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In-vivo study of quetiapine fumarate superporous hydrogels

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***Abstract*---**This study aims to design and evaluate a gastroretentive drug delivery system using second generation Superporous hydrogels using Factorial design approach. Optimized formulation was assessed for pharmacokinetic parameters by In-vivo study. Pharmacokinetic analysis of Quetiapine Fumarate plasma concentration–time data provided the following pharmacokinetic parameters like Cmax values ranging (690.58 ± 1.1 ng/mL to 524.37 ± 1.6 ng/mL), Tmax values ranging (1.5 ± 0.0 to 6.0 ± 0.0 Hours), AUC values ranging (5345.67 ± 11.34 h.ng/mL to 5345.67 ± 4.59 h.ng/mL). Results obtained for the formulated product prepared with superporous hydrogel technology shows prolonged release while maintaining Q Value with reduce plasma drug fluctuations in comparison to the Pure drug.

***Keywords*---**superporous hydrogel, gastro retentive drug delivery system, quetiapine fumarate, in-vivo, pharmacokinetics.

Introduction

The gastro retentive drug delivery system (GRDDS) is designed to stay in the stomach for a long time and release its active ingredients, ensuring continuous and prolonged drug delivery to the upper digestive tract[1]. It is well known that many factors affect the gastric emptying of human conventional dosage forms, and the time required for treatment varies greatly between patients and within individuals[2]. In turn, this variability can lead to unpredictable timing of maximum plasma levels and drug bioavailability, because many drugs are more absorbed in the upper small intestine[3]. Superporous hydrogel (SPH) is a promising method of gastric retention[4]. Hydrogels are cross-linked hydrophilic polymers with acidic, basic, or neutral monomer networks that can absorb large amounts of water[5]. The swelling performance of hydrogel mainly depends on the elasticity of the network, the degree of crosslinking and the porosity of the polymer. A new generation of

hydrogels have been developed, which can quickly swell and absorb water. New Generation Superporous Hydrogel (SPH), which can swell to equilibrium size in a short time[6]. Superporous hydrogel (SPH) is a three-dimensional network of chemically and physically connected cross-linked polymers. Hydrogels with effective pore diameters greater than 10 µm are called ultra-porous hydrogels[7]. They are hydrophilic polymer networks, which do not dissolve due to the interconnected micropores, and absorb a large amount of water in a short time. Due to its porous structure, SPH has a larger surface area and therefore a smaller diffusion distance. They will swell quickly in contact with water. These systems not only have the characteristics of rapid swelling, but also have the characteristics of lubricity, biodegradability, biocompatibility, high mechanical strength, and stability in the acidic environment of the stomach[8]. Quetiapine Fumarate (QF) is a psychotropic drug used to treat sudden onset of schizophrenia, bipolar disorder, mania, or depression associated with bipolar disorder[9]. Quetiapine Fumarate is a BCS Class II drug[10]. In the current study, it was decided to administer the drug in a controlled manner in the form of a Superporous hydrogel (SPH).

Method

Experimental Design

Quetiapine Fumarate (QTP-F) based Superporous Hydrogels were prepared by using factorial design. A 3-factor two-level factorial design was employed to study the effect of independent variables on dependent variables as shown in Table 1. A total of 8 formulations were prepared according to the experimental design[11].

Table 1
Quetiapine Fumarate SPH formulations

S. No.	Ingredient	F1	Fa	Fb	Fab	Fc	Fac	Fbc	Fabc
1	Acrylic acid 50%v/v (ml)	2	2	2	2	2	2	21	2
2	Acrylamide 50%w/v (ml)	3	3	3	3	3	3	3	3
3	Chitosan 6%w/v (ml)	4	4	4	4	4	4	4	4
4	BIS 2.5%w/v (ml)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
5	Span 80 10%v/v (ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
6	Ammonium persulphate 20%w/v (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
7	TEMED 16.7%w/v (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8	HPMC K4M (g)	0	0.240	0	0.240	0	0.240	0	0.240
9	HPMC K100M (g)	0	0	0.240	0.240	0	0	0.240	0.240
10	Quetiapine fumarate (g)	10	10	10	10	10	10	10	10
11	Sodium bicarbonate (g)	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9
12	Stirring time (sec)	20	20	20	20	30	30	30	30

