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Formulation of Sustained Release Pellets of Quetiapine Fumarate by Fluidized Bed Coating Process

[1,] K.Anusha, [2,] Mr.G.Kishore Babu, [3,] Dr.P.Srinivasa Babu
Department Of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur Dist, Andhra Pradesh, India.

ABSTRACT: *Multiparticulate drug delivery systems are especially useful for controlled or delayed release oral formulations to obtain different release patterns. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations. Recently multiparticulate dosage forms are gaining much favor over single-unit dosage forms in pharmaceutical applications. In the present investigation QUETIAPINE FUMARATE was employed in the sustained drug delivery system for extending the drug release for a prolonged period of time. Quetiapine Fumarate is an Anti-Psychotic drug and is used in the treatment of depression and anxiety disorders.*

Quetiapine Fumarate sustained release pellets were prepared by using sugar pellets with EC and Cellulose diacetate as sustained release polymers, the pellet coating was performed by fluidized bed coating technique. The physicochemical characterization like SEM, DSC and Invitro dissolution studies were performed for all the formulations. It was found that among the various batches of formulations EC-4, EC-5 and CDA-4, CDA-5 were found to release the drug over an extended period of time, i.e. upto 16 hrs. As the concentration of the polymer increased the drug release from the pellet formulations was reduced. The sustained drug release profile has been maintained. So the present technique is successful in developing a sustained release pellet formulation for the Quetiapine fumarate.

KEYWORDS: *Sustained release, pellets, Quetiapine Fumarate, EC, Cellulose diacetate, Fluidized bed Coating.*

I. INTRODUCTION:

Since decades, Oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally, oral dosage forms are classified as single unit and multiple unit dosage forms. It was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphagia, etc.) comes along with the single dose formulations. This soon led to the dividing of monolithic dosage forms into multiples. The concept of this multiple unit dosage forms answers many formulating problems and is a common strategy to control the release of drug as showing the reproducible release profiles when compared to SUDFs. These MUDFs, can either be filled in to hard capsules or compacted in to bigger tablets or can be dispensed in a dose pouches or packets.

In the present investigation QUETIAPINE FUMARATE was employed in the sustained drug delivery system for extending the drug release for a prolonged period of time. Quetiapine Fumarate is an Anti-Psychotic drug and is used in the treatment of depression and anxiety disorders. The antipsychotic effect of Quetiapine is thought by some to be mediated through antagonist activity at dopamine and serotonin receptors. Specifically the D1 and D2 dopamine, the alpha 1 adrenoreceptor and alpha 2 adrenoreceptor, and 5-HT1A and 5-HT2 serotonin receptor subtypes are antagonized. Quetiapine also has an antagonistic effect on the Histamine H1 receptor. QUETIAPINE FUMARATE sustained release pellets were prepared by using sugar pellets with EC and Cellulose diacetate as sustained release polymers, the pellet coating was performed by fluidized bed coating technique.

II. MATERIALS AND METHODS:

MATERIALS:

Quetiapine Fumarate was obtained as gift sample from Sun pharmaceuticals Pvt. Ltd., Mumbai, India. Ethyl Cellulose, Cellulose diacetate, Povidone k-30, Acetyl tributyl citrate, Crosspovidone XL-10 ,Tween-80 were obtained as gift samples from Dow Chemicals Asia pvt. Ltd., Mumbai. Hypromellose phthalate, Talc, Isopropyl alcohol, Titanium dioxide, Acetone were obtained from Loba chemi pvt ltd., Mumbai.

METHODS:

Quetiapine Fumarate sustained release pellets were prepared by Direct Pelletization method using sugar pellets with EC and Cellulose diacetate as sustained release polymers, the pellet coating was performed by fluidized bed coating technique.

Standard Calibration curve of Quetiapine Fumarate:

A simple, sensitive, specific, rapid, accurate and precise RP-HPLC method was developed for the estimation of Quetiapine Fumarate. Quetiapine was chromatographed on a reverse phase C_{18} Welchrome column with dimensions (4.6 x 250 mm I.D.,particle size 5µm) in a mobile phase consisting of phosphate buffer (pH 3.0 adjusted with orthophosphoric acid) and acetonitrile in the ratio 40:60 v/v. The mobile phase was pumped at a flow rate of 0.8ml/min with detection at 291nm. The detector response was linear in the concentration of 20-120µg/mL.

Chromatographic Conditions:

The mobile phase consisting of phosphate buffer (pH 3.0 adjusted with orthophosphoric acid) and acetonitrile were filtered through 0.45µ membrane filter before use, degassed for 15minutes and was pumped from solvent reservoir into the column at a flow rate of 0.8 ml/min. The detection was monitored at 291nm and run time was 5 mins.The volume of injection loop was 10µL.Prior to the injection of the drug solution, the column was equilibrated for at least 30mins with mobile phase flowing through the system. The column and the HPLC system were kept in ambient temperature.

Procedure:

Stock solution of Quetiapine Fumarate was prepared by dissolving 50mg of drug in 50ml Standard volumetric flask containing 25ml of mobile phase and the solution was sonicated for 15 min. and then made up to the mark with mobile phase to get concentration of 1000µg/mL. Subsequent dilutions of this solution were made with mobile phase to get concentration of 20-120µg/mL.The Standard solutions prepared as above were injected into the 10µL loop and the chromatogram was recorded.

