



Research Article

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FORMULATION DESIGN AND IN-VITRO EVALUATION OF ANTIPSYCHOTIC DRUG QUETIAPINE FUMARATE

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ABSTRACT

Although the drug delivery system has been changing with time, the conventional tablet preparation is still dominating in dosage form preparation. Conventional tablet has more advantages than the other formulations such as low cost of manufacture, package, easier shipment, tamper proof and stability for longer duration. Schizophrenia is a severe illness with substantial effects on individual and social functioning. First-line treatment in these patients is the use of atypical antipsychotics. The atypical antipsychotic Quetiapine was approved in 1997 by the US Food and Drug Administration (FDA), and has been available since 2007. The treatment of schizophrenia has changed considerably with the introduction of atypical antipsychotics. Quetiapine is among the most widely used atypical antipsychotics, and along with clozapine has the least propensity to induce extrapyramidal motor symptoms. It is thought that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D₂) and serotonin type 2 (5HT₂) receptor antagonisms. The main objective of this work is to develop a pharmaceutical equivalent, stable, robust immediate release tablet. The tablets were prepared by using wet granulation method with sodium starch glycolate and micro crystalline cellulose used intra and extra granularly. The dosage form was prepared and evaluated based on various parameters such as bulk, tapped density, sieve analysis, drug uniformity, disintegration and dissolution etc.

Keywords: Schizophrenia, Quetiapine, Dopamine, Serotonin.

INTRODUCTION

The chemical formula of Quetiapine Fumarate is 2-[2-(4-dibenzo [b, f][1,4] thiazepin-11-yl-1-Piperazinyl) ethoxy] ethanol hemifumarate (Figure 1). It is Antipsychotic drug which is white or almost white powder, soluble in water and soluble in methanol & 0.1N HCl. It is used to treat psychosis associated with Parkinson's disease and chronic schizophrenia^{1,2,3}. The mode of action of Quetiapine Fumarate, as with other drugs used to treat schizophrenia, is unknown. However, it is thought that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D₂) and serotonin type 2 (5HT₂) receptor antagonisms^{4,5}. Antagonism at receptors other than dopamine and serotonin may explain some of the other effects of it due to Antagonism at histamine (H₁) receptors^{6,7} and may be explained by the following reasons:

- Antagonism at adrenergic (α_1) receptors may explain orthostatic hypotension.
- Antagonism at muscarinic (M₁) receptors may explain anticholinergic effects.

MATERIALS AND METHODS

Quetiapine Fumarate was donated by Alkem Laboratories Ltd, India, hydroxypropyl methylcellulose by Colorcon Asia, India, PVP K30 (Noveon, Inc., USA.) and Magnesium Stearate by Zydus Cadila, India. Microcrystalline cellulose, Dicalcium Phosphate Dihydrate, Lactose Monohydrate, Sodium Starch Glycolate, talc were gifted from Mankind Pharmaceutical

Limited. All other chemicals and reagents used were of analytical grade and purchased from Merck Ltd., India.

Formulation of Immediate Release tablets of Quetiapine, containing 25 mg equivalent weight of Quetiapine Fumarate were prepared by wet granulation⁸⁻¹⁰ technique. The composition of each tablet is shown in Table 1. All the components were screened and then thoroughly mixed with intragranular excipients including drug for period of 15 min. The powder mix was granulated with water and povidone appropriate quantity. The wet mass was passed through # 12 and the granules were dried at 50°C till it dried in a hot air oven. The extra-granular excipients passed through # 40 and added with the dried granules which were passed through # 20. The blending of mixture was done for 25 min. The step followed by lubrication with magnesium stearate and finally talc was added to the blend, further blending for 5 min. Compression was done on 5.5mm punches with 16 station Cadmach tablet compression machine.

Evaluation of pre-compression parameters of powdered blend

Angle of Repose

The material was poured through a funnel; the tip of the funnel should be held close to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reaches a predetermined height or the base a predetermined width. Measure the angle¹¹⁻¹³ of the resulting cone directly; divide the height by half the width

of the base of the cone. The inverse tangent of this ratio is the angle of repose.

$$\tan\theta = h/r$$

Bulk Density

The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed.

