Research Article

Preformulation and Formulation Studies of Novel pH Independent Controlled Release Drug Delivery System of Quetiapine Fumarate

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ABSTRACT

Advent of pharmacology, combinatorial chemistry and High Through Put Screening offered large number of synthetic drugs as a therapeutic substances. These molecules are potent to elucidate their pharmacological activity. However, pharmacokinetic properties of such molecules are rate limiting factors for its safety as well as efficacy. Most of the synthetic drug available so far in market are either weakly acidic or basic in nature, such molecules are possess narrow range of absorption profile, when administered orally for systemic therapies. The erratic and poor absorption of these molecules are closely related with different physiological pH of gastrointestinal tract. There is a continuous need for improving bioavailability of such molecules. pH independent matrix drug delivery system is one such approach that can not only improve the dissolution and absorption of weakly basic or weakly acidic drug but also release the drug for prolonged period of time. Quetiapine fumerate was selected as a model drug for our present investigation. Quetiapine shows pH dependent solubility i.e. it is soluble in acidic aqueous media but solubility of drug decreases with increase in pH of media, which can result in pH dependent release of drug from drug delivery system. Eudragit L30 D55 an enteric polymer was selected to control the release in acidic medium and facilitate the release in basic medium by providing acidic microenvironment to release the drug independent of pH. Sodium alginate and HPMC was used as retarding and matrix forming agent, respectively. The prepared granules and tablets were characterized for its pharmaceutical properties, drug release studies and release kinetics. The ratio of HPMC and sodium alginate was studied and found suitable in ratio of 1:1, 1: 1.5, and 1.5: 1 when used with 10 % acidifying and granulating agent to achieve not only desired release profile but also for better pharmaceutical standards. The present pre-formulation and formulation studies of pH independent matrix tablet had shown promising potential for delivery of pH dependent drugs that can improve the bioavailability and clinical success of dosage form.

Key words: Preformulation ; pH Independent Controlled Release Drug Delivery System ; Quetiapine Fumarate

1. INTRODUCTION

The high cost involved in the development of new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of new drug delivery systems (1). Oral administration of drug to patients at a controlled release rate; preferably at a constant linear release rate is advantageous in various clinical applications (2). Many drugs (e.g. weakly acidic and basic drugs) demonstrate pH dependent solubility in the pH range of the gastrointestinal tract. The rate at which a drug goes into the solution when it is dissolved in a medium is proportional to the solubility of the drug in medium. Hence, pH dependent solubility in the pH range of the gastrointestinal tract lead to different dissolution rates in the different parts of the gastrointestinal tract. pH dependent drug release from controlled release dosage form

could result in reduced and variable bioavailability (3). Several articles have been published on different approaches to overcome the problem of pH dependent drug release from controlled release dosage forms. Most of the approaches for pH independent drug delivery of weakly acidic or weakly basic drugs are based on presence of buffer systems or organic acids within the drug formulation (4-11).

The most commonly used method of modifying drug release is to include it in matrix system (12). Hydrophilic polymer matrix system are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance (13). Alginates have been used for preparation of controlled release formulations previously with or without addition of other release controlling polymers (14). Sodium alginate is a water soluble natural linear polysaccharide with 1, 4' – linked D mannuronic acid and L-guluronic acid residues either as blocks of the same units or as a random sequence of these two sugar residues that is soluble at near neutral pH, forms alginic acid at below pH 3. Sodium alginate forms a hydrogel upon contact with calcium ions in aqueous medium due to the physical crooslinking between the carboxylate anions of guluronate units in alginate and the calcium ions. This cross linking property of alginate has been utilized for the development of various pharmaceutical formulations such as pulsatile release from calcium alginate beads, entrapment of macromolecules in alginate-poly-L-lysine microspheres and alginate compressed matrices as extended release dosage forms (15-17).

