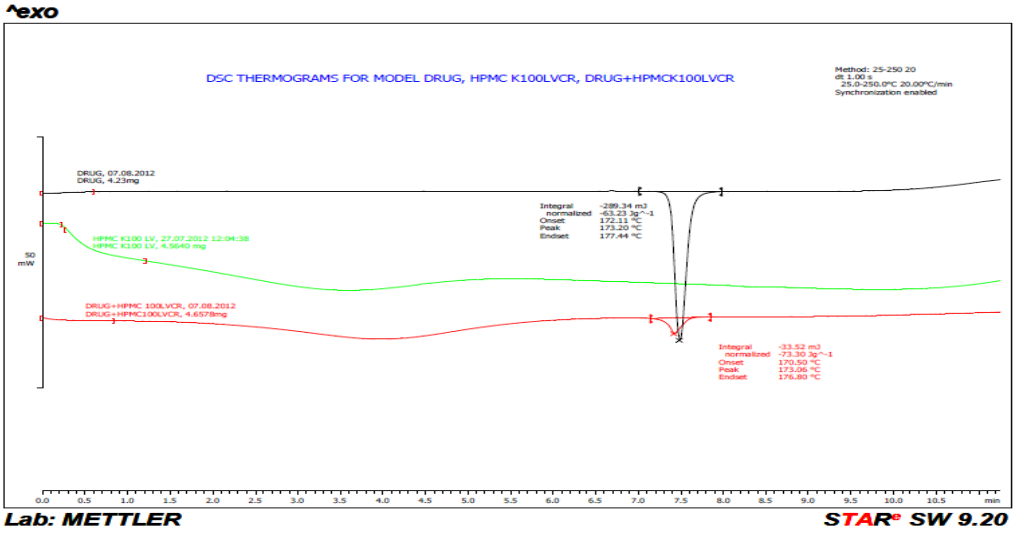


Figure 4: DSC Thermograms of API and HPMC K100LVCR Physical Mixture.

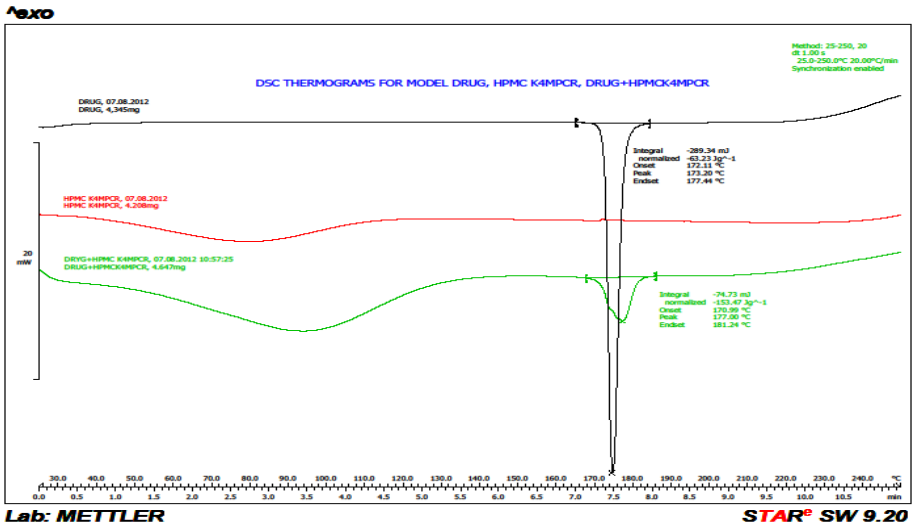


Figure 5: DSC Thermograms of API and HPMC K4M PCR Physical Mixture.

