ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and Development of pH Independent Once Daily Matrix Tablet of Quetiapine Fumarate

R Mohapatra*[1], S Senapati[1], C Sahoo[1], S Mishra[1], A Dinda[1], and DK Sahoo[2]

[1] Department of Pharmaceutics, School of Pharmaceutical Sciences, Siksha o Anusandhan University, Kalinga Nagar, Bhubaneswar, Odisha, India: 751003.
[2]Dr. Reddy's Laboratories Ltd, Greenlands, Ameerpet, Hyderabad - A.P., India: 500016.

ABSTRACT

The major huddle in formulating weakly acidic and basic drugs is pH dependant solubility in the pH range of gastro intestinal tract. To overcome such a problem several approaches have been adopted. Use of pH dependant polymer for the extended release formulation is one of them which facilitate transition of drug from stomach to colon irrespective of any pH condition. Quetiapine Fumarate (QF) is an atypical psychotropic agent. Multimedia solubility measurements of QF were conducted in the pH range 1.2 to 7.4 at 37^0C ± 0.5^0C. Solubility of QF was found to be within the limit in water, 0.1N HCl and 4.5 acetate buffers where as in case of 6.8 phosphate buffer its solubility was low. pH dependent stability study conducted at pH range from 1.2 to 7.4 revealed maximum 2 % degradation as compared to initial concentration. Trial batches (TB) of QF matrix tablets (TB1-TB16) were formulated using suitable combinations of pH dependant polymers like Eudragit NE 30D and Polyethylene oxide (POLYOX WSR 205) along with PVK K 30, lactose monohydrate, sodium citrate and magnesium Stearate. The physical appearance, weight variation, friability study, hardness and thickness study of all the formulations were satisfactory. From *in-vitro* drug release study optimum release was observed from the formulations containing 10 % Polyox WSR 205 with 15 % Eudragit NE 30D (T_7) and 20 % of Poly ox WSR 303 & 5 % of Polyox WSR 205 (T_{15}) with lactose. FT-IR spectra (Shimadzu, Japan), DSC thermogram (DSC- 61000, Seiko Instruments, Japan) and XRD defractogramme (Philips PW 1700 with Cu Kα) supported the compatibility of API with polymers.

Keywords: Quetiapine Fumarate (QF), matrix tablets, pH dependant polymers, Eudragit NE 30D and Polyethylene oxide (POLYOX WSR 205).

Corresponding author

ISSN: 0975-8585

INTRODUCTION

The oral route of drug delivery is typically considered as the preferred and most patient convenient means of drug administration. The normal goal of an oral sustain release formulation is to maintain the therapeutic blood level over an extended period of time. To achieve this rate of drug entry to the systemic circulation must be retarded by suitable agents. In recent years many drugs (weakly acidic and basic drugs) demonstrate pH dependant solubility in the pH range of gastro intestinal tract [1-2]. Many articles have been published on different approaches to overcome the problem of pH dependant drug release from control release doses forms. Most of the approaches for pH independent drug delivery of weakly acidic or weakly basic drugs are based on the presence of buffer system or organic acids within the formulation [3-4]. The pH of human gastro intestinal tract was increase progressively from stomach (1.2-3), small intestine (6.5-7) to the colon (7.7-8). It has also been studied from different article that the average gastric emptying rate was (1-2) hrs in fasted state and (2-4) hrs in fed state and small intestinal transit was found to be 3-4 hrs .Therefore a drug which is designed as controlled release should reach the colon within 4-8hrs. During the transition of drug from stomach to colon there is change in pH. Therefore pH dependant polymer was used for the extended release formulations [5-6].

QF is an atypical psychotropic agent of dibenzothiazepine class [7]. It is used for the treatment episodes associated with bipolar I disorder and treatment of schizophrenia. It has mean elimination half-life about 6 hours so it is administered twice or thrice a day to maintain therapeutic plasma level. Once a day controlled release formulation of QF may improve patient compliance and clinical efficacy of treatment [8]. QF shows pH dependent solubility of drug from drug delivery system.

The main goal of present work was to develop once a day matrix tablets formulation for pH independent drug release from the system throughout the gastrointestinal tract [9]. It should be suitable for drugs having pH dependent solubility i.e. highly soluble in acidic pH and less soluble in alkaline pH. The objective is to test the suitable combination of polymers [10], eudragit NE 30D and polyethylene oxide (POLYOX) for pH dependant study [11-12].

MATERIALS

QF was obtained as a gift sample from Glenmark pharmaceuticals Pvt.Ltd. (Mumbai, India), PVP K-30 (Glenmark Mumbai, India), Eudragit NE 30D (Degussa, Germany), Polyox WSR 205 & Polyox WSR 303 (Colorcon Asia Pvt.Ltd.), Sodium Citrate (JRS Pharma), Magnesium Stearate (Fuji Chemicals, Japan), Avicel PH 101 (Colorcon Asia Pvt.Ltd.). All other chemicals and reagents used in the study were of analytical grade.

METHODS

Drug-excipients compatibility study

Instrumental analysis (FT-IR, DSC and XRD) of drug polymer mixture were carried out to confirm drug and polymer compatibility.

Fourier transforms infrared spectroscopy (FT-IR)

The FT-IR study was performed using FT-IR spectrometer (Shimadzu 2800, Japan). The samples (QF / polymer/ excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix in 1:5 (sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Thirty scans were obtained at resolution of 2 cm^{-1} from 4500 to 400 cm^{-1}.