Quetiapine Fumarate (QF) is an atypical psychotropic agent of dibenzothiazepine class. It is used for the treatment of acute manic 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 (18). Once a day controlled release formulation of Quetiapine may improve patient compliance and clinical efficacy of treatment. Quetiapine shows pH dependent solubility i.e. it is soluble in acidic aqueous media but solubility of drug decreases with increase in pH of media, which can result in pH dependent release of drug from drug delivery system.

The objective of present study was to develop once a day matrix tablet formulation for pH independent drug release from the system throughout the gastrointestinal tract It should be suitable for drugs having pH dependent solubility i.e. highly soluble in acidic pH and less soluble in alkaline pH. In this work, the objective is to test the suitability of combination of enteric polymer, Eudragit L30D 55 (preferably as granulating and acidifying agent), sodium alginate and HPMC. The effect of in-situ crosslinking of sodium alginate with calcium ions and magnesium aluminometasilicate was also studied for its effect on swelling and erosion behaviour of the tablet and dissolution profile.

2. MATERIALS AND METHODS

2.1. Materials

Quetiapine fumarate was obtained as a gift sample from Sun pharmaceuticals Pvt.Ltd. (Mumbai, India), Eudragit L30 D55 (Degussa, Germany), HPMC K 100 MCR (Colorcon Asia Pvt.Ltd.), Sodium alginate HVCR (ISP, UK), Calcium sulphate dihydrate (Compactrol, JRS Pharma), Magnesium aluninometasilicate (Neusilin, Fuji Chemicals, Japan). All other chemicals and reagents used in the study were of analytical grade.

2.2. Methods

2.2.1. Solubility of drug

Solubility measurements of QF were conducted in the pH range 1.2 to 7.4 at $37^0C \pm 0.5^0C$. An excess of drug was added to 0.1 N HCl, 4.5 acetate buffer, 6.8 phosphate buffer and 7.4 phosphate buffer (19). After equilibrium was reached, the solution was filtered through 0.45 µm membrane filters and concentration of drug was determined spectrophotometrically at 250 nm (Evolution 300 BB, Thermo Electron Corporation, Japan). The samples are analyzed in triplicate.

2.2.2.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 $37^0C \pm 0.5^0C$. in a well labelled volumetric flask and then sample was withdrawn after a predetermined time intervals. The concentration of drug was determined spectrophotometrically at 250nm (Evolution 300 BB, Thermo Electron Corporation, Japan). The samples are analyzed in triplicate.

2.2.3. Preparation of QF matrix Tablets

Quetiapine fumarate (equivalent to 200 mg. Quetiapine) was dry blended with appropriate quantity of diluent and granulated using Eudragit L30D 55 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.$50^0 C \pm 5^0 C$ for half an hour and sieved through a sieve # 20 (ASTM). Excipients (sodium alginates, HPMC, calcium sulphate and magnesium aluninometasilicate) were mixed with granules obtained by wet granulation as per compositions given in Table 1. Thoroughly mixed blend was lubricated with magnesium stearate for 2-3 minutes and lubricated blend was compressed using 10 mm standard concave punches (Clit Jemkey Eng.Pvt.Ltd. Ahmedabad, India). The

formulation ingredients of various batches are summarized in Table1.

2.2.4. Characterization of Granules

Flow property of pre-compression blends was evaluated by measuring angle of repose using fixed cone method. Bulk density; tap density, compressibility index and Hausners ratio of blends were measured using tap density apparatus (Electrolab ETD-1020, Mumbai, India). Moisture content was determined using moisture balance equipped with an infrared unit (Sartorius MA-45). The characteristics of granules and matrix tablets of optimized batches of Quetiapine are summarized in Table 3.

2.2.5. Characterization of tablets

The properties of the compressed matrix tablet, such as hardness, friability, weight variation and assay were determined using reported procedure. Briefly; hardness was determined by using Erweka hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation was performed according to the IP procedure. Assay was determined by weighing 10 tablets individually, and the drug was extracted from an accurately weighed amount of powdered granules (200 mg) with 0.1N HCl. The solution was sonicated for half an hour and filtered through 0.45 µm membrane filter and absorbance was measured at 250 nm after suitable dilution.