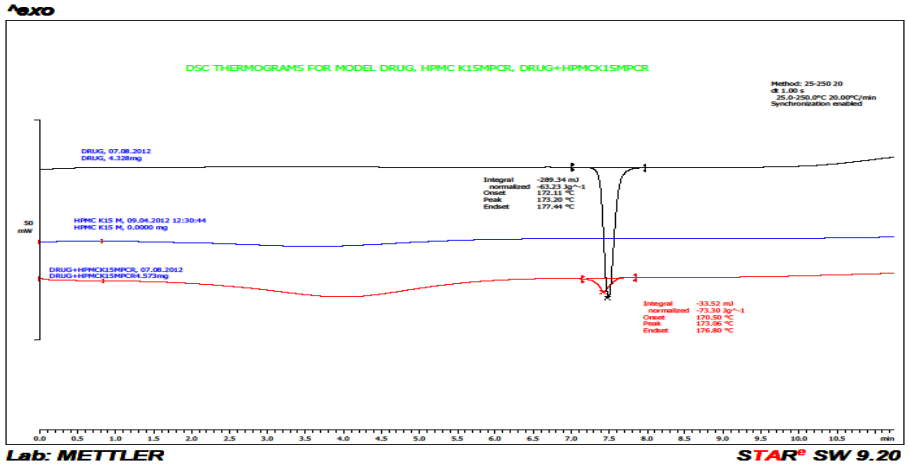


Figure 6: DSC Thermograms of API and HPMC K15MPCR Physical Mixture.

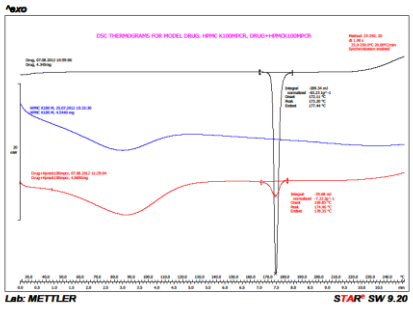


Figure 7: DSC Thermograms of API and HPMC K100M PCR Physical Mixture.

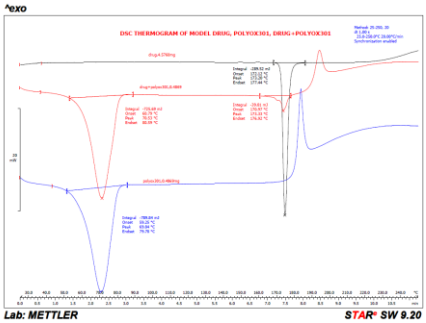


Figure 8: DSC Thermograms of API and PEO WSR 301 Physical Mixture.

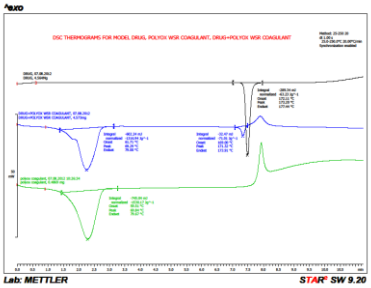


Figure 9: DSC Thermograms of API and PEO WSR Coagulant Physical Mixture.

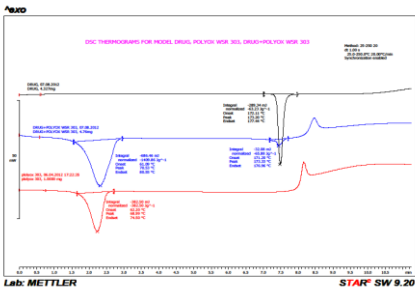


Figure 10: DSC Thermograms of API and PEO WSR 303 physical mixture.

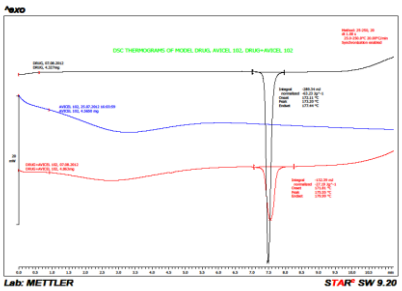


Figure 11: DSC Thermograms of API and AVICEL pH 101 physical mixture.