Tapped Density

The tapped density of a powder is the ratio of the mass of a tapped powder sample and its volume.

- Pour (or Bulk) density = Mass / Untapped volume
- Tapped density = Mass / Tapped volume
- Hausner ratio = Tapped density / Pour density
- Carr's Index = (Tapped density – Bulk density) / Tapped density x 100

Evaluation of tablets

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, disintegration, dissolution and stability studies.

Thickness

Twenty tablets were randomly selected from formulations and thickness was measured individually by using vernier calipers. It was expressed in millimeters and average was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness¹⁴ of the tablets was determined using Dr. Schleuniger hardness tester. It was expressed in Newton (N). Ten tablets were randomly selected from each formulation and hardness of the same was determined. The average value was also calculated.

Friability

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). About 6.5 g tablets (W-initial) were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or 100 revolutions. The tablets were dedusted and weighed again (W_{final}). The percentage friability was calculated by,

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

% Friability of tablets less than 1 % was considered acceptable.

Weight Variation

Twenty tablets were randomly selected from each formulation and weighed individually to check for weight variation. The percentage deviation in weight variation according to USP was allowed.

Drug Content Estimation

Twenty tablets were weighed and powdered. An amount of powder equivalent to 25mg of Quetiapine Fumarate was dissolved in 100 ml of pH 6.8 phosphate buffer and

filtered properly. Then it was diluted with suitable solvent and analyzed for drug content^{15,16} at 254 nm using UV-Visible spectrophotometer.

Disintegration Time

It was carried out by Electrolab Disintegration Apparatus, USP in which 900ml beaker was used and 6 test tubes were attached with 10 mesh screen at a temperature of 37°C±0.5°C. In each test tubes one tablet was placed and time was noted.

In Vitro Dissolution Study

The Quetiapine Tablets were subjected to *in vitro* drug release studies in water for 45 min. The drug release¹⁷ studies carried out in dissolution test apparatus using 900 ml of dissolution medium with paddle speed at 100 rpm, maintained at 37°C ± 0.5°C. Then they were subjected to match in other two media i.e. pH 4.5 acetate buffer and in 0.1 N HCl. Samples withdrawn were filtered through Whatmann filter paper (no.41), suitably diluted with , and analyzed at 258.80 nm, using UV-Visible double beam spectrophotometer.

Comparison with Marketed Product

The developed product was quantitatively evaluated and assessed for a tablet's properties and product quality was monitored for various specifications. The standards or quality control tests were carried out on marketed tablets for comparative evaluation of developed and marketed product¹⁸. The observations were reported in Table 2.

FTIR Studies

IR spectra for Quetiapine Fumarate and formulation of tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr. (Figure 2)

DSC Studies

DSC scans of about 5mg; using an automatic thermal analyzer system was performed. Accurately weighed Quetiapine Fumarate and drug with excipients were taken for study as shown in Table 3 and Table 5 (DSC 60, Shimadzu, Japan). Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at scanning rate of 10°C/min from 50-300°C. (Figure 3)

XRD Studies

The XRD pattern of the Quetiapine Fumarate (Figure 4) and different ingredients, granules, compressed tablet were recorded. The XRD spectra show no significant changes in peak of different formulations hence it was confirmed that excipients are compatible with Quetiapine Fumarate as shown in Table 4.

Compatibility Study

Quetiapine Fumarate with different excipient were taken in different proportion in vials and were kept in accelerated stability condition for 2 and 4 weeks and

evaluated for appearance, moisture content and assayed to confirm the compatibility.

