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Research Article

FORMULATION AND EVALUATION OF QUETIAPINE IMMEDIATE RELEASE FILM COATED TABLETS

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ABSTRACT

The scenario of pharmaceutical drug delivery is rapidly challenging, but conventional pharmaceutical dosage forms are still dominating. Tablets formulations are mostly preferred because of low cost of manufacture, package, shipment, increased stability and virtual tamper resistance. The main goal of this study was to develop a stable formulation of antipsychotics Quetiapine as an immediate-release tablet. Quetiapine has beneficial calming properties and successfully treats the symptoms of aggression, anxiety and hostility that can accompany acute exacerbations of schizophrenia. The atypical antipsychotic Quetiapine was approved in 1997 by the US Food and Drug Administration (FDA), for formulation. Furthermore, while current prescribing information recommends that Quetiapine can be administered at doses up to 750mg/day (800mg/day in the USA and Canada), there is growing evidence that dosing up to 1600mg/day of Quetiapine has been well tolerated in some patients. The task of developing immediate release tablet is accomplished by using a suitable diluent and super-disintegrants. Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in less time. The formulation development work was initiated with wet granulation. The granules were evaluated for angle of repose, bulk density, compressibility index, tapped density and Hausner ratio. The tablets for the formulations i.e.F1to F8 were subject to hardness, thickness, friability, weight variation test, drug content uniformity and *in vitro* disintegration time, *in vitro* drug release studies and stability studies. The granules showed satisfactory flow properties and good compressibility. all the tablet formulations i.e.F1 to F8 showed acceptable pharmacotechnical properties and complied with in-house specifications for tested parameters. From the all formulations, F8 was optimised and *in vitro* disintegration time and *in vitro* drug release studies were found to be 4.0 (min) and 98.5 % respectively. The optimized formulation is further selected and compared with the release profile of the innovator product and similarity factor was conducted. The result was found to be more than 50%.The optimized,formulation, F8 was conducted for stability studies according to ICH guideline. The results indicate that there were insignificant changes during studies. Hence, the results suggest the feasibility of developing immediate release tablets consisting of Quetiapine, which has an excellent tolerability profile offering high patient acceptability that may promote patient adherence to medication and an improved quality of life.

Keywords: Quetiapine, antipsychotics, immediate release, *in vitro* drug release studies.

INTRODUCTION

Immediate release drug delivery system are based on single or multiple-unit reservoir or matrix system, which is designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systemic effect. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulation, mainly because of patient acceptance, convenience in administration and cost effective manufacturing process.

The chemical formula of Quetiapine fumarate is2-[2-(4-dibenzo [b, f][1,4] thiazepin-11-yl-1-Piperazinyl) ethoxy] ethanol hemifumarate. It is an antipsychotic drug which is a 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[2,3,4]. 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[5,6]

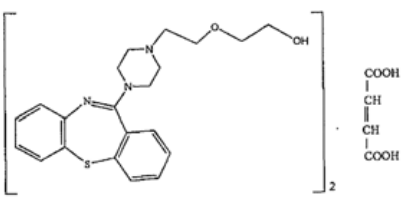

Figure1: Structure of Quetiapine Fumarate

The main goal of this study was to develop a stable formulation of antipsychotics Quetiapine as an immediate-release tablet.

MATERIALS AND METHOD

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 and talc were gifted by Mankind Pharmaceutical Limited. All other chemicals and reagents used were of analytical grade and purchased from Merck Ltd., India.

Drug – Excipients compatibility study

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. The results shown are shown in Fig. no. 03

DSC Studies

DSC scans of about 5mg using an automatic thermal analyzer system were performed. Accurately weighed Quetiapine Fumarate and drug with excipients were taken for study. (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 a scanning rate of 10°C/min from 50-300°C. The results are shown in Fig. no. 04

XRD Studies

The XRD pattern of the Quetiapine Fumarate 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. The results are shown in Fig. no. 05

Formulation of Immediate release Tablets of Quetiapine Fumarate

Wet granulation method [7, 8, 9]:

