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FABRICATION OF MICROPARTICULATE CARRIER SYSTEMS FOR EFFECTUAL DELIVERY OF ATYPICAL ANTIPSYCHOTIC DRUG

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ABSTRACT

Purpose: To prepare and evaluate Quetiapine Fumarate microspheres for prolonged release.
Methods: Quetiapine Fumarate microspheres were prepared by emulsion solvent evaporation method using various polymers, including ethylcellulose (EC), hydroxypropyl methylcellulose (HPMC), carbopol 934 (CA) .The process variables, viz, drug/polymer ratio, type of polymer on the mean particle size, drug entrapment efficiency, yield, drug content, micromeritic properties and drug release of the microspheres were studied.
Results: It was observed that as the microsphere size decreased and there is an increase in drug release rate with the polymer combination of EC and HPMC with good flow properties. Invivo data revealed that Quetiapine Fumarate loaded microspheres was able to inhibit stereotypy reactions as that of standard e drug.
Conclusion: Amongst the developed microspheres, F7 exhibited maximum prolonged drug release for 8h. This oral Quetiapine Fumarate formulation could potentially improve the bioavailability of the drug as well as patient compliance.
Keywords: Quetiapine Fumarate, Microspheres, Prolonged release, Solvent evaporation, Ethyl cellulose, Hydroxy propyl methylcellulose, Carbopol

INTRODUCTION

Antipsychotics (also known as neuroleptics or major tranquilizers) are a class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations, or disordered thought), in particular in schizophrenia and bipolar disorder, and are increasingly being used in the management of non-psychotic disorders. Schizophrenia is a chronic, severe and disabling brain disease. Approximately 1% of the world population suffers from schizophrenia during their lifetime [1, 2].

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The treatment for schizophrenia is with compounds generally classified as antipsychotics, neuroleptics and major tranquilizers. Drug maintenance therapy is a very important strategy to prevent relapse, after an acute psychotic episode has resolved and the patient is free of overt psychotic symptoms. Quetiapine fumarate belongs to groups of atypical antipsychotics. This medication is used to treat certain mental/ mood conditions (such as schizophrenia, bipolar disorder, mania or depression associates with bipolar disorder. Quetiapine is known as an anti-psychotic drug (atypical type). It works by helping to restore the balance of certain natural substances (neurotransmitters) in the brain. Quetiapine fumarate is an antipsychotic drug with plasma half life of 6 h and poor oral bioavailability (9%) due to extensive first-pass metabolism [3]Quetiapine fumarate is approximately 83% bound to plasma proteins.[6] Possible methods to avoid first-pass metabolism

include transdermal, buccal, rectal, and parenteral routes of administration. Oral route is the most commonly used and preferred route for the delivery of drugs, although several factors like pH of GIT, residence time, and solubility can affect drug absorption or availability by this route . Developing an oral controlled –release for highly acidic soluble drugs has been always a problem, if these systems have not been formulated properly they may release drug at faster rate and cause undesirable effects. Hence selections of polymers play an important role in designing such a drug delivery systems. In the present study, Quetiapine fumarate microspheres were prepared by emulsion-solvent evaporation method. Surface morphology, particle size, encapsulation efficiency and drug release profile of the prepared microspheres have been investigated

MATERIALS AND METHODS

Quetiapine fumarate was obtained as a gift sample from Aurobindo Labs, Hyderabad and all the other reagents used were of analytical grade.

METHOD:

Microspheres were prepared by emulsification – solvent evaporation technique which involves two steps as given below

A) Preparation of Aqueous phase:

Aqueous phase was prepared by taking 160ml of water. To it appropriate concentrations of Tween 20 and polyvinyl alcohol were added as emulsifiers.

B) Preparation of organic phase:

Accurately weighed amounts of ethyl cellulose, hydroxyl propyl methyl cellulose and carbopol were dissolved in 20ml of organic solvent mixture containing Dichloromethane and acetone.