Table 1: Different Formulation of Quetiapine Tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	Q11
Intra-granular											
Quetiapine Hemi Fumarate (USP/NF)	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8
MCC	11.6	11.6	11.6	11.6	11.6 (PH-102)	-	-	-	-	12.1	12.1
Dicacium Phosphate dihydrate	8.01	9.3	11.1	11.1	11.1	-	-	-	-	10.1	10.1
Lactose Mono Hydrate 200 M	4.37	4.37	4.37	4.37	4.37	4.06	4.06	4.06	26.05 (DCL-21)	4.37	4.37
SSG Type-A	4.00	3.00	1.25	1.25	1.25	1.25	2.5	2.5	1.25	1.87	1.00
Povidone (Kollidon-30)	1.25	1.25	0.63	1.25	0.63	1.0	1.0	1.0	2.0	1.25	1.25
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Extra-granular											
SSG Type-A	1.0	0.75	1.25	1.25	1.25	-	-	1.25	2.5	0.63	1.00
MCC	2.1	2.1	2.1	2.1	2.13 (PH-102)	18.9 (PH-102)	17.6 (PH-102)	16.4 (PH-102)	-	2.1	2.3
Povidone (Kollidon-30)	-	-	-	-	-	-	-	-	0.63	1.25	1.25
Dicalcium Phosphate Dihydrate	-	-	-	-	-	7.25	7.25	7.25	-	-	-
Magnesium stearate	1.25	1.25	1.25	0.63	1.25	1.25	1.25	1.25	1.25	-	-
Core tablet weight	65	65	65	65	65	65	65	65	65	65	65
Insta Coat brown	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total Weight	68	68	68	68	68	68	68	68	68	68	68

Table 2: In-process Data Compilation of all Formulations

S N	Parameter	Observation											
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	
1	L.O.D.(%w/w)	2.97	2.65	2.51	3.1	2.28	2.68	1.78	3.51	3.23	3.11	2.31	
2	Bulk Density(gm/ml)	0.5322	0.44	0.421	0.5	0.432	0.4931	0.485	0.526	0.521	0.4626	0.5611	
3	Tapped Density(gm/ml)	0.6611	0.572	0.59	0.64	0.552	0.5962	0.654	0.663	0.635	0.6184	0.6921	
4	Compressibility index (%)	20.74	23.5	28.9	20.6	21.7	17.71	19.87	20.82	15.23	26.14	20.32	
5	Hausner Ratio	1.27	1.308	1.4	1.26	1.28	1.21	1.25	1.27	1.171	1.352	1.246	
6	Sieve analysis (%)	30#	2.01	0.6	3.75	13.3	6.8	17.21	11.36	4.27	5.21	11.52	5.41
		60#	18.11	15.7	10	14.1	20.89	30.91	19.41	27.12	49.67	18.54	11.02
		80#	18.86	27.2	6.3	2.6	11.58	5.13	5.82	5.81	3.68	4.97	4.12
		100#	25.11	6.2	1	4.1	17.32	7.89	11.89	11.98	4.93	8.31	5.01
		collector	34.89	49.8	77.5	64.5	42.45	37.01	50.01	46.92	31.21	56.55	74.22
7	Core Tablet	Weight variation (mg)	65.0±1.5	65.0±1.5	65.0±2.0	65.0±1.5	65.0±1.5	65.0±1.3	65.0±1.3	65.0±1.4	65.0±1.3	65.0±1.3	65.0±1.4
		Hardness (N)	66-74	65-72	69-82	70-76	60-72	41-47	48-58	30-48	41-47	68-77	61-76
		Thickness (mm)	2.52-2.59	2.6-2.65	2.48-2.54	2.51-2.55	2.54-2.59	2.51-2.55	2.46-2.54	2.50-2.54	2.54-2.57	2.50-2.55	2.46-2.49
		D.T. (min)	4.15-4.45	4-4.3	4.1-4.4	5.1-5.3	3.15-3.30	7-7.45	4.15-4.45	3.15-3.30	5.10-5.30	4.4-4.15	5.20-5.35
		Friability	0.038	0.053	0.032	0.028	0.021	0.162	0.01	0.102	0.11	0.034	0.138
		% Build up	2.99	3.02	2.94	3.12	2.98	3.01	2.98	2.97	3.08	2.99	3.01
8	Coated Tablet	Weight variation (mg)	68 ± 1.5	68 ± 2.0	68 ± 1.5	68 ± 1.5	68 ± 2.0	68 ± 2.0	68 ± 1.4	68 ± 1.5	68 ± 1.3	68.0 ± 1.4	68.0 ± 1.5
		Hardness (N)	79-87	78-84	80-87	80-92	74-90	48-56	65-78	62-73	62-75	81-92	77-88
		Thickness (mm)	2.68-2.73	2.70-2.76	2.50-2.59	2.54-2.6	2.60-2.64	2.56-2.60	2.59-2.62	2.63-2.66	2.63-2.67	2.57-2.61	2.54-2.57
		D.T. (min)	5-5.20	4.4-5	5-5.2	6-6.4	4.2-4.4	9.45-10.30	6.0-6.15	4-4.50	6.40-7.0	4.45-5.10	6.10-6.25
		% Build up	2.99	3.02	2.94	3.12	2.98	3.01	2.98	2.97	3.08	2.99	3.01