The calibration curve was constructed by plotting concentration Vs peak area ratio. The amount of Quetiapine fumarate present in the sample was calculated from the standard calibration curve. The peak area ratios of the drug Vs concentration were found to be linear and the results are furnished in the given **table no.3**.

Preformulation Studies:

Preformulation studies are conducted for stability and excipient compatibility. The drug and polymers are mixed in geometric dilution and they are taken into PE/PVC polybag , after thorough mixing they are loaded into stability chambers maintained at 40^0 C $\pm 2^o$ C, 75%±5%RH.The samples were withdrawn periodically and assayed to check the purity. Results are given in **table no. 4 .**

Preparation of Sugar spheres

Ingredients required:

1. Pharma grade sugar #40/45(B.P.)
2. P.G. Sugar for solution (B.P.)
3. Starch for solution(B.P.)
4. Purified water(B.P.)
5. Milled P.G. sugar for loading(B.P.)

Manufacturing procedure:

1. Mill the P.G. Sugar (#24 pass) by using micronizer with 0.5mm screen.
2. **Binder solution preparation:**
   Take Pharmagrade sugar for solution (#24 pass), starch and purified water in a container. Switch on homogenizer and mix for 10min. and filter through #40 mesh into a container.
3. Take pharma grade sugar #40/50 into coating pan and load P.G. Sugar while spraying binding solution till the P.G. Sugar loading is completed and rotate the pan for 30min after completion.
4. Load the pellets into treys uniformly and dry at specified temperature(40-50 ^{0}C) for about 20 hours.
5. Sift the dried pellets and collect good fraction.
6. Re sift the good fraction quantity after Q.C. analysis and approval to get required sizes.

III. PREPARATION OF PELLETS BY FLUID BED COATING

General Procedure:

Equal quantities of Quetiapine Fumarate and Crosspovidone XL-10 were taken in to bowl and mixed with gloved hand. To the mixture another equivalent quantity of Quetiapine Fumarate was added and mixed with help of gloved hand then remaining quantity of drug was loaded in to the blender and mixed for 10 mins.

Preparation of Povidone Solution:

Isopropyl alcohol, PVP K-30 and Tween 80 were taken into the container and switched on the stirrer and mixed for 10mins. The solution was filtered through nylon cloth into another container.

Drug Loading:

Sugar pellets were loaded into the pan. On to the sugar pellets Quetiapine Fumarate and Crosspovidone XL-10 blends prepared earlier were loaded. While spraying the povidone solution Pan was allowed to rotate for about 10 mins until uniform drug loading occurs.

Drying:

The drug loaded pellets from the pan were spread on to the trays uniformly and dried at 60°C temperature for about 3hrs. After drying the pellets were sifted by using vibro sifter to remove fines and collect the uniform sized pellets.

Talc loading:

Drug loaded pellets were loaded into the coating pan. On to the drug loaded pellets, talc was loaded while spraying remaining povidone solution. Agitate the bed to avoid lumps manually till the drug loading is completed and rotate the pan for 15 min.

Drying:

The talc loaded pellets from the pan were spread on to the trays uniformly and dried at 60°C temperature for about 2hrs. After drying, the pellets were sifted by using vibro sifter to remove fines and the uniform sized pellets were collected.

Preparation of Cellulose diacetate Solution:

Cellulose diacetate and water were taken into the container and mixed for 10mins. Povidone and IPA were taken in separate containers and mixed well for 10 mins. Now the Povidone solution was added to Cellulose diacetate solution with continuous stirring. The solution was then filtered through nylon cloth into a container.

Sub Coating:

The drug loaded pellets were charged in to fluidization basket. Cellulose diacetate polymer solution was atomized on to the materials while the air is allowed to circulate into the basket to keep the materials under fluidized state. The process of fluidization was continued for 10 mins.

Preparation of Hypromellose Phthalate Solution:

Hypromellose phthalate, titanium dioxide, acetone and isopropyl alcohol were taken into a container and mixed for 10 mins at 1300 rpm and filtered through nylon cloth into another container.

Polymer Loading:

The Cellulose diacetate coated pellets were charged in to fluidization basket. Polymer solution was atomized on to the materials while the air is allowed to circulate into the basket to keep the materials under fluidized state. The process of fluidization was continued for 10 mins.

Preparation of EC Solution:

Ethyl cellulose, Acetyl tributyl citrate, talc, IPA and acetone were taken into a container. They were mixed in homogenizer for 15 mins and filtered through nylon cloth into another container.

Polymer loading:

The Hypromellose phthalate coated pellets were charged in to fluidization basket. EC Polymer solution was atomized on to the materials while the air is allowed to circulate into the basket to keep the materials under fluidized state. The process of fluidization was continued for 10 mins.