C) FABRICATION OF MICROSPHRES:

Microspheres were prepared by emulsion-solvent evaporation method. The drug and Ethyl cellulose were dissolved in a mixture of acetone and dichloromethane. The 0.5%polyvinyl alcohol solution was prepared as emulsifier and to it aqueous phase containing HPMC solution was added. In a polymer combination trails various ratios of carbomer and HPMC were employed as aqueous phase along with the PVA solution. The organic phase was added to the aqueous phase the solvent mixture was stirred for a period of 5min in ultra-turrax for initial size reduction and for the formation of uniform dispersion of the two phases. Stirring is carried out at 10000 rpm. After that the dispersion was transferred to a homogenizer and the stirring was continued at 1000 rpm with the aid of heat for initial 20-25 min followed by the removal of heat for a period of 4 hours for complete evaporation of the solvent and the emulsification to occur. Small amount of magnesium stearate was added to reduce the aggregation of microsphres.The emulsion so obtained, was further stirred continuously for 3 hr at 30 ºC for evaporation of solvent. After three hours, the microspheres were recovered and washed with distilled water. The resultant emulsion was filtered to collect the microspheres. The microspheres were repeatedly washed with successive amounts of purified water to remove the solvent remnants on the surface of microspheres. The collected microspheres were dried in a desiccator for further evaluation purpose.

CHARACTERIZATION OF MICROSPHERES

Drug excipient compatibility study by FT-IR spectroscopy and DSC:

The FT-IR spectrum of the pure drug Quetiapine fumarate and in combination with polymers like EC, HPMC and carbopol were taken and the spectra of the drug and polymers were shown in the **fig1, 2, 3, 4** respectively.

MICROMERITIC PROPERTIES OF DRUG:

Angle of Repose:

The frictional force in a loose powder can be measured by the angle of repose It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\mathbf{Tan\ \theta = h / r}$$

Tan θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Bulk Density:

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, V0, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula,

$$\mathbf{Bulk\ Density = M / V0,}$$

Where M – weight of sample,

V0 - apparent volume of powder

Tapped Density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides

100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tapped density = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measure of Compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Hausner's ratio

Hausner ratio were calculated using following equation

Hausner ratio = TD/BD

Where, BD = Bulk Density

TD= Tapped Density

Evaluation of entrapment efficiency and percentage yield:

Microspheres (50 mg) were treated with 50 ml. of phosphate buffer (pH 6.8), in 100 ml. amber coloured vial with stirring at 250 rpm. The temperature was maintained at 37 ± 0.2 ºC. At the end of 2 h, it was filtered and the filtrate analyzed spectrophotometrically (n = 3) at 256 nm .Drug entrapment efficiency & yield were calculated using

Drug entrapment (%) = (A/T)100

where A is actual drug concentration and T is the theoretical drug concentration.

Yield (%) = (Wm/Wdp)100

where Wm,weight of microspheres ,Wdp is the expected total weight ofdrug and polymer

***In vitro* Drug Release Studies**

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Microsphres were placed in the vessel and the vessel was covered the apparatus was operated for 8hours. The dissolution is carried in 0.1NHcl medium for 2hrs followed by pH6.8 Phosphate buffer was taken and process was continued for 8 hrs at 75 rpm. At definite time intervals of 5 ml of the fluid was withdrawn, filtered and again 5ml fluid was replaced. Suitable dilutions were done with the sample fluid and analyzed by spectrophotometrically at 256 nm using UV-spectrophotometer

Application of Release Rate Kinetics to Dissolution Data [4]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Hixson-Crowell release model and Korsmeyer- Peppas release model.

***IN VIVO* ANTIPSYCHOTIC STUDIES OF MICROSPHRES**

Inhibition of apomorphine induced stereotypy in rats: [5]

The antipsychotic activity was performed *Invivo* in 24 animals. Animals were selected and divided into 4 groups each containing 6 animals. [Normal - Dist.Water, I.P; Disease control - apomorphine HCl, 1.5mg/kg,SC; Standard - Olanzapine, 2 mg/kg,I.P; Test - Formulation F7, 2mg/kg]. The test drug or the standard was administered 60 min prior to apomorphine dosage. Apomorphine HCl was injected SC at a dose of 1.5mg/kg. The animals were placed in individual plastic cages. A 10s observation period was used to measure the presence of stereotypic activity such as sniffing, licking and chewing 10 min after apomorphine administration. The data of stereotypic reactions in test groups was compared to standard group. From the obtained data, we can assure that test formulation had potential to inhibit the stereotypic reactions [7, 8.9]

Groupings of the animals:

Control Group – Animals of this group will receive distilled water I.P

Group II- Animals of this group will receive standard drug Olanzapine, 2 mg/kg,I.P