2.2.6. 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 $37^0C \pm 0.5^0C$ and at 75 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 900 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 lmax 250 nm in 0.1 N HCI and at lmax 250 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.

2.2.7. Determination of swelling and eroding behavior

The medium uptake into the preparation and erosion were determined after immersion in the medium. Weighed samples were placed in dissolution vessels and continued as per dissolution method. After a selected time interval each dissolution basket was withdrawn, blotted to remove excess water, and weighed on an analytical balance. The wetted samples were then dried in an oven at 70°C for 24 hours, allowed to cool in desiccators, and finally weighed until constant weight was achieved (final dry weight). The increase in weight of the wet mass represents the medium uptake [2].

Swelling (%) and erosion (%) were calculated according to the following formulas:

The percentage increase in weight due to absorbed liquid or water uptake was estimated at each time point from following equation:

$$\% \text{ Weight change} = W_1 - W_0 / W_0 * 100 \quad \text{—} \quad (1)$$

$$\% \text{ Erosion} = W_0 - W_2 / W_0 * 100 \quad \text{—} \quad (2)$$

where W_1 is the weight of the matrix after swelling, W_2 is the weight of the eroded matrix, and W_0 is the initial weight of the matrix.

Three different samples were measured for each time point, and fresh samples were used for each individual time point. All experiments were done in triplicate.

2.2.9. Kinetic modeling 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 (21)

$$M_t / M_f = k \cdot t^n \quad \text{———} \quad (3)$$

where M_t / M_f 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 (21).

The dissolution profile of all the batches was fitted to first-order (22-23),Higuchi, (24-26) Hixon-Crowell (27), Korsemeyer and Peppas,(21, 28-29) and Bekker and Lonsdale (30-31) to ascertain the kinetic modeling of drug release. All the mathematical models were fitted as per the

review Modeling and comparison of dissolution profiles by Paulo Costa et al (32).

3. RESULT AND DISCUSSION

3.1. Solubility of drug

QF is highly soluble in 0.1 N HCl, having quantitative solubility 35.6 mg/ml. As pH increased, solubility decreased significantly (fig.1), i.e. pH 4.5 acetate buffer (5.8 mg /ml), pH 6.8 phosphate buffer (2.1 mg/ml), and pH 7.4 phosphate buffer (1.3 mg/ml). It showed pH dependent solubility, highly soluble in acidic pH but poorly soluble in alkaline pH.

3.2. pH dependent stability of drug

Drug solution was prepared with the concentration 300 ppm in 0.1 N HCl, 4.5 aceaate buffer, pH 6.8 phosphate buffer and 7.4 phosphate buffer. And observed for 24 hrs at predetermined time intervals. Drug is stable at pH range from 1.2 to 7.4 and showed the maximum 2 % degradation as compared to initial concentration (table 2).

3.3. Characterization of QF matrix tablets

Different combinations of sodium alginate and HPMC were used to prepare the matrix tablets for sustained release of QF. All physical parameters were acceptable due to granule flowability and compressibility properties in all eleven formulations (table 3a and 3b). Tablet weight of all the formulations were in the range of 400 ± 5 mg. Tablet thickness of all the formulations were observed in the range of 5.07 ± 0.1 mm. Hardness of the tablets was in the range of 70-90 N. Percentage weight loss in the friability test was found to be 0.2 to 0.5 % in all the cases. All the prepared matrix tablets were found to be non-disintegrating in water, 0.1 N HCl and phosphate buffer of pH 6.8. The tablets of all the prepared batches contained Quetiapine fumarate equivalent to quetiapine within 100 ± 5 % of the labeled content

3.4. Selection of granulating agent

QF was sticky in nature with poor flow properties (Table 3) and the formulation without wet granulation was difficult to compress uniformly (Batch I and II). Hence wet granulation method was selected for the development QF eroding tablet by improving overall granulation properties.