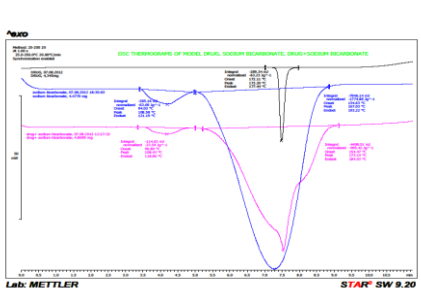


Figure 12: DSC Thermograms of API and sodium bicarbonate physical mixture

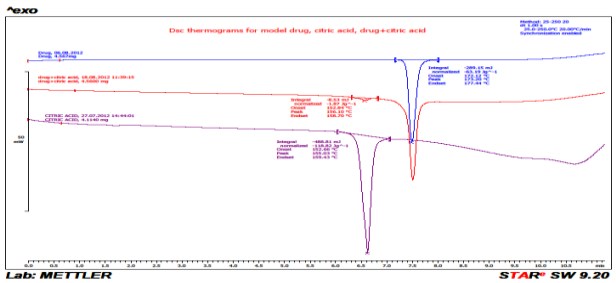


Figure 13: DSC Thermograms of API and CITRIC ACID physical mixture.

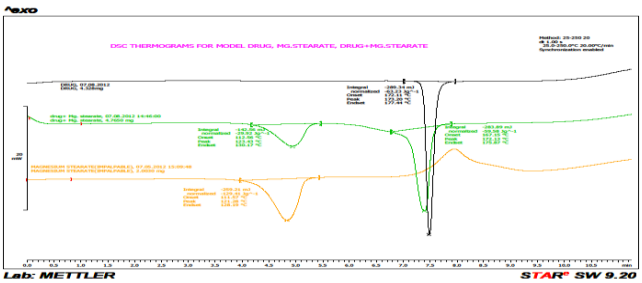


Figure 14: DSC Thermograms of API and MAGNESIUM STEARATE physical mixture.

Physical characteristics of Quetiapine Fumarate floating tablets

The floating tablets were prepared using Wet Granulation method and prepared tablets were evaluated for physical parameters like weight variation, Thickness, Tablet density, hardness, friability, and drug content. All the parameters lie within the limits.

Table 3: physicochemical properties for Formulations (Mean±SD; n = 3).

Batch No	Weight variation (mg)	Thickness (mm)±SD	Density (g/cc)	Hardness (kp)±SD	Friability (%)	Drug content (%)±SD
F1	650.5-651.6	6.5±0.03	0.897	5.82±0.01	0.52	99.89±0.73
F2	650.2-651.5	5.8±0.02	0.897	5.81±0.05	0.61	100.56±0.78
F3	648.2-650.5	5.9±0.01	0.880	5.87±0.11	0.54	100.88±0.54
F4	649.6-651.2	6.9±0.15	0.897	5.82±0.10	0.59	99.98±0.28
F5	650.5-651.9	5.8±0.14	0.872	5.91±0.02	0.68	100.21±0.26
F6	648.8-650.4	5.7±0.12	0.895	5.84±0.04	0.58	99.67±0.42
F7	649.2-652.8	6.4±0.14	0.884	5.88±0.02	0.59	100.32±0.51
F8	650.1-651.2	5.9±0.12	0.888	5.87±0.12	0.62	100.65±0.12
F9	650.5-652.8	6.5±0.16	0.865	5.95±0.14	0.52	100.81±0.92
F10	648.8-651.1	5.9±0.11	0.895	5.84±0.06	0.64	100.97±0.24
F11	650.9-651.9	5.8±0.10	0.840	5.16±0.08	0.51	99.98±0.18
F12	649.8-651.1	6.1±0.12	0.882	5.34±0.19	0.59	99.89±0.16
F13	648.9-651.8	5.7±0.11	0.875	5.42±0.14	0.58	100.78±0.98
F14	650.7-651.2	5.8±0.14	0.858	5.49±0.16	0.65	99.79±0.20
F15	649.8-651.1	6.2±0.21	0.866	5.48±0.04	0.64	99.24±0.24
F16	649.4-651.6	6.0±0.25	0.877	5.42±0.02	0.53	100.68±0.89
F17	649.5-651.9	5.9±0.02	0.884	5.39±0.10	0.55	100.54±0.32
F18	649.8-651.1	6.2±0.21	0.878	5.46±0.06	0.59	99.84±0.24
F19	650.4-651.6	6.0±0.25	0.879	5.44±0.09	0.51	100.18±0.89
F20	649.5-650.9	5.8±0.04	0.859	5.38±0.20	0.52	100.34±0.32

The floating lag time and the total floating time

The tablet swelled radially and axially during *in vitro* buoyancy studies. All the batches of tablets were found to exhibit short floating lag times in the artificial gastric fluid and the floating time of all the formulation were more than 20h except for formulations except F1, F2, F3, F4, F13 and F14 (showed a floating time of 10h, 14h 16h, 16h, 14 and 18h respectively).