Differential scanning calorimetry (DSC)

The DSC measurements were performed on a DSC- 61000 (Seiko Instruments, Japan) differential scanning calorimeter with thermal analyzer. All accurately weighed samples (about 5 mg of QF, Polymers and Formulation) were placed in a sealed aluminium pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10 ºC per min from 25 to 200 º C. An empty aluminium pan was used as reference.

X- Ray diffraction (XRD)

The X-ray powder diffraction patterns were obtained by using Philips PW 1700 with Cu Kα (λ = 1.54056Aº) radiation and a crystal monochromator, voltage: 45 mV and current: 20 A. The diffraction patterns were run at 2º per min in terms of 2θ angle.

Solubility of drug

For the pH dependant study solubility of the drug takes an important role. Solubility measurements of QF were conducted in the pH range 1.2 to 7.4 at 370C ± 0.50C. An excess of drug was added to 0.1 N HCl, 4.5 acetate buffer, 6.8 phosphate buffer and 7.4 phosphate buffer (15). After equilibrium was reached, the solution was filtered through 0.45 µm membrane filters and concentration of drug was determined spectrophotometrically at 291 nm (Evolution 300 BB, Thermo Electron Corporation, Japan). The samples were analyzed in triplicate.

***pH* dependent stability of drug**

The solution of 300 ppm was prepared in 0.1 N HCl, 4.5 acetate buffer, 6.8 phosphate buffer and 7.4 phosphate buffers. The solution was filtered through 0.45 µm membrane filters and initial concentration of drug was determined by spectrophotometrically at 250nm. The solutions are then maintained at 370C ± 0.50C. In a well labelled volumetric flask and then sample was withdrawn after a predetermined time intervals. The concentration of drug was determined spectrophotometrically at 250 nm (Evolution 300 BB, Thermo Electron Corporation, Japan). The samples are analyzed in triplicate.

Preparation of matrix tablets

QF (equivalent to 300 mg. Quetiapine) was dry blended with appropriate quantity of diluents , Sodium Citrate, Polyox and granulated using PVP K 30 (Batches 1-4, 9-16), Eudragit

NE 30D (5-8) dispersion in a planetary mixture (Kenwood). The wet mass was passed through a sieve # 12 (ASTM). The wet granules were dried in a tray dryer at a temp.500 C ± 50 C for half an hour and sieved through a sieve # 30 (ASTM). Thoroughly mixed blend was lubricated with magnesium Stearate for 2-3 minutes and lubricated blend was compressed using 19.5 mm standard concave punches (Clit Jemkey Eng.Pvt.Ltd. Ahmedabad, India). The formulation ingredients of various batches are summarized in Table.

Physical characterization of tablets

The formulated tablets were subjected to different physical characterisation studies. The hardness was determined by using Erweka hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation was performed according to the USP procedure. Assay was determined by weighing 10 tablets individually, and the drug was extracted from an accurately weighed amount of powdered granules (300 mg) with 0.1N HCl. The solution was sonicated (Bath type) for half an hour and filtered through 0.45 µm membrane filter and absorbance was measured at 291 nm after suitable dilution.

***In-vitro* drug release studies**

Drug release studies were carried out on the matrix uncoated tablets using the USP type II (Paddle) apparatus (Electrolab, Mumbai, India) at 370C ± 0.50C and at 50 rpm. The dissolution studies were performed in a 0.1 N HCI for initial 2 hours followed by pH 6.8 phosphate buffer with 1% w/v sodium lauryl sulphate from 0-20 hrs using 1000 ml media. An automatic sampling system (Electrolab, Mumbai, India) was used for sampling at fixed time intervals. Samples (5 mL) were withdrawn at predetermined time intervals, filtered through a 0.45 mm membrane filter, diluted suitably (absorbance in the normal range of 0.2 to 0.8), and analyzed spectrophotometrically., An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the volume. Dissolved drug content was determined by UV-Visible spectrophotometer (Evolution 300 BB, Thermo Electron Corporation, Japan) at 291 nm in 0.1 N HCI and at 291 nm pH 6.8 phosphate buffer with 1% w/v sodium lauryl sulphate. Percentage of drug dissolved at different time intervals was calculated using the equation generated from the standard curve. The release studies were conducted in triplicate.

Kinetic modelling of drug release

To study the release kinetics from polymeric matrix tablets, the release data in dissolution media were fitted to the well-known exponential equation (power law or Korsmeyer–Peppas equation), which is often used to describe the drug release behaviour from polymeric systems when the mechanism is not well known or when more than one type of release phenomenon is involved.

$$M_t / M_f = k . t^n \quad \text{.....(Equation 1)}$$

where Mt / Mf is the drug released fraction at time t, k is a constant incorporating the structural and geometric characteristics of the matrix tablets, n is the release exponent, indicative of the drug release mechanism. In case of Fickian release (diffusion controlled-release); the n has the limiting values of 0.45 for release from cylinders. Case II transport or relaxation controlled delivery; the exponent n is 0.89 for release from cylinders. The non-Fickian release or anomalous transport of drug occurred when the n values are between the limiting values of Fickian and Case II transport. The non-Fickian kinetics corresponds to coupled diffusion/ polymer relaxation. Occasionally, values of n > 0.89 for release from cylinders have been observed, which has been regarded as Super Case II kinetics. The dissolution profile of all the batches was fitted to first order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas, and Bekker and Lonsdale to ascertain the kinetic modelling of drug release.