The finally coated pellets were dried at ambient conditions for 2hrs and sifted through vibro sifter to collect uniform sized pellets. The composition of various QUETIAPINE FUMARATE sustained release pellets were given in **table no.1 and 2.**

Table No. 1: Composition Of Various Quetiapine Fumarate Pellets Prepared By Fluid Bed Coating Method

Ingridients for 10gms	EC-1	EC-2	EC-3	EC-4	EC-5
Quetiapine Fumarate	5	5	5	5	5
Povidone K-30	0.275	0.275	0.275	0.275	0.275
Ethyl Cellulose	0.010	0.012	0.014	0.016	0.018
Cellulose diacetate	0.014	0.014	0.014	0.014	0.014
Hypromellose Pthalate	0.135	0.135	0.135	0.135	0.135
Titanium dioxide	0.015	0.015	0.015	0.015	0.015
Acetyl tributyl citrate	0.01	0.01	0.01	0.01	0.01
Acetone	2.308	2.308	2.308	2.308	2.308
IPA	5	5	5	5	5
Talc	0.037	0.037	0.037	0.037	0.037
Crosspovidone XL-10	0.06	0.06	0.06	0.06	0.06
Sugar Spheres	4.420	4.418	4.416	4.414	4.412
Purified Water	1.84	1.84	1.84	1.84	1.84
Tween-80	0.024	0.024	0.024	0.024	0.024

Ingredients for 10gms	CDA-1	CDA-2	CDA-3	CDA-4	CDA-5
Quetiapine Fumarate	5	5	5	5	5
Povidone K-30	0.275	0.275	0.275	0.275	0.275
EC	0.12	0.12	0.12	0.12	0.12
Cellulose diacetate	0.010	0.012	0.014	0.016	0.018
Hypromellose phthalate	0.010	0.012	0.014	0.016	0.018
Titanium dioxide	0.015	0.015	0.015	0.015	0.015
Acetyl tributyl Citrate	0.016	0.016	0.016	0.016	0.016
Acetone	2.308	2.308	2.308	2.308	2.308
IPA	5.543	5.543	5.543	5.543	5.543
Talc	0.037	0.037	0.037	0.037	0.037
Crosspovidone XL-10	0.06	0.06	0.06	0.06	0.06
Sugar Spheres	4.43	4.425	4.421	4.417	4.413
Purified Water	1.847	1.847	1.847	1.847	1.847
Tween-80	0.027	0.027	0.027	0.027	0.027

Table No. 2: Composition Of Various Quetiapine Fumarate Pellets Prepared By Fluidized Bed Coating Technique.

EXPERIMENTAL:

Physical Parameters of Quetiapine Fumarate Pellets Prepared by Fluidized Bed Coating

a) % yield:

All the batches of sustained release Quetiapine Fumarate pellets prepared by fluidized bed coating were evaluated for percentage yield of the pellets. The actual percentage yields of pellets were calculated by using the following formula**.** The % yield of various batches of pellets was given in **table no.7**.

$$\text{Percentage yield of pellets} = \frac{\text{Practical yield of pellets}}{\text{Theoritical yield of pellets}} \times 100$$

b) Particle Size Determination:

The average particle size of the pellets was analyzed by simple sieve analysis method. The Micromeritic properties like Bulk density, Tapped density, Compressibility index, Hausner's ratio were carried out for the prepared pellets, based upon these properties Capsule size was estimated. Dose of the drug is 250mg. Pellets (equivalent to dose) are then filled into the **triple zero size** capsules. Micromeritic Characterization and particle size of various batches of pellets were given in **table no. 6 and table no.7** .

c) Drug Content:

Take sample pellets equivalent to about 50mg of Quetiapine Fumarate into 50ml volumetric flask, dissolve in 25ml Acetonitrile and 10ml Mobile phase. Sonicate for 20min and makeup to the volume with mobile phase and shake well. Filter the solution, from the stock solution prepare the required dilutions. Inject the samples into HPLC monitored at 290nm .From the peak area of the Chromatogram obtained and standard Calibration curve of Quetiapine Fumarate drug content was calculated.

Results were given in **table no.7.**

INVITRO DISSOLUTION STUDIES:

Dissolution studies for each formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA), equipped with paddles (USP apparatus II method) employing 900ml of distilled water as a medium. The paddles were operated at 75 rpm and the temperature was maintained at 37± 1^0C throughout the experiment. Samples were withdrawn at regular intervals upto 18 hrs and replaced with equal volume of dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by chromatographically at 291nm. The dissolution studies on each formulation were conducted for three times.

CHARACTERIZATION:

Based on the dissolution studies performed on all the batches of pellets, some of the optimized formulations were selected and further investigated for DSC and SEM studies.

Scanning Electron Microscopy (SEM):

The samples were coated with a thin gold layer by sputter coater unit (SPI, Sputter, USA). Then, the SEM photographs were taken by a scanning electron microscope (Scanning electron microscope JSM-6390, Japan) operated at an accelerated voltage of 10000 Volt. The SEM photographs of fluidized bed coated pellets given in **Figure No.12.**

Differential Scanning Calorimetry (DSC):

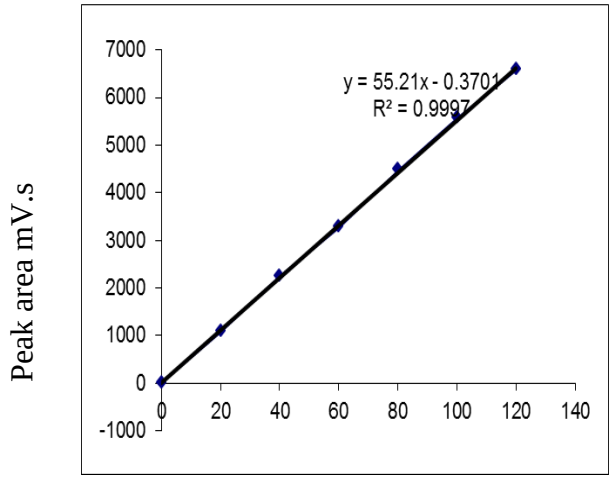
A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curves of Quetiapine Fumarate Pellets prepared by fluidized bed coating. About 3.052mg of sample was weighed in a standard open aluminum pan, and scanned from 30-450^{o}C, at a heating rate of 10^{o}C/minute while being purged with dry nitrogen. Results given in **table no.5 .**