Table 4: Floating properties for formulations

Batch Number	Floating lag time (seconds) ± SD	Floating time(hrs)	Matrix Integrity
F1	20 ± 0.11	10	+
F2	35 ± 0.21	14	+
F3	50 ± 0.41	16	+
F4	20 ± 0.51	16	+
F5	40 ± 0.21	24	+
F6	80 ± 0.61	24	+
F7	95 ± 0.71	24	+
F8	105 ± 0.81	24	+
F9	110 ± 0.11	24	+
F10	120 ± 0.13	24	+
F11	140 ± 0.41	24	+
F12	20 ± 0.51	14	+
F13	30 ± 0.81	18	+
F14	50 ± 0.08	24	+
F15	20 ± 0.41	20	+
F16	40 ± 0.60	24	+
F17	60 ± 0.42	24	+
F18	50 ± 0.41	24	+
F19	55 ± 0.60	24	+
F20	75± 0.42	24	+

Swelling studies

The swelling studies were performed in 0.1N Hydrochloric acid. The complete swelling was achieved by the end of 8h, so percent swelling was determined at the end of 8 h for all the developed formulations. It was inferred that formulations F7, F8 and F20 showed highest swelling indices throughout the study period. In all the set of formulations the swelling index increased with increase in the polymer concentration. This may be related to high viscosity grades of polymer.

Table 5: Swelling studies for formulations.

S No.	Batch Number	Swelling ratio							
		1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr
1	F1	Tablets showed maximum extent of erosion							
2	F2	Tablets showed maximum extent of erosion							
3	F3	Tablets showed maximum extent of erosion							
4	F4	0.75	1.98	2.08	2.12	2.24	2.48	2.65	2.92
5	F5	1.15	2.05	2.17	2.26	2.41	2.86	3.33	3.96
6	F6	1.86	2.32	2.39	2.43	2.56	3.07	3.60	4.03
7	F7	1.99	2.28	2.46	2.64	2.90	3.16	3.57	4.03
8	F8	2.22	2.41	2.58	2.78	3.04	3.28	3.89	4.24
9	F9	2.29	2.56	2.69	2.91	3.18	3.49	4.12	4.52
10	F10	2.31	2.68	2.94	3.28	3.64	4.01	4.42	4.82
11	F11	2.52	2.86	3.19	3.46	3.84	4.39	4.86	5.12
12	F12	3.13	3.38	3.57	3.69	3.84	3.99	4.06	4.14
13	F13	3.25	3.44	3.69	3.83	3.96	4.04	4.13	4.29
14	F14	3.34	3.58	3.77	3.92	4.04	4.16	4.25	4.34
15	F15	3.24	3.38	3.57	3.99	4.34	4.56	4.76	4.95
16	F16	3.45	3.64	3.89	4.14	4.35	4.59	4.84	5.12
17	F17	3.67	3.88	3.97	4.22	4.44	4.68	4.95	5.24
18	F18	3.15	3.44	3.70	4.24	4.60	4.91	5.24	5.41
19	F19	3.39	3.74	4.16	4.48	4.83	5.05	5.34	5.58
20	F20	3.55	3.87	4.24	4.67	4.95	5.17	5.46	5.74

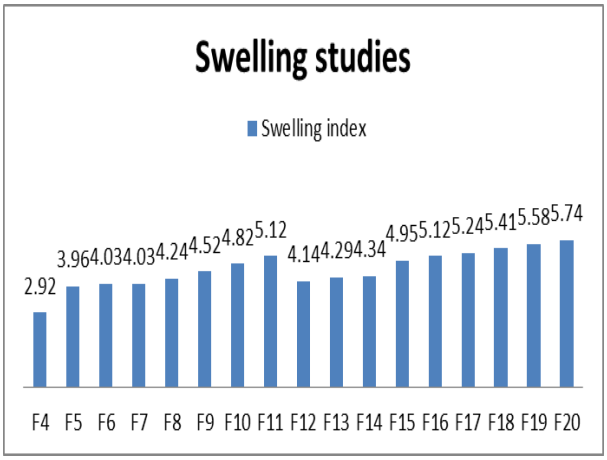


Figure 15: Swelling index values of stable formulations.

