ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

Human Journals
Research Article
June 2019 Vol.:15, Issue:3

Design and Evaluation of Quetiapine Fumarate Nanoparticles Loaded Transdermal Patches

ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

ASHA RANI M *[1], LAKSHMI CSR [2], NARGUND LVG [3]

[1] *Department of Pharmaceutics, Nargund College of pharmacy, Bangalore-85, Karnataka, India.*

[2] *Professor and Head, Department of Pharmaceutics, Nargund College of pharmacy, Bangalore-85, Karnataka, India.*

Submission: 26 May 2019
Accepted: 31 May 2019
Published: 30 June 2019

Keywords: Nanoparticles, Quetiapine Fumarate, Schizophrenia, PLGA, Transdermal patches

ABSTRACT

Antipsychotic drugs loaded PLGA nanoparticles (P-NPs) were prepared by nanoprecipitation method. The prepared PLGA nanoparticles were characterized for particle size, shape, zeta potential, and encapsulation efficiency. PLGA Nanoparticles were further loaded into matrix type transdermal patches which were prepared by solvent casting method using different grades of hydrophilic (HPMC 15cps, HPMC 50cps) and hydrophobic (Eudragit RS 100) polymeric combinations, dibutyl phthalate (10% w/w dry weight of the polymer) as a plasticizer and Olive oil (1% w/w dry weight of the polymer) as a penetration enhancer. All the patches were smooth, flexible and transparent. Among all the patches the best formulation was subjected to *in-vivo* studies using New Zealand white rabbits. The results showed significantly higher plasma concentration (C_{max}), time for maximum plasma concentration (T_{max}) and area under the curve (AUC) as 13.23±1.44ng/ml, 8hrs and 96532.67ng.hr/ml respectively for test Quetiapine fumarate loaded PLGA nanoparticles transdermal patches when compared with standard Quetiapine fumarate solution. Thus developed transdermal patches produced a sustained effect for a prolonged period of time for the management of psychosis and improve patient compliances.

INTRODUCTION:

Antipsychotics are the drugs that are used to reduce or relieve symptoms of psychosis (including delusions or hallucinations, as well as disordered thoughts), particularly in schizophrenia and bipolar disorder. Formerly known as major tranquilizers and neuroleptics, antipsychotic medications are the main class of drugs used to treat people with schizophrenia. Antipsychotic medications can help to calm and clear confusion in a person with acute psychosis within hours or days but can take up to four or six weeks to reach their full effect. Combining antipsychotic medication with other therapy and support can help people to manage symptoms and improve quality of life [1]. It has been suggested that nanoparticles could be used in various psychiatric diseases like schizophrenia, endogenous depression, and bipolar disorder. This is mainly because of the small size of nanoparticles. In neurology and psychiatry practice, one of the major challenges that physicians have so far been faced with was the inability of many medications to pass through the blood-brain barrier [2]. Many of the drug substances have a short half-life, poor bioavailability, poor water solubility, and extensive first-pass metabolism. Nanoparticles are one such universal approach to improve the pharmacokinetic profile of poorly water-soluble, low bioavailable and highly toxic drugs. Possible methods to avoid first-pass metabolism include transdermal, buccal, rectal, and parenteral routes of administration [3]. Transdermal Drug Delivery System (TDDS) are adhesives drug contains devices of defined surface area that delivers a predetermined amount of drug to the intact skin at a preprogrammed rate [4]. Transdermal patches offer various advantages over another type of conventional dosage forms like improved bioavailability, uniform plasma level, reduced dosing interval, user-friendly, avoid first-pass metabolism and GI irritation, convenient, painless, offering multi-day dosing, thereby resulting in improved patient compliance[5]. Transdermal delivery provides convenient and pain-free and self-administration for patients. It eliminates frequent dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain constant drug concentrations and a drug with a short half-life can be delivered easily. All this leads to enhanced patient compliance, especially when long-term treatment is required and avoid hepatic first-pass metabolism. It has been observed that many psychotropic drugs are non-compliant because of the large and diverse array of adverse effects and drug adherence problems and transdermal drug delivery may be useful in achieving patient compliance [6] [7].

The aim of this work was to prepare PLGA nanoparticles of antipsychotic drug using the nanoprecipitation method. The encapsulated PLGA nanoparticles are formulated into matrix type transdermal patches of using the hydroxypropyl methylcellulose (HPMC 15cps, HPMC 50cps) and Eudragit RS 100 to enhance its bioavailability and sustain its action.

MATERIALS AND METHODS:

Materials:

Quetiapine fumarate was a gift sample from Micro Labs Ltd, Bangalore. Ziprasidone HCL was a gift sample from Apotex Pharmachem, Bangalore. All other reagents and chemicals were of analytical grade.

The study was carried out after taking approval from the Institutional Animal Ethics Committee (IAEC) of Radiant Research, Bangalore, Karnataka.

Reg.No. 1803/PO/RcBi/S/2015/CPCSEA/RR/IAEC/56-2018.

Method:

PLGA Nanoparticles loaded matrix type transdermal patches of Quetiapine fumarate were prepared by solvent casting method using different grades of hydrophilic (HPMC 15cps, HPMC 50cps) and hydrophobic (Eudragit RS 100) polymeric combinations.

Drug Excipient Compatibility Study:

1. **Fourier Transform Infrared Spectroscopy (FTIR):** Drug- excipient interaction plays a vital role in the release of drug from the formulation. Fourier transform infrared spectroscopy (FTIR) has been used to study the physical and chemical interactions between the drug and the excipients using KBr pellets method.

2. **Differential scanning calorimeter (DSC):** DSC was performed by Indian Institute of Science (IISc) using METTLER-TOLEDO DSC1 instrument. DSC scan was recorded for the pure drug and polymers combinations at a heating rate of 10^0C/min in the temperature range of 10^0 – 300^0 C.

Preparation of PLGA Nanoparticles (P-NPs): [8][9]

P-NPs of Quetiapine fumarate (QP) were prepared by nanoprecipitation method. Drug and polymer poly(DL-lactide-co-glycolide) (PLGA)(50:50) in the ratio of 1:1were dissolved in the different volume of organic solvent acetone (0.5, 1 and 2ml). The organic phase was added dropwise into the aqueous phase containing 10 ml various concentrations of poloxamer 188 (0.5, 1 and 1.5%) as a stabilizing agent and stirred continuously using magnetic stirrer at a speed of 500 rpm. The above mixture was stirred on a magnetic stirrer for 3 hrs at a speed of 500 rpm to evaporate the organic solvent (Table 1,2).

Similarly, blank nanoparticles were prepared by using the above technique without the drug.

Table No. 1: Formulation consideration of PLGA nanoparticles with different volume of acetone

Sr. No.	Ingredients	QP1	QP2	QP3
1	Drug (100mg): Polymer (PLGA) (100mg)	1:1	1:1	1:1
2	Acetone (ml)	0.5	1	2
3	Poloxamer 188 (%)	1	1	1
4	Water (ml)	10	10	10
5	Stirring speed (rpm)	500	500	500

Table No. 2: Formulation consideration of PLGA nanoparticles with different concentration of stabilizer

Sr. No.	Ingredients	QP4	QP5	QP6
1	Drug (100mg): Polymer (PLGA) (100mg)	1:1	1:1	1:1
2	Acetone (ml)	0.5	0.5	0.5
3	Poloxamer 188 (%)	0.5	1	1.5
4	Water (ml)	10	10	10
5	Stirring speed (rpm)	500	500	500

Preparation of transdermal patches [10]

PLGA Nanoparticles loaded matrix type transdermal patches of Quetiapine fumarate were prepared by solvent casting method using different grades of hydrophilic (HPMC 15cps, HPMC 50cps) and hydrophobic (Eudragit RS 100) polymeric combinations. The required amount of polymers were dissolved in 5mL of acetone solvent. Quetiapine fumarate loaded

PLGA nanoparticles were added slowly into the polymeric solution and stirred with the help of magnetic stirrer to obtain a uniform solution dibutyl phthalate (10% w/w dry weight of the polymer) was used as a plasticizer and Olive oil (1% w/w dry weight of the polymer) was used as the penetration enhancer (Table 3). The solution was poured into the Petri dish covered with aluminum foil. The solvent was allowed to evaporate for 6 h in a thermostatically controlled oven at 60^0 C. The patches were removed by peeling and cut into squares with dimensions of 2 X 2 cm^2. These patches were kept in desiccators for further evaluation.