Group III – Animals of this group will receive apomorphine HCl I.P

Group IV- Animals of this group will receive Formulation F7, 2mg/kg

RESULTS & DISCUSSION:

QF microspheres were prepared by emulsion solvent evaporation method. After evaporation the microspheres were obtained as

free flowing, white in colour, spherical in shape (as confirmed by images, **Fig: 07, 08**. The percentage recovery of the microspheres was increased with the increase in concentration of EC; HPMC: Carbopol (Table: 05 F6, F7, F8) whereas the chance of aggregation and cake formation are higher with the increase in polymer ratio. So 0.5% Tween 80 was used in the preparation to minimize the aggregation and to increase the emulsification. Initial high stirring speed in ultra turrax resulted in obtaining smaller microspheres whereas stirring speed less than 1000rpm caused the adherence of materials to the walls of beaker which results in loss of recovered microspheres.

The % Yield and entrapment efficiency were increased when EC:HPMC concentration was increased but the microspheres containing higher concentration of carbopol results in lower % yield and entrapment efficiency as the hydrophilic nature of HPMC from the dispersed phase into continuous was higher which hinders the entrapment of carbopol with the remaining polymers as given by the **Table No 06.** The micromeritic properties of all the 8 formulations were expressed in the term of bulk density, tapped density, carr's index, Hausner's ratio as given in the **Table No 04.** There was a decrease in bulk density with increased polymer concentration. The values of cars index was less than 25%, Hausner's ratio below 1.5% and angle of repose was less than 30^0 for all the 8 formulations indicating the microspheres were free flowing in nature.

Figure showed no significant difference in the FTIR spectra of pure Quetiapine fumarate and QF loaded EC/HPMC/Carbopol microspheres. FTIR spectra exhibited a broad characteristic as indicated in **Table No 03**. Thermal analysis using DSC has revealed the exothermic peak at 171^0 c , the same thermal behavior was also observed in QF loaded microspheres was less sharp which suggested that QF was encapsulated in molecularly dispersed microspheres as shown in **Fig 09**. *In vitro* drug release was investigated at pH 1.2 for 2 hrs and pH 6.8 phosphate buffers for 6 hrs. **Fig 10, 11, 12, 13** represents the drug release profile of all formulations for different kinetic models. Formulations with individual polymers showed abrupt release for only 6 hrs but whereas polymer combinations prolonged the release for 8 hrs due to increased polymer proportions. In polymer combinations EC: HPMC combination in 1:2 ratios was found to be satisfactory compared to that of other combinations. When the data was fitted to different release kinetic models, the kinetic model with highest value of coefficient of determination (r^2) was considered to be as suitable model for all dissolution profiles. The results of kinetic analysis provided the evidence for zero order as best fit model for the dissolution data of all formulations at different pH conditions. All the other models exhibited curvilinear plots having low r^2 values when compared with that of zero order.

Drug release mechanisms were also investigated from these microspheres using korsemeyer-peppas equation. The value of "n" was higher than 0.5 indicating the mechanism of drug release is following zero order in the release of Quetiapine fumarate (**Table 06**). With the increase in the polymer concentration the surface pores permits the escape of drug that may contribute in prolonging the release of drug from polymeric microspheres. It has been evident from the kinetic data that initial drug release containing polymers alone follows anomalous mode but with the passage of time ,microspheres are able to swell by uptake of the water leading to decreased erosion prolonging the release rate of the drug. The presence of carbopol934 in combination with EC and HPMC hinders the release rate by eroding the microspheres in the due course of dissolution testing where as the use of EC and HPMC controls the balance between erosion and swelling of microspheres as it is a combination of hydrophobic and hydrophilic nature.

The ideal combination of both the polymers through the data prolongs the drug release with desired therapeutic effect and minimizes the chance of side effects. *In vivo* results largely pointed out the fact that QF loaded microspheres significantly reduced the stereotypy reactions like sniffing, licking, chewing and biting similar to that of standard olanzapine drug. Apomorphine affects the dopamine and serotonin receptors and produces stereotypy reactions. Psychosis is characterized by stereotypy reactions due to dopamine excess. Similar results were also observed in our disease control group by apomorphine treatment. However both standard Olanzapine and QF loaded microspheres formulation (F-7) significantly prevented the occurrence of stereotypy in treatment group animals as shown in the **Table 07**.