RESULTS AND DISCUSSION:

Table No.3: Calibration data of Quetiapine Fumarate:

Concentration (µg/mL)	Peak area (n=6)
20	1074.667
40	2241.898
60	3266.782
80	4472.625
100	5552.404
120	6577.053

Figure No.1: Calibration Curve of Quetiapine Fumarate:



Preformulation Studies:

Table No.4: Preformulation Studies

S.no	*Description*	*Method Evaluated*	*0th day*	*1 month*	*3 months*
1	**Quetiapine Fumarate**	Physical Evaluation	White crystalline powder	White crystalline powder	White crystalline powder
2	**Ethyl cellulose**	Physical Evaluation	White powder	White powder	White powder
3	**Cellulose diacetate**	White powder	White powder	White powder	White powder
4	**Quetiapine Fumarate**	Assay by HPLC method	Complied	Complied	complied
5	**Quetiapine Fumarate**	DSC Studies	Melting isotherm was observed at 178.1°C	Complied	Complied
6	**Quetiapine Fumarate+ Cellulose diacetate + EC**	DSC Studies	Melting isotherm was observed at 178.2°C	Complied	Complied

DSC Analysis:

Table No.5: DSC Thermo gram interpretation.

	QUETIAPINE FUMARATE	QUETIAPINE FUMARATE PELLETS
Peak Temperature	**178.1°C**	**178.2°C**
Nature of Peak	**Broad Endothermic**	**Broad Endothermic**
Inference	**Melting point**	**Melting point**

Figure No.2: DSC curve of Quetiapine Fumarate

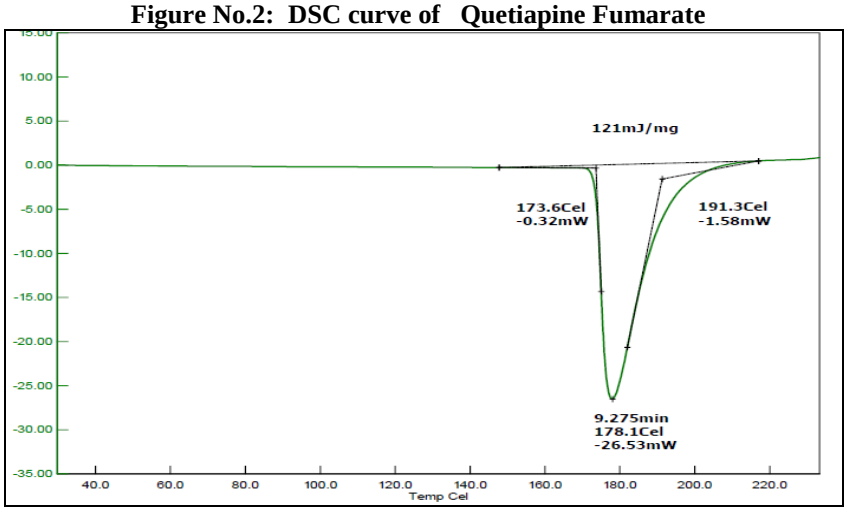
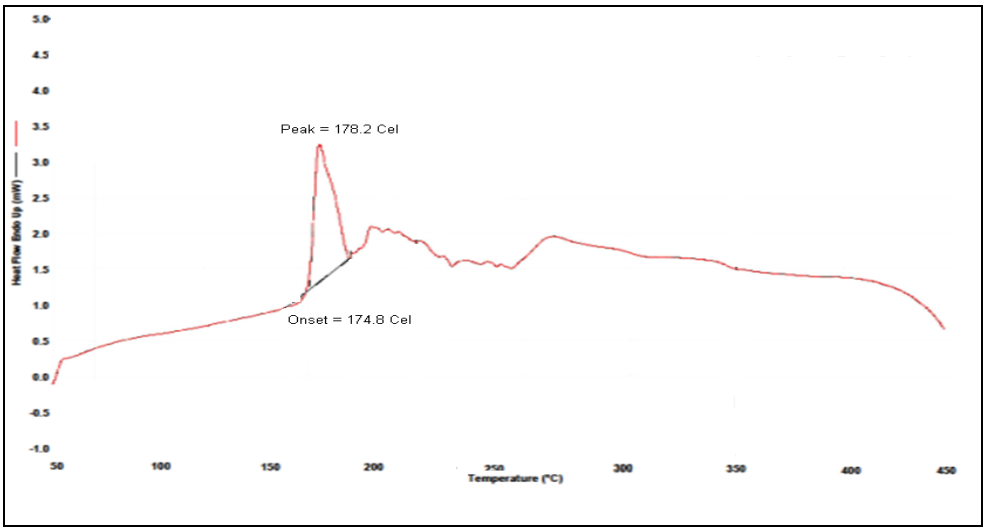


Figure No.3: DSC curve of Quetiapine Fumarate along with polymers



Physical parameters of Quetiapine fumarate pellets prepared by fluidized Bed coating process