Table No. 3: Formulations of transdermal patches

Sr. No.	Ingredients	QE1	QE2	QE3
1	HPMC 15cps (mg)	200mg	600mg	--
2	HPMC 50cps (mg)	200mg	--	600mg
3	Eudragit RS 100 (mg)	200mg	--	--
4	Dibutyl phthalate	10 %	10 %	10 %
5	Olive oil	1%	1%	1%
6	Acetone	5ml	5ml	5ml

Characterization:

Characterization of PLGA Nanoparticles:

Shape and Surface Morphology: The shape and surface morphology of the Quetiapine fumarate loaded PLGA nanoparticles were visualized by transmission electron microscopy (TEM).The nanoparticle suspensions were diluted 10 folds with distilled water. One drop was deposited on a copper grid and the excess was drawn off with a filter paper. Samples were subsequently stained with 2% of uranyl acetate solution for 30 sec. The image was magnified and focused on a layer of photographic film.

Particle Size and Zeta Potential Measurement: The average particle size, polydispersity index (PDI) and zeta potential of the formulated nanoparticles were determined using HORIBA scientific nanoparticle, nanoparticle analyzer SZ-100 at 25ºC. 1 ml of the sample of nanoparticles dispersion was placed in disposable cuvettes for particle size measurements.

Samples were diluted with double distilled water. Each experiment was conducted in triplicate.

Entrapment Efficiency (EE): The drug-loaded nanoparticles were ultracentrifuged (Eppendorf) at 12,000 rpm and 4^0C for 30 min and the supernatant was assayed for non-bound drug concentration. The absorbance of the unencapsulated drug was evaluated in the supernatant using a UV-VIS spectrophotometer (UV-1800 Shimadzu) against plain PLGA nanoparticles as the blank which have also been prepared and treated similarly to the drug-loaded nanoparticles. The analysis was carried out in triplicate and the mean was taken. The drug entrapment of the nanoparticles was calculated by the following equation.

$$EE = \frac{\text{Amount of total drug} - \text{Amount of free drug in supernatant}}{\text{Amount of total drug}} X\ 100$$

Total drug content: The drug content of nanoparticles was determined by dissolving 1 ml of the nanoparticle formulation in 9ml acetone and further dilution were made with the mobile phase. The amount of drug was estimated by HPLC method using a C-18 column with a flow rate of 1mL/min and injection of 20µL.

Chromatographic condition for Quetiapine fumarate:

Mobile phase: methanol: acetonitrile: phosphate buffer (pH 7) – (1:2:2)

UV detection: 254 nm

Retention time: 9 min

Evaluation of transdermal patches

Weight variation and thickness: For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated and thickness of the film was measured at six different points using digital vernier calipers.

Folding endurance: The folding endurance of patches was determined by repeatedly folding a strip of film at the same place until it tends to break. The number of times, the film could be folded and unfolded at the same place without breaking, gives the value of folding endurance.

Percentage moisture content: The prepared patches were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches were reweighed and the percentage moisture content was determined by using the given formula.

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X } 100$$

Percentage moisture uptake: The weighed patches were kept in a desiccator at room temperature for 24 hrs containing the saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the patches were reweighed and the percentage moisture uptake was determined using the given formula.

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{ X } 100$$

Total drug content:

HPLC method: The drug content of Quetiapine fumarate loaded PLGA nanoparticle transdermal patches were determined by dissolving 4 cm^2 patches in 10ml acetone and further dilution were made with the mobile phase. The amount of drug was estimated by HPLC method using a C-18 column with a flow rate of 1mL/min and injection of 20µL.

Chromatographic conditions for Quetiapine fumarate:

Mobile phase: methanol: acetonitrile: phosphate buffer (pH 7) – (1:2:2)

UV detection: 254 nm

Retention time: 9 min

***In-vitro* drug release studies:**

Modified Franz diffusion cell*:*

In-vitro permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 50 ml. The treated synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into the size of 4cm^2 and placed over the cellophane membrane and the

receptor compartment of the diffusion cell was filled with pH 7.4 phosphate buffer. The whole assembly was placed on a magnetic stirrer with continuously stirred at 50 rpm, the temperature was maintained at 37 ± 1^0C. The samples of 2 ml were withdrawn at a time interval of 1, 2, 3, 4, 6, 8, 10, 12, and 24 h, analyzed for drug release by using UV spectrophotometer. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The experiment was performed in triplicate, and the mean value was calculated.

Dissolution apparatus*:*

In-vitro drug release studies were carried out using USP-7 dissolution apparatus (reciprocating disk) and 900 ml of pH 7.4 phosphate buffer as the dissolution medium. Dry patches of known thickness were cut, weighed and fixed over the reciprocating disk with an adhesive. This reciprocating disk was placed in the basket at an equilibrium temperature of 37°C ± 0.5°C and operated at a speed of 30 rpm. 5 ml of samples were withdrawn at different time intervals up to 12h. The drawn samples were replaced with an equal volume of fresh dissolution medium to maintain sink condition and analyzed for drug content using UV-visible spectrophotometer. The experiment was performed in triplicate, and the mean value was calculated.

Pharmacokinetic studies:

Animals: Healthy male New Zealand white rabbits (weighing 1.5 kg) were housed under temperature 22± 3ºC, relative humidity 30-70%, 12 hour light, and 12-hour dark cycle. Animals were housed in a stainless steel cage having facilities for pelleted food and drinking water in the bottle. Normal chow diet was provided to all the animals throughout the experiment. Aqua guard online water was provided *ad libitum*. Animals had continuous access to fresh, potable, uncontaminated drinking water.

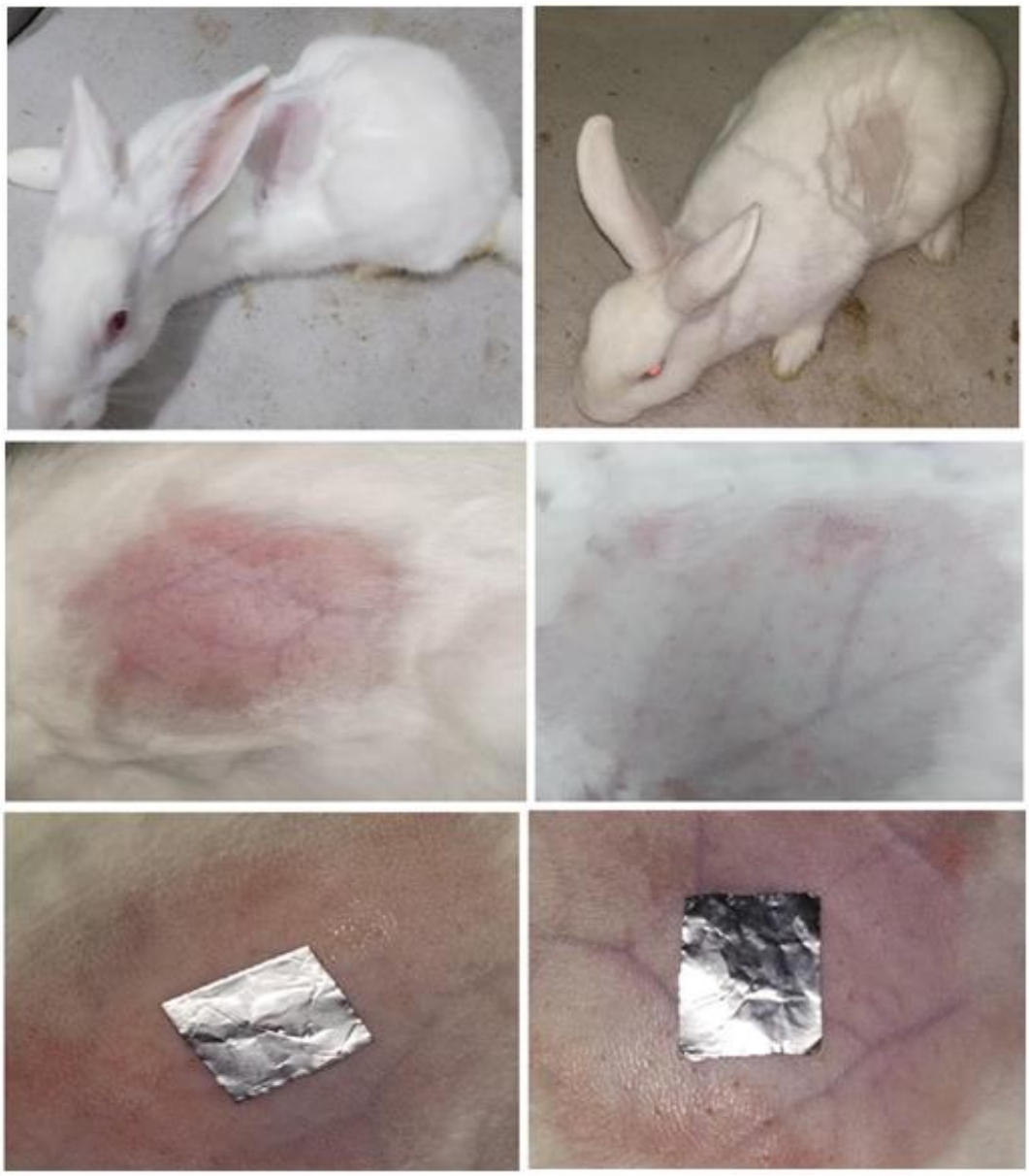
Grouping: Male New Zealand white rabbits (weighing 1.5 kg) were divided into three groups, each group consisting of 6 animals. The dose of test drug (QE1) and reference standard (Quetiapine fumarate solution) was 1.92 mg/ 1.5 kg body weight.