Characterization of Superporous Hydrogels

It was envisioned that Superporous hydrogels would be formed and evaluated using Quetiapine Fumarate (BCS Class II). Specifically, the present study examined the response of porosity, mechanical strength, and dissolution to a modified method of preparing superporous hydrogels. It was observed that superporous hydrogels prepared with quetiapine fumarate showed no impact of release retarding polymers. This may be due to the poor solubility of drug, resulted in non-uniform dispersion of drug in HPMC. A multi-criteria decision optimization of approaches was employed for formulation optimization with desired responses. Optimization was performed with constraints of Mechanical strength in the range of 185 – 500 g/sq.cm, Q1h in the range of NMT 35%, Q4h in the range of 45-65% and Q8h in the range of NLT 80%, to get optimized formula solutions with higher desirability function. The response Mechanical strength, Porosity and Dissolution followed interactive (3FI) model and the summary of Analysis of variance (ANOVA) results with coefficient in terms of coded factors given by the Design-Expert®. The optimized formulation which will fit into the model is (Fc)[12].

Animal Ethics

All animal experiments approved and performed in Jeeva Life Sciences accordance with the guidelines of Institutional Animal Ethics Committee (CPCSEA Registration No: 1757/PO/RcBiBt/S/14/CPCSEA).

Animal Husbandry and Maintenance

Healthy adult male Wistar strain albino rats (weighing 200-300 g, 4-5 weeks of age) were obtained from Animal house; Standard laboratory diet, water and libitum were provided to the caged animals. Animals should be individually housed. The temperature of the experimental animal room should be 20°-26°C for rats. Although the relative humidity should be at least 30% and preferably not exceed 70%, other than during room cleaning, the aim should be 50-60%. Lighting should be artificial, the sequence being 12 hours light, 12 hours dark. For feeding, conventional laboratory diets may be used with an unrestricted supply of drinking water. Only healthy animals were assigned for these studies according to OECD Guidelines 404 (OECD Guidelines,1981) Approval to carry out these studies was obtained from the Institutional Animal Ethics Committee and an experiment was performed in compliance with the Principles of Laboratory Animal Care (NIH Publication 85-23, revised 1985) (Public health guidelines,1985). All of the animal experimental protocols were in accordance with the guidelines of the committee for the purpose of control and supervision of experiments on animals, Ministry of Forest and Environment, Government of India.

LC conditions

The LC system consisted of a Waters 515 pump and an autosampler (Waters 717 plus Autosampler, Waters Instruments, MA). The analytical column was a Phenomenex Luna C18 column (2.0 mm 150 mm, i.d., 5 mm), and the column

was maintained at room temperature. The mobile phase was composed of 85% CH3CN(aq) with 1 mM NH4OAc and 0.1 mM HCOOH. The flow rate was 0.3 mL/min and the injection volume was 5 mL[13].

Mass spectrometer conditions

A Quattro Ultima triple-quadrupole mass spectrometer (Micromass) equipped with ESI was used, and the detection was performed in positive ionization mode. Capillary voltage and cone voltage were set at 3200 and 60 V, respectively. The temperature of ion source was 80°C with ultra-high-purity nitrogen as cone gas and nebulizer gas (150 L h-1). Desolvation gas was heated to 320°C and set at a flow rate of 560 L/h. With argon as collision gas, selected reaction monitoring was applied to detect quetiapine and clozapine by monitoring the ion transition of m/z 384.1-253.1 and 327.0-270.0, respectively. The collision energy for quetiapine and clozapine was set at 23 eV and 38 eV. Data acquisition was performed using Mass Lynx 3.5 software (Micromass Ltd.)[13].

Choice of internal standard

A number of substances have been confirmed for the decision of internal standard (IS). Clozapine used to be selected as essentially the most compatible IS, on account that the plasma samples showed no interference at its retention time and the peak height used to be additionally good resolved from the Clozapine. Furthermore, it is a stable compound and does not exist endogenously within the plasma. In addition, a large expertise of that IS used to be its elution time which used to be shorter than that of Quetiapine Fumarate[14].