Table 3: Differential Scanning Calorimetric (DSC) Study

Sample	Initial QF006A	Water Granules QF006A	105 ° C QF006B	1M 40°C/75%RH QF006C	3M 40°C/75%RH QF006D	Compressed Sample QF006E
Peak	173.47°C	174.22°C	174.54°C	174.19°C	174.24°C	174.09°C

Table 4: X-Ray Diffraction (XRD) Study

	Initial QF006A	Water Granules QF006A	105 ° C QF006B	1M 40°C /75%RH QF006C	3M 40°C /75%RH QF006D	Compressed Sample QF006E
θValue	5.46089	5.42547	5.46320	5.43522	5.40790	5.44601
d-value	(16.2189)	(16.3247)	(16.2112)	(16.2952)	(16.3781)	(16.2627)
θValue	4.43607	4.41414	4.43791	4.42337	4.40105	4.41871
d-value	(19.9996)	(20.10)	(19.9912)	(20.0622)	(20.1604)	(20.079)
θValue	4.22047	4.19098	4.21494	4.19809	4.17990	4.20287
d-value	(21.0326)	(21.1823)	(21.0605)	(21.1460)	(21.2391)	(21.1217)
θValue	3.81653	3.79543	3.81551	3.80343	3.78799	3.80236
d-value	(23.2883)	(23.4196)	(23.2946)	(23.3696)	(23.4662)	(23.3763)

Inference: The above table shows there is no polymorph form in various condition.

Table 5: Compiled Data from DSC Study

Drug + excipient	Ratio	Peak value for Quetiapine	Remarks
Quetiapine	1	173.46°C	
Quetiapine + MCC	1:1	172.82°C	Compatible
Quetiapine+SodiumStachGlycolate	1:0.5	172.23°C	Compatible
Quetiapine+Dicalsium Phosphate Dihydrate	1:0.05	171.69°C	Compatible
Quetiapine+Lactose Monohydrate	1:0.5	174.25°C	Compatible
Quetiapine + Povidone	1:0.5	174.12°C	Compatible
Quetiapine+ Mag.Stearate	1:0.05	171.13°C	Compatible
Quetiapine+ Titanium Dioxide	1:0.05	171.78°C	Compatible
Quetiapine + Yellow iron Oxide	1:0.05	172.82°C	Compatible
Quetiapine + Red iron Oxide	1:0.05	171.61°C	Compatible