In vitro release data

The dissolution was carried out with different grades of HPMC and PEO in different ratios. in all these formulations F5, F7 F14, F16, and F18 are selected as optimized formulations which shows satisfactory drug release during final period of study.

Retardation of drug release for different grades of HPMC was found to be:

HPMCK 100MPCR > HPMCK15MPCR > HPMC K4MPCR> HPMC K100LVCR

Retardation of drug release for different grades of polyethylene oxides were found to be:

PEO WSR 303 > PEO COAGULANT > PEO WSR 301

Table No 6: In Vitro drug release for formulations F1 to F11.

Time (hrs)	Cumulative % Drug released									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F
1	25.98±0.12	23.19±0.17	20.75±0.22	21.62±0.11	19.70±0.21	18.31±0.23	18.48±0.23	15.87±0.42	13.25±0.33	17.09
2	40.11±0.32	29.82±0.21	28.77±0.37	29.30±0.31	28.33±0.13	24.76±0.23	28.77±0.34	26.86±0.23	19.88±0.23	24.94
3	60.17±0..31	39.06±0.32	37.15±0.29	37.15±0.22	36.97±0.21	34.53±0.32	36.80±0.52	27.55±0.43	25.46±0.24	29.82
4	71.33±0.24	48.31±0.26	45.17±0.21	46.91±0.34	44.12±0.22	42.03±0.41	43.08±0.33	34.18±0.54	30.69±0.42	37.15
6	81.80±0.32	61.04±0.32	53.02±0.32	55.63±0.25	51.80±0.14	49.36±0.16	50.58±0.43	43.25±0.13	35.40±0.2	44.65
8	88.43±0.16	73.43±0.28	60.52±0.42	63.66±0.27	60.34±0.15	56.51±0.27	60±0.24	50.23±0.28	45.17±0.11	53.19
10	95.58±0.41	81.45±0.29	69.41±0.41	72.73±0.15	67.15±0.16	66.10±0.28	69.24±0.22	56.51±0.25	52.84±0.33	60.34
12	100.11±0.28	86.68±0.19	76.22±0.20	77.44±0.33	74.30±0.21	69.94±0.32	75±0.21	62.79±0.34	60.17±0.41	64.88
14		93.31±0.25	84.76±0.33	85.110±.2	78.83±0.23	75.34±0.25	81.45±0.35	72.38±0.35	66.10±0.25	70.81
16		100.46±0.36	93.13±0.11	91.56±0.11	82.5±0.32	80.05±0.35	84.06±00.36	77.44±0.36	71.33±0.32	78.13
18			100.29±0.41	98.37±0.12	87.03±0.29	83.89±0.43	86.68±0.45	80.58±0.19	74.65±0.21	81.80
20					93.13±0.28	88.77±0.41	91.04±0.46	84.76±0.29	77.79±0.24	84.94
24					99.06±0.23	92.61±0.46	96.62±0.19	89.87±0.36	80.05±0.42	89.65

Table No 7: In Vitro drug release for formulations F12 to F20.