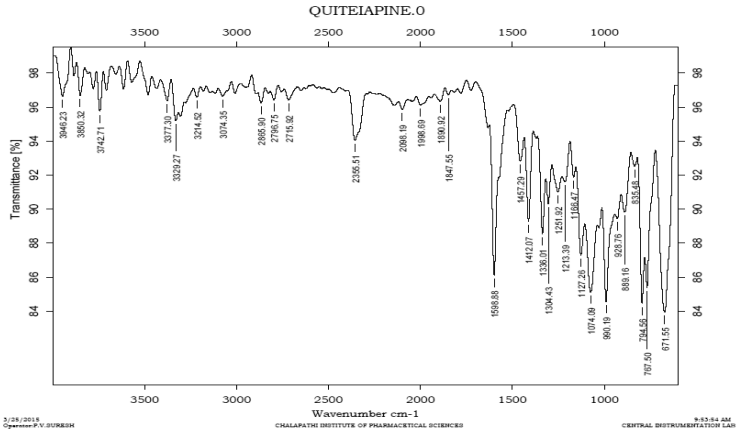

Fig no 1: FTIR Spectra of Pure drug (Quetiapine fumarate)

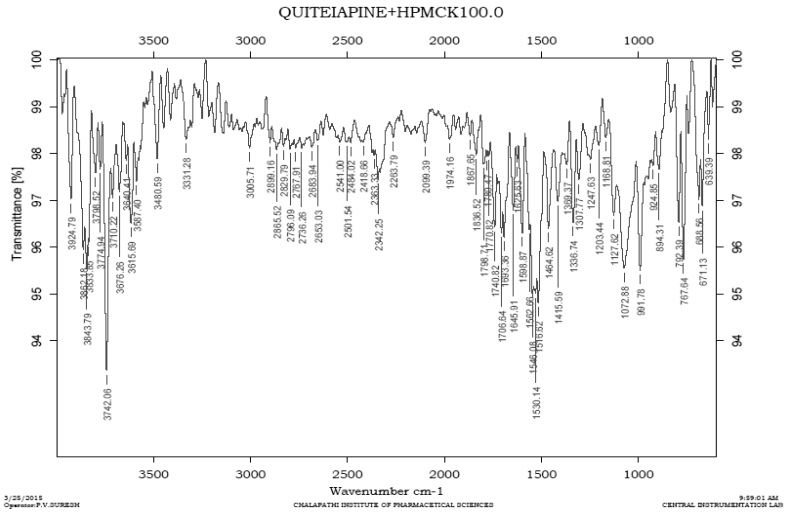

Fig no 2: FTIR Spectra of Drug with HPMC K100

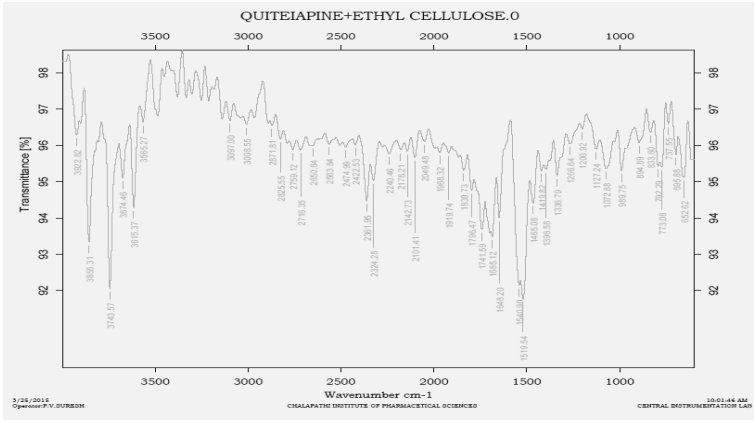

Fig no 3: FTIR Spectra of Drug with Ethyl Cellulose

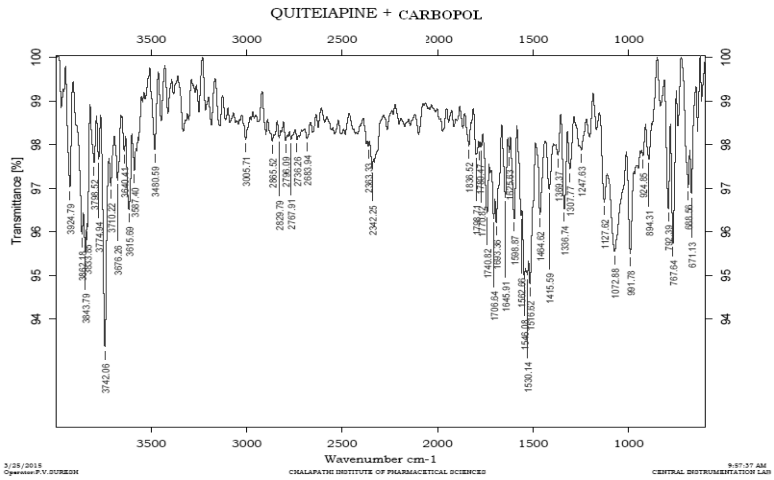

Fig no 4: FTIR Spectra of Drug with carbopol

Table no 1: Formulation variables of Quetiapine Fumarate microspheres

Formulation code	QF	EC:HPMC:CARBOPOL	PVA 0.5%	Tween 80 (ml)	Magnesium stearate (mg)
F1	100	1:0:0	50ml	0.1	0.1
F2	100	0:1:0	50ml	0.1	0.1
F3	100	0:0:1	50ml	0.1	0.1
F4	100	1:1:0	50ml	0.1	0.1
F5	100	0:1:1	50ml	0.1	0.1
F6	100	1:0:1	50ml	0.1	0.1
F7	100	1:2:0	50ml	0.1	0.1
F8	100	1:3:0	50ml	0.1	0.1

Table no.2: Calibration Curve of Quetiapine Fumarate in 0.1N HCl

S.NO	Concentration (µg/ml)	Absorbance (at 246 nm)	
		pH 1.2 Buffer	pH 6.8 Buffer
1	0	0	0
2	5	0.256 ± 0.0015	0.201± 0.005
3	10	0.418 ± 0.004	0.391 ± 0.01
4	15	0.653 ± 0.0043	0.579 ± 0.01
5	20	0.817 ± 0.004	0.717 ± 0.022
6	25	0.975 ± 0.004	0.948 ± 0.004

