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(RESEARCH ARTICLE)

Preparation and characterization of quetiapine fumarate loaded transfersome as a novel drug delivery system

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Abstract

Modern medicine delivery techniques like transdermal patches are vital for treating numerous disorders. With the aid of TDDS, first pass metabolism is prevented, which aids in achieving effective bioavailability. Drug molecules are also released into the systemic circulation at a controlled and predetermined rate. The objective of this study was creating matrix-type Quetiapine fumarate loaded transdermal patches with water bath method using different polymers like HPMC 5 cps, HPMC 15 cps, and Ethyl cellulose in different ratios. Polyethylene glycol-400, Dimethyl sulfoxide (DMSO) as a plasticizer and permeation enhancer, Solvents including methanol and chloroform in 1:1 ratio employed. FT-IR study indicated that pure drug and excipients are compatible with each other. The formulated patches are evaluated for thickness, weight variation, folding endurance, percentage moisture content, percentage moisture uptake, drug content and *In vitro* diffusion studies. A transfersomal formulation containing 25 mg of the drug and 10 mg of span 80 was concluded as the optimized formulation (F1) as it showed maximum drug entrapment (84.8%) and cumulative percent drug release (98.51%)

Keywords: Transdermal drug delivery; Transferosomes; Quetipaine Fumarate; Stratum corneum

1. Introduction

Schizophrenia is a chronic and severe mental disorder that affects a person's thoughts, feelings, and behavior and it is characterized by positive symptoms such as Hallucinations and delusions, negative symptoms such as disruption to normal emotions, and difficulties in cognitive actions. About 12 million male and 9 million females are affected by schizophrenia and 50% of the people are not receiving proper treatment for schizophrenia.

AstraZeneca (formerly Zeneca) Pharmaceuticals researchers created quetiapine in 1985. Both the US Food and Drug Administration and the German government officially approved it in September 1997 and 2000, respectively. Since that time, over 70 nations have utilized quetiapine to treat severe mental illness, including Canada, the majority of Western European nations, and Japan.

Quetiapine fumarate (QF) is a dibenzothiazepine derivative, an atypical antipsychotic with demonstrated efficacy in acute schizophrenia. It is indicated for the treatment of schizophrenia as well as for the treatment of acute manic episodes associated with bipolar disorder, Quetiapine has major affinity to cerebral serotonergic (5HT2A), histaminergic (H1), and dopaminergic D1 and D2 receptors, moderate affinity to 1 and 2-adrenergic receptors, and minor affinity to muscarinergic M1 receptors.

Quetiapine fumarate (QF) has poor oral bioavailability (9%) due to extensive first pass metabolism. Possible methods to avoid first pass metabolism include transdermal, rectal, buccal and parenteral routes of administration. Stratum

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corneum is a superficial layer of the skin comprises of keratinized, flattened residues of dividing epidermal cells which restricts drug molecules into the skin

The word Transfersomes was introduced by Gregor Cevc in 1991, Transfersome is a combination of two words Transfere and soma. Transfere means to carry across and soma means body. Transfersomes are ultradeformable vesicles that are able to squeeze themselves into the stratum corneum and they penetrate as intact stratum corneum spontaneously by intracellular route .

2. Material and methods

Quetiapine Fumarate is obtained as a gift sample from Nosch laboratories Pvt. Ltd, Hyd, HPMC 15 cps, HPMC 5 cps was obtained from Research lab fine chem limited, Hyd. Surfactants including Tween-85, Tween-80, Span-80 and Span-20 are obtained from Fluka company. All other chemicals and reagents were of analytical grade.

2.1. Preformulation studies of Quetiapine Fumarate (QF)

2.1.1. Identification of Drug

Physical appearance, color and nature of drug were evaluated

2.2. Solubility studies

2.2.1. Solubility study of QF in various solvents

Solubility studies of quetiapine are performed in various solvents like ethanol,methanol, chloroform, distilled water and 0.1N Hcl. Take 1 mg of drug in volumetric flask and add the 5 ml of the ethanol, methanol, chloroform, distilled water and 0.1N Hcl separately. Shake vigorously and keep aside for some time and note the solubility of the drug in various solvents at room temperature.