Table No. 4: Groups of animals used for pharmacokinetic studies.

Sr. No.	No of animal	Group	Description	Dose
1	6	Group I	Control	Normal saline
2	6	Group II	Standard solution (Quetiapine fumarate)	1.9 mg/1.5 kg b.w
3	6	Group III	Test (QE1)	1.9 mg/1.5 kg b.w

Procedure: Healthy male New Zealand white rabbits whose body weight of 1.5 kg was selected. After acclimatization for 1 week, the animals were divided into three groups of 6 rabbits in each group and average body weight was less than 20% in each group at randomization. Group, I was treated with normal saline. Group II received standard drug solution (1.92 mg/ 1.5 kg) orally. Group III was treated with topical application of the Quetiapine fumarate loaded PLGA nanoparticle transdermal patches at a dose of 1.92 mg/ 1.5 kg body weight. 200µL of blood samples were collected by marginal ear vein route into centrifuge tubes containing EDTA at different time intervals of 0, 1, 2, 4, 8, 12, 24, 36 and 48 hrs. All the samples were centrifuged at 5000 rpm for 10 minutes at 4 ± 2ºC within 1 h of collection. After centrifugation plasma samples were separated. Plasma samples were stored below -20ºC until bioanalysis. Bioanalysis was performed using LC-MS/MS method for the quantification of Quetiapine fumarate in rabbit plasma.

LC-MS Determination: 200µl of plasma was mixed with 1000µl of methyl tert-butyl ether and vortex for 5min, centrifuge for 10min at 6800rpm. From the above solution 800µl of supernatant was transferred and evaporated in nitrogen evaporator at 40˚C. Reconstitute in 200µl of diluent (Methanol: water 1:1). The chromatographic separation was achieved on a AQUITY UPLC BEH C18 (2.1x50mm, 1.7µm). A mixture of 5mM ammonium formate in water-acetonitrile (60:40, *v/v*) was used as mobile phase at a flow rate of 0.4 ml/min.



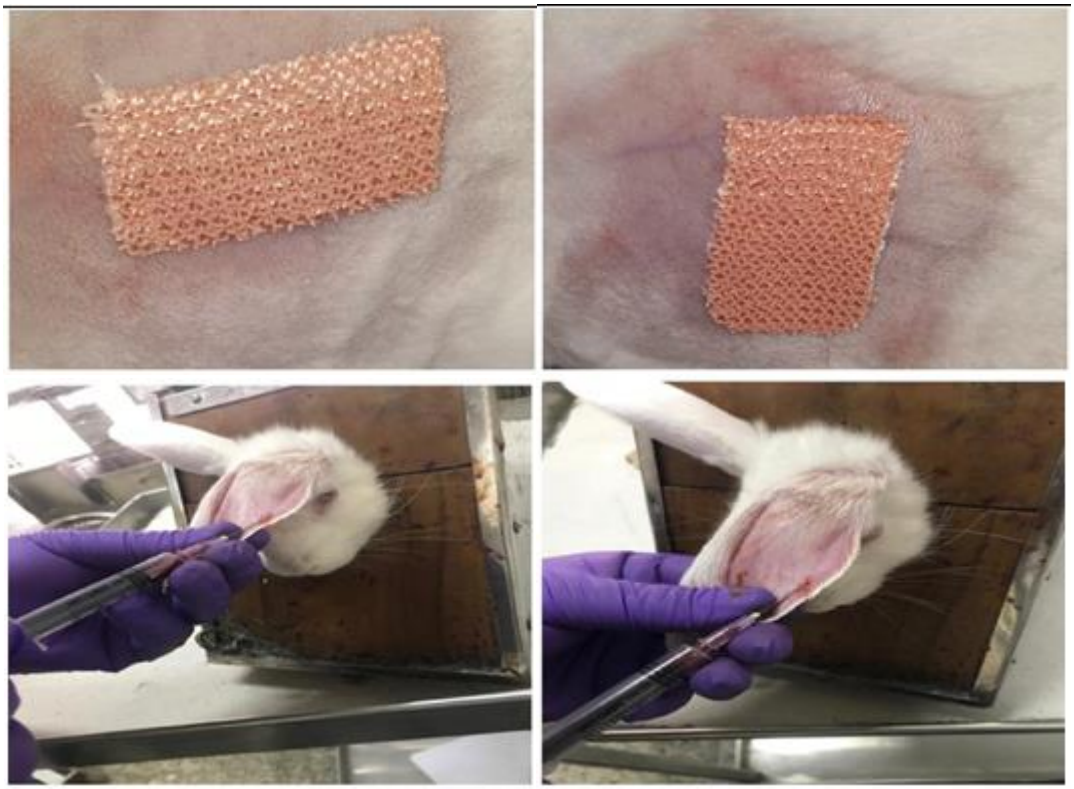


Figure No. 1: Quetiapine fumarate nanoparticle transdermal patches on rabbits

Stability Studies [10]

The stability studies were carried out according to ICH guidelines. The most satisfactory formulations were stored at 25°C ± 2°C and 60% RH ± 5% relative humidity (RH) for 6 months and analyzed for evaluation parameters like folding endurance, thickness, and % drug content. All the experiments were performed in triplicate.

RESULTS AND DISCUSSION:

RESULTS:

Results of Quetiapine fumarate loaded PLGA nanoparticles

Surface Morphology, Particle size and Zeta Potential Measurement of nanoparticles:

The morphology of drug-loaded PLGA nanoparticles was round in shape with a smooth surface (Figure 4). The particle size and zeta potential of the PLGA nanoparticles were analyzed by HORIBA scientific nano Partica, nanoparticle analyzer SZ-100. Six formulations were prepared with various concentrations of acetone and stabilizer. The values

for the average particle size, zeta potential, polydispersity index and encapsulation efficiency (Table 5) and drug content by HPLC method are tabulated (Table 6).

Table No. 5: The values for the average particle size, zeta potential, polydispersity index, and entrapment efficiency

Sr. No.	Formulation	Average particle size ± S.D (nm)	Zeta Potential ± S.D (mV)	Polydispersity Index ± S.D	Entrapment Efficiency ± S.D (%)
1	QP 1	20.9 ± 1.0	-40.5 ± 1.4	0.37 ± 0.2	89±1.4
2	QP 2	45.0 ± 0.9	-24.8 ± 2.1	0.30 ± 1.6	78±1.9
3	QP 3	51.6 ± 1.3	-31.3 ± 1.0	0.24 ± 2.9	75±0.7
4	QP 4	43.9 ± 1.5	-20.2 ± 2.5	0.32 ± 1.4	74±1.3
5	QP 5	20.9 ± 1.0	-40.5 ± 1.4	0.37 ± 0.6	89±1.4
6	QP 6	58.2 ± 0.5	-31.3 ± 2.2	0.32 ± 2.4	77±2.8

n=3; Values are the mean ± standard deviation

Table No. 6: The values for the drug content of Quetiapine fumarate loaded PLGA nanoparticles using HPLC method

Sr. No.	Formulation code	Drug content ± S.D (%)
1	QP 1	96.69±1.8
2	QP 2	96.14±1.3
3	QP 3	95.82±1.4
4	QP 4	96.01±0.5
5	QP 5	95.71±1.1
6	QP 6	95.89±0.9

n=3; Values are mean ± standard deviation

HORIBA Scientific

HORIBA SZ-100 for Windows [Z Type] Ver2.00

SZ-100

201701071642004.nsz

Measurement Results

Date	:	Wednesday, June 07, 2017 4:42:59 PM
Measurement Type	:	Particle Size
Sample Name	:	QP 1
Scattering Angle	:	173
Temperature of the holder	:	25.3 °C
T% before meas.	:	37570
Viscosity of the dispersion medium	:	0.890 mPa·s
Form Of Distribution	:	Standard
Representation of result	:	Scattering Light Intensity
Count rate	:	2304 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	28.3 nm	7.2 nm	29.0 nm
2	—	— nm	— nm	— nm
3	—	— nm	— nm	— nm
Total	1.00	28.3 nm	7.2 nm	29.0 nm