Time (Hrs)	Cumumlative % Drug released								
	F12	F13	F14	F15	F16	F17	F18	F19	F20
1	13.87±0.21	11.12±0.21	10.46±0.21	14.12±0.23	12.73±0.16	10.81±0.21	15.87±0.21	13.43±0.25	11.86±0.32
2	29.47±0.31	24.59±0.32	22.15±0.23	23.89±0.32	21.10±0.23	17.09±0.23	23.54±0.32	22.67±0.35	16.74±0.24
3	39.76±0.42	32.96±0.45	30.69±0.23	34.70±0.43	27.55±0.19	23.72±0.27	30.69±0.46	29.12±0.28	23.02±0.35
4	50.23±0.32	41.33±0.41	39.06±0.43	41.16±0.39	32.79±0.28	30±0.35	38.02±0.26	35.40±0.19	29.47±0.35
6	58.77±0.43	50.75±0.22	47.79±0.24	53.02±0.35	43.60±0.23	40.63±0.26	47.96±0.32	45.17±0.32	39.41±0.37
8	68.72±0.33	58.25±0.43	57.03±0.29	64.70±0.26	53.02±0.42	48.83±0.12	57.73±0.37	55.46±0.25	46.22±0.27
10	77.79±0.42	66.45±0.55	64.36±0.28	73.77±0.25	61.39±0.15	56.51±0.17	67.15±0.28	63.13±0.26	52.84±0.19
12	86.68±0.45	73.77±0.35	72.55±0.17	81.62±0.36	68.72±0.26	64.18±0.28	74.47±0.19	71.86±0.26	58.77±0.32
14	92.96±0.35	83.02±0.41	80.75±0.23	88.43±0.27	75.87±0.26	74.30±0.27	80.93±0.32	79.18±0.15	64.18±0.22
16	99.59±0.32	87.73±0.32	86.33±0.27	93.66±0.24	80.23±0.15	77.44±0.24	85.11±0.25	82.5±0.31	69.06±0.45
18		93.13±0.24	91.39±0.37	97.32±0.26	86.16±0.27	80.40±0.43	88.95±0.31	84.41±0.28	74.65±0.33
20		100.4±0.27	94.70±0.26	100.6±0.27	93.31±0.27	85.81±0.25	93.48±0.22	88.77±0.18	77.61±.042
24			99.24±0.32		99.59±0.23	94.53±0.32	100.1±0.26	92.79±0.23	82.52±0.23

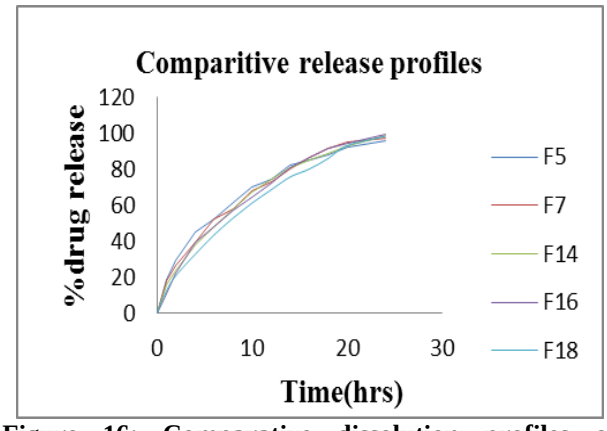


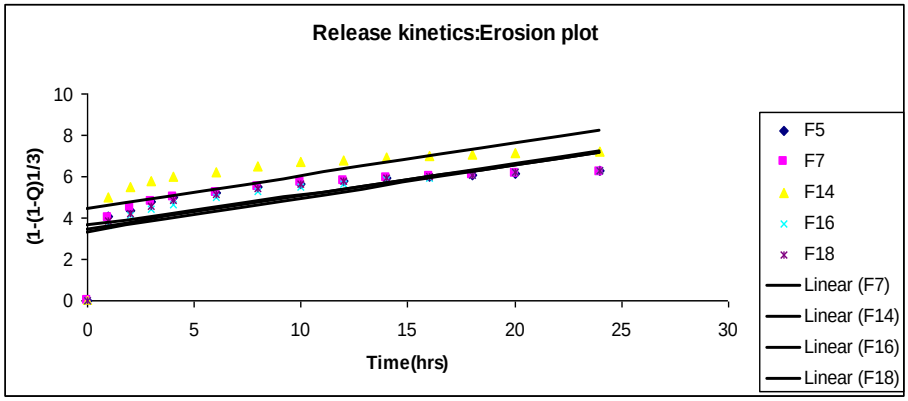
Figure 16: Comparative dissolution profiles of Optimized formulations.