2.2.2. Solubility study of QF in various surfactants

Solubility studies of QF are performed in various surfactants like Span 80, Tween 80, Tween 85 and Span 20. An excess amount of quetiapine fumarate was added to each tube containing

2 ml of each surfactant and mixed by vortexing in order to facilitate proper mixing. Tubes were shaken for 35-48 hrs in a shaking incubator until equilibrium was achieved and the sample was then diluted with 10 ml of ethanol and spectrophotometrically analyzed for solubility.

2.3. Calibration curve of Quetiapine Fumarate in Ethanol

An accurately weighed quantity of 10 mg of Quetiapine Fumarate was transferred into a 100 ml volumetric flask with sufficient quantity of ethanol and sonicated. The volume was made up to the mark with ethanol. Aliquots of this standard stock solution of Quetiapine were diluted with ethanol and scanned over the UV range of 200-400 nm..Drug showed maximum absorbance at 254 nm. Standards of Quetiapine have concentrations of 1,2,3,4 and 5 µg/ml and are plotted against Concentration vs Absorbance.

2.4. Drug excipient compatibility studies by FT- IR

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker alpha. The solid powder sample was pressed in a mortar with 100 times the amount of potassium bromide to produce the potassium bromide pellets using a KBr press. Then, a stainless steel die was used to compress the finely ground powder between polished steel anvils. The spectra were captured between the wavelengths of 4000 and 400 cm^{-1}

2.5. Preparation of Quetiapine Fumarate loaded transfersomes:

Soya PC (0.5, 1.0, 1.5, 2.0, 2.5, 3.0% w/v) and span-80 were dissolved in 10 ml of ethanol and heated up to 30 ±1 °C in a water bath in a closed vessel. Drug is dissolved in 10 ml of distilled water, which is previously heated up to 30± 1 °C. Drug solution was added slowly in a fine stream to the above ethanolic lipid solution with continuous mixing using a magnetic stirrer at 900 rpm. Mixing was continued for another 5 minutes and finally, the vesicular dispersions resulted was left to cool at room temperature about 25 ±1 °C for 45 minutes

2.6. Formulation of transdermal patch of QF

Matrix-type transdermal patches were prepared by solvent casting technique. HPMC (cps-5, cps-15), Ethylcellulose as polymers, chloroform: methanol (1:1) as a solvent system polyethylene glycol- 400 (PEG) as a plasticizer and DMSO was used as a permeation enhancer.

A fixed amount of 150 mg of Ethyl cellulose and HPMC were dissolved in 20 ml of a mixture of solvents (chloroform : methanol) in the 1:1 ratio and a specified amount of tranfersome suspension (0.2 ml)is then added to the polymer solution with the gentle stirring to get a uniform homogenous mixture using a magnetic stirrer for 20 minutes at a temperature of 32 ± 0.5 °C. It is mixed well and then kept aside to eliminate air Bubbles for a short period and lastly PEG-400(0.4 ml) and DMSO(0.2 ml) are added into the solid mixture

Then, the solution was moved to clean the Petri plates. These patches were dried at room temperature for 24 hours and an inverted funnel was kept over the Petri dish to control the evaporation of solvent. The patches were removed by peeling and cut into squares with dimension of 4 x 4 cm^2 until the evaluation assessments were accomplished

Figure 1 Transdermal patch of Quetiapine Fumarate

Table 1 Formulation table of quetiapine fumarate loaded transfersomes

Table 1a Optimization of Lipid ratios

Formulation code	Soya PC (%w/v)	Span-80 (mg)	Ethanol (ml)	Drug (mg)	Average vesicle size (nm)	% Entrapment efficiency
F1	0.5	10	10	25	158.5	84
F2	1.0	15	10	25	328.5	69.1
F3	1.5	20	10	25	280.9	76
F4	2.0	10	10	25	248.2	74
F5	2.5	15	10	25	253.3	72.8
F6	3.0	20	10	25	380.8	68