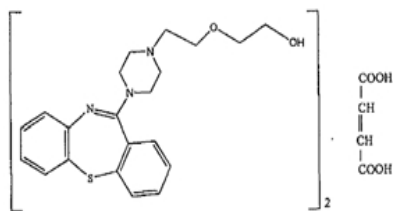


Figure 1: Structure of Quetiapine Hemifumarate

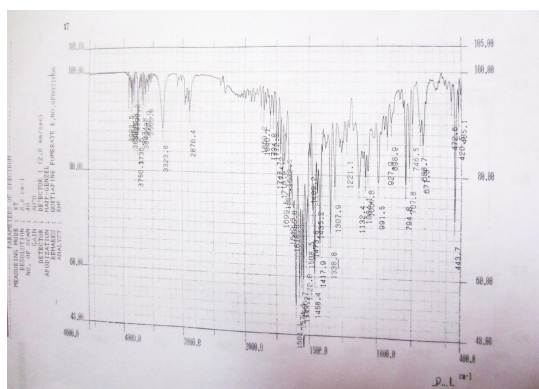


Figure 2: IR Spectrum of Quetiapine Fumarate

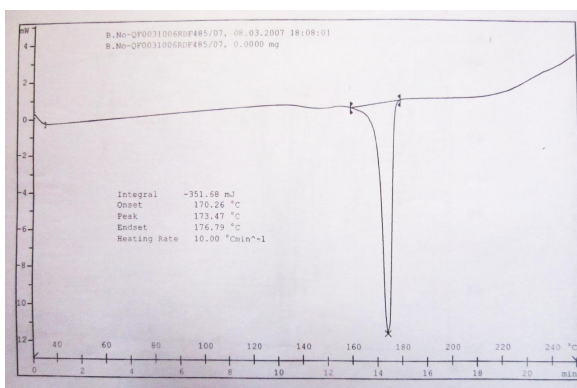


Figure 3: DSC of Quetiapine Fumarate

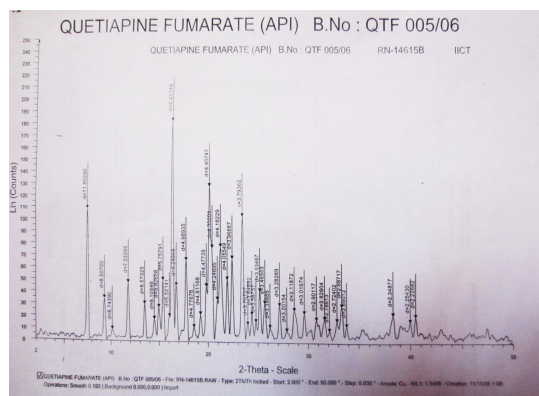


Figure 4: XRD study of Quetiapine Fumarate

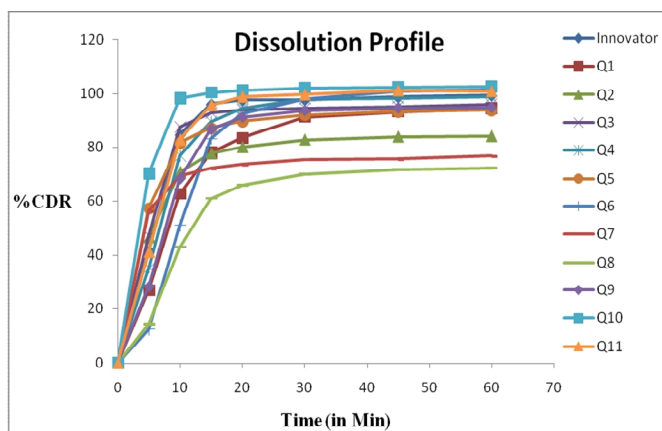


Figure 5: Dissolution Study

RESULT AND DISCUSSION

The present investigation was carried out to develop immediate release tablet dosage form of Class -II drug, Quetiapine. Drug-Excipient compatibility study of Quetiapine with different categories of excipients was carried out. The study was carried out at different conditions of temperature and humidity like 40°C/75%RH, 2–8°C, room temperature & found their physical appearance, impurity level and water content after 2 week, 4 weeks and compared with initial value. The result showed that impurity level with same drug and excipient combination increases and also slightly changes in appearance but except Cross carmellose sodium all were compatible with Quetiapine. Excipients were considered compatible only if the total impurities do not exceed 2 times the impurities of initial (Table 3, 4, 5). The pH dependent solubility study was carried out by using different pH buffer solution ranging pH 1.2 (0.1 N HCl), pH 2.1 acid buffer, pH 4.5 acetate buffer, pH 5.5 acetate buffer and pH 6.8 phosphate buffer. Study shows solubility of Quetiapine was higher in pH 1.2 (0.1 N HCl) i.e. 17.17 mg/ml. Water was used as dissolution medium as used by innovator. Evaluation was divided mainly in Pre compression parameters and Post compression parameters.

Pre Compression Parameters

Loss on Drying (LOD)

As calculated, theoretical moisture content of drug and excipient was 2%w/w, at 80°C. LOD of dried granules maintained in that level NMT ± 1% variation by drying at 60°C and optimizing drying time to achieve LOD in particular limit.