Table No.6: Micromeritic characterization of Quetiapine fumarate pellets

S.no	Formulations	BD	TD	CI	HR	Bulkiness
1	**EC-1**	0.397	0.443	10.384	1.116	2.519
2	**EC-2**	0.386	0.431	10.441	1.117	2.591
3	**EC-3**	0.381	0.426	10.563	1.118	2.625
4	**EC-4**	0.379	0.422	10.190	1.113	2.639
5	**EC-5**	0.376	0.42	10.476	1.117	2.660
6	**CDA-1**	0.371	0.413	10.169	1.113	2.695
7	**CDA-2**	0.369	0.41	10.000	1.111	2.710
8	**CDA-3**	0.365	0.409	10.758	1.121	2.740
9	**CDA-4**	0.362	0.403	10.174	1.113	2.762
10	**CDA-5**	0.361	0.401	9.975	1.111	2.770

BD = Bulk density, **TD** = Tapped density, **CI** = Compressibility index, **HR** = Hausner's ratio

Table No.7: Physical parameters of Quetiapine fumarate pellets prepared by FBC Technique

S.no	Formulations	%Yield ± SD, n = 3	Particle Size ± SD, n=3(μ)	% Drug Loading ± SD n=3
1	EC-1	91.5 ± 0.2	1072 ± 20	98.2 ± 0.3
2	EC-2	92.6 ± 0.6	1063 ± 25	97.6 ± 0.6
3	EC-3	91.6 ± 0.5	1069 ± 16	99.5 ± 0.4
4	EC-4	93.9 ± 0.2	1061 ± 24	101.9 ± 0.2
5	EC-5	90.2 ± 0.2	1082 ± 34	98.0 ± 0.5
6	CDA-1	94.8 ± 0.3	1084 ± 24	99.8 ± 0.4
7	CDA-2	92.7 ± 0.4	1091 ± 27	97.7 ± 0.4
8	CDA-3	92.4 ± 0.3	1088 ± 29	99.4 ± 0.3
9	CDA-4	92.8 ± 0.5	1077 ± 21	102.8 ± 0.5
10	CDA-5	92.6 ± 0.2	1073 ± 19	98.6 ± 0.4

Table No.8: Drug release profile of Quetiapine Fumarate pellets prepared by FBC (EC)

S.No	*Time (hrs)*	*Cumulative % drug release*				
		EC-1	EC-2	EC-3	EC-4	EC-5
1	0	0	0	0	0	0
2	1	52.71	37.21	24.23	18.34	16.35
3	2	61.34	56.25	42.56	30.45	25.45
4	4	67.87	62.86	55.48	43.65	37.42
5	6	75.15	70.42	68.24	56.24	53.14
6	8	84.24	79.56	75.35	67.46	63.14
7	10	92.45	87.64	83.34	75.32	71.26
8	12	97.24	91.47	89.58	84.34	79.15
9	14	-	96.82	94.56	90.56	83.47
10	18	-	-	96.32	94.25	86.35

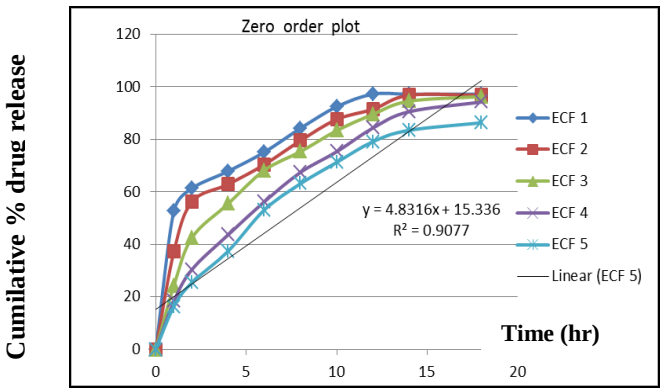


Figure No.4 : Zero Order Plots of Quetiapine Fumarate Pellets prepared by Fluidized bed Coating Process

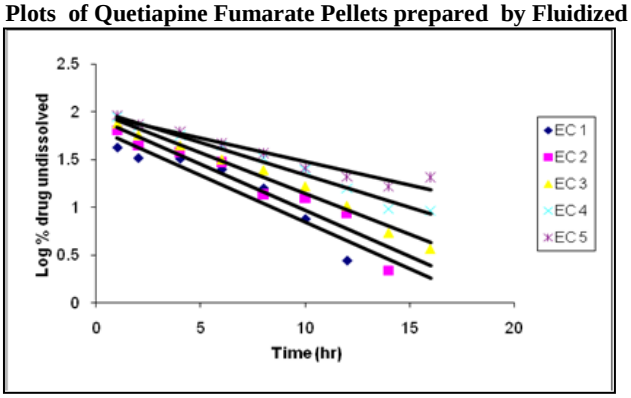


Figure No.5 : First Order Plots of Quetiapine Fumarate Pellets prepared by Fluidized bed Coating Process