Table 1b Optimization of Ethanol ratios

Formulation code	Soya PC (%w/v)	Span-80(mg)	Ethanol (ml)	Drug (mg)	Average vesicle size (nm)	% Entrapment efficiency
F7	0.5	10	5	25	862.4	66.64
F8	0.5	10	10	25	162.3	83
F9	0.5	10	15	25	278.9	81
F10	0.5	10	20	25	395.5	78

Table 1c Optimization of Stirrer time

Formulation code	Soya PC (%w/v)	Span-80 (mg)	Ethanol (ml)	Stirrer time (min)	Drug (mg)	Average vesicle size (nm)	% Entrapment efficiency
F11	0.5	10	10	5	25	176	81
F12	0.5	10	10	10	25	274.1	76
F13	0.5	10	10	15	25	428.4	71

3. Results and discussion

3.1. Pre-formulation studies

3.1.1. Organoleptic studies

Table 2 Organoleptic characters of Quetiapine

Properties	Results
Description	Powder
Taste	Tasteless
Color	White

Discussion: The organoleptic properties of Quetiapine Fumarate were found to be white to off white in color and slightly unpleasant in taste and were as per the specifications.

3.1.2. Solubility study of Quetiapine in various solvents:

Quetiapine Fumarate showed highest solubility in Ethanol, 0.1N Hcl followed by Methanol, Chloroform and Distilled water

Table 3 Solubility study of Quetiapine in various solvents

Solvents	Concentration (µg/ml)
Ethanol	77.76 ±1.46
0.1N Hcl	76.30 ±1.75
Methanol	68.02 ±1.35
Chloroform	66.8 ±1.41
Distilled water	29.76 ±2.23

Values are expressed as µg/ml ± SD (n=3)

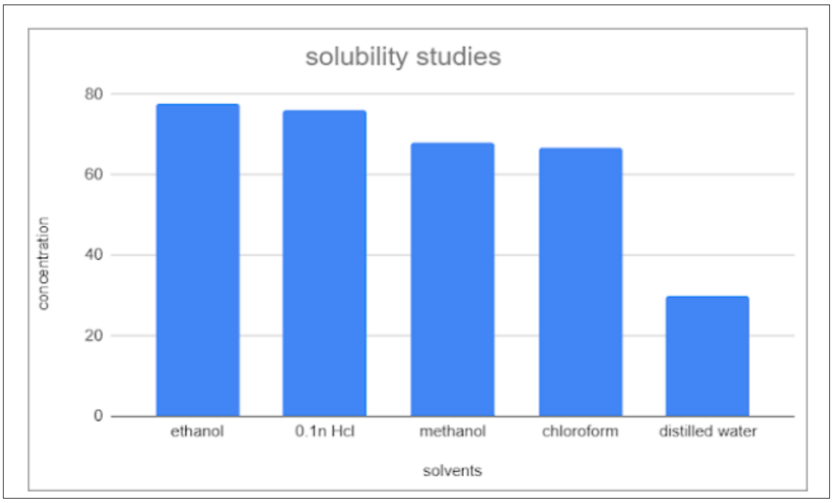


Figure 2 Solubility study of Quetiapine in various solvents

3.1.3. Solubility of Quetiapine in various surfactants:

Among all surfactants, Span-80 showed highest solubility (71.83) followed by Tween-80 (33.5) and Tween-85 (32.2) and showed low solubility in Span-20 (5.58)

Table 4 Solubility of Quetiapine in various surfactants

Surfactants used	Concentration (µg/ml)
Span 80	71.83 ±3.3
Tween 80	33.53 ±2.98
Tween 85	32.2 ±1.88
Span 20	5.58 ±0.54