Table 1: Formulation compilation

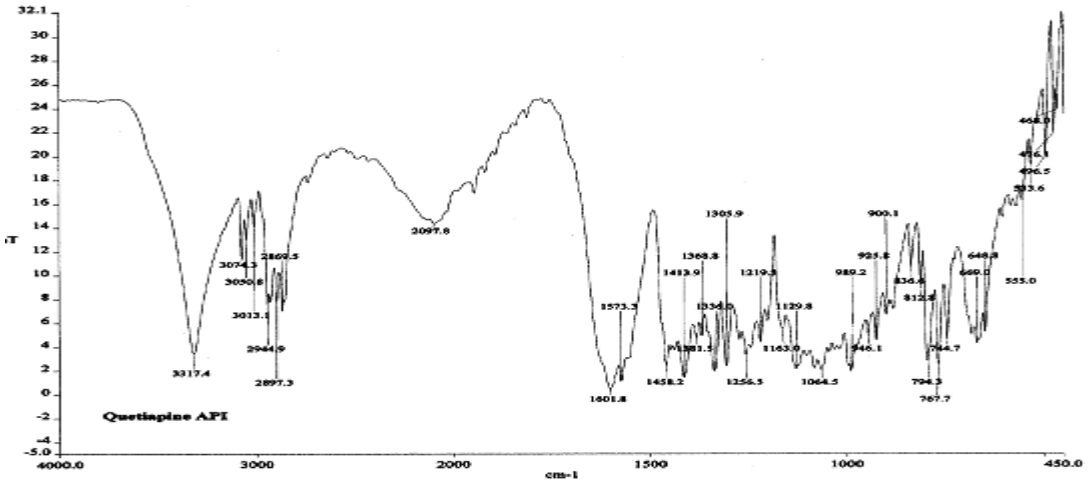
	TB1	TB2	TB3	TB4	TB5	TB6	TB7	TB8	TB9	TB 10	TB 11	TB 12	TB 13	TB 14	TB 15	TB16
Q.F	345 .38	345. 38	345. 38	345. 38	345. 38	345. 38	345. 38	345. 38	345. 38	345. 38	345. 38	345. 38	345.3 8	345. 38	345. 38	345. 38
L.M	80	80	60	100	80	60	60	100	80	80	60	100	80	80	80	120
AVICEL PH101	166.6 2	126.62	106.6 2	146.6 2	110.6 2	90.62	90.6	130.6 2	166.6 2	126.6 2	106.6 2	146.6 2	166.6 2	126.6 2	126.6 2	166.62
PVP K 30	40	40	42	40	16	16	16	16	40	40	40	40	40	40	40	40
POLYOX WSR 205	56	80	120	120	56	80	56	80	-	-	-	-	24	24	56	24
POLYOX WSR 303	-	-	-	-	-	-	-	-	56	80	120	120	40	80	40	80
SOD.CITRA-TE	80	80	80	-	80	80	80	-	80	80	80	-	80	80	80	-
EUDRAGIT 30D	-	-	-	-	80	80	120	80	-	-	-	-	-	-	-	-

ISSN: 0975-8585

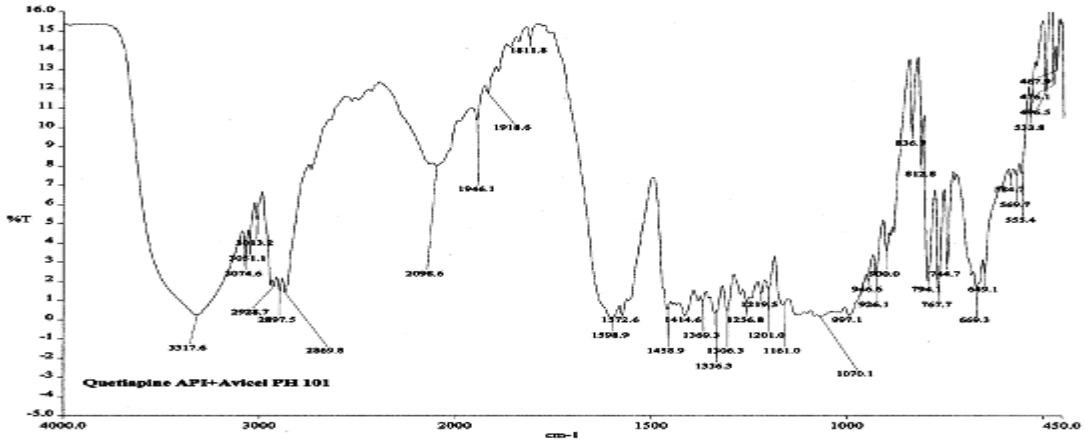
RESULT AND DISCUSSION

FT- IR study

FT-IR studies were performed to detect the possible interaction between the QF and excipients. The characteristic peaks of QF, polyox WSR 205, polyox WSR 303, eudragit NE 30D and their formulations were given below in the following figures. Comparing the spectra of drug, excipients and polymers it has been revealed that there were no significant differences in the positions of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between pure drug and polymer in their formulations.