Preparation of calibration standards and quality control samples

A stock solution of 0.5 mg/mL for quetiapine was prepared in 50% methanol and serially diluted with 50% methanol to give a series of standard working solutions with concentrations of 0.02, 0.06, 1, 2, 6, 10, 12, 18, 24, 30 and 100 ng/mL. A stock solution of 0.5 mg/mL for clozapine was prepared in 50% methanol and then further diluted with 50% methanol to yield a working solution of 0.5 ng/mL. Plasma calibration standards of quetiapine (1, 50, 100, 300, 600, 900, 1200 and 1500 ng/mL) were prepared by spiking the appropriate amount of the standard solutions in blank plasma. Quality control (QC) samples were prepared from a pool of blank plasma at the concentrations of 1, 3, 500, 1300 and 1500 ng/mL and were used in pre-study validation[13].

Sample preparation

To an aliquot of 100 mL plasma sample, 50 mL of 0.5 ng/mL clozapine solution was added as an IS. 50 mL of 0.1N NaOH was added and vortexed for 1 min. The mixture was then vortexed for 3 min to ensure adequate mixing followed by an addition of 3 mL diethyl ether. After 5 min of centrifugation, the organic layer was transferred into another tube. The samples were then evaporated to dryness under N2 stream and reconstituted in 1 mL of 50% MeOH. Finally, 5 mL of aliquots were injected onto LC–MS-MS[13].

Calibration solutions

The linearity was confirmed by plotting the peak area ratio of quetiapine (Y) to the internal standard versus quetiapine concentration (X). The unknown sample concentrations were calculated from the equation y = mx + b. The calibration curve was obtained by weighted (1/x) least-squares regression analysis[13].

Plasma extraction procedure

Liquid–liquid extraction was necessary and important because this technique not only purifies but also concentrates the samples. Diethylether was used because of its high extraction efficiency and low interference[13].

Application of the method

The LC–MS/MS procedure was developed to determine quetiapine concentrations in rat plasma 0–24 h. After an initial period of acclimatisation for one week to laboratory conditions, the rats were randomly divided into 2 groups of 3 subjects each. All the rats were fasted for twelve hours with impromptu access to water before the experiment. Dose of drug was administered according to Animal Equivalent Dose Calculations[15].

Maximum Dose Per Day- 800mg/Day/60kg-13.33mg/kg
AED = 13.33/0.162 = 82.2 mg
Group 1: Administered with pure drug
Group 2: Administered with Formulated Optimized Superporous Hydrogel
These rats were administered with pure drug, dissolving in normal saline.
The Superporous Hydrogels were administered at the rear of the throat using a stomachic canulation tube (made of silicone rubber) with one Superporous Hydrogels on the tip of tube and immediately 5 ml of water was administered through the tube to facilitate swallowing of the hydrogel. Animal had access to food 4 h after dose administration. Concerning 0.2 ml of blood sample was withdrawn from tail vein into heparinized Eppendorf tubes at time intervals of 0 (pre-dose), 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 18 and 24hrs post administration (USFDA guidelines 2003).

Discussion

Quetiapine Fumarate (QTP-F) based hydrogels were prepared by using factorial design, where a three-factor and two-level design was employed to study the relationship between selected independent variables and dependent variables. By using the response surface graphs HPMC K4M (g) (X1); HPMC K100M (g) (X2); and Stirring time (seconds) (X3) selected as independent variables. The FT-IR spectra of the drug and polymer showed that there was no shift in the major peaks. Mechanical strength, Porosity, and the Dissolution were selected as the dependent variables. The obtained Mechanical strength was found to be in the range of 185 g/ sq.cm to 510.35g/ sq.cm, the calculated porosity was about 17.15% to 87.29%, while the dissolution was estimated at 3 different time periods Q1h, Q4h and Q8h and results are found around 29 to 100%. As per ANOVA results of software mechanical strength was significant as F-value is 60.54 and P-

valve (<0.0001) is less than 0.05. and porosity was significant as F-value is 4.27 and P-valve (0.0001) is less than 0.05. Design-Expert® software had given that SPH with 0 mg HPMC K4M & 0 mg HPMC K00M with 30 seconds stirring time as optimized formula (Fc).

HPLC Chromatograms of Pharmacokinetic Study

The chromatograms and retention times of Blank plasma, Quetiapine Fumarate, Internal Standard (Clozapine), plasma spiked with Quetiapine Fumarate and Clozapine are shown in figures 1,2,3,4 and Table 2. From the retention times of all the plasma samples, it has been observed that blank plasma has no interference from endogenous substance at the retention times of IS and analyte. The retention time minutes for IS and minutes for Quetiapine Fumarate showing good resolution between IS and analyte. The retention time for the plasma samples collected after 2 hours from the subject administered via oral administration are found to be similar indication no interference between the analyte and plasma.