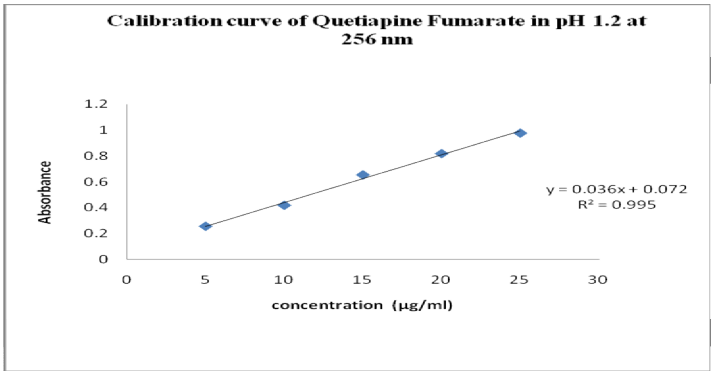

Fig no 5: Calibration Curve of Quetiapine Fumarate in 0.1N HCl

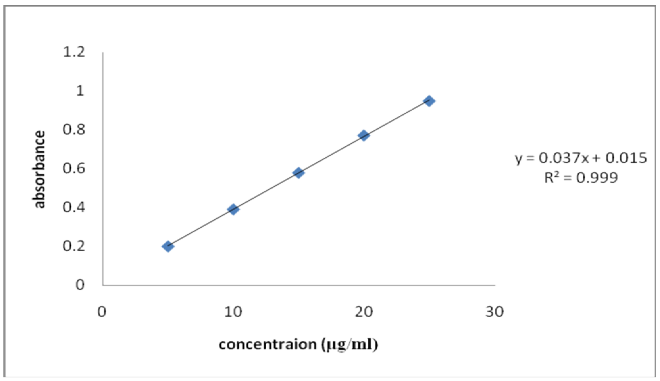

Fig no 6: Calibration Curve of Quetiapine Fumarate in pH 6.8 Phosphate Buffer

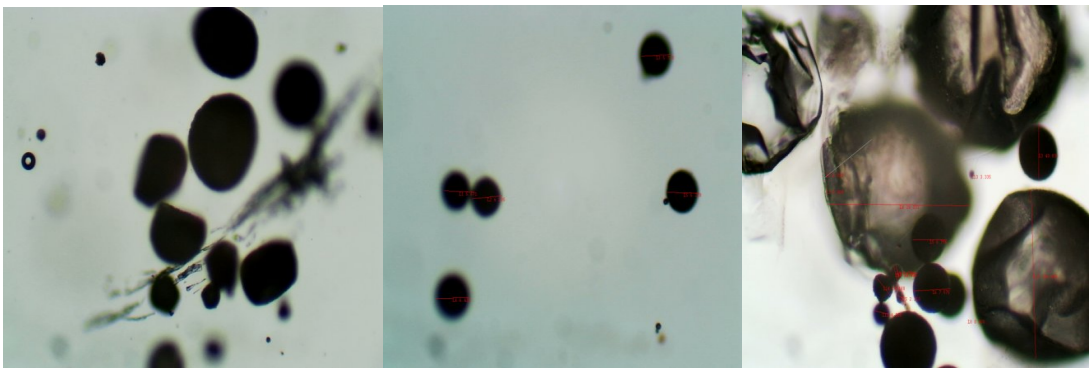

Fig no 7: Blank microspheres images (Binocular microscope olympus system)
A)Ethyl Cellulose B)Ethyl Cellulose And HPMCk100
C)Ethyl Cellose + Carbopol+HPMCk100

Table 3: Infrared spectra of quetiapine fumarate

S.NO	Peak (cm^{-1})	Functional group
1	3705	-OH-
2	2974	Ar-H-
3	2880	-CH-
4	1598	C-N
5	793	Substituted benzene ring

Table no: 04 Micromeritic properties of prepared microspheres

Formulation code	Angle of Repose	Bulk density(g/ml)	Tapped density (g/ml)	Carrs's index	Hausner's ratio
F1	12.99	0.4	0.5	25	1.3
F2	21.80	0.3	0.5	16	1.2
F3	42.58	0.62	0.8	22	1.2
F4	30.96	0.71	0.1	9.5	1.1
F5	32.75	0.50	0.5	11	1.11
F6	24.98	0.60	0.66	15	1.05
F7	22.34	0.55	0.55	25	1.33
F8	17.98	0.55	0.55	20	1.25