Values are expressed as µg/ml ± SD (n=3)

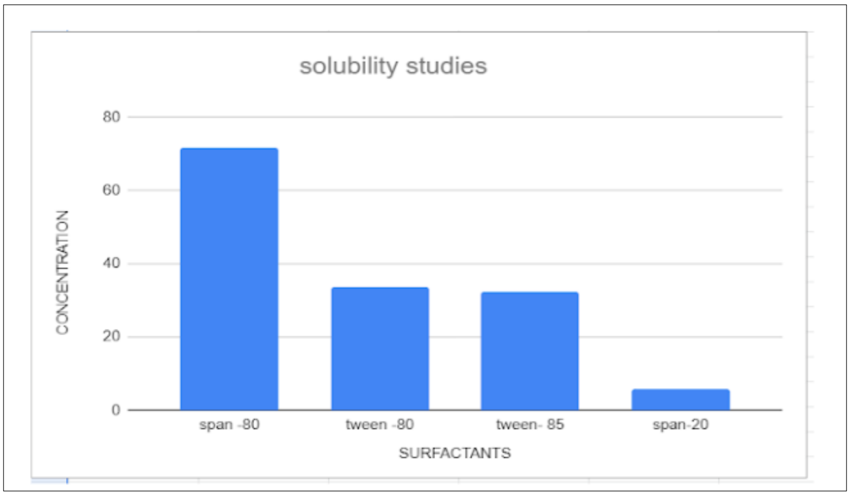
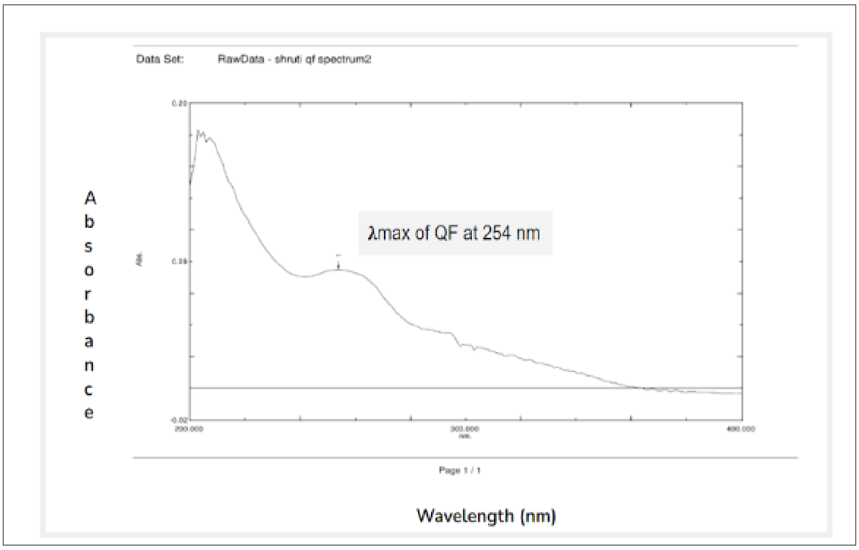


Figure 3 Solubility of Quetiapine in various surfactants

3.1.4. UV spectrum of Quetiapine fumarate in Ethanol

When examined in the range of 200 nm to 400 nm, Quetiapine showed an absorption maximum (λmax) at 254 nm. Different concentrations were prepared in ethanol solution and absorbance maximum at λmax (254 nm) were noted. The calibration curves displayed a correlation coefficient of $R^2 = 0.999$