Table 2
Retention Time of Chromatograms

S. No.	Name of the Sample	Retention Time
1	Blank Plasma	0.0
2	Analyte (Quetiapine Fumarate)	5.18
3	IS (Clozapine)	7.07
4	Blank + Quetiapine Fumarate + Clozapine	0.0 + 5.23 + 7.11

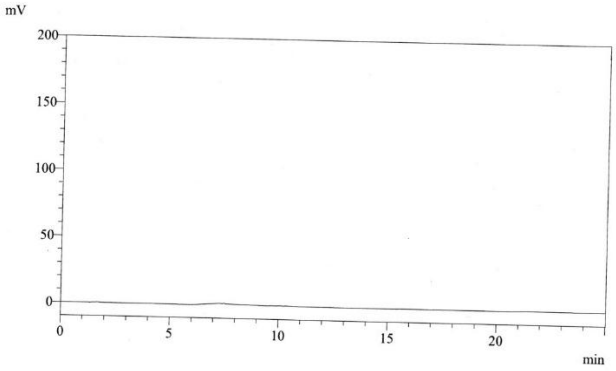

Figure 1. Chromatogram of Blank plasma

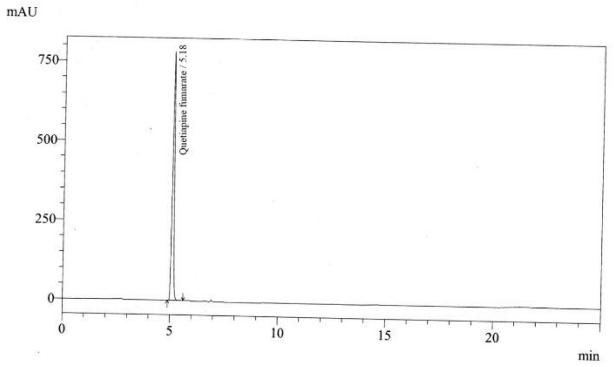

Figure 2. Chromatogram of Quetiapine Fumarate

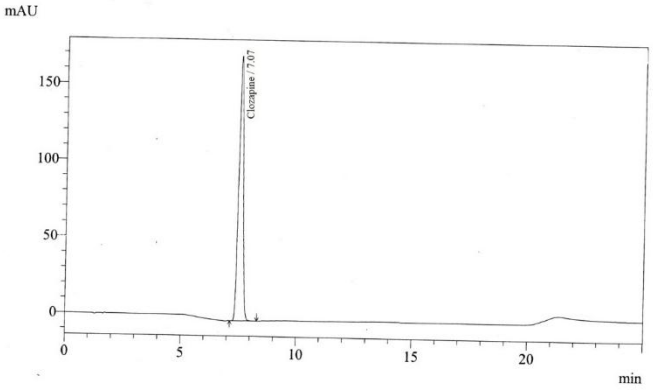

Figure 3. Chromatogram of IS Clozapine

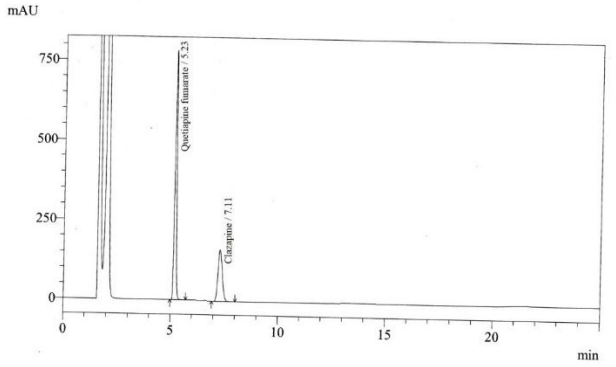

Figure 4. Chromatogram of plasma spiked with Analyte & Internal Standard

Standard Linearity Curve of Quetiapine Fumarate Hydrochloride

The calibration curve results observed over the concentration range of 1 to 1500 ng/ml were satisfactory. The regression equation was found to be y = 119.7x + 1523 with a regression coefficient of 0.9989. The linearity of results was depicted in Table 3 and Figure 5.