Cumulant Operations

Z-Average	:	20.9 nm
PI	:	0.377

Molecular weight measurement

Molecular weight	:	---
Mark-Houwink-Sakurada parameters	:	---

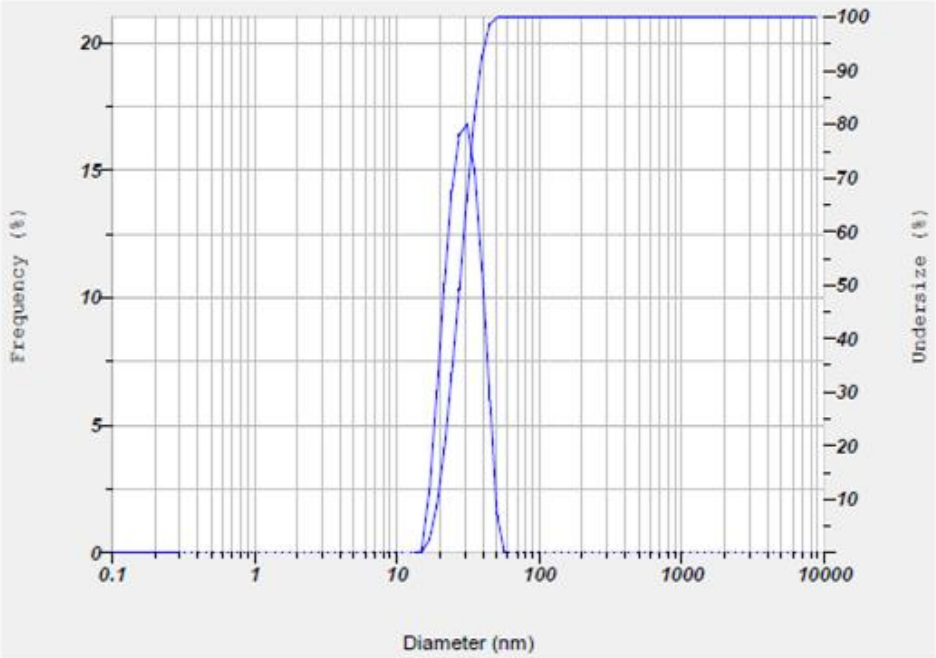


Figure No. 2: Particle size analysis

HORIBA Scientific

HORIBA SZ-100 for Windows [Z Type] Ver2.00

SZ-100

Measurement Results

201606222017006.nzt

Measurement Results

Date	:	Wednesday, June 07, 2017 8:17:47 PM
Measurement Type	:	Zeta Potential
Sample Name	:	QP 1
Temperature of the Holder	:	25.2 °C
Dispersion Medium Viscosity	:	0.891 mPa·s
Conductivity	:	0.780 mS/cm
Electrode Voltage	:	3.3 V

Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-40.5 mV	-0.000315 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean) : -40.5 mV

Electrophoretic Mobility Mean : -0.000315 cm^2/Vs

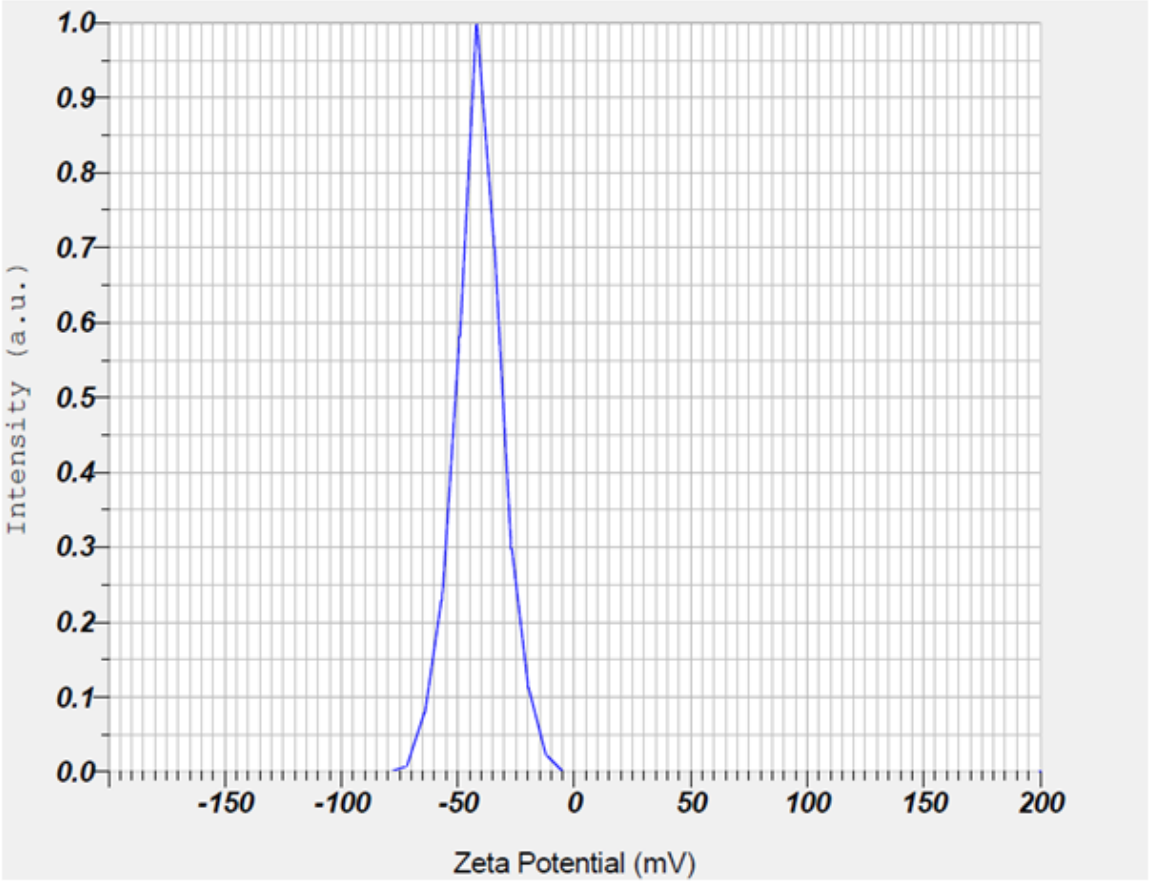


Figure No. 3: Zeta potential analysis

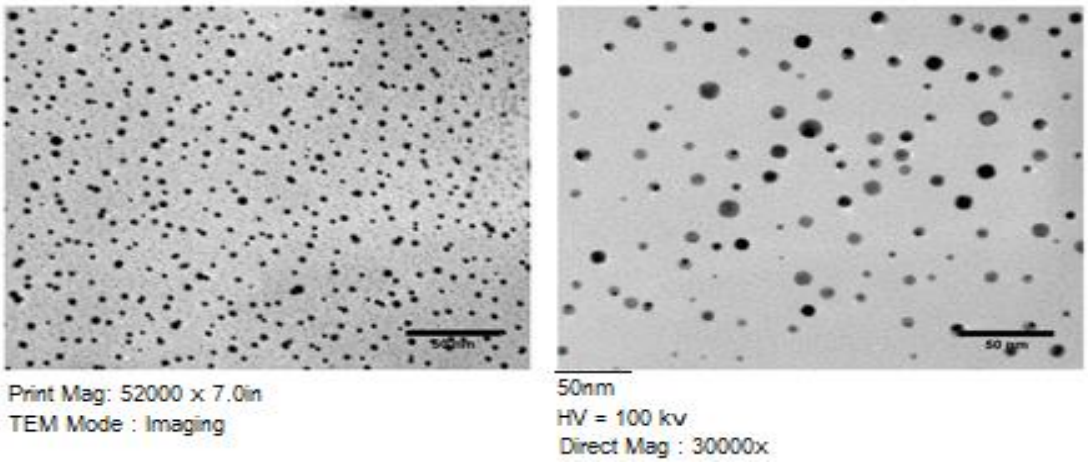


Figure No. 4: TEM images of Quetiapine Fumarate (QP 1) loaded P-NPs

Results of Quetiapine fumarate loaded PLGA nanoparticle transdermal patches

The results of physicochemical properties like weight variation, thickness, folding endurance, percentage moisture content, percentage moisture uptake and drug content of the transdermal patches are tabulated (Table 7).