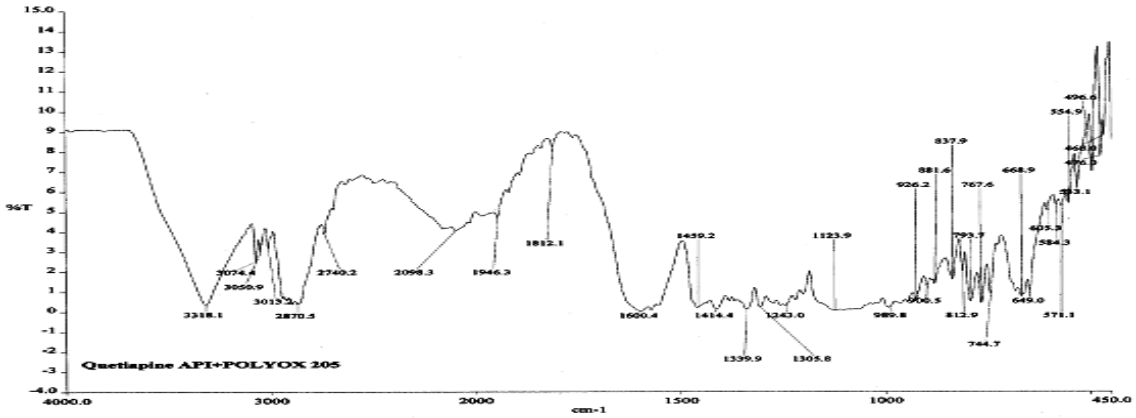


Graph 1: FT-IR spectra of API

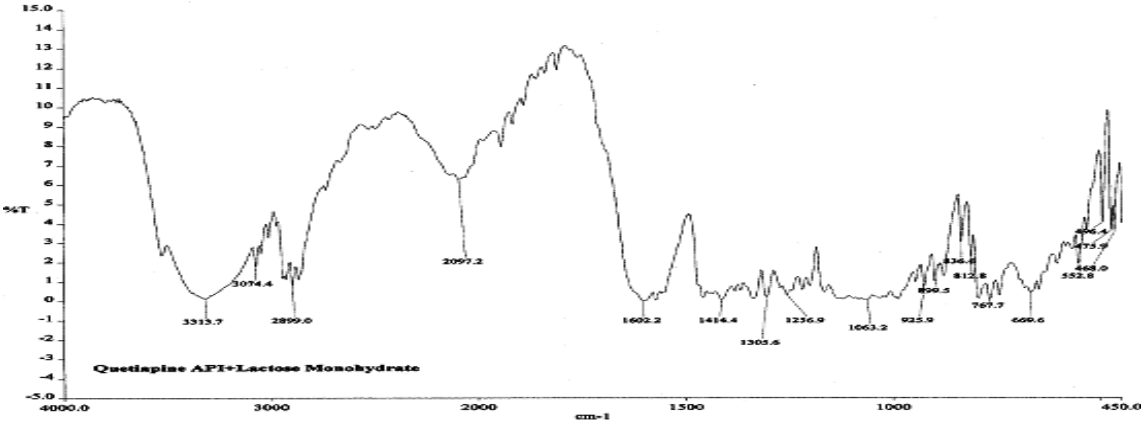


Graph 2: FT-IR spectra of API + Avicel PH 101

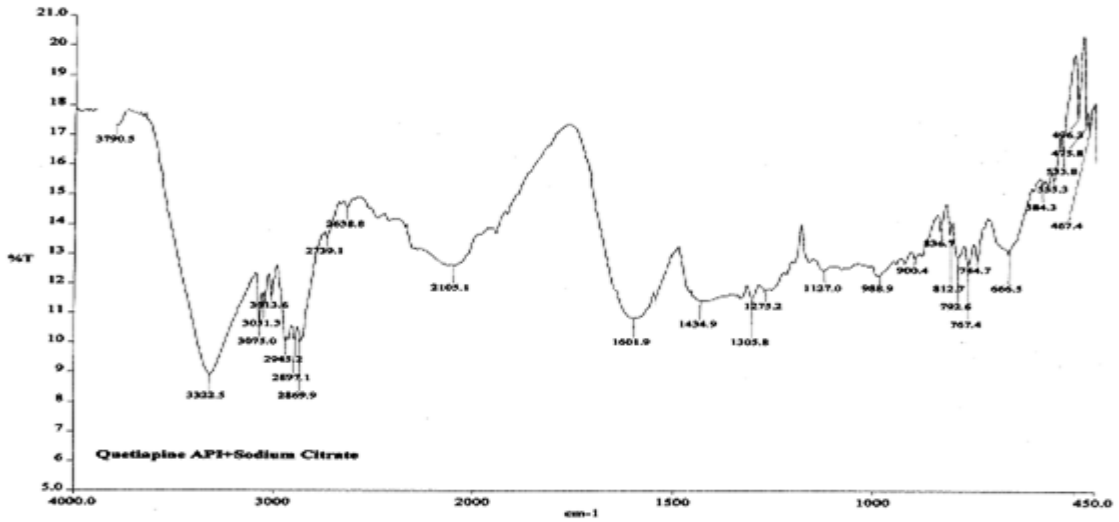
ISSN: 0975-8585



Graph 3: FT-IR spectra of API + Polyox 205

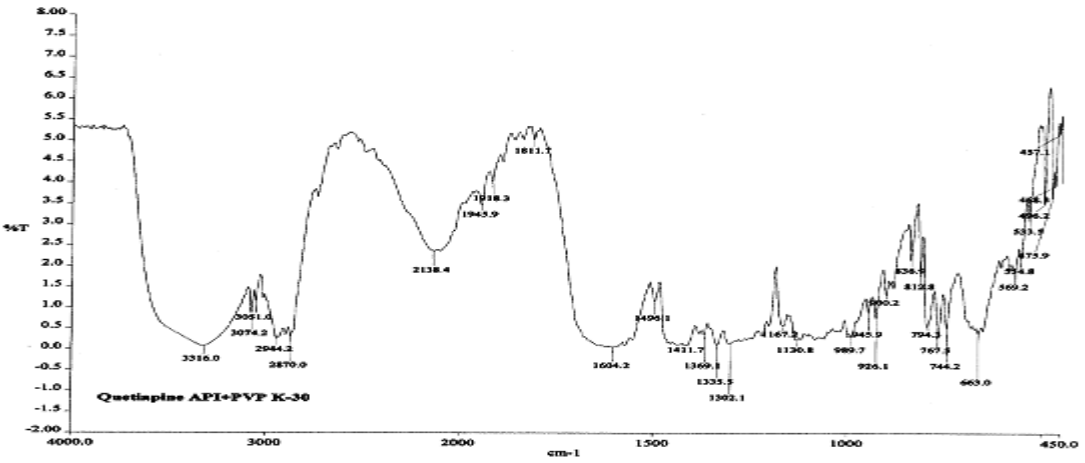


Graph 4: FT-IR spectra of API + Lactose monohydrate

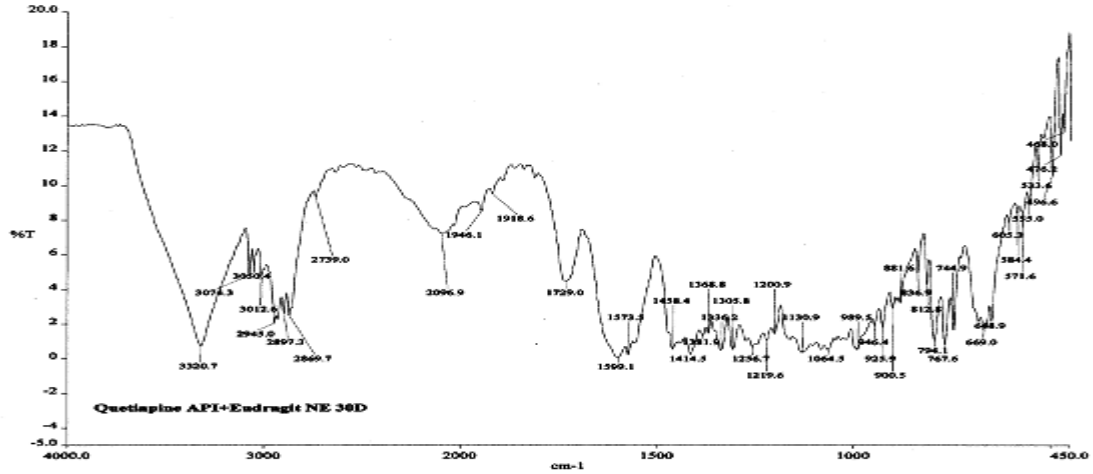


Graph 5: FT-IR spectra of API + Sodium Citrate

ISSN: 0975-8585



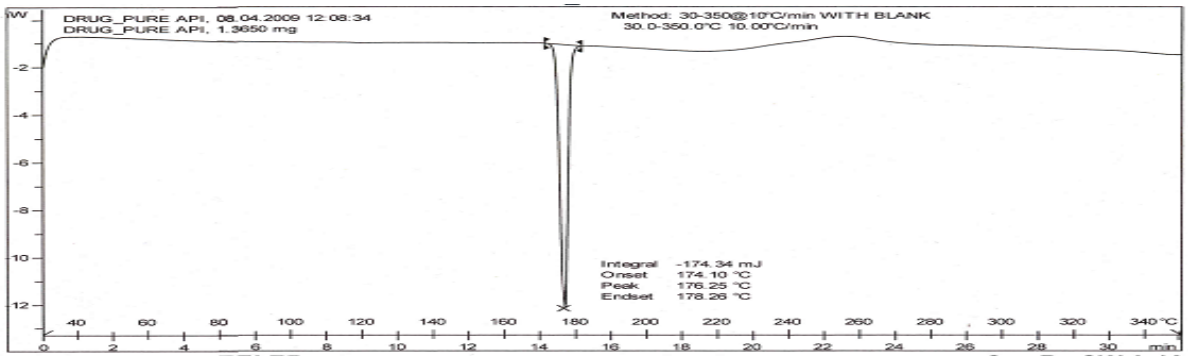
Graph 6: FT-IR spectra of API + PVP K 30



Graph 7: FT-IR spectra of API + Eudragit NE 30D