Table 3
Calibration curve of Quetiapine Fumarate

S. No.	Concentration ng/ml	Peak Area
1	1	166
2	50	7531
3	100	13582
4	300	39161
5	600	74120
6	900	106142
7	1200	149184
8	1500	179157

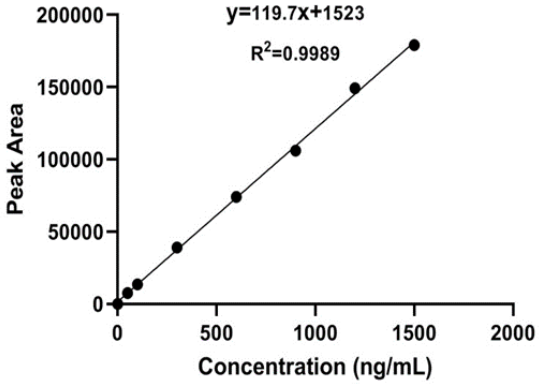

Figure 5. Linearity of Quetiapine Fumarate

Table 4
QC Samples for Quetiapine Fumarate

Amount Added (ng/mL)					
Amount Found	1	3	500	1300	1500
	1.20 ± 0.01	3.00 ± 0.14	499.3 ± 6.4	1300.7 ± 28.1	1501.0 ± 37.5
	1.10 ± 0.02	3.10 ± 0.17	500.8 ± 3.7	1301.0 ± 34.0	1500.8 ± 45.3
	0.99 ± 0.01	2.97 ± 0.10	498.1 ± 8.9	1299.1 ± 44.5	1498.4 ± 28.6
	0.98 ± 0.10	3.20 ± 0.21	502.3 ± 5.6	1300.5 ± 51.6	1502.2 ± 14.7
	1.20 ± 0.05	2.94 ± 0.31	500.6 ± 9.1	1301.1 ± 47.3	1500.0 ± 39.1
	1.30 ± 0.02	2.87 ± 0.19	501.4 ± 5.9	1298.2 ± 31.8	1499.5 ± 62.2
Mean	1.12 ± 0.06	3.01 ± 0.28	500.4 ± 9.7	1300.16 ± 32.6	1500.51 ± 41.7
Standard Deviation	0.127	0.118	1.503	1.248	1.355

Table 5
Experimental Mean Plasma Concentration Values of Pure Drug

First group of Rats Administered with Pure Drug (Quetiapine Fumarate)
Concentration ng/mL

Time in Hours	Subject			Mean	Standard Deviation
	1	2	3		
0	0	0	0	0	0
0.5	225.32	224.16	223.45	224.31	0.94
1	510.65	508.28	511.21	510.04	1.55
1.5	689.26	692.12	690.36	690.58	1.44
2	550.25	550.69	549.27	550.07	0.72
2.5	490.28	491.09	490.24	490.53	0.47
3	410.41	413.64	411.32	411.79	1.66
3.5	340.33	340.01	341.81	340.71	0.96
4	285.14	284.25	285.66	285.01	0.71
6	198.81	198.06	199.68	198.85	0.81
8	105.11	103.58	103.35	104.01	0.95
10	89.28	89.34	88.47	89.03	0.48
12	71.08	69.08	71.333	70.49	1.23
14	58.32	58.73	57.21	58.08	0.78
18	32.12	30.51	31.07	31.23	0.81
24	18.69	18.49	17.62	18.26	0.56

Table 6
Experimental Mean Plasma Concentration Values of Optimized (Fc) Superporous Hydrogel

Experimental Mean Plasma Concentration values of Optimized (Fc) Superporous Hydrogel					
Concentration ng/mL					
Time in Hours	Subject			Mtailean	Standard Deviation
	1	2	3		
0	0	0	0	0	0
0.5	92.16	93.74	91.19	92.36	1.28
1	121.16	119.74	122.19	121.03	1.23
1.5	183.18	183.54	182.15	182.95	0.72
2	230.29	231.56	230.01	230.62	0.82
2.5	295.89	294.34	296.27	295.5	1.02
3	353.18	352.74	352.91	352.94	0.22
3.5	427.24	425.16	428.06	426.82	1.49
4	489.26	487.89	489.54	488.89	0.88
6	524.47	523.29	525.35	524.37	1.03
8	451.17	452.54	451.29	451.66	0.75
10	370.02	371.01	369.04	370.023	0.98
12	310.21	310.23	312.21	310.88	1.14
14	265.87	263.15	265.1	264.70	1.40
18	195.11	194.56	195.22	194.96	0.35
24	127.34	127.89	126.18	127.13	0.87