***In-vitro* drug release studies:** Permeability studies of pure drug and drug-loaded PLGA nanoparticle transdermal patches through cellophane membrane are shown in Table 8, Figure 5. *In vitro* drug release for the drug-loaded PLGA nanoparticle transdermal patches by the dissolution method is shown in Figure 6. The transdermal patches showed slow and sustained release over a period of 24 h (Table 9). The drug release from transdermal patches varied with respect to the polymer composition and nature. *In vitro* drug release ranges from 8.9 ± 0.12% to 92.4 ± 0.25%. Among all the formulations, a patch containing HPMC 15cps (200mg), HPMC 50cps (200mg) and Eudragit RS 100 (200mg) showed maximum drug release of 92.4±0.25% over a period of 24 h.

Table No. 7: Physical characteristics of transdermal patches

Formulation code	Weight variation (mg)	Thickness (mm)	Folding endurance	% moisture content	% moisture uptake	Drug content (%)
QE1	210±0.02	0.21±0.02	210	2.4±0.09	1.1± 0.05	94.75±0.05
QE2	207±0.08	0.19±0.09	219	3.8±0.03	1.4±0.03	91.77±0.01
QE3	209±0.03	0.20±0.04	218	3.3±0.06	0.7±0.09	92.20±0.03

n=3; Values are a mean ± standard deviation

Table No. 8: Permeability studies of pure drug and nanoparticle transdermal patches through cellophane membrane

Time (hr)	Pure drug	Nanoparticle transdermal patches		
		QE1	QE2	QE3
0	0	0	0	0
1	10.56±0.23	10.5±0.13	9.7±0.27	10.1±0.31
2	23.14±0.41	19.3±0.22	17.4±0.41	22.3±0.17
3	44.09±0.13	28.3±0.28	30.2±0.4	32.3±0.16
4	75.48±0.54	40.2±0.15	45.7±0.25	43.5±0.29
6		49.7±0.17	50.4±0.19	51.7±0.17
8		57.4±0.29	62.2±0.36	68.2±0.29
10		61.7±0.13	68.5±0.23	73.6±0.25
12		72.4±0.29	79.4±0.18	78.4±0.36
24		86.8±0.26	78.6±0.24	77.4±0.17

n=3; Values are the mean ± standard deviation

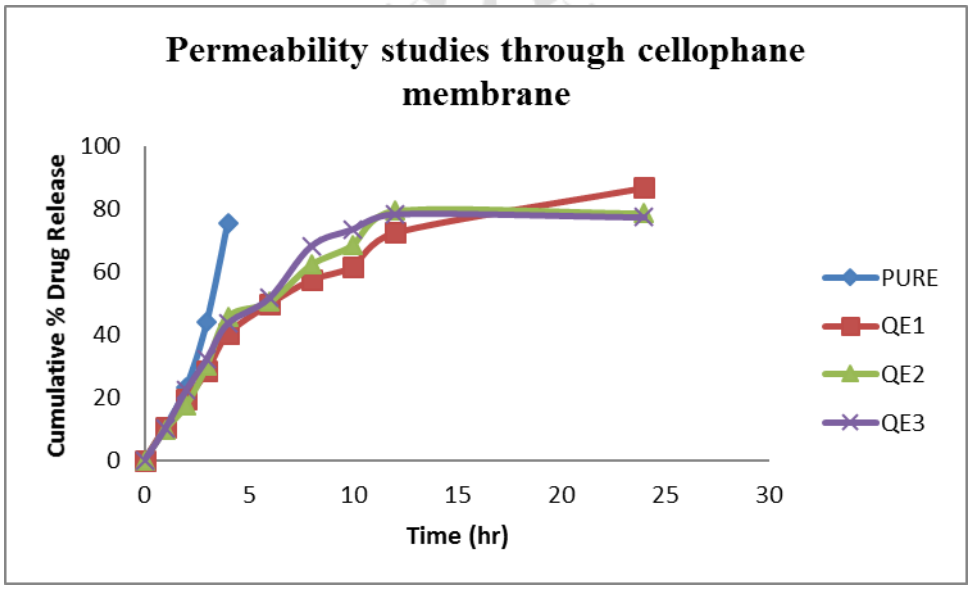


Figure No. 5: Permeability studies through cellophane membrane

Table No. 9: *In-vitro* release studies of the Quetiapine fumarate loaded PLGA nanoparticle transdermal patches by dissolution method

Time (hr)	Formulation code Cumulative % Drug Release		
	QE1	QE2	QE3
0	0	0	0
1	10.2±0.8	9.3±0.7	8.9±0.12
2	17.9±0.27	15.3±0.18	16.3±0.28
3	29.1±0.32	27.3±0.25	26.3±0.33
4	40.3±0.43	39.2±0.26	37.3±0.18
6	56.9±0.16	51.4±0.34	49.3±0.26
8	68.7±0.28	63.5±0.16	60.6±0.14
10	77.4±0.51	70.3±0.13	70.8±0.33
12	88.6±0.13	81.2±0.28	79.5±0.16
24	92.4±0.25	77.2±0.04	74.4±0.37

n=3; Values are mean ± standard deviation

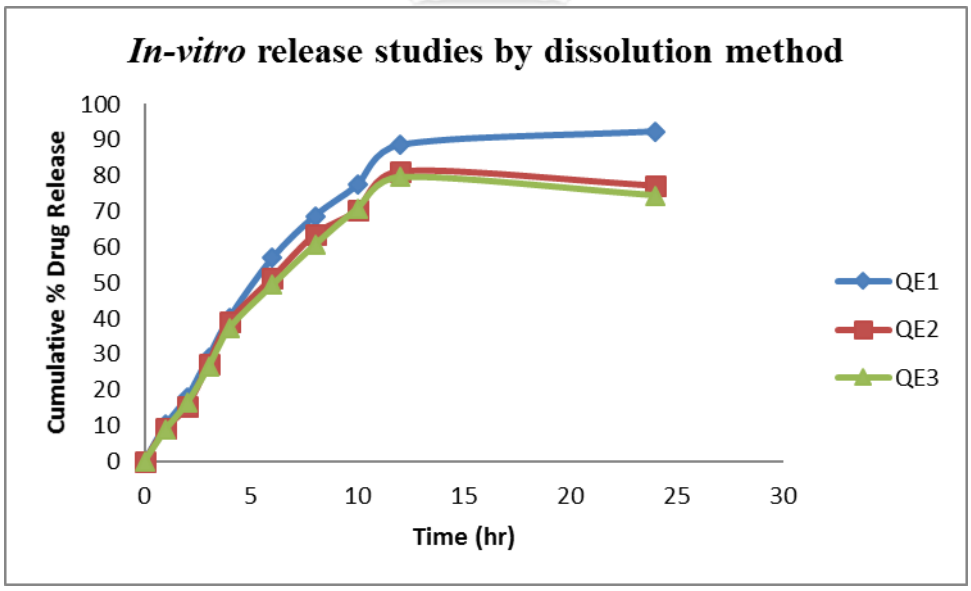


Figure No. 6: Cumulative % Drug release of Quetiapine fumarate loaded PLGA nanoparticle transdermal patches

Pharmacokinetic Study:

Pharmacokinetic evaluation of nanoparticle transdermal patch (QE1) in comparison with standard drug solution (Quetiapine fumarate) was done by LC-MS method of extraction. The plasma concentration-time profiles for standard and test were listed in Table 10, Table 11and Fig. 7. The maximum plasma concentration (C_{max}) for the standard group was found to be 2.80±1.32 ng/ml, whereas, in the test group, the maximum plasma concentration (C_{max}) was found to be 13.23±1.44 ng/ml. The pharmacokinetics parameters such as the area under the curve (AUC), average concentration and maximum plasma drug level (C_{max}) and time taken to reach (T_{max}) ware presented in tables 12. The graphical representation is given in figure 8 and figure 9.