Calculate and Weigh Quetiapine based on its potency. Dispense all other ingredients as per batch formula and sift Quetiapine Fumarate, Dicalcium phosphate dihydrate, Micro Crystalline Cellulose (PH-101), Sodium Starch Glycolate and Pharmatose 200 M through # 40 . Prepare binder solution using PVP K- 30 in warm water .Prepare granule in RMG by using above shifted mix and binder solution .Dry the above granule at 60 C in dryer and then pass it in (#20) . Pass the Extra granular Blend (#40) and mix to the granules above obtained for 20min in blender. Finally Magnesium Stearate (#60) is mixed for 5min.Compression is carried out using 5.5mm Punch. The different formulations of tablets are given in Table no. 01

Process flow diagram

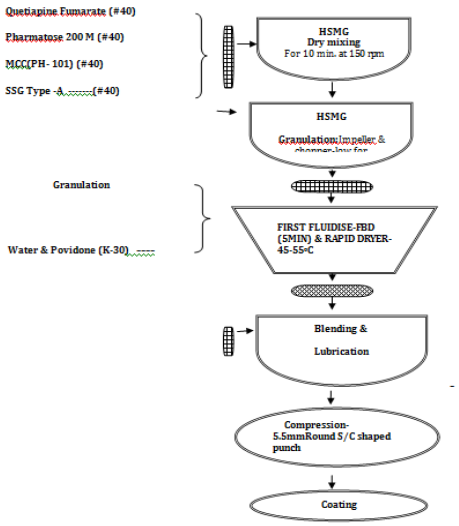

Figure2: Flow diagram of Process

Evaluation of Tablets of Quetiapine
Pre-compression parameters [10, 11, 12] :

The pre-compression parameters were evaluated for loss on drying, angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results are shown in Table no .02

Loss on drying (LOD)

The moisture content of the lubricated granules was analyzed by using the Halogen Moisture Analyzer. Approximately one gram of the blend was heated at 105°C until the change in the weight was n o more observed by the instrument. The percentage (%) of weight loss was recorded.

% LOD=100 (Initial Weight - Final Weight) / Initial Weight

Angle of repose

Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to interparticulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\theta = \tan^{-1} h / r$$

Where, θ = angle of repose, h = height of heap, r = radius of base of heap circle.

Density analysis

The volume of powder packing was determined on an apparatus consisting of a graduated cylinder mounted on a mechanical tapping device that has a specially cut rotating cam. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Initial volume of powder was noted and the sample subjected to tapping (500, 750 or 1250 tappings) until no further reduction in volume was noted or the percentage of difference in volume was not more than 2 %. A sufficient number of taps should be employed to assure reproducibility for the material in question. The tappings should not produce particle attrition or a change in the particle size distribution of the material being tested.

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by sample in ml}}$$

Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and Hausner ratio are determined by measuring both bulk density and the tapped density of a powder.

$$\text{Compressibility Index} \quad \frac{\text{Tapped density – Bulk density}}{\text{Tapped density}}$$

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post-compression parameters

The compressed tablets were evaluated for hardness, thickness, friability, weight variation, drug content uniformity, *In-vitro* disintegration time and *In vitro* dissolution studies.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Dr. Schleuniger hardness tester. It was expressed in Newton's (N). Ten tablets were randomly selected from each formulation and hardness was determined thereof.The average value was also calculated**.** The results are shown in Table no. 02

Thickness

Tablets of each batch were selected and measured for thickness and diameter using the digital vernier calipers. It was expressed in millimeters and average was calculated**.** The results are shown in Table no. 02

Friability test

The friability of the tablets was determined by using the Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. The tablets were weighed again (W_{final}).

The percentage friability was then calculated using the equation

$$F=[(W_{initial} - W_{final}) / W_{initial}] \times 100$$

Percentage of Friability of tablets less than 1% is considered acceptable. The friability was expressed as the loss of mass and was calculated as a percentage of the initial mass. The results are shown in Table no. 02

Weight Variation Test

Twenty tablets selected at random were weighed and the average weight was calculated. Not more than two of the individual weights deviated from the average weight by more than the percentage. The results are shown in Table no. 02

Drug Content Estimation[13-14]

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, filtered properly. Then it was diluted with suitable solvent and analyzed for drug content at 254 nm using UV-Visiblespectrophotometer.