Table 7
Pharmacokinetic parameters of Pure Drug and Formulated Superporous Hydrogel

Parameters	Pure Drug	Optimized (Fc) Superporous Hydrogel
C_{max} (ng/mL)	690.58 ± 1.1	524.37 ± 2.3
T_{max} (Hours)	1.5	6.0
$AUC_{(0-24)}$ (h.ng/mL)	2580.31 ± 11.34	5345.67 ± 4.59
$T_{1/2}$ (Hours)	5.4 ± 0.1	8.5 ± 0.8
Ke (hr-1)	0.128 ± 0.00387	0.081 ± 0.00124

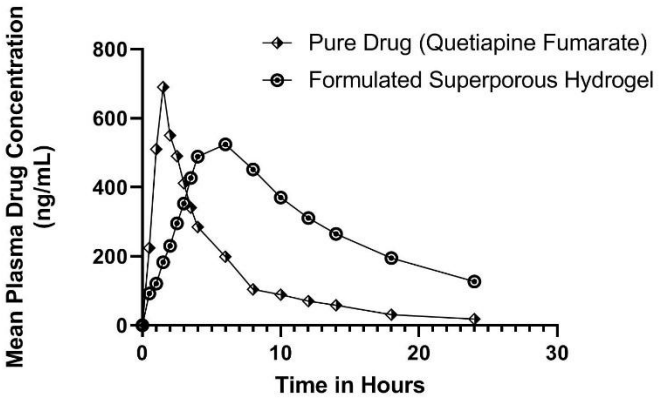

Figure 6. Mean plasma concentration time profile in Wistar Rats obtained after single dose oral administration of Quetiapine Fumarate API and Formulated Superporous Hydrogel

The mean ± SD plasma Quetiapine Fumarate concentration time curve after oral administration of pure drug and formulated Superporous hydrogels were administered to 2 groups of 3 healthy subjects each is illustrated in Figure 6. Pharmacokinetic analysis of Quetiapine Fumarate plasma concentration–time data provided the following pharmacokinetic parameters like Cmax values ranging (690.58 ± 1.1 ng/mL to 524.37 ± 1.6 ng/mL), Tmax values ranging (1.5 ± 0.0 to 6.0 ± 0.0 Hours), AUC values ranging (5345.67 ± 11.34 h.ng/mL to 5345.67 ± 4.59 h.ng/mL) and other pharmacokinetic parameters are depicted in Table 7. It is evident from the data obtained in Table 7 demonstrates the variability in pharmacokinetic parameters like Tmax, Cmax, T1/2 (Hours), AUC & Ke. It has been observed that increased Tmax value (6 hours), Half Life (8.5 ± 0.8 Hours) and AUC Value with decreased Cmax value (524.37 ± 1.6 ng/mL) and Ke (0.081 ± 0.00124 hr-1) values obtained for the formulated product prepared with superporous hydrogel technology shows prolonged release while maintaining Q Value with reduce plasma drug fluctuations in comparison to the Pure drug.

Conclusion

The study demonstrated that optimized test formulation could significantly control certain mental/mood conditions for a period of 24hrs. The Tmax value of optimized test formulation was found to be 6hrs, which was increased in comparison to pure drug, where tmax was achieved in 1.5 hour. Also a significant increase in AUC_{0-24} of optimized test formulation was observed (1 fold), in comparison to pure drug. This indicates the presence of optimized test formulation in the blood plasma for about 24 hrs. This further

indicates the capability of Quetiapine Fumarate Superorous Hydrogels release the drug in the body over prolonged period of time and proves the formulation to be extended release. The developed formulation is successful in staying in the stomach for prolonged time, thereby maintaining the drug concentration in blood, by getting absorbed slowly, and giving better pharmacodynamics and pharmacokinetic effect. It can be concluded that the drug delivery of such drugs can be improved, which results in increase in bioavailability of the drug. Also, the duration of action of drug can be extended, resulting in possible reduction in dose, less side effects, low overall cost of therapy and hence, better patient compliance.

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