As the drug is freely soluble in acidic medium and poorly soluble in basic medium, Eudragit L30 D55 an enteric polymer was selected to control the release in acidic medium and facilitate the release in basic medium by providing acidic microenvironment to release the drug independent of pH. The batches I and II were prepared without granulation using Eudragit L 30 D 55, showed the burst release in acidic media. Eudragit L 30D 55 was selected as granulating agent and also provides the acidic microenvironment in alkaline pH where solubility of drug is minimum.

3.5. Selection of polymers

Sodium alginate is an anionic linear polysaccharide that is soluble at pH 3 and does not appear to swell at pH 1.2. SA shows a pH dependent release when it was used extra granularly, to further retards the release in acidic medium. However rapid swelling and erosion observed at pH 6.8. Calcium cross-linking with sodium alginate significantly affect the release profile.

HPMC K100 MCR, a non-ionic pH independent polymer was used to form a rapid gel formation, which prevents wetting of the interior and disintegration of the tablet core. It encourages a strong, tight gel formation compared to other cellulosic polymers.

3.6. Swelling study

Swelling pattern was studied at dissolution media which was used for in vitro release profile i.e. at pH 1.2 for 2 hrs and pH 6.8 with 1% SLS (table 4). In batch No. I the swelling was comparatively slow with batch II. SA is slowly hydrated as compared to HPMC but slowly disintegrated. B. No. I disintegrated after 4 hrs while B. No. II after 3 hrs.

B. No. III, with Eudragit L 30 D 55 (10%) and HPMC (7.5%), was showed the optimum swelling around 235 % for initial 2 hrs and maintained at 178 % after 8 hrs. It showed that HPMC was required for initial get strength but did not erode in alkaline pH. B. No. IV, with Eudragit L 30 D 55 (10%) and sodium alginate (7.5%), was showed swelling around 335 % and completely disintegrated after 4 hrs. It showed that SA required for initial swelling as well as erosion in alkaline pH. From swelling data of these two batches, the combination of SA and HPMC was essential for initial swelling where drug is highly soluble as well as slowly and controlled erosion in alkaline media where drug is less soluble than acidic pH. When the ratio of HPMC and sodium alginate was 1: 1.5, it showed the desirable swelling and erosion as compared with ratio of 1.5: 1. When the ratio of HPMC and sodium alginate was 1: 1 in B. No. IX, it showed the desirable swelling and erosion as compared with ratio of 1.5: 1

B. No. V showed the optimum swelling in initial 2-3 hours and then swelling get reduced. It showed the 80 % erosion in 8 hrs, which was desirable to provide the pH independent release for the drugs having pH dependent solubility.

3.7. Erosion Study

The result of erosion study (table 5) showed that formulation containing sodium alginate alone was not intact in acidic medium but erodes fast in basic medium. In the basic medium there was visible break in swelling profile and completely eroded within 3 hrs, while formulation of sodium alginate and HPMC with enteric polymer shows less erosion as compared to sodium alginate or HPMC alone. The HPMC with enteric

Table 1; Composition for Quetiapine Fumarate matrix tablets

Ingredients	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Quetiapine Fumarate	58.09	58.09	58.09	58.09	58.09	58.09	58.09	58.09	58.09	58.09	58.09
Lactose anhydrous	33.41	33.41	23.41	23.41	18.41	13.41	13.41	18.41	18.41	15.91	10.91
Eudragit L30 D55	0	0	10	10	10	10	10	10	10	10	10
HPMC K100 CR	7.5	0	7.5	0	7.5	7.5	7.5	5.0	6.25	7.5	7.5
Sodium alginate	0	7.5	0	7.5	5	5	5	7.5	6.25	5	5
Calcium sulphate	0	0	0	0	0	5	0	0	0	2.5	7.5
Magnesium aluninometasilicate	0	0	0	0	0	0	5	0	0	0	0
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1
Tablet weight (mg)	400	400	400	400	400	400	400	400	400	400	400