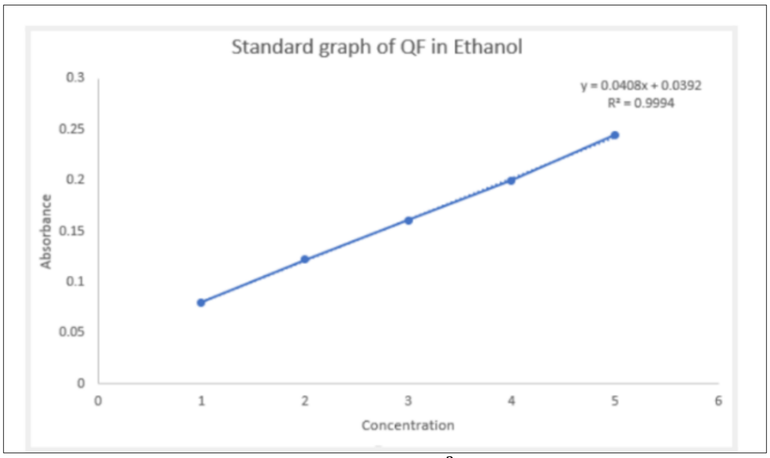
Maximum absorption was found at 254 nm

Figure 4 UV spectrum of Quetiapine Fumarate in Ethanol

Table 5 Calibration curve of Quetiapine Fumarate in Ethanol

S.NO	Concentration (µg/ml)	Absorption
1	1 ppm	0.080 ±0.002
2	2 ppm	0.122 ±0.002
3	3 ppm	0.161 ±0.002
4	4 ppm	0.20 ±0.01
5	5 ppm	0.245 ±0.002

Values are expressed as µg/ml ± SD (n=3)



Graph was found to be linear and R^2 was found be 0.9994

Figure 5 Calibration curve of Quetiapine Fumarate in Ethanol

The linear regression analysis was done on Absorbance data points. The results are as follow for standard curve

Slope = 0.0408

The intercept = 0.0392

The correlation coefficient (R^2) = 0.9994

3.2. Formulation of transferosome

Span 80 was selected as the edge activator for the transfersome formulation as it is Bio-compatible and pharmaceutically acceptable so Soya-Phospholipid was used as the biolayer-forming agent and ethanol was used as the hydrating agent because ethanol is known to alter the barrier property of the intracellular lipoidal route thereby allowing higher drug permeation.

3.3. Drug excipient compatibility studies

Drug excipient compatibility studies were performed using the FTIR spectrophotometer. FTIR data of the pure drug and the drug with excipients (span-80 and Soya lecithin) suggested that there was no interaction between the drug and excipients used.