Table No. 10: Plasma Concentration for Standard group

SL. NO.	Time (hr)	AUC (ng.hr/ml)	The average concentration of the standard (ng/ml)
1	0	5111.667	0.00±0.00
2	1	10923	2.80±1.32
3	2	8457.667	2.16±0.35
4	4	5194.333	1.36±0.05
5	8	6072.333	1.56±0.11
6	12	5491	1.40±0.26
7	24	6117	1.60±0.30
8	36	4818.333	1.26±0.37
9	48	4254.667	0.86±0.75

n=6; Values are the mean ± standard deviation

Table No. 11: Plasma Concentration for Test group

SL. NO.	Time (hr)	AUC (ng.hr/ml)	The average concentration of formulation (ng/ml)
1	0	1504	0.00±0.00
2	1	2609.667	0.40±0.69
3	2	3112.667	0.90±0.81
4	4	4166.667	1.43±0.05
5	8	96532.67	13.23±1.44
6	12	3188.667	1.13±0.05
7	24	3498	1.03±0.89
8	36	4580	1.13±1.10
9	48	1912	0.00±0.00

n=6; Values are the mean ± standard deviation

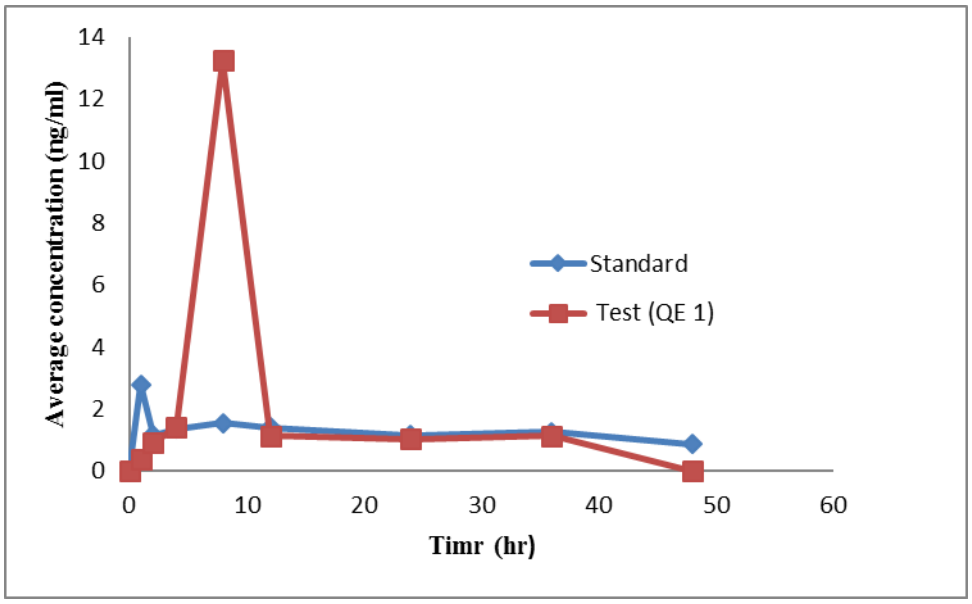


Figure No. 7: Plasma Concentration for Standard and Test (QE1)

Table No. 12: Pharmacokinetic parameters for standard and test (QE 1) in plasma

Sr. No.	Parameters	Standard	Test (QE 1)
1	**Tmax (hr)**	**1**	**8**
2	**Cmax (ng/ml)**	2.80±1.32	13.23±1.44
3	**AUC (ng.hr/ml)**	10923	96532.67

n=6; Values are mean ± standard deviation

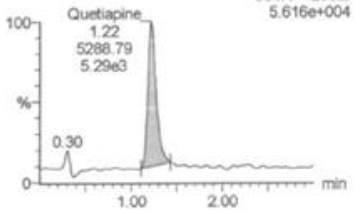
Quantify Compound Report **MassLynx MassLynx V4.1 SCN940** Page 1 of

Dataset: E:\Quetiapine.PRO\PeakDB\1811330_1811356.qld

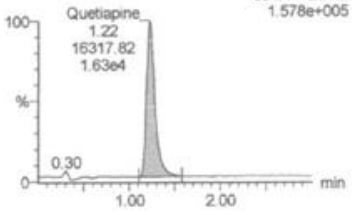
Last Altered: Wednesday, December 05, 2018 17:58:02 India Standard Time
Printed: Wednesday, December 05, 2018 18:47:21 India Standard Time

Method: E:\Quetiapine.PRO\MethDB\quetiapin.mdb 29 Nov 2018 12:14:16
Calibration: E:\Quetiapine.PRO\CurveDB\EXT_CC -02.cdb 29 Nov 2018 13:55:26

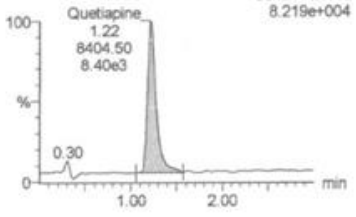
Sample Name: Quetia_EXT_02_012
1811330 Diluent1 MRM of 3 channels,ES+ 384.1 > 253.2 5.616e+004



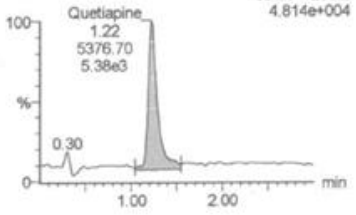
Sample Name: Quetia_EXT_02_013
1811331 1811331 MRM of 3 channels,ES+ 384.1 > 253.2 1.578e+005



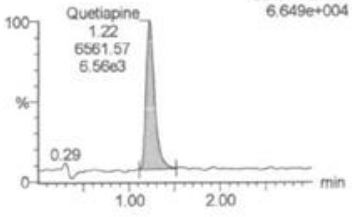
Sample Name: Quetia_EXT_02_014
1811332 1811332 MRM of 3 channels,ES+ 384.1 > 253.2 8.219e+004



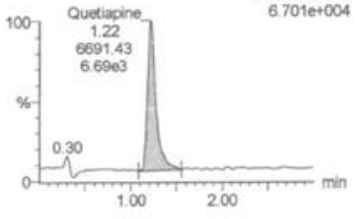
Sample Name: Quetia_EXT_02_015
1811333 1811333 MRM of 3 channels,ES+ 384.1 > 253.2 4.814e+004



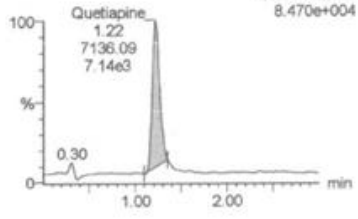
Sample Name: Quetia_EXT_02_016
1811334 1811334 MRM of 3 channels,ES+ 384.1 > 253.2 6.649e+004



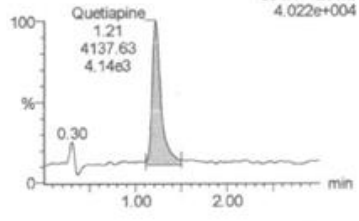
Sample Name: Quetia_EXT_02_017
1811335 1811335 MRM of 3 channels,ES+ 384.1 > 253.2 6.701e+004



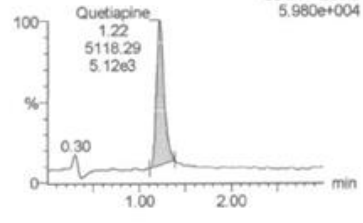
Sample Name: Quetia_EXT_02_018
1811336 1811336 MRM of 3 channels,ES+ 384.1 > 253.2 8.470e+004



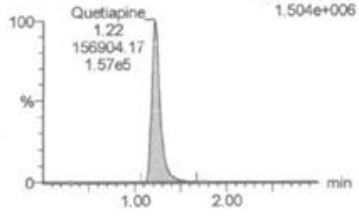
Sample Name: Quetia_EXT_02_019
1811337 1811337 MRM of 3 channels,ES+ 384.1 > 253.2 4.022e+004



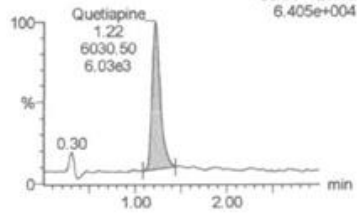
Sample Name: Quetia_EXT_02_020
1811338 1811338 MRM of 3 channels,ES+ 384.1 > 253.2 5.980e+004



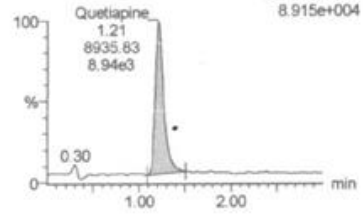
Sample Name: Quetia_EXT_02_021
QC QC MRM of 3 channels,ES+ 384.1 > 253.2 1.504e+006



Sample Name: Quetia_EXT_02_022
1811339 1811339 MRM of 3 channels,ES+ 384.1 > 253.2 6.405e+004



Sample Name: Quetia_EXT_02_023
1811340 1811340 MRM of 3 channels,ES+ 384.1 > 253.2 8.915e+004