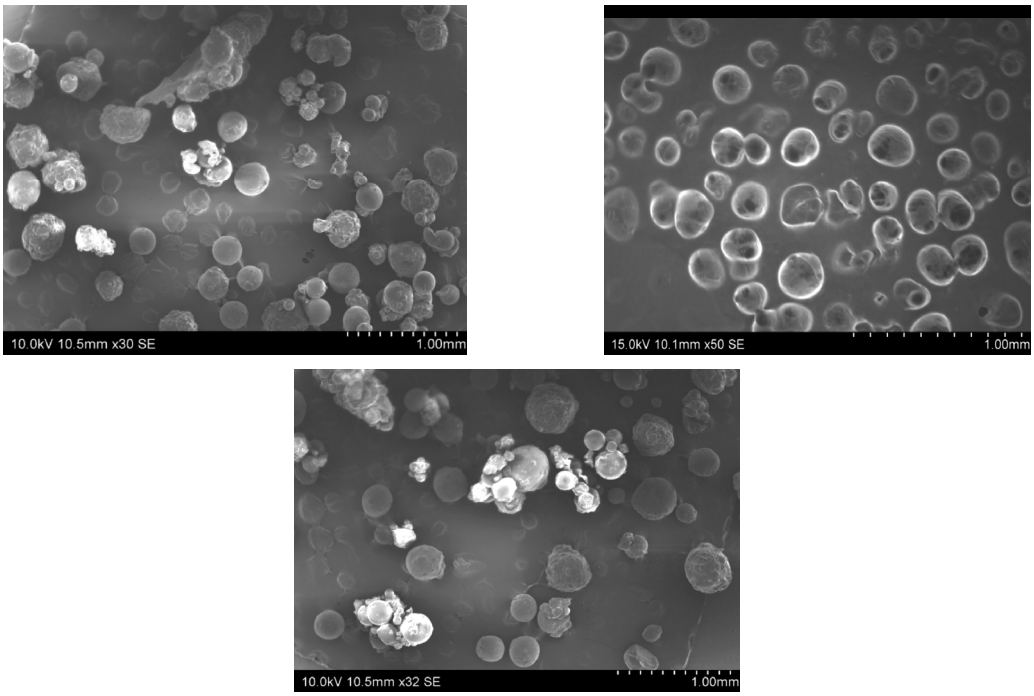

Fig 8: SEM images of Drug loaded microspheres F7

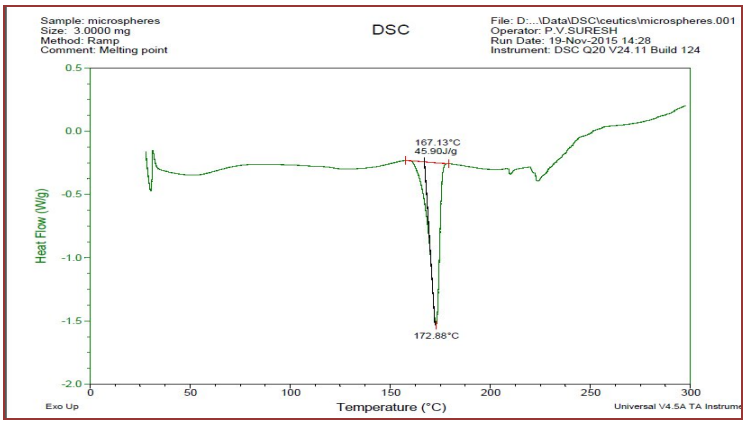

Fig 9: DSC thermogram of F-7 formulation

Table no: 06 Release Kinetic data of formulations F1 – F8

Formultion code	Ko	R2	r2	K1	R2	r2
F1	14.05	0.820	0.9185	0.262	0.724	0.8813
F2	11.61	0.871	0.9119	0.2256	0.643	0.8321
F3	6.528	0.750	0.8813	0.099	0.616	0.9157
F4	9.093	0.930	0.9734	0.1543	0.802	0.9221
F5	9.741	0.922	0.9733	0.1473	0.978	0.9896
F6	5.031	0.883	0.9513	0.0621	0.819	0.9245
F7	9.528	0.844	0.9404	0.2095	0.641	0.8452
F8	7.730	0.769	0.9063	0.1404	0.601	0.8206

Formulation code	K_H	R2	r2	K_k	R2	r2	n
F1	24.76	0.604	0.8204	1.036	0.795	0.8918	1.018
F2	22.52	0.610	0.8189	0.859	0.796	0.8926	1.058
F3	14.39	0.537	0.7819	0.941	0.836	0.9148	0.746
F4	20.42	0.717	0.895	1.195	0.972	0.9860	0.771
F5	23.12	0.945	0.983	0.885	0.953	0.9765	1.100
F6	11.21	0.657	0.8603	0.975	0.859	0.9271	0.633
F7	20.94	0.606	0.8406	1.258	0.924	0.9613	0.684
F8	16.77	0.530	0.7955	1.267	0.870	0.9331	0.541