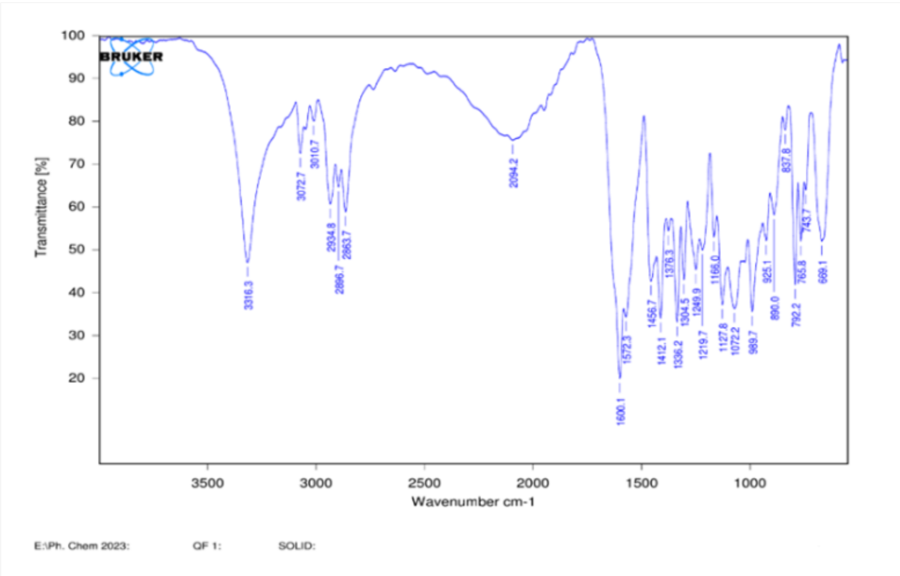


Figure 6 FTIR spectra of quetiapine fumarate pure drug

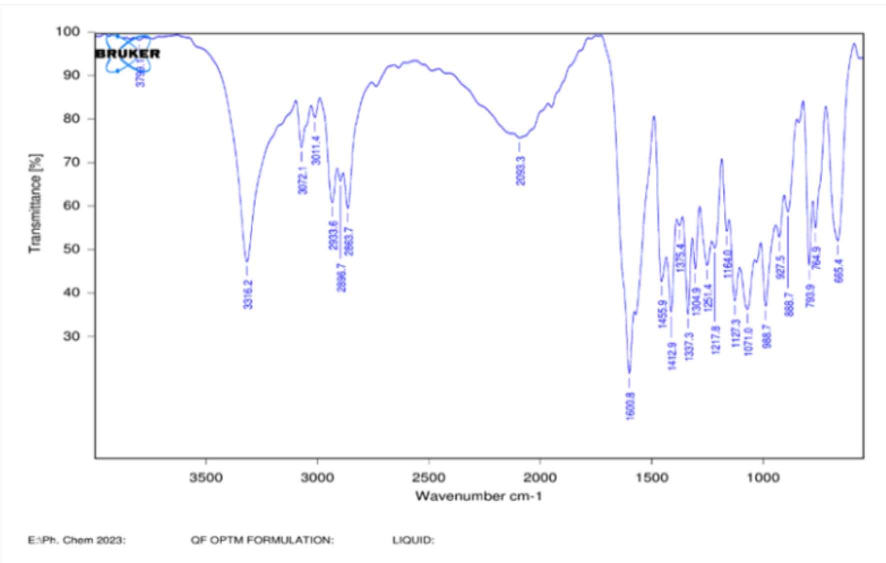


Figure 7 FTIR spectra of optimised formulation (F1)

Table 6 Interpretation of Pure drug (QF) and optimized formulation (F1)

S.No	Wave number of drug (cm^{-1})	Wave number of optimized formulation (cm-1)	Interpretation
1	1336.2	1337.3	O-H (bending)
2	1412.1	1412.9	S=O (bending)
3	1600.1	1600.8	C=C(stretching)
4	2863.7	2863.7	C-H (stretching)
5	2934.8	2933.6	N-H (stretching)
6	3072.7	3072.1	C-H (stretching)
7	3316.3	3316.2	N-H (stretching)

Discussion: The FTIR spectra of pure QF showed sharp peaks at 1336.2 cm^{-1} (O-H bending), 1412.1 cm^{-1} (S=O bending), 1600 cm^{-1} (C=C stretching) and 3316.3 cm^{-1} (N-H stretching). Pure drug with excipients i.e.. Optimized formulation (F1) showed sharp peaks at 1337.3 (O-H bending), 1412.9 cm-1 (S=O bending) 1600.8 cm^{-1}(C=C stretching) and 3316.2 cm^{-1} (N-H stretching). FTIR bands of the drug with excipients indicates that there is no unwanted interaction between QF pure drug and excipients in the formulations

3.4. Vesicle size and zeta potential

The vesicle size for the formulations (F1-F13) were obtained in the range of 158.5 to 428.5nm. It is observed that %EE decreased With increasing the concentration of ethanol and on increasing the time of stirring due to the leaching out of the drug from the vesicles on increasing the mechanical force by stirrer.