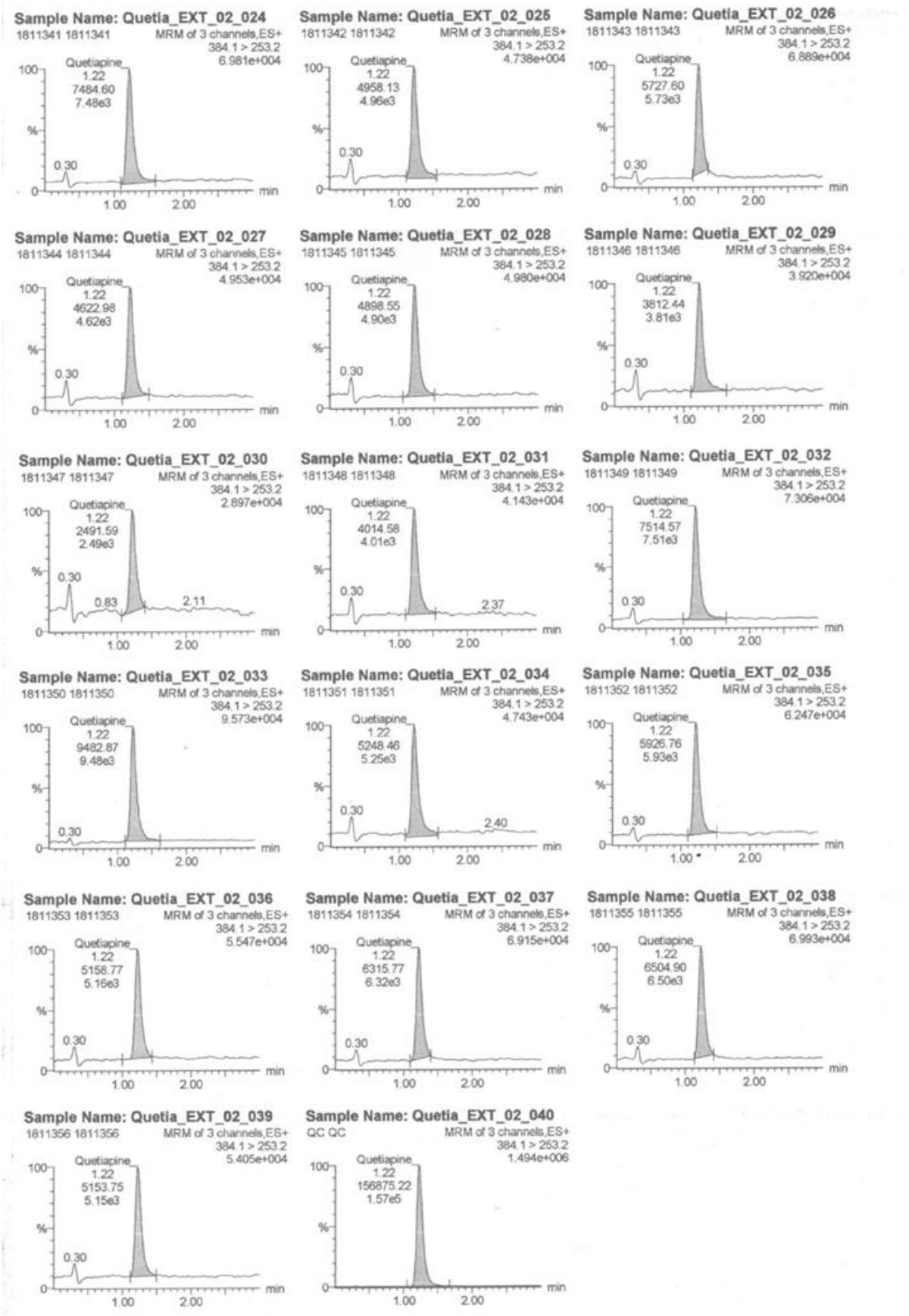


Figure No. 8: LC-MS chromatograph of standard Quetiapine fumarate solution

Quantify Compound Report **MassLynx MassLynx V4.1 SCN940** Page 2 of

Dataset: E:\Quetiapine.PRO\PeakDB\1811303_1811329.qld

Last Altered: Wednesday, December 05, 2018 18:45:18 India Standard Time
Printed: Wednesday, December 05, 2018 18:46:53 India Standard Time

Sample Name: Quetia_EXT_01_024
1811315 1811315 MRM of 3 channels,ES+ 384.1 > 253.2 4.705e+004
Quetiapine 1.23 4401.69 4.40e3

Sample Name: Quetia_EXT_01_025
1811316 1811316 MRM of 3 channels,ES+ 384.1 > 253.2 3.870e+004
Quetiapine 1.22 3587.68 3.59e3

Sample Name: Quetia_EXT_01_026
1811317 1811317 MRM of 3 channels,ES+ 384.1 > 253.2 3.420e+005
Quetiapine 1.23 36277.24 3.63e4

Sample Name: Quetia_EXT_01_027
1811318 1811318 MRM of 3 channels,ES+ 384.1 > 253.2 4.366e+004
Quetiapine 1.23 4091.11 4.09e3

Sample Name: Quetia_EXT_01_028
1811319 1811319 MRM of 3 channels,ES+ 384.1 > 253.2 8.285e+004
Quetiapine 1.22 8413.83 8.41e3

Sample Name: Quetia_EXT_01_029
1811320 1811320 MRM of 3 channels,ES+ 384.1 > 253.2 2.373e+004
Quetiapine 1.22 2146.14 2.15e3

Sample Name: Quetia_EXT_01_030
QC QC MRM of 3 channels,ES+ 384.1 > 253.2 1.189e+006
Quetiapine 1.23 125138.89 1.25e5

Sample Name: Quetia_EXT_01_031
1811321 1811321 MRM of 3 channels,ES+ 384.1 > 253.2 2.009e+004
Quetiapine 1.22 1735.03 1.74e3

Sample Name: Quetia_EXT_01_032
1811322 1811322 MRM of 3 channels,ES+ 384.1 > 253.2 2.722e+004
Quetiapine 1.22 2376.44 2.38e3

Sample Name: Quetia_EXT_01_033
1811323 1811323 MRM of 3 channels,ES+ 384.1 > 253.2 3.493e+004
Quetiapine 1.22 3290.46 3.29e3

Sample Name: Quetia_EXT_01_034
1811324 1811324 MRM of 3 channels,ES+ 384.1 > 253.2 4.126e+004
Quetiapine 1.23 3989.94 3.99e3

Sample Name: Quetia_EXT_01_035
1811325 1811325 MRM of 3 channels,ES+ 384.1 > 253.2 2.085e+006
Quetiapine 1.23 217575.64 2.18e5

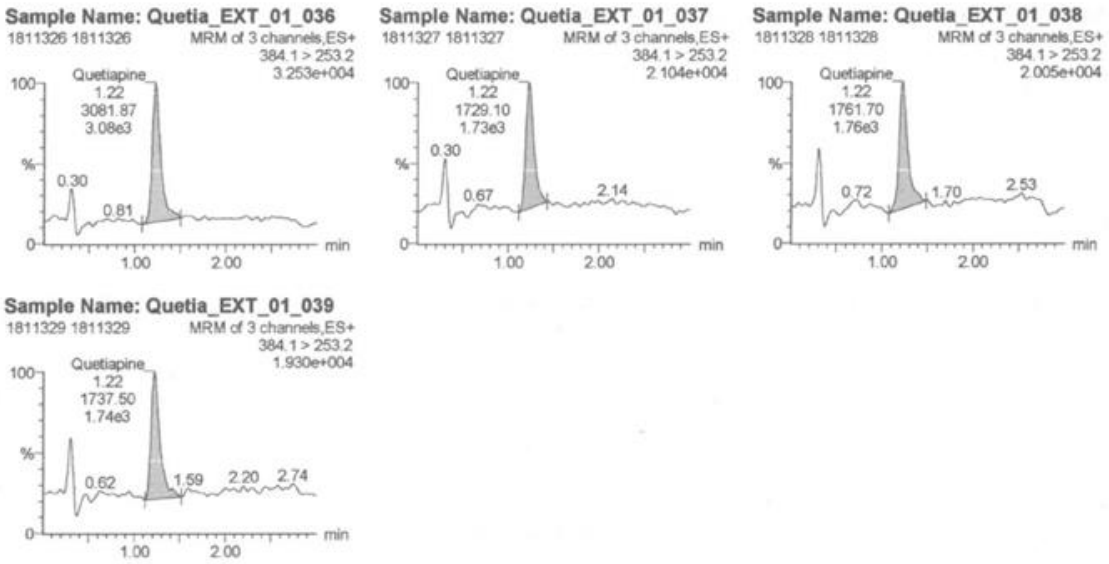


Figure No. 9: LC-MS chromatograph of Test formulation (QE 1)

- **Stability studies**

Stability studies were carried out for the formulation of QE1 as per ICH guidelines. The results were satisfactory without any physical change (Table 12).