Table 2; pH dependent stability of drug from 300-ppm solution (percentage variation in assay w.r.t 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

Table 3; Properties of granules and tablet

Parameters/ Batch	Pure drug	I	II	III	IV	V
Granules						
Angle of Repose (^{0})	38.50± 0.6	32.08± 0.8	35.21± 0.5	23.2± 0.3	25.21± 0.5	23.± 0.8
Bulk Density (gm/ml)	0.54	0.45	0.50	0.47	0.53	0.60
Tap Density (gm/ml)	0.82	0.74	0.91	0.78	0.88	0.74
Carr'Index	40.5± 0.5	38.7± 0.3	45.0± 0.3	18.7± 0.3	20.0± 0.3	18.8± 0.3
Hausners Ratio	2.14± 0.4	1.6± 0.3	1.3± 0.5	1.6± 0.3	1.3± 0.5	1.2± 0.3
Moisture Content (%)	-	-	-	1.54± 0.2	1.37± 0.4	1.3± 0.2
Total drug content (%)	-	98.0	102.3	100.2	98.6	99.4
Tablets						
Weight Variation (%)	-	± 7.0	± 5.0	± 5.0	± 3.0	± 3.0
Friability (%)	-	0.27	1.07	0.47	0.62	0.20
Hardness (N)	-	80 ± 5	90 ± 5	85 ± 5	85 ± 5	85 ± 5
Drug content (%)	-	103.2	98.6	99.4	99.0	100.1

Table 4:Swelling study of Quetiapine fumarate matrix tablet

Time (Hrs)	Percentage swelling										
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**
1	247.3	263.0	208.5	248.5	215.1	439.0	220.3	218.7	188.9	274.6	248.4
2	273.0	365.0	235.0	335.0	240.0	408.0	272.3	255.3	245.3	345.2	367.5
3	313.6	CE	315.0	384.3	301.0	CE	341.0	321.0	310.8	**CE**	**CE**
4	CE		228.2	**CE**	220.6		336.4	250.6	278.5		
6			198.0		255.0		377.0	225.0	235.2		
8			178.5		CE		433.7	188.7	198.5		

Table 5: Erosion study of Quetiapine fumarate matrix tablet

Time (Hrs)	Percentage erosion										
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**
1	45.0	44.5	16.6	40.5	14.2	60.0	19.2	12.2	20.8	57.8	54.2
2	62.0	61.5	20.2	66.7	23.7	64.0	31.5	25.7	28.4	68.7	65.5
3	71.0	**CE**	25.7	78.4	29.3	**CE**	46.0	30.8	36.2	**CE**	**CE**
4	87.8		34.5	**CE**	39.2		51.3	37.3	40.7		
6	**CE**		58.3		61.5		53.4	62.5	68.5		
8			84.8		81.0		58.0	83.0	88.2		

polymer shows less erosion as compared to sodium alginate with enteric polymer. The formulation comprising cross linking of sodium alginate and calcium shows more erosion while the formulation with 5% MAS showed very less erosion in all the studied batches.

The erosion experiments with enteric polymer, HPMC and sodium alginate demonstrated that drug release was controlled by initial swelling for 2-3 hours and then followed by erosion in alkaline pH. It was achieved because of acid insoluble nature of sodium alginate and Eudragit L30 D55, which showed less or no erosion in acidic medium. The addition of pH independent HPMC K100 MCR along with other polymers showed increase in get strength at initial 2-3 hrs and predictable, controlled erosion in alkaline pH to facilitate the drug release independent of pH.