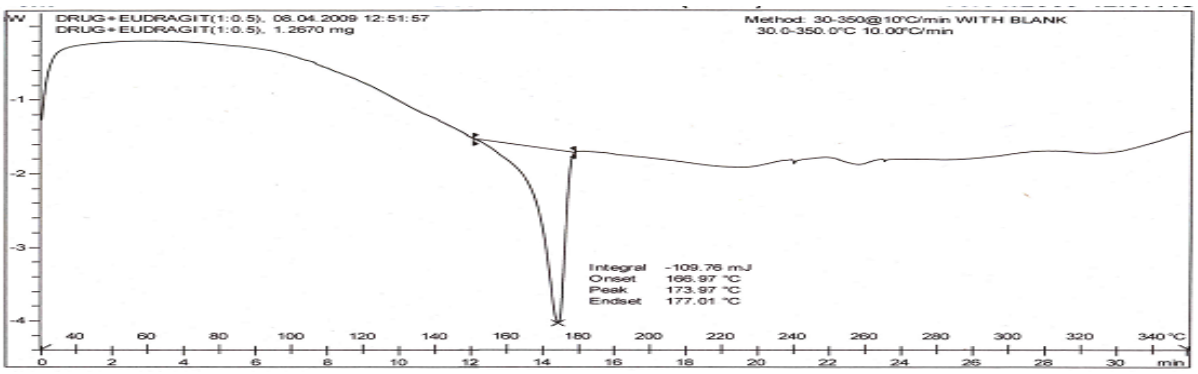
DSC study

DSC study was performed on the pure drug, polymer used in the study in different ratios and on the drug: polymer complex to access whether there is any interaction between drug and polymer. The thermogram of pure QF gave a melting endotherm at 176.25ºC. But the thermogram of polyox gave a melting endotherm at 69.08ºC. The thermogram of optimized formulation gave the same melting endotherm. So from the DSC curve it has been confirmed that there is no change in endothermic peak of the drug. And hence the drug and polymers are well compatible with each other.