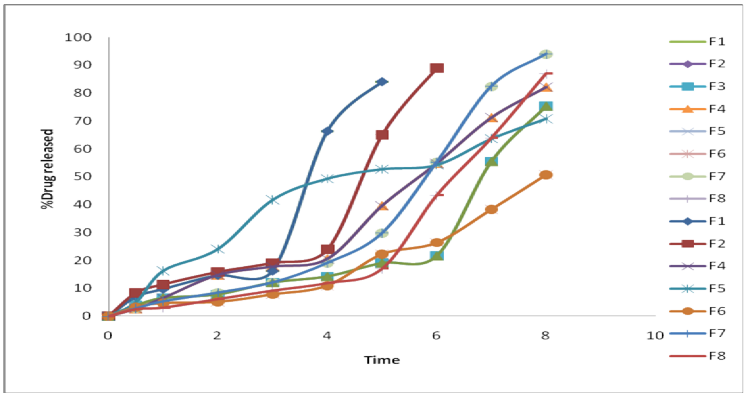

Fig-10: zero order release profile of F1 – F8

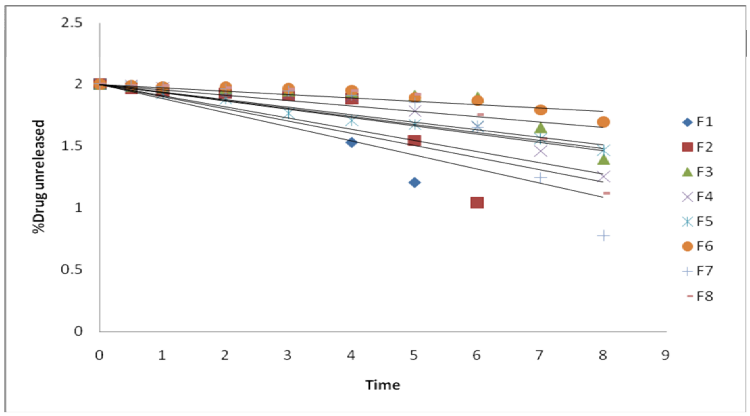

Fig-11: First order release profile of F1 – F8

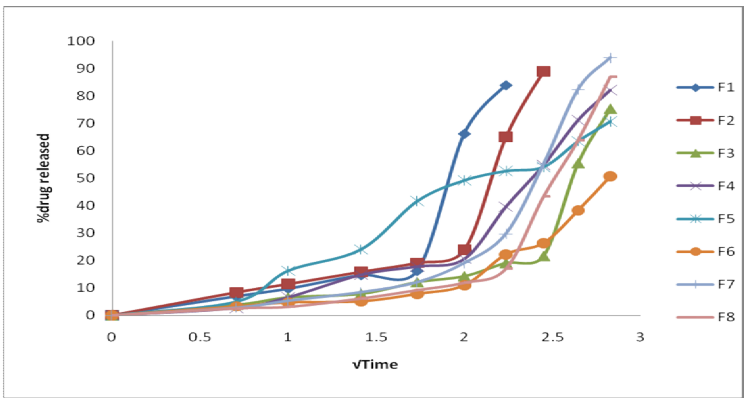

Fig-12: Higuchi matrix order plots of all formulations

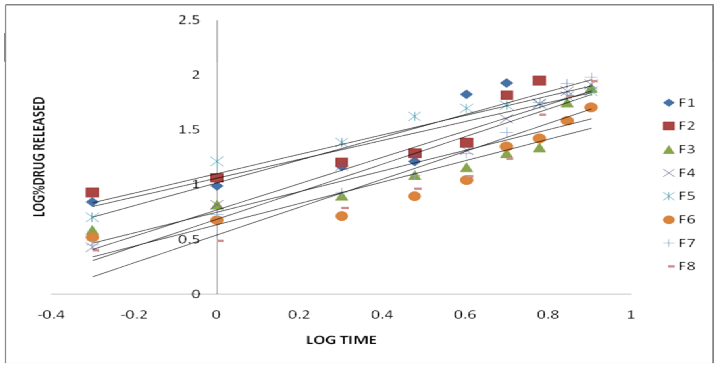

Fig-13: Korsemeyer –peppas plots of all formulations

Table no: 05 Characterization of prepared microspheres

Formulation code	Particle size (µm)	Percentage yield (%)	Entrapment efficiency (%)
F1	129	80	80
F2	210	77.5	79
F3	215	70	65
F4	222	83.3	80
F5	228	79	71
F6	230	60	50
F7	258	91	89
F8	314	85	86

Table no: 07 Effect of formulation F7 on rats by measuring their stereotypic score

Groups (Dose: mg/kg, I.P)	Stereotypic scores(min)				
	10	30	60	90	120
Control	0.79±0.15	0.79±0.20	0.78±0.31	0.75±0.45	0.9±0.24
Disease control	19±0.25	6.5±0.78	7.8±0.5	7.5±0.5	5.5±0.5
Standard	0.34±0.12	4.23±0.54	4.5±0.67	3.5±0.5	2.6±0.7
Test	0.46±0.22	4.12±0.34	3.78±0.5	2.8±0.4	2.0±0.21

CONCLUSION:

Quetiapine microspheres were successfully prepared using Emulsion solvent evaporation technique and their release profiles proved that a combination of EC and HPMC at a ratio of 1:2 possess good entrapment efficiency and prolonging the drug release for about 8hrs.Invivo data further assured that prepared Quetiapine fumarate microspheres were able to inhibit stereotype reactions as a promisable antipsychotic formulation.

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