3.8. Drug release study

Results showed that erosion plays a significant role and coincides with drug release during dissolution process (figure 2). The formulation swells without significant erosion in acidic medium for 2 hrs where release control is required for drugs having higher solubility in acidic pH and then erosion of the polymer started in alkaline pH. For the desired release profile, tablet should erode in 8 hrs with percentage erosion more than 80%. It gave the controlled erosion with desirable pH independent release profile for drug having pH dependent solubility. The ratio of HPMC and sodium alginate was studied and found suitable in ratio of 1:1, 1: 1.5, and 1.5: 1 when used with 10 % acidifying and granulating agent. This is the unique combination to control the initial burst release for highly soluble drug in acidic pH as well provide pH independent release in alkaline pH by erosion where drug solubility is minimum.

Based on release profile shown by B. No. V, VIII and IX clearly showed that release rate and rate of erosion progress in a similar rate and drug released completely independent of pH (figure 3, 4, and 5)

3.9. Kinetics of drug release

The mechanism of drug release from matrix tablets during dissolution tests in 0.1 N HCl and phosphate buffer pH 6.8 was determined using zero-order, first-order, and Higuchi

equation (table 6). These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix (33).

Therefore, the dissolution data were also fitted to the well-known exponential equation (Korsmeyer–Peppas equation), which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved (33)

The n values for all the formulations ranged from 0.4759 to 0.49635, indicating that the release mechanism was non-Fickian or anomalous release. It can be inferred that the release was dependent on both drug diffusion and polymer relaxation. Because the values of n were closer to 0.5, in most cases, good correlation coefficients (r values ranged from 0.9920 to 0.9956) were obtained for the kinetic parameters based on Korsmeyer–Peppas equation. It can be concluded that the drug release was totally based on diffusion, and erosion. Based on the swelling and erosion studies, it was observed that the matrix tablets undergo swelling (Figure 6) as well as erosion (Figure 7) during the dissolution study, which indicates that polymer relaxation had a role in the drug release mechanism. However, it can be concluded that the effect of diffusion on drug release was more than the effect of polymer relaxation as the values of n were nearer to 0.5.

Table 6; Dissolution data model fitting

Release equation	V	VIII	IX
Diffusion coefficient (n)	0.4759	0.4963	0.4955
Korsmeyer–Peppas (r^2)	0.9956	0.9920	0.9939
	k = 26.55	k = 26.55	k = 26.55
First order (r^2)	0.9660	0.9622	0.9578
Higuchi (r^2)	0.9947	0.9920	0.9939
Baker and Lonsdale (r^2)	0.9770	0.9654	0.9653
Hixon and crowell (r^2)	0.9451	0.9479	0.9441