The result of formulation for F1 was considered as optimized formation and the average vesicle size of optimized formulation (F1) observed as 158.5 nm, zeta potential was observed as -32.8mV and %EE was found as 84.8%

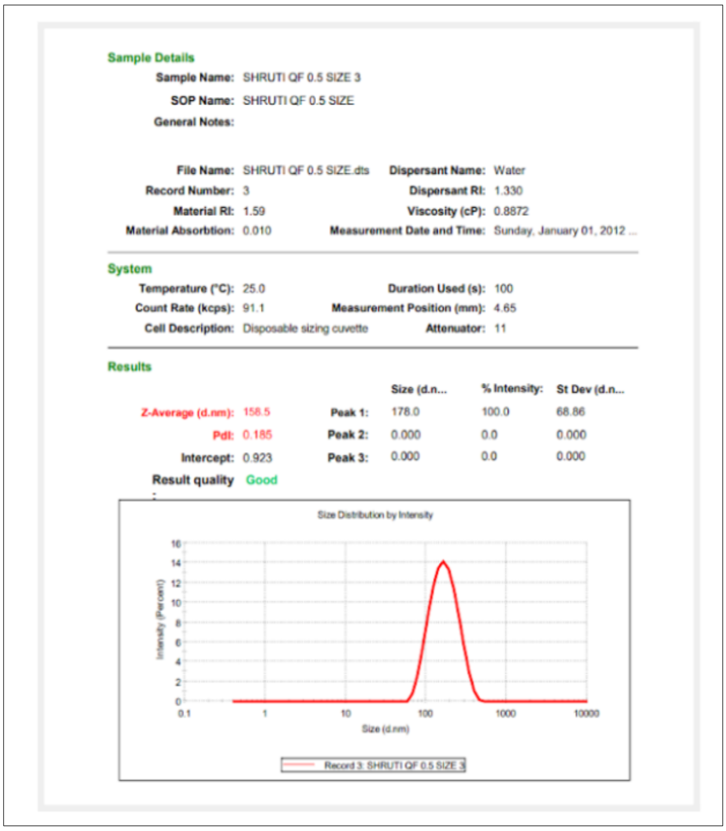


Figure 8 Average vesicle size of optimized formulation (F1)

Table 7 Size, Pdi and Zeta of F1

Formulation code	Average vesicle size (nm)	PDI	Zeta potential (mV)
F1	158.5	0.185	-32.8

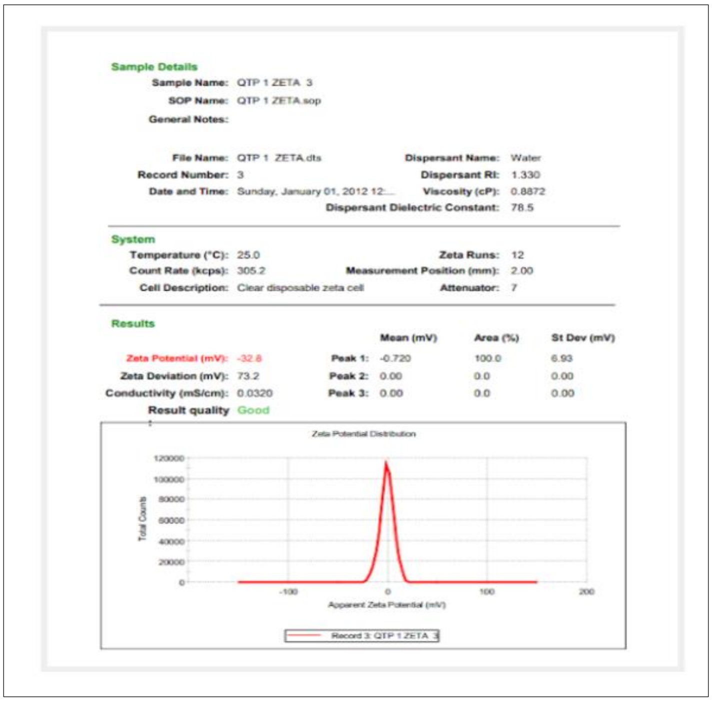


Figure 9 Zeta potential of optimized formulation (F1)

3.5. Entrapment efficiency

Percentage entrapment efficiency of deformable vesicles was found to be in the range of 68 to 84.8%Percentage entrapment efficiency of Quetiapine was found to be maximum with the formulation (F1) of 84.8%. The entrapment efficiency of the drug decreased with increasing surfactant concentration and thus increased with increasing lipid concentration.