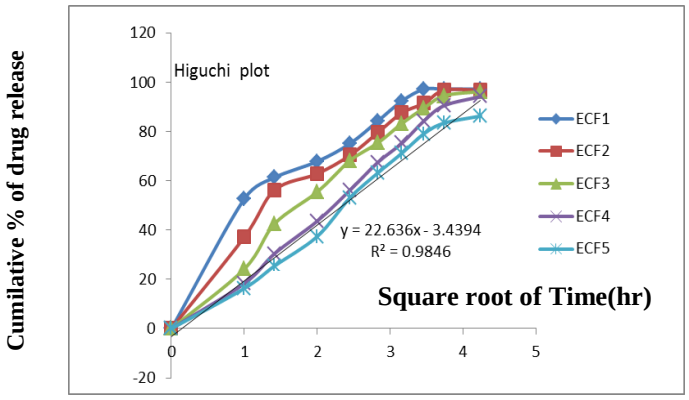


Figure No.6 : Higuchi plots of Quetiapine Fumarate Pellets prepared by FBC

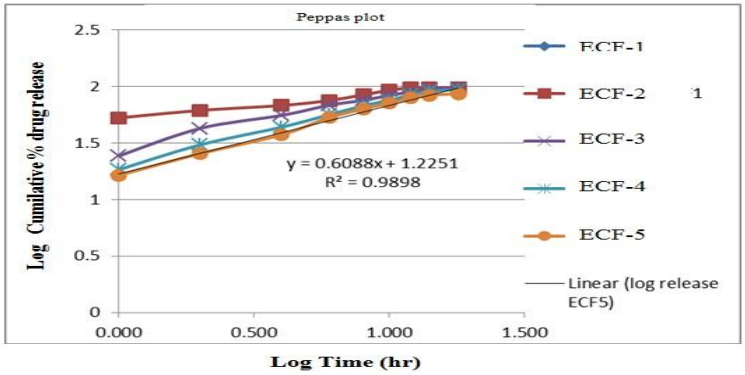


Figure No.7 : Peppas plots of Quetiapine Fumarate Pellets prepared by Fluidized bed Coating

Table No.9: Drug release profile of Quetiapine Fumarate pellets prepared by FBC (CDA)

S.no	*Time (hrs)*	*Cumulative % drug release*				
		CDA-1	**CDA-2**	**CDA-3**	**CDA-4**	**CDA-5**
1	1	56.32	35.32	20.14	9.21	7.25
2	2	67.72	47.25	38.51	27.35	22.34
3	4	75.56	64	44.62	35.62	31.16
4	6	83.43	70.51	64.72	50.32	46.32
5	8	86.64	78.54	75.26	65.24	62.33
6	10	91.34	84.15	81.24	72.28	70.66
7	12	95.62	89.47	88.32	81.88	78.13
8	14	-	93.15	92.45	87.12	84.33
9	18	-	96.47	95.42	92.34	89.32

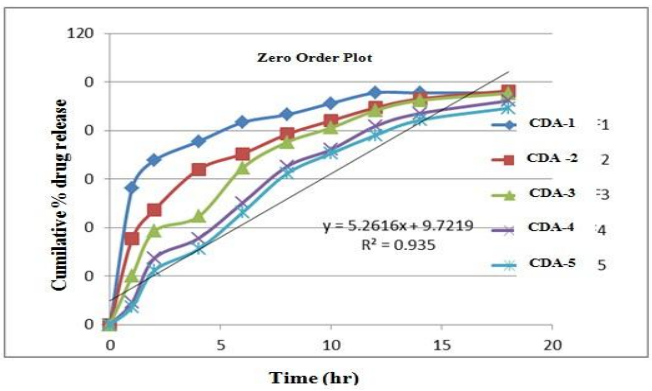


Figure No.8: Zero Order Plots of Quetiapine Fumarate pellets prepared by FBC (CDA)

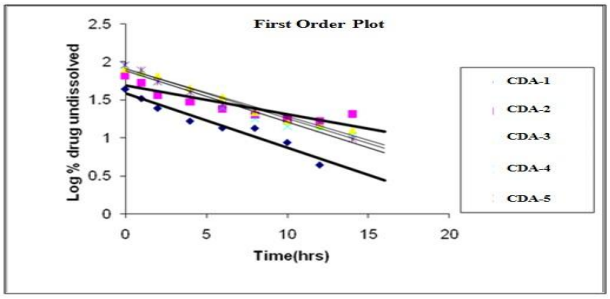


Figure No.9: First Order Plots of Quetiapine Fumarate Pellets prepared by FBC (CDA)

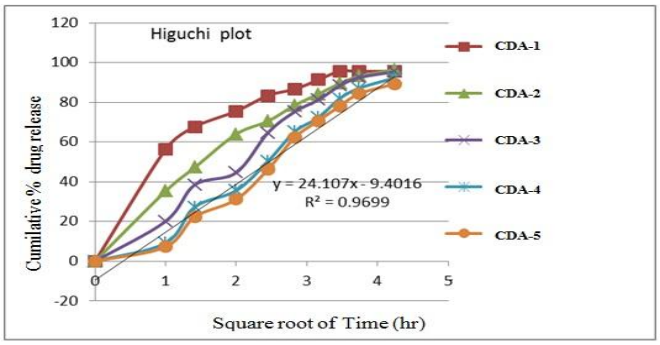


Figure No.10 : Higuchi plots of Quetiapine Fumarate Pellets prepared by FBC (CDA)