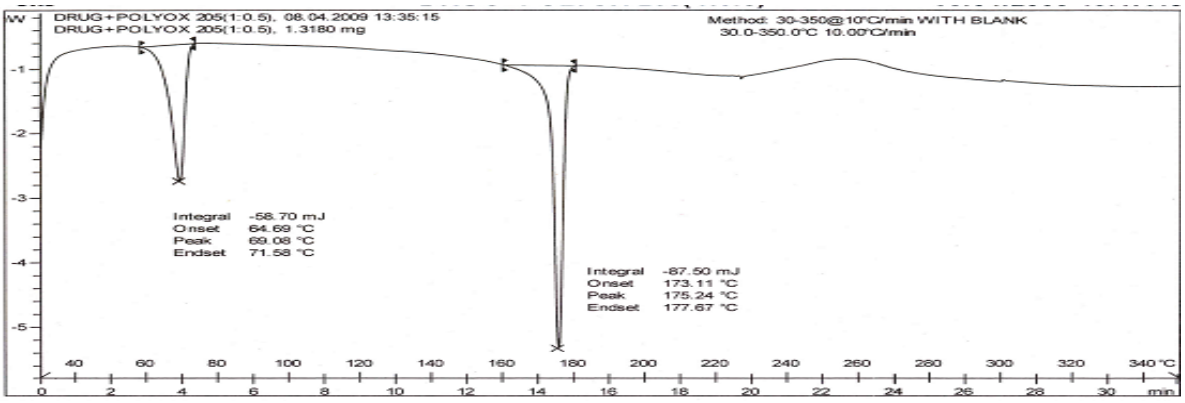


Graph 8: DSC Endotherm of API

ISSN: 0975-8585



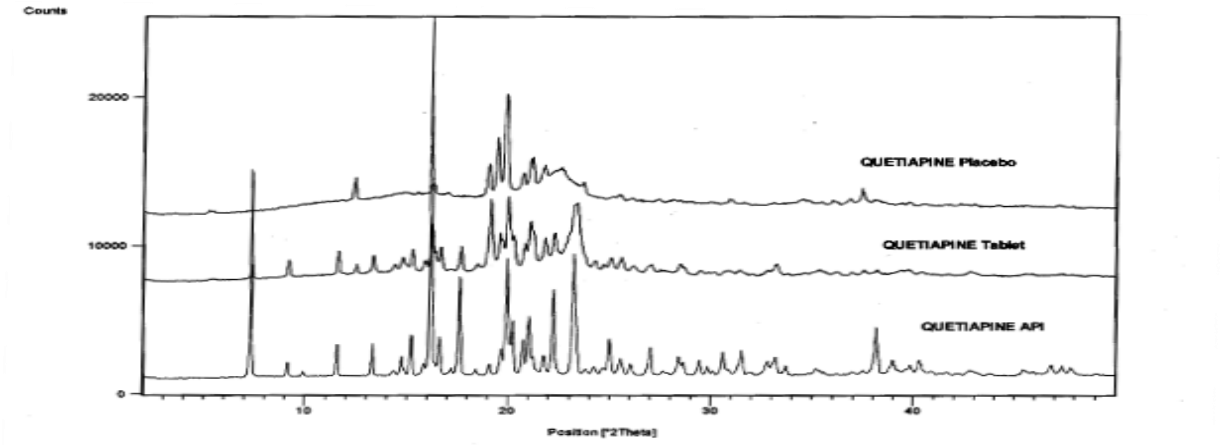
Graph 9: DSC Endotherm of API + Eudragit NE 30D



Graph 10: DSC Endotherm of API + Polyox 205

XRD study

The presence of numerous distinct peaks in the X-ray diffraction pattern indicate that QF as crystalline material with characteristic diffraction peaks appearing at a diffraction angle of 2θ at 7.82, 15.99, 22.5, 26.11 & 38.6. Formulation also exhibits a distinct pattern with diffraction peaks at diffraction angle of 2θ at 7.82, 15.99 and 22.5. The diffraction pattern of placebo was found to differ in comparison with drug. Some peaks were disappeared, some peaks were appeared & some peaks heights were decreased. Overall diffraction pattern revealed that there is no change in polymorphic properties of the drug and the drug is well distributed throughout the formulations.



Graph 11: XRD of Drug, Tablet, Placebo.

ISSN: 0975-8585

Solubility of drug

The solubility study of QF in different ph range was done. Solubility of Quetiapine was found to be within the limit in water, 0.1N HCl and 4.5 acetate buffers where as in case of 6.8 phosphate buffer its solubility was low. From the above datas it has been confirmed that Quetiapine shows pH dependant solubility that means its solubility decreases with increase in pH and falls under BCS class II.

Table 2: Multimedia solubility compilation

SL. NO.	MEDIA	BCS SOLUBILITY (% ASSAY)	MG/250 ML	BCS SOL. STABILITY (% ASSAY 24 HRS)
1	Water	101.86	470.75	99.77
2	0.1N HCl	100.47	463.18	99.99
3	4.5 Acetate Buffer	99.58	457.39	98.66
4	6.8 Phosphate Buffer	39.71	183.18	39.54

pH dependent stability of drug

Drug solution was prepared with the concentration 300 ppm in 0.1 N HCl, 4.5 acetate buffers, pH 6.8 phosphate buffers and 7.4 phosphate buffer and observed for 24 hrs at predetermined time intervals. Drug is stable at all pH ranges from 1.2 to 7.4 and showed the maximum 2 % degradation as compared to initial concentration. From the pH dependent stability studies which is shown below, has been confirmed that the drug was stable throughout 24 hrs in entire pH range.