Drug release kinetics

The optimized formulations were studied for drug release kinetics using zero order, first order, higuchi, korsmeyer-peppas and R^2 values of all the formulations were tabulated in table. Model drug with HPMC and PEO formulations showed Zero Order release kinetics with correlation coefficient (R^2) values indicating drug release rate does not depends on its concentration. Korsmeyer-Peppas release kinetics with correlation coefficient (R^2) values and n value $0.45<n<0.89$ indicating Anomalous diffusion or non-Fickian diffusion i.e. both diffusion and erosion controlled rate release.

Table No 7: Evaluation of drug release kinetics for optimized formulations.

Formula	R^2 values(Correlation coefficient)				
	Zero order	First order	Higuchi	osion	Korsmeyer- Peppas n values
F5	0.9111	0.83	0.9967	8675	0.5149
F7	0.9124	0.8413	0.9933	0.8519	0.5174
F14	0.9315	0.8734	0.9904	0.8519	0.6778
F16	0.9573	0.8144	0.992	0.8901	0.784
F18	0.9311	0.8598	0.994	0.871	0.7226



Stability Studies

The controlled stability samples showed comparable. Drug content and dissolution profile with the initial release, but there was slight drop in drug content and dissolution profile after the stability period. This was attributed to the curing effect produced by high temperature and humidity during the stability study. The drug content and dissolution profile was still in acceptance with the official compendia.

Table 8: Drug content Estimation for optimized formulations During Accelerated Stability studies.

Formula	%drug content					
	4week		8weeks		12weeks	
	initial	40°C/ 75%RH	initial	40°C/ 75%RH	initial	40°C/ 75%RH
F5	98.78	98.39	98.69	98.03	98.54	97.83
F7	99.19	98.81	99.14	98.65	98.14	98.85
F14	99.59	98.95	99.55	98.63	99.15	97.93
F16	99.73	98.93	99.67	98.21	99.27	97.71
F18	99.68	98.77	99.64	98.56	99.34	97.96

Table 9: Comparative drug release profile of optimized formulations after 12weeks of accelerated stability study

Time	F5		F7		F14		F16		F18	
(hrs)	Intial	40°C/75%RH	Initial	40°C/75%RH	initial	40°C/ 75 %RH	Initial	40°C/75%RH	initial	40°C/75%RH
1	18.7	18.48	17.96	18.31	15.87	12.45	10.46	12.05	12.73	15.67
2	29.33	28.77	26.33	27.67	23.54	21.15	22.15	21.7	21.1	22.4
4	45.11	43.08	39.41	42.08	38.02	38.06	39.06	31.79	32.79	37.02
6	52.2	50.58	51.97	49.58	47.96	47.5	47.79	43.76	43.6	46.96
8	61.32	60	58.08	59.1	57.73	56.02	57.03	53.82	53.02	59.73
10	69.89	69.24	67.84	67.84	67.15	67.15	64.36	61.32	61.39	65.33
12	74.34	75	73.08	74.5	74.47	72.55	72.55	68	68.72	72.47
14	82.12	81.45	79.88	78.95	80.93	80.93	80.75	73.57	75.87	79.39
16	84.97	84.06	86.33	86.06	85.11	84.33	86.33	79.23	80.23	83.11
18	87.89	86.68	91.91	91.91	88.95	88.95	91.39	87.98	86.16	88.53
20	92.3	91.04	95.05	94.37	93.48	96.7	94.7	93.31	93.31	92.48
24	96.27	95.57	97.62	97.62	99.14	98.2	99.48	98.59	98.51	97.01

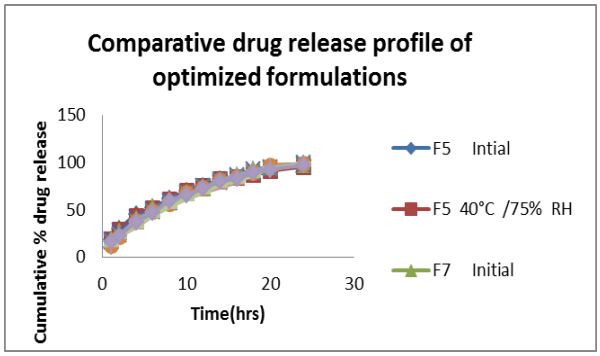


Figure 18: In-vitro release study of optimized formulations after stability for a period of 12weeks.