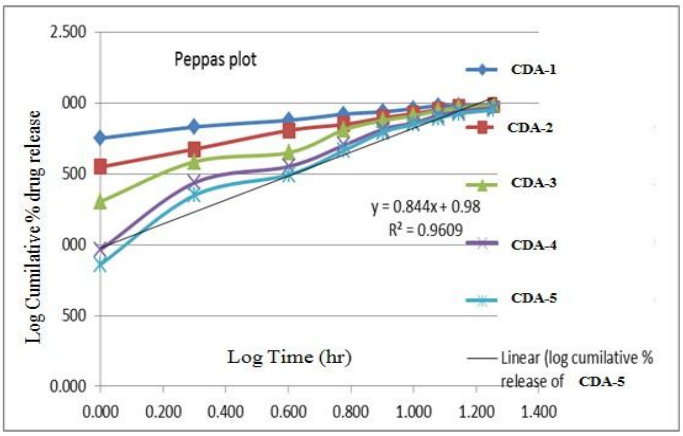


Figure No.11 : Peppas plots of Quetiapine Fumarate Pellets prepared by FBC (CDA)

Table No.10: Pharmacokinetic parameters

FORMULATIONS	ZERO ORDER		FIRST ORDER		HIGUCHI	PEPPAS
	K	R^2	K	R^2	R^2	K
EC-1	4.135	0.911	0.200	0.675	0.888	0.971
EC-2	4.465	0.953	0.188	0.758	0.942	0.970
EC-3	4.921	0.985	0.181	0.835	0.978	0.971
EC-4	5.134	0.986	0.158	0.912	0.980	0.993
EC-5	5.134	0.908	0.115	0.895	0.985	0.990
CDA- 1	3.718	0.925	0.151	0.818	0.930	0.980
CDA- 2	4.500	0.995	0.168	0.882	0.970	0.989
CDA- 3	5.100	0.992	0.172	0.885	0.964	0.967
CDA- 4	5.293	0.992	0.145	0.925	0.982	0.955
CDA- 5	5.261	0.930	0.126	0.903	0.982	0.961

n-values									
EC-1	**EC-2**	**EC-3**	**EC-4**	**EC-5**	**CDA-1**	**CDA-2**	**CDA-3**	**CDA-4**	**CDA-5**
0.49	0.57	0.63	0.77	0.81	0.52	0.61	0.68	0.73	0.80

SEM Analysis:

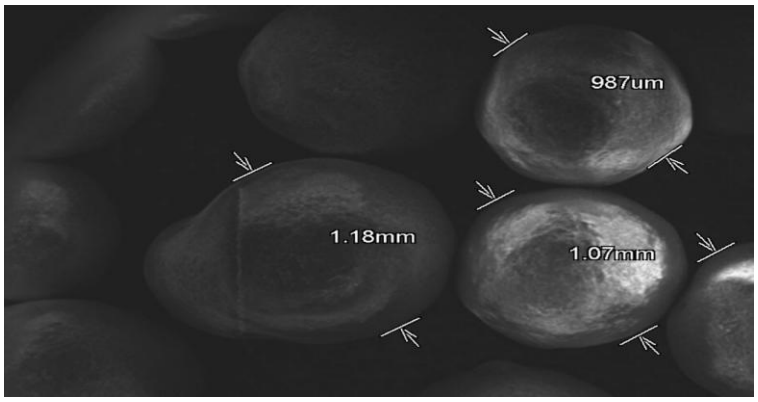


Figure No.12: SEM photograph of Quetiapine Fumarate pellets prepared by FBC method

DISCUSSION

Development of Calibration curve for Quetiapine Fumarate:

A simple, sensitive, specific, rapid , accurate and precise RP-HPLC method was developed for the estimation of Quetiapine Fumarate. Quetiapine was chromatographed on a reverse phase C_{18} Welchrome column with dimensions (4.6 x 250 mm I.D.,particle size 5µm) in a mobile phase consisting of phosphate buffer (pH 3.0 adjusted with orthophosphoric acid) and acetonitrile in the ratio 40:60 v/v. The mobile phase was pumped at a flow rate of 0.8ml/min with detection at 291nm. The detector response was linear in the concentration of 20-120µg/mL.

The calibration curve was constructed by plotting concentration Vs peak area ratio.The amount of Quetiapine fumarate present in the sample was calculated from the standard calibration curve. The peak area ratios of the drug Vs concentration were found to be linear.

Preformulation Studies:

The preformulation studies performed on Quetiapine Fumarate and Quetiapine Fumarate along with excipient admixtures were found to be stable with no physical changes in the colour and amorphous nature. The drug content estimated in the admixtures by HPLC method was linear with the standard curve values. It was further confirmed that there was no interaction observed between drug and the polymers.

DSC thermo graphic peak for Quetiapine Fumarate was observed at temperature 178.1^{o}C. It was also observed that similar thermograph at same temperature with the drug and excipient mixture at 178.2^{o}C was obtained.

The preformulatory studies thus indicated that there were no drug and excipient incompatibilities. Based upon these studies suitable polymers were selected and Quetiapine Fumarate sustained release pellets were formulated.

Physical parameters of Quetiapine fumarate pellets prepared by fluidized bed coating method:

% yield, Particle size and drug content of prepared pellets were found to be stable with the change in the concentration of polymer. % yield for all the pellets were in the range of 90-94.5% and the average particle size range of 1079 µ.The drug content in the all pellet formulations were in the range of 95-105% .