Table 3: *pH* dependent stability of drug from 300-ppm solution (% variation in assay with respect to initial drug content)

MEDIA	TIME (Hrs)							
	1	2	4	6	8	10	12	24
0.1 N HCl	0.86	0.58	0.50	0.80	0.28	0.85	0.81	1.70
4.5 Acetate Buffer	0.77	0.50	0.85	0.57	0.64	0.16	1.74	1.13
6.8 Phosphate Buffer	0.74	0.63	0.24	0.47	0.38	0.44	0.17	0.76
7.4 Phosphate Buffer	1.69	0.13	0.26	0.84	0.61	0.45	1.35	0.28

Physical characterisation of tablets

The physical appearance, weight variation, friability study, hardness, thickness study of all the formulation were satisfactory as can observed from the table below. All the characterisation study of tablet was found to be in the range of USP limit.

ISSN: 0975-8585

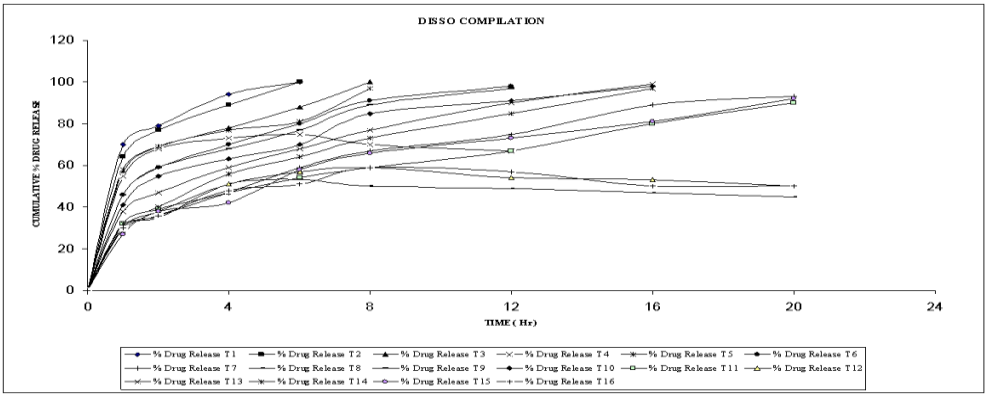
Table 4: physical characterisation compilation				
TRIAL BATCH	**WEIGHT VARIATION(MG)**	**FRIABILITY (%)**	**HARDNESS (NEWTONS)**	**THICKNESS**
TB1	798±2.35	0.14	240-251	5.47±0.1
TB2	801±2.04	0.12	237-245	5.51±0.1
TB3	800±2.03	0.17	241-250	5.47±0.1
TB4	802±2.06	0.2	239-251	5.49±0.1
TB5	798±2.41	0.24	244-249	5.47±0.1
TB6	801±2.13	0.26	239-247	5.48±0.1
TB7	802±2.35	0.23	251-258	5.45±0.1
TB8	803±2.15	0.24	249-257	5.47±0.1
TB9	799±2.38	0.28	250-256	5.49±0.1
TB10	798±2.35	0.15	248-256	5.49±0.1
TB11	801±2.04	0.22	244-251	5.47±0.1
TB12	800±2.03	0.27	251-258	5.48±0.1
TB13	804±2.06	0.25	246-251	5.48±0.1
TB14	799±2.41	0.19	241-252	5.45±0.1
TB15	803±2.35	0.23	240-250	5.47±0.1
TB16	801±2.04	0.21	242-254	5.49±0.1

In-vitro release

The *In vitro* dissolution study was carried in four batches. The first batch of dissolution was carried out by QF with polyox wsr 205 and among this four batch (T1-T4) T3 shows 98% of release within 8 hrs ,though t4 gives release up to 12 hrs but fails to meet desired concentration. Similarly second (T5-T8), third (T9-T12) and fourth (T13-T16) batch of dissolution was carried out with eudragit 30d, polyox wsr 303,and combination of polyox wsr 205 and polyox wsr 303 was used with QF. In the second batch *In vitro* dissolution study T7 shows 93% of release upto 20 hrs, although T8 sustain release upto 20 hrs but fails to meet desired concentration. In the third and fourth batch of dissolution study T11 shows 90%release in 20 hrs and T15 shows 92%release up to 20 hrs.