Tablet dropped | **Formation of effervescence** | **Tablet rising in 70 sec's** | Tablet floating | After 20 hours.

Fig 18: Pictures of optimized formulation.

Fourier Transform Infrared Spectroscopy (FTIR) studies

FTIR Studies: The FTIR spectra of optimized formulations showed characteristic peaks same as that of the pure drug at characteristic wave numbers. This indicates that there was no interaction between drug and polymer during accelerated stability conditions.

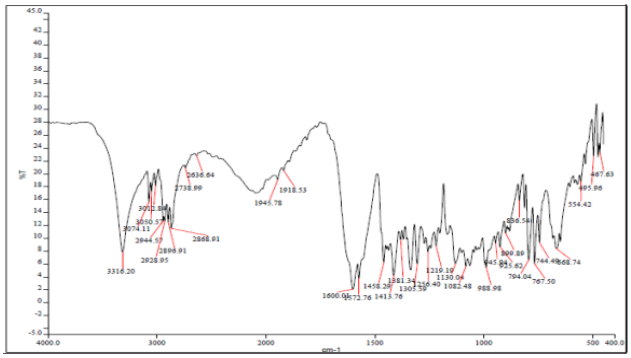


Figure 19: FTIR Spectrum of Quetiapine Fumarate.

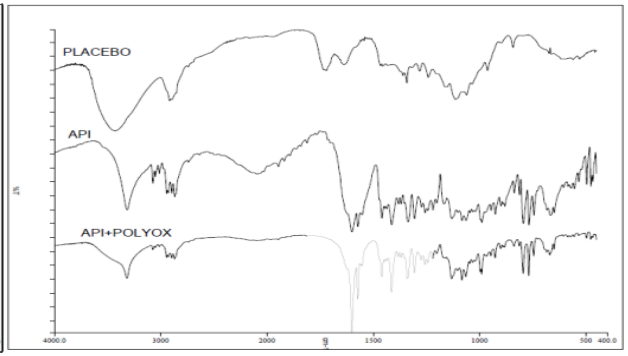


Figure 20: IR Spectra of Drug, Placebo and Optimized formulation with Polyox

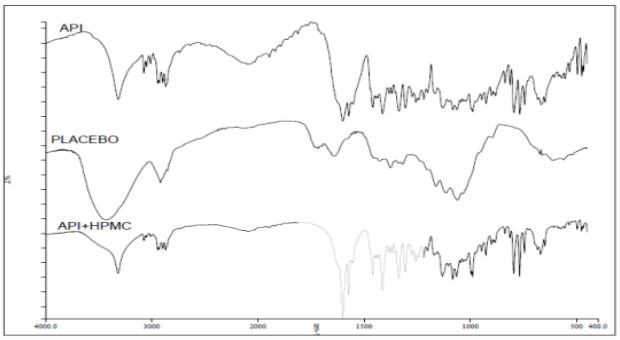


Figure 21: IR Spectra of Drug, Placebo and Optimized formulation with HPMC.

CONCLUSION

The region selective floating tablets of Quetiapine Fumarate were successfully formulated by effervescent technique. The tablets with good floating properties and matrix integrity were subjected to swelling & in vitro drug release studies. From this study there is a direct relationship was observed between Swelling index and nature of polymer and polymer concentration. Formulations F5, F7, F14, F16 & F18 were considered as optimized formulations based on drug release profiles as they were able to give 100% drug release at desired period of time (24hr). In vitro release data of optimized formulations were fitted to various kinetic models like zero order, first order, Higuchi, korsmeyer-peppas. It was evident from the results that correlation coefficient value of Zero order was closer to unity for most of formulations. Therefore it was ascertained that drug release from the formulations followed Zero order kinetics & mechanism of drug release predominantly followed non-fickian diffusion for all the polymers.

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