Powder Flow Characteristics

Initially some flow problem arises in direct compression method. Powder blend shows poor flow which causes weight variation and problem in content uniformity; But Wet granulation method shows good flow properties of granules and final blend.

- Bulk density was in the range 0.54 – 0.57 gm/ml
- Tapped density was in the range 0.65-0.69 gm/ml,
- Carr's Index ranging 16-23%

- Hausner ratio was in the range 1.2-1.3 which shows the good flow characteristics.

Sieve Analysis: Sieve Analysis by Mechanical shaker showed that there was good blend of fines and granules which result in good flow and reduces weight variation problems.

Post Compression Parameters

Weight Variation

Initially in same trails, weight variation was observed, but in final trial tablet ranging 67.5-69.5 mg (Target weight – 68.0mg/Tablet) for 25 mg tablet formulation, which was less than 5% and indicates that the variation in the weight of the tablets is within standard official limits.

Thickness Evaluation

Thickness of tablets was observed by Vernier Caliper. Thickness of tablet does not show any measurable deviation in both strengths.

Hardness Test

Hardness of the tablet was measured in 'Newton' unit in digital harness tester. The hardness of tablets was found to be uniform within range 65 N to 80 N for 25mg, which indicates that the prepared tablets are mechanically stable.

Disintegration Test

Disintegration test was carried out in Electro lab (ED-2AL). Disintegration time for 6 tablets was found to be 6-6.25 min for 25 mg. since this was less than 15 min, indicating that disintegration time is within the specification limit.

Friability Test

The friability test was carried out by using Roche Friabilator. The percentage friability of tablet was ranging 0.03% - 0.08% for 25mg. This is less than the standard limit of 1%, which indicates that the prepared tablets are mechanically stable.

Drug Content Uniformity

In the initial trials drug content uniformity was found to be outside limit, but after that in each trial drug contents range from 98% - 101.2% which is within the range of

92.5 – 105% for Quetiapine. It indicates uniform distribution of drug in the tablets of each formulation.

In Vitro Drug Release Studies

The Quetiapine Tablets were subjected to in vitro drug release studies in water for 45 min. The drug release studies carried out in dissolution test apparatus using 900 ml of dissolution medium, maintained at 37°C ± 0.5°C which profile is shown in Figure 5. Among all trials dissolution profile of 4 trials i.e. Trial - 3, Trial - 4, Trial – 9 and Trial - 11 matches with innovator in water medium. Then they were subjected to match in other two media i.e. pH 4.5 acetate buffer and in 0.1NHCl, but Trial – 4 and Trial - 9 failed to match in 0.1N HCl medium with innovator. Trial – 3 and 11 match in 0.1N HCl, thus they were tried for pH 4.5 acetate buffer media with innovator. Only Trial – 11 matches with innovator. Then it was also studied for other media with innovator. Thus, Trial - 11 was finalized and taken as final formula.

Exposure Study

Exposure studies were carried out of selected trial. In exposure study, our trial and innovator formulation was subjected to different environmental stress¹⁹ conditions like 80°C for 2 days and in autoclave at 121°C for 15 min. The result shows similar behavior between our trial and innovator in different conditions.

Stability Study

The stability studies of final trial were done for 6 months by packing in HDPE container in humidity chamber (40°C/75% RH). The result for 1 month, 2 months, 3 months and 6 months was obtained. All parameters of formulation including physical parameters, impurity profile²⁰, content uniformity²¹ or dissolution profile were within specification limit. So it indicates optimized formulation was stable.

CONCLUSION

Here an attempt was made to prepare a bioequivalent immediate released solid oral dosage form of Quetiapine Fumarate. The present formulation has identical dissolution profile as that of Innovator Seroquel tablet of AstraZeneca. Newer antipsychotics have superior tolerability profiles compared with conventional agents; however, clear differences in tolerability exist among the new generation antipsychotics. Quetiapine has an excellent tolerability profile offering high patient acceptability that in turn, may promote patient adherence to medication and an improved quality of life. As such, we consider Quetiapine to be a first choice antipsychotic for the treatment of acute exacerbations of schizophrenia.

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