In-Vitro Disintegration time

The disintegration time for all formulations was carried out using a tablet disintegration test apparatus. Six tablets were placed individually in each tube of the disintegration test apparatus and the disks were placed. The water was maintained at a temperature of 37±2°C and the time taken for the entire tablet to disintegrate completely was noted. The results shown in Table no. 02

Table1: Composition of Quetiapine Immediate release tablets

Sl No.	Ingredients(Mg/Tablet)	Batch Number							
		F1	F2	F3	F4	F5	F6	F7	F8
1.	Intra-granular Quetiapine emifumarate	28.8	28.8	28.8	28.8	28.8	28.8	28.8	28.8
2.	MCC	11.66	11.66	11.625	11.625	11.625	-	-	-
3.	DicaciumPhosphate dihydrate	8.01	9.26	11.118	11.118	11.118	-	-	-
4.	Lactose Mono Hydrate 200 M	4.375	4.375	4.375	4.375	4.375	4.06	4.06	4.06
5	SSG Type-A	4.00	3.00	1.25	1.25	1.25	1.25	2.5	1.25
6	Povidone(Kollidon-30)	1.25	1.25	0.625	1.25	0.625	1.0	1.0	1.0
7	Purified water	qs	qs	qs	qs	qs	qs	qs	qs
8.	SSG Type-A	1.0	0.75	1.25	1.25	1.25	-	-	1.25
9.	MCC	2.08	2.08	2.125	2.125	2.125	18.87	17.62	16.37
10.	Povidone(Kollidon-30)	-	-	-	-	-	-	-	-
11	DicaciumPhosphate dihydrate	-	-	-	-	-	7.25	7.25	7.25
12.	Magnesium stearate	1.25	1.25	1.25	0.625	1.25	1.25	1.25	1.25
	Total weight (mg)	62.5	62.50	62.50	62.5	62.5	62.5	62.5	62.5
	Coating Solution								
13	Insta Coat brown	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
14.	Purified water	qs	qs	qs	qs	q.s	q.s	q.s	q.s
	Total weight (mg)	65.5	65.5	65.5	65.5	65.5	65.5	65.5	65.5

Table 2 : Parameters for Evaluation of Designed Formulation

Sl	Parameter		Formulation code							
			F1	F2	F3	F4	F5	F6	F7	F8
1	L.O.D.(%w/w)		2.97	2.65	2.51	3.1	2.28	2.68	1.78	3.51
2	Bulk Density(gm/ml)		0.53	0.44	0.42	0.5	0.43	0.49	0.48	0.52
3	Tapped Density(gm/ml)		0.66	0.57	0.59	0.64	0.55	0.59	0.65	0.66
4	Compressibility index(%)		20.74	23.5	28.9	20.6	21.7	17.71	19.87	18.82
5	Hausner Ratio		1.27	1.308	1.4	1.26	1.28	1.21	1.25	1.27
6.	Angle of repose		22.32	27.17	21.72	22.50	24.39	21.82	23.42	22.35
7	Core Tablet	Weight variation (mg)	62.5± 1.5	62.5±1. 5	62.5± 2.0	62.5±1. 5	62.5± 1.5	62.5± 1.3	62.5±1. 3	62.5±1.4
		Hardness(N)	66-74	65-72	69-82	70-76	60-72	45-57	48-58	40-48
		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	2.50-2.63
		DisintegrationTime(min)	4.15–4.45	4– 4.3	4.1–4.4	5.1–5.3	3.25-3.30	7 -7.45	4.15-4.45	3.15-3.30
		Friability	0.038	0.053	0.032	0.028	0.021	0.162	0.01	0.102
8	Assay		98.2	99.3	100.2	99.1	97.3	98.3	99.7	99.1
9	Coated Tablet	Weight variation (mg)	65± 1.5	65±2.0	65± 1.5	65± 1.5	65± 2.0	65± 2.0	65± 1.4	65± 1.5
		Hardness(N)	79-87	78-84	80-87	80-92	74-90	58-65	65-78	62-73
		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
		Disintegration Time(min)	5-5.20	4.4-5	5-5.2	6--6.4	4.2-5.4	9.45-10.30	6.0-6.15	4-4.50
		%Build up	2.99	3.02	2.94	3.12	2.98	3.01	2.98	2.97