Table No. 13: Stability studies of formulation QE 1

Sr. No.	Sampling Interval	Formulation QE 1		
		Thickness (mm)	Folding Endurance	Drug content (%)
1	Initial	0.18±0.03	209	93.59±0.09
2	30 days	0.17±0.04	211	92.37±0.14
3	60 days	0.17±0.12	210	92.14±0.25
4	90 days	0.16±0.06	215	92.04±0.16

DISCUSSION

Drug-loaded PLGA nanoparticles were successfully formulated using PLGA as a polymer with different concentrations of acetone as a solvent and poloxamer 188 as a stabilizer by nanoprecipitation method. These nanoparticles were characterized using the HORIBA scientific nano Partica, nanoparticle analyzer SZ-100. Drug-excipient compatibility studies were carried out using FTIR and DSC, and it was observed that there was no interaction between the drug and polymer. The particle size distribution of prepared PLGA nanoparticles ranged from 20.9 ± 1.0nm to 58.2 ± 0.5nm. By increasing the volume of acetone from 0.5ml

to 1ml, an increase in the particle size was observed. By increasing the concentration of stabilizer from 0.5% to 1%, decrease in the particle size was observed and by further increasing the concentration from 1% to 1.5%, increase in the particle size was observed. The zeta potential of the prepared PLGA nanoparticles ranged from -20.2 ± 2.5 to -40.5 ± 1.4 mV. Particle aggregation is less likely to occur in cases of high zeta potential due to electric repulsion. The entrapment efficiency of drug loaded P-NPs ranged from 74 ± 1.3 to 89 ± 1.4%. The optimum formulation of Quetiapine fumarate (QP1) containing drug and polymer in the ratio of 1:1 with 0.5 ml of acetone and 1% stabilizer showed better results. The particle size of nanoparticles was 20.9 ± 1.0 nm (Figure 2), zeta potential -40.5 ± 1.4 mV (Figure 3), encapsulation efficiency of 89 ± 1.4% and drug content of 96.69 ± 1.8%.

PLGA nanoparticles loaded matrix type transdermal patches of Quetiapine fumarate were prepared by a solvent evaporation method using different grades of hydrophilic (HPMC 15cps, HPMC 50cps) and hydrophobic (Eudragit RS 100) polymeric combinations. Drug-excipient compatibility studies were carried out using FTIR and DSC, and it was observed that there were no interactions between drugs and polymers. All the patches were found to be similar in weights and thickness. Folding endurance value of all the patches was found to be more than 200 which assures that patches prepared using dibutyl phthalate (10% w/w dry weight of the polymer) as a plasticizer and Olive oil (1% w/w dry weight of the polymer) as a penetration enhancer have acquired excellent flexibility and were not brittle. The small moisture content in the formulation helps them to remain stable and prevents from drying and forming the brittle film. A low moisture uptake preserves the material from microbial contamination and bulkiness of the patches. Drug content of the patches by the HPLC method ranged from 91.77 ± 0.01% to 94.75 ± 1.3%. The results indicate that the process employed to prepare transdermal patches in this study was capable of producing formulations with uniform drug content and minimal patch variability. Permeability studies were carried out for pure drug through a cellophane membrane. The cumulative percentage drug release for the pure drug was found to be 75.48 ± 0.54% at the end of 4 hours. Permeability studies for Quetiapine fumarate loaded PLGA nanoparticle transdermal patches were found to be 86.8 ± 0.26% for Quetiapine fumarate (QE1) at the end of 24 hours. The optimum formulation of Quetiapine fumarate (QE1) nanoparticulate transdermal patches containing HPMC 15cps, HPMC 50cps and Eudragit RS 100 as polymers, dibutyl phthalate as a plasticizer and Olive oil as a penetration enhancer showed better results. The cumulative percentage drug release for Quetiapine fumarate loaded PLGA nanoparticle transdermal

patches by dissolution method at the end of 24 hours was found to be 92.4±0.25%. Pharmacokinetic evaluation of Quetiapine fumarate loadedPLGA nanoparticle transdermal patch (QE1) in healthy male Newzealand white rabbit (weighing 1.5 kg) was carried out in comparison with standard drug solution (Quetiapine fumarate) and these were analyzed by LC-MS method. Plasma concentration versus time was plotted and different pharmacokinetics parameters were determined. The maximum plasma concentration (C_{max}) for the standard group was found to be 2.80±1.32 ng/ml, whereas 13.23±1.44 ng/ml for the test group. The time taken to reach the maximum plasma concentration (T_{max}) is 1 hour for the standard group and 8 hours for the test group. The area under the curve (AUC) for the standard group was found to be 10923ng.hr/ml and 96532.67ng.hr/ml for the test group for a 48h study period. Stability study data obtained showed that the prepared formulation of Quetiapine fumarate nanoparticulate transdermal patches (QE1) was found to be stable without any physical change with respect to thickness, folding endurance, and drug content.

CONCLUSION

The Quetiapine fumarate loaded PLGA nanoparticles (QP1) containing drug and the polymer in the ratio of 1:1 with 0.5 ml of acetone as a solvent and 1% poloxamer 188 as stabilizer are considered as best formulations compared to other formulations. PLGA Nanoparticles loaded matrix type transdermal patches of Quetiapine fumarate were prepared by solvent evaporation method using different grades of hydrophilic (HPMC 15cps, HPMC 50cps) and hydrophobic (Eudragit RS 100) polymeric combinations, dibutyl phthalate (10% w/w dry weight of the polymer) as a plasticizer and Olive oil (1% w/w dry weight of the polymer) as a penetration enhancer which produces smooth, flexible and transparent patches. It was concluded that transdermal patches containing Quetiapine fumarate with HPMC 15cps (200mg), HPMC 50cps (200mg) and Eudragit RS 100 (200mg) polymer combination were found to be best compared to the other formulations in terms of drug release, permeation and better bioavailability of transdermal drug delivery system when compared with oral drug delivery system. The pharmacokinetic studies of transdermal patches were better than the oral standard solution. The formulations were sustained for a prolonged period by transdermal route for the management of psychosis. These patches are likely to enhance patient compliance as it would eliminate the need for repeated dosing, enhance the bioavailability and sustain the action of the drug. The developed Quetiapine fumarate loaded

PLGA nanoparticle transdermal drug delivery system proves to be a better alternative to conventional dosage forms.

ACKNOWLEDGMENT

We thank Vision Group of Science and Technology, Government of Karnataka and the management and principal, Nargund College of Pharmacy, Bangalore for their immense support in accomplishing the work.

REFERENCES

1. Centre for Addiction and Mental Health, Understanding psychiatric medications-Antipsychotics. 2012; 1-17.
2. Dimitrijevic I and Pantic I. Application of nanoparticles in psychophysiology and psychiatry research. Reviews on advanced materials science. 2014; 38: 1-6.
3. Jawahar N, Meyyanathan SN, Senthil V, Gowthamarajan K, Baruah UK, Elango K.Improved oral bioavailability of PLGA-Nanoparticles containing the atypical antipsychotic agent.International journal of biological & pharmaceutical research. 2013; 4(12): 938-45.
4. Bookya P, Raparla R, Sriramula H, and Tarigopula S.Formulation development and evaluation of Clopidogrel Bisulfate transdermal patches. International journal of pharmaceutical sciences and research.2018; 9(1): 250-5.
5. Namdeo A, Garud N, Garud A. Development and evaluation of transdermal patches of quetiapine fumarate for the treatment of psychosis. International journal of drug delivery. 2012; 4: 470-6.
6. Aggarwal G and Dhawan S. Psychotropic drugs and transdermal delivery: An Overview. International journal of pharma and biosciences. 2010; 1(2): 1-12.
7. Isaac M and Holvey C. Transdermal patches: the emerging mode of drug delivery system in psychiatry. Therapeutic advances in psychopharmacology. 2012; 2(6):255–63.
8. Liu Y, Wu X, Mi Y, Zhang B, Gu S, Liu G, Li X. PLGA nanoparticles for the oral delivery of nuciferine: preparation. Physicochemical characterization and *in-vitro/in-vivo* studies. Drug Delivery. 2017; 24(1): 443–51.
9. Sahin A, Esendagli G, Yerlikaya F, Caban-Toktas S, Yoyen-Ermis D, Horzum U. A small variation in the average particle size of PLGA nanoparticles prepared by nanoprecipitation leads to considerable change in nanoparticles characteristics and efficacy of intracellular delivery. Artificial Cells. Nanomedicine and Biotechnology. 2017: 1-8.
10. Peddapalli H, Ganta R P, Boggula N. Formulation and evaluation of transdermal patches for the antianxiety drug.Asian journal of pharmaceutics. 2018; 12 (2): 127-36.