Dissolution Studies:

Dissolution studies were performed on all the sustained release pellets by using U.S.P paddle method (apparatus II). The drug release from the pellet formulations were extended upto 18 hrs in majority of the formulations. EC-1 and CDA-1 formulations were failed to release the drug up to 18 hrs. Formulations EC-1 and CDA-1 extended the drug release upto 8hrs where as the formulation EC-2 extended the drug release up to 10hrs. The drug release rate decreases as the concentration of EC polymer composition increased.

Among all formulations EC-3, EC-4 and CDA-2, CDA-3 and CDA-4 showed extended drug release i.e. > 90 % at the end of 18hrs. The formulations EC-5, and CDA-5 showed very slow drug release (i.e. <85%) in 18hrs. It was observed that increase in the concentration of polymer Ethyl Cellulose resulted in delay in the drug release. The increase in the Cellulose diacetate polymeric concentration in formulations showed initial delay in drug release. Among the various batches of formulations EC-4,EC-5 and CDA-4 and CDA-5 prepared by fluid bed coating were found to release the drug over an extended period of time, i.e. upto 18 hrs and meeting USP Quetiapine Fumarate extended release test profiles once a day administration.

The release exponent (n values) for all the pellet formulations were in the range of 0.45 to 0.8, indicated that the drug release was by non-Fickian diffusion. Thus the drug release from the pellet formulations was by diffusion of the drug from the polymeric matrix followed by erosion of the polymer. Thus mechanism of drug release from all the pellet formulations was by both polymer erosion and diffusion of the drug from the matrix systems.

SEM Analysis:

SEM analysis was performed for the pellets prepared by fluid bed coating. The pellets prepared by FBC were having smooth surface with minimal pores indicated the uniform coating of the pellets.

DSC Analysis:

DSC analysis was performed for the pure drug and pure drug with polymers. There was a characteristic endothermic peak (down) at 178.1^{o} C for the pure drug and temperature cycle is maintained at 20^{0} C/min.

For the pure drug and the polymers, the DSC curve shows characteristic endothermic peak (up) at 178.2^{0} C and the temperature cycle was maintained at 50^{0} C/min. Thus both the DSC curves are exhibiting the characteristic endothermic peak at the same temperature which infers that there is no interaction between the drug and the polymers used.

SUMMARY

In the present investigation Quetiapine Fumarate was employed in the sustained drug delivery system for extending the drug release for a prolonged period of time. Quetiapine Fumarate is an used in the treatment of depression and anxiety disorders. Quetiapine Fumarate is a white to off-white crystalline solid and is soluble in cold water, practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane and mixtures of methanol and dichloromethane. Quetiapine Fumarate is well absorbed and extensively metabolized in the liver. The relative bioavailability of Quetiapine Fumarate from a pellet was 100%.

Based on their biopharmaceutical properties, QUEITIAPINE FUMARATE was selected as a candidate for the preparation of sustained release pellets by using sugar pellets with EC and

Cellulose diacetate as Sustained release polymers the pellet coating was performed by fluidized bed coating techniques. The following conclusions were drawn from the present investigation.

1. Preformulation studies were performed on the drug and polymers used in the formulations were found to be compatable. No drug and excipient reactions were observed.
DSC analysis was performed for the pure drug and pellets the results revealed that there were been no major interaction between the drug and the polymers used.
2. % yield, Particle size and drug content of prepared pellets were found to be stable with the % yield for all the pellets were in the range of 90-94.5% and the average particle size range of 1079µ.The drug content in the all pellet formulations were in the range of 95-105%.
3. The *invitro* dissolution studies were performed for various pellets. It was found that among the various batches of formulations **EC-4,EC-5 , CDA-4 and CDA-5** prepared by fluid bed coating were found to release the drug over an extended period of time, i.e. up to 18 hrs and meeting USP Quetiapine Fumarate extended release test profiles for once a day administration.
4. SEM analysis was performed for the pellets prepared by fluid bed coating. The pellets prepared by FBC were having smooth surface with minimal pores which indicated the uniform coating on the pellets.

IV. CONCLUSION & RECOMMENDATIONS

Conclusion:

The Quetiapine fumarate sustained release pellets were prepared by fluidized bed coating process. Ten formulations were prepared by using EC and Cellulose diacetate polymers as release retardants. The polymers chosen showed no significant interaction with drug which was evident from DSC studies. The physicochemical characterization of pellets was studied by SEM analysis. The i*nvitro* dissolution studies have been performed for all the formulations. Good correlation and reproducible results were obtained with formulations EC-4, EC-5, CDA-4 and CDA-5 thus showing good *in-vitro* dissolution profile.

As the concentration of the polymer increased the drug release from the pellet formulations was reduced. The sustained drug release profile has been maintained. So the present technique is successful in developing a sustained release pellet formulation for the Quetiapine fumarate.

Recommendations:

The scalability of multiparticulate systems facilitates the formulation of these type of dosage forms more easy for industrialists. The advantages of uniformity in size and shape avoids the weight variation and drug dissolution problems when compared to single unit dosage forms such as tablets or capsules. Formulation of Quetiapine fumarate pellets for sustained drug release can be adopted in large scale. With the advantage of requirement of small polymer concentrations to get sufficient sustained effect, one can drastically reduce bio burden of polymers and eventually their relative side effects. Due to requirement of small polymer quantities the formulations can also be cost effective.

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