Table 03 : Stability studies

Sl. No.	Parameters	Condition					
		RT	40º±2ºC /75±5%RH				
		Initial	15Days	30 days	60 days	90 days	180days
1	Description	RoundS/C peachcolor tablet	Round S/C peach color tablet	Round S/C peach color tablet	Round S/C peach color tablet	Round S/C peach color tablet	Round S/C peach color ablet
2	Hardness (N)	62-73	62-72	61-70	60-70	60-70	58-69
3	DisintegrationTime (min)	4.0-4.50	4.0-4.50	3.8-4.40	3.8-4.50	4.0-4.40	3.8-4.30
4	Assay (%)	101.42	100.52	100.24	100.16	100.08	100.03
5	In-Vitro Dissolution	98.8	98.5	98.37	98.15	98.05	97.8

***In-Vitro* Dissolution Study[15-16]**

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 with

paddle speed at 100 rpm, maintained at 37°C ± 0.5°C. Then they were subjected to match in other two medium 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 254 nm, using UV-Visible double beam spectrophotometer. The results shown in Fig. no.06

Calculation of dissimilarity (f_1) & similarity (f_2) factor

Dissimilarity factor (f_1)

It was calculated in comparison with reference or with the innovator product to know the dissimilarity.

$$f_1 = \frac{\sum R_t - T_t}{\sum R_t} \times 100 \quad \text{.....(i)}$$

The dissimilarity factor (f_1) should be always less than 15 (f_1<15)

Similarity factor (f_2)

The similarity factor (f_2) was defined as the logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products. This was calculated to compare the test with reference release profiles.

$$f_2 = 50 \times \log 10 \times \frac{1}{\sqrt{1 + 1/n \times \sum (R_t - T_t)^2}} \times 100 \quad \text{..... (ii)}$$

Where, n= numbers of sampling points

The similarity factor (f_2) should be always greater than 50 (f_2>50) The method is adequate to compare dissolution profiles when more than three or four dissolution time points are available and can only be applied if average difference between R_t and T_t is less than 100. If this difference is higher than 100, normalization of data is required.

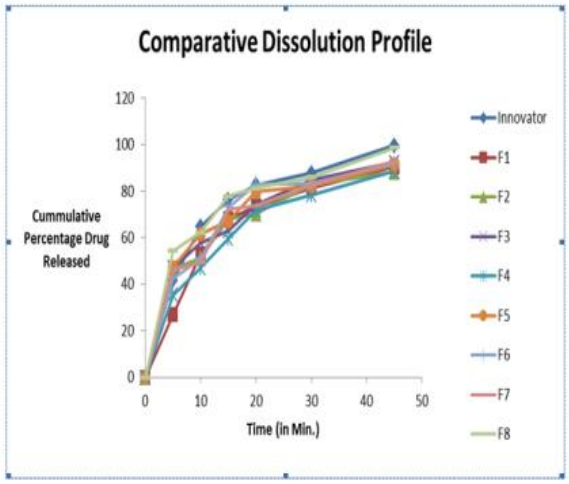

Figure 6: Comparative Dissolution profile of Innovator product and Formulations F1- F8.

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 following standards or quality control tests were carried out on marketed tablets i.e Seroquel tablet of Astrageneca and observations were reported in Fig. no. 07.

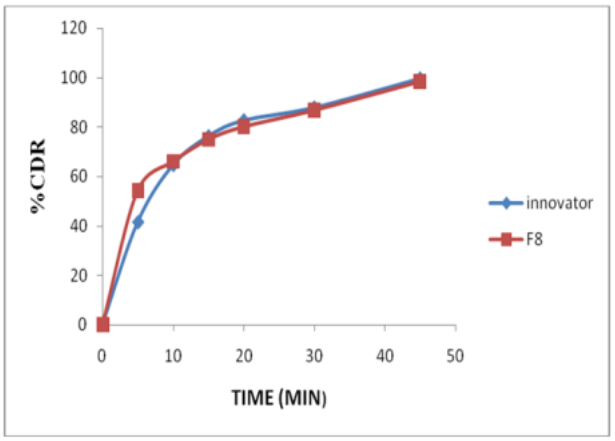

Figure7: Comparative Dissolution profile of innovator product and optimised formulation, F8

Stability Studies [9, 17]:

The stability studies were performed on the most promising tablet formulation i.e. F8. The purpose of stability testing is to provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions and shelf lives to be established.