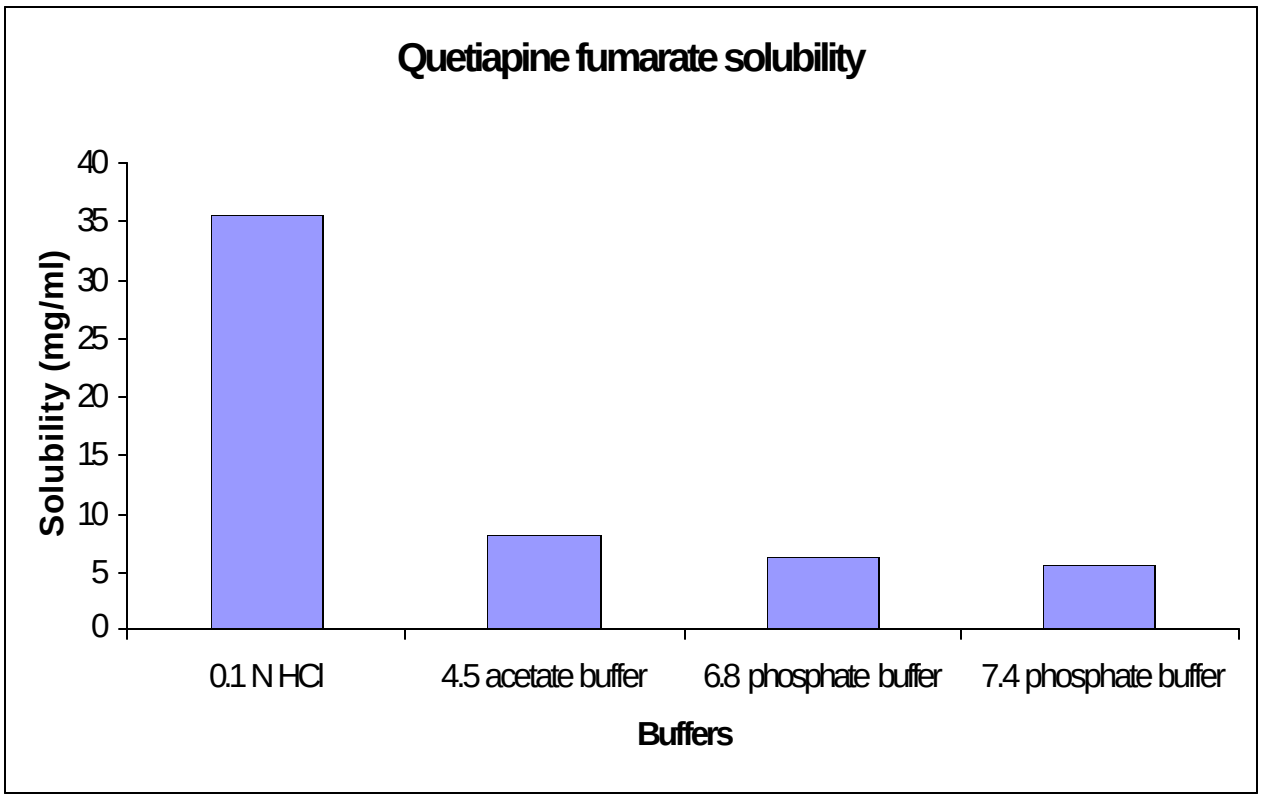

Figure 1; Quetiapine fumarate quantitative solubility

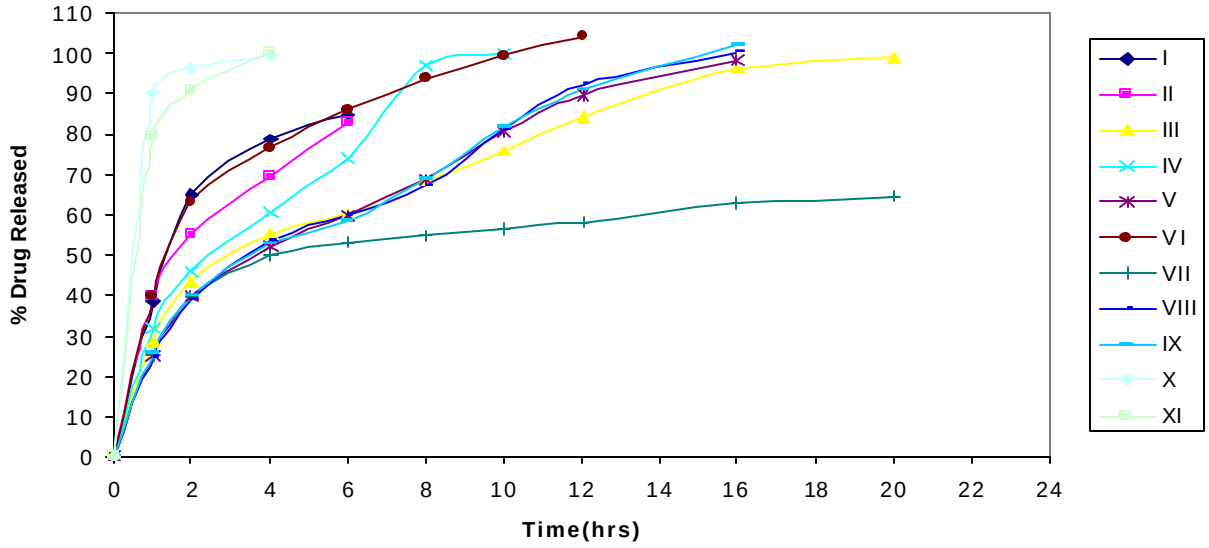

Figure 2: Dissolution profile of Quetiapine Fumarate matrix tablets

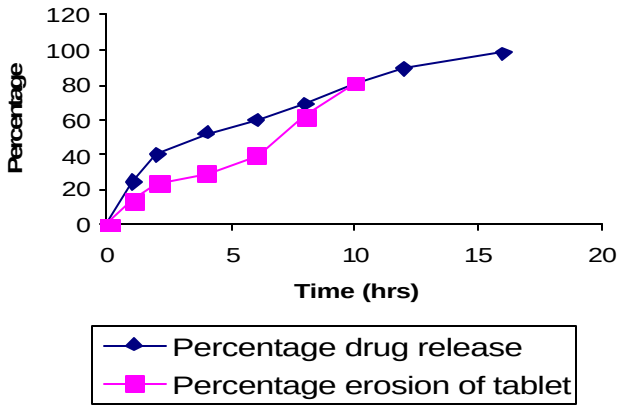

Figure 3: Correlation of drug release and erosion B. No. V

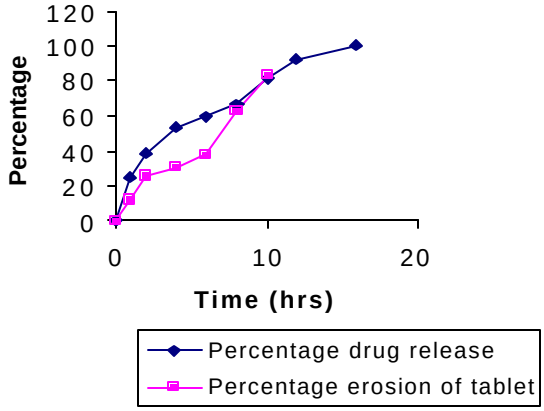

Figure 4:Correlation of drug release and erosion B. No. VIII

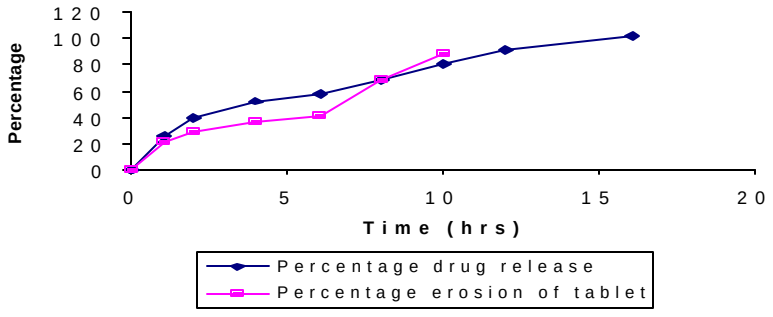

Figure 5; Correlation of drug release and erosion B. No. IX

4.0. CONCLUSION

From the results from present study it appears that the release of Quitiapine Fumarate having pH dependent solubility was significantly influenced by the characteristic of the polymers used. Because Eudragit L30 D55 is enteric polymer and sodium alginate is acid insoluble polymer, both controls release in acidic medium and facilitate drug release in basic medium. As a result, release of Quetiapine from these formulations was completed within 10-12 hrs. The combination of enteric polymer Eudragit L30 D55, pH dependent sodium alginate and pH independent HPMC K100 MCR gives optimum release profile by providing controlled erosion, with good intactness to the tablet. Addition of magnesium aluminuminosilicate significantly retards the release of drug. The effect of cross linking between divalent calcium and sodium alginate significantly affect the release profile showing need of optimization of the ratio to give desired dissolution with good intactness. This can be expected that modified release QF matrix tablet will reduce the variability and reduced bioavailability.

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