Table 5: *In-vitro* release compilation																
TIME (HR)	CUMULATIVE % DRUG RELEASE															
-	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	70	64	57	55	58	46	29	31	46	41	32	30	38	32	27	30
2	79	77	69	68	69	59	36	35	59	55	39	38	47	40	38	36
4	94	89	78	73	77	70	47	51	68	63	47	51	59	56	42	48
6	100	100	88	75	81	80	59	53	77	70	54	57	68	64	58	51
8	-	-	100	70	97	91	67	50	89	85	59	59	77	73	66	59
12	-	-		67	-	98	75	49	97	91	67	54	90	85	73	57
16	-	-	-	-	-	-	89	47	-	98	80	53	99	97	81	50
20	-	-	-	-	-	-	93	45	-	-	90	50	-	-	92	50

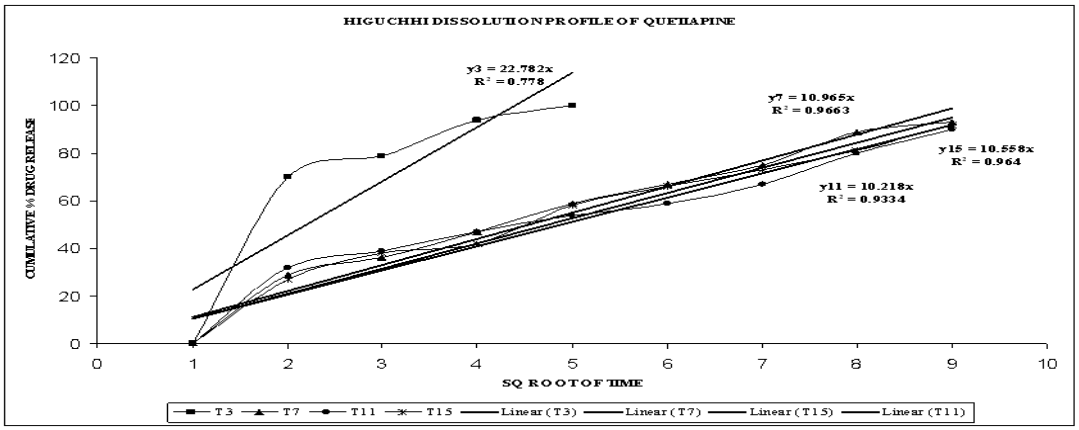
ISSN: 0975-8585



Graph 12: *In-vitro* release compilation

Kinetic modelling of drug release

The release mechanism and kinetics of the release profiles were analysed by zero order, first order, Korsmeyer-Peppas and Higuchi model. The model fitting of zero order, first order dissolution profiles of formulation T_3,T_7,T_{11},T_{15}, shows 93%,90%,92% respectively drug release up to 20 hrs. The r^2 value is grater in T_7 in zero order and r^2 value is greater in T_{11} in First order. The Korsmeyer-Peppas and Higuchi model shows the r^2 value is grater in T_7 .from the four model fitting shows that the Higuchi model shows best model fitting.



Graph 13: Kinetic modelling of drug release

Table 6: r^2 value compilation of different kinetic models				
RELEASE EQUATIONS	**T_3**	**T_7**	**T_{11}**	**T_{15}**
Zero order (r^2)	0.3561	0.5495	0.5375	0.4478
Zero order (k)	15.165	5.823	5.6015	5.405
First order (r^2)	1.6611	2.6009	3.3493	2.6509
First order (k)	1.00	0.66	0.65	0.64
Korsmeyer–Peppas (r^2)	0.6536	0.8389	0.7919	0.5045
Higuchi (r^2)	0.778	0.9663	0.9642	0.9334
Higuchi (k)	22.782	10.965	10.558	10.218

ISSN: 0975-8585

CONCLUSION

It was thus concluded that the desired drug dissolution profile could be achieved by formulating Quetiapine Fumarate as matrix SR tablets using polyox WSR 303 & polyox WSR 205 combinations. During course of study various sustained released tablet formulations (T_1-T_{16}) of QF were formulated by using eudragit NE 30D as matrix forming agent. Different percentages of polyox WSR 303 & polyox WSR 205 were used and the amount of drug was 300 mg in all batches. The tablets were evaluated for physical properties, *in-vitro* dissolution test and stability studies. After observing all the formulation for physical parameters viz. hardness, friability, weight variation and drug content. It was concluded that all of them fulfil the Indian pharmacopoeal limits. To find the most promising formulation all of them were evaluated for *in-vitro* drug release at different *pH* conditions like 1.2 for first two hours and pH 6.8 for remaining hours. From *in-vitro* drug release, optimum release was observed from the formulations containing 10 % polyox WSR 205 with 15 % eudragit NE 30D (T_7) and 20 % of poly ox WSR 303 & 5 % of polyox WSR 205 (T_{15}) with lactose. T7 batch gives desired release profile. Release kinetic studies indicated that T_7 followed the Higuchi release model.

REFERENCES

[1] JB Dressman, M Vertzoni, K Goumas, C Reppas. Adv.Drug Del Rev 2007; 59 (7): 591-602.
[2] G Ottaviani, DJ Gosling, C Patissier, S Rodde, L Zhou, B Faller Eur J Pharm 2010; 41 (3): 452-457.
[3] A Streubel, J Siepmann, A Dashevsky, R Bodmeirer. J Contr Rel 2000;67(1): 101-110.
[4] H Kranz, C Guthmann, T Wagner, R Lipp, J Reinhard. Euro J Pharm 2005; 26 (1): 47-53.
[5] H Kranz, T Wagner. Eur J Pharm Biopharm 2006;62 (1): 70-76.
[6] MVS Varma, AM Kaushal, S Garg. J Contr Rel 2005;103 (2): 499-510.
[7] SJ Baldessarini and FI Tarqz. McGraw-Hill, New York, 2001, pp.485-520.
[8] A Dinda, I Biswal, D Das, S Si, Sanjay Kumar, BB Barik, MM Safhi. Intl J Drug Del 2011; 3: 371-380.
[9] SA Charman and WN Charman. Marcel Dekker, New York, 2003, pp.1-10.
[10] V Pillay, R Fassihi. J Contr Rel 1999);59 (2): 229-242.
[11] JR Howard and P Timmins. US Patent US 4792452, 1988.
[12] M Dimitrov, N Lambov. Int J Pharm 1999;189 (1): 105-111.