The conditions and time duration for these studies as per ICH Q1A (R2) guidelines are given in the table.

Study	Storage conditions	Minimumtime period covered by data at submission.
Long term	25 ± 2°c / 60 ± 5% RH	12 months
Intermediate	30 ± 2°c / 65 ± 5% RH	6 months
Accelerated	40 ± 2°c / 75 ± 5% RH	6 months

The present study was performed by keeping the prepared tablets in air tight high density polyethylene bottles at 40° C and relative humidity of 75% for 3 months. Samples withdrawal schedule was 15th, 30th, 60th and 90th day. Tablets were analyzed for physical appearance, hardness, thickness, percent drug content *in vitro* dissolution studies.

RESULTS AND DISCUSSION

Compatibility Study

Drug–Excipients compatibility study of Quetiapine with different categories of excipients was carried out. The result indicates that there was no chemical interaction between drug and excipients. The results are shown in Fig No. 03,04& 05.

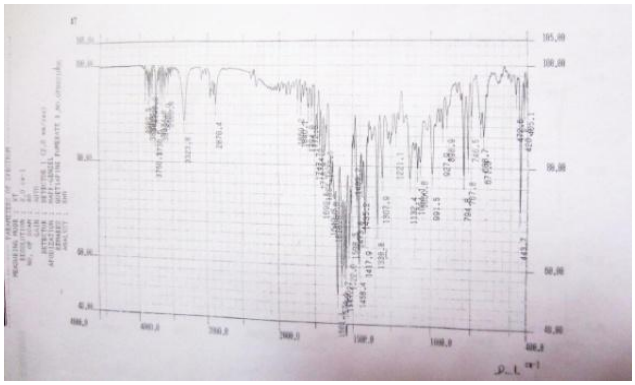

Figure 3: IR Spectrum study of Quetiapine Fumarate

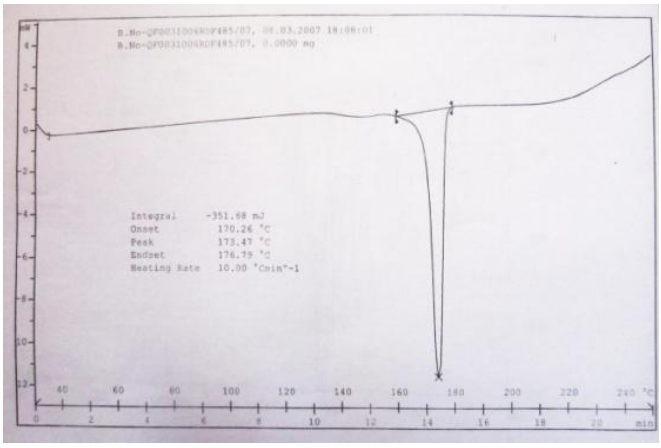

Figure 4: DSC study of Quetiapine Fumarate

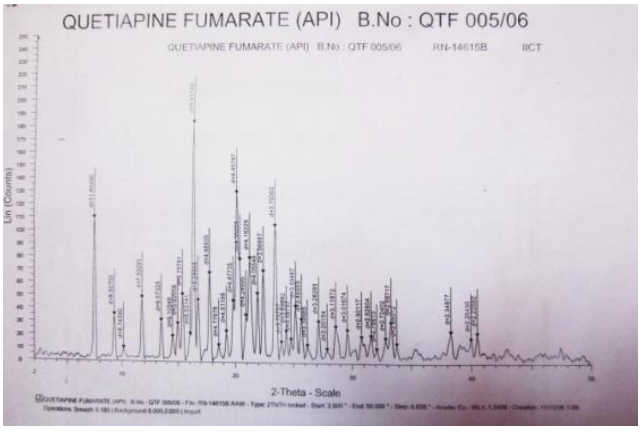

Figure 5: X-RD study of Quetiapine Fumarate

pH Dependent Solubility Study

pH of Quetiapine in 10% solution (water)) was found to be slightly acidic. 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 more in pH 1.2 (0.1 N HCl) i.e. 17.17 mg/ml. Hence, 0.1 N HCl was selected as ideal dissolution medium to carry out *in -vitro* release profile of Quetiapine.

Pre Compression Parameters

Loss on Drying (LOD)

As calculated, theoretical moisture content of drug and excipient which was 2%w/w, 80 LOD of dried granules maintained in that level NMT ± 1% variation by drying at 60°C and optimum drying time to achieve LOD in particular limit. The LOD was in the range of 1.78% to 3.51% w/w. The results are shown in Table no. 02

Powder Flow Characteristics

The flow properties of the drug candidate are important for the selection of suitable method for granulation of the powder mixture. Therefore, the flow of drug was analyzed before the selection of granulation technique. Initially some flow problem arises in direct compression method. Powder Blend shows poor flow which causes weight variation, problem in content uniformity; But Wet Granulation Method shows good flow properties of granules and final blend. Bulk density is in the range of 0.42 to 0.53 gm/ml. Tapped density is in the range of 0.55-0.66 gm/ml. Carr's Index is in the range of 17.71 to 28.9%. Hausner's ratio is in the range of 1.21 to 1.30 and angle of repose is in the range of 21.82^0 to 27.17^0. The results indicate that all properties are showing the good flow characteristics and suitable for compression into tablets. The results are shown in Table no. 02

Post Compression Parameters

Hardness and Friability

Tablets required certain amount of strength, or hardness and resistance to friability. It is necessary or important to withstand mechanical shocks of handling in manufacture, packaging and shipping. Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. Using tablets hardness tester, hardness of the tablets was checked. By using of superdisintegrant (sodium starch glycolate) the hardness and friability of formulations F1 to F8 were found to be in the range of 40 to 82 (N) & 0.01 to 0.10% respectively. The results are shown in Table no. 02. From the above studies it was found that hardness and friability are within the pharmacopeia limits.

Weight variation test

The results indicated that the content of Quetiapine in all the formulations i.e F1 to F8 were found to be in the range of 62.5 ± 1.3% to 62.5 ± 2.0% which are within the Pharmacopeia limits. The results are shown in Table no.02

Drug Content Uniformity

The results indicated that the content of Quetiapine in all the formulations i.e F1 to F8 were found to be in the range of 97.3% to 100.2% which are within the Pharmacopeia limits. The results are shown in Table no.02

***In- Vitro* Disintegration time**

During the formulation development of immediate release tablet, the selection of suitable disintigrant and its concentration is very important. In this experiment sodium starch glycolate was considered as disintegrant with various concentrations. The disintegration time for innovator tablet was 15 min., which was very high. Similarly the disintegration time was found for formulations F1 TO F8 was 4.0 to 10.30 min. The results indicate that the disintegration time increases as the concentration of superdisintegrant. Increases. The results are shown in Table no.02

***In-Vitro* Dissolution study**

Dissolution rate studies showed that about 88 to 98.8% drug release within 45 minutes for all formulations with using using superdisintegrant of sodium starch glycolate , showed complete release i.e. 99 % of drug in 45 minutes. The results are shown in Fig 6 . The results indicate that the formulation, F8which was prepared using superdisintegrant of sodium starch glycolate , showed the complete drug released within 45 minutes. The *in-vitro* drug releases of all developed formulations were within the acceptable ranges of values as given in official compendia but it was observed that the physical properties of F8 was best comparable with marketed preparation. The result indicates that the drug release increases with increase in concentration of superdisintegrant. The results are shown in Fig no.06.

From the dissolution profile, the dissimilarity (f_1) and similarity (f_2) factor**s** were also calculated in comparison with test and innovator product i.e Seroquel tablet of Astrageneca. The result indicates that test and innovator release profile are similar.

Among all formulations, formulation F8 shows F2 – value 86.83 in D.M. water medium and when it subjected to pH 4.5 acetate buffer and 0.1 N HCl media it shows F2 – values 64.84 and 57.34 respectively. This value indications formulation F8 shows good release profile in all media. So it was chosen as final formulation.

Stability Study

The stability studies of optimized formulation F8 were done for 3 months by packing in HDPE container in humidity chamber (40°C/75% RH).

The results are given in table for 1 month, 2 months, 3 months and 6 months. All parameters of formulation including physical parameters, hardness, content uniformity and *in-vitro* dissolution

profile were within specification limit. So it indicates optimized formulation was stable. The results are shown in Table no .03

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 Astrageneca. 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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