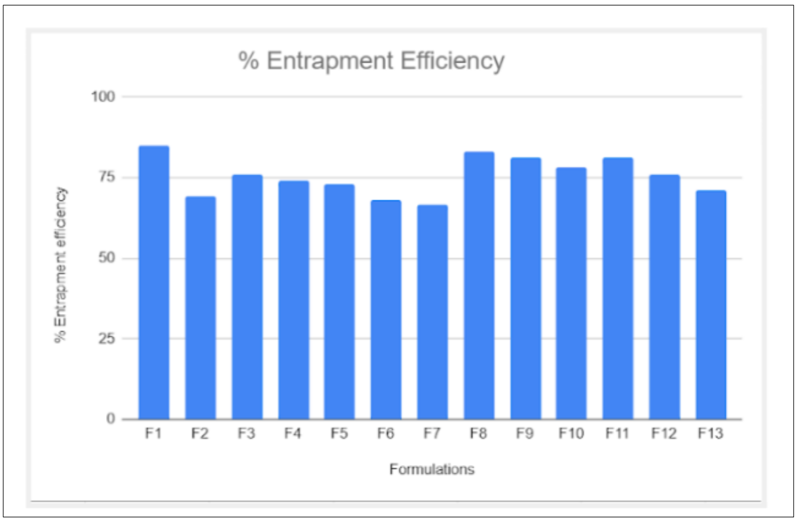


Figure 10 Entrapment efficiency of formulations (F1- F13)

3.6. Evaluation of patches

Table 8 Evaluation tests of Transferosomal Patches of Quetiapine Fumarate

Parameters	F1	F2	F3	F4	F5	F6
Weight variation	126 ± 1.69	118 ± 3.68	122 ± 2.05	120 ± 2.49	119 ± 2.05	122 ± 1.69
Thickness	0.28 ± 0.01	0.25 ± 0.249	0.25 ± 0.032	0.24 ± 0.020	0.27 ± 0.024	0.31 ± 0.012
Folding endurance	304 ± 2.49	301 ± 2.05	302 ± 0.81	301 ± 2.05	300 ± 1.63	298 ± 2.44
Drug content uniformity	97.4 ± 0.82	96.1 ± 1.30	91.6 ± 1.20	92.8 ± 0.98	90.2 ± 1.14	91.2 ± 1.37
% Moisture content	8.84 ± 0.02	7.07 ± 0.04	4.7± 0.124	3.06 ± 0.03	3.64 ± 0.04	5.82 ± 0.23
% Moisture uptake	8.06 ± 0.02	6.55 ± 0.028	4.61 ± 0.024	5.5 ± 0.12	5.8 ± 0.12	6.45 ± 0.02

Parameters	F7	F8	F9	F10	F11	F12	F13
Weight variation	124 ± 2.054	119 ± 2.054	115 ± 2.449	118 ± 2.94	114 ± 1.247	115 ± 1.247	108 ± 1.247
Thickness	0.28 ± 0.020	0.32 ± 0.0124	0.30 ± 0.0124	0.25 ± 0.024	0.23 ± 0.020	0.25 ± 0.032	0.24 ± 0.028
Folding endurance	302 ± 2.44	301 ± 1.63	301 ± 2.05	298 ± 2.44	299 ± 2.86	300 ± 2.94	298 ± 1.63
Drug content uniformity	94.7 ± 1.55	94.8 ± 1.04	93.7 ± 0.89	95.4 ± 1.28	94.4 ± 2.06	95.8 ± 0.41	91.8 ± 1.63
% Moisture content	5.61 ± 0.124	7.64 ± 0.036	7.8 ± 0.314	6.82 ± 0.016	6.91 ± 0.012	6.78 ± 0.037	7.87 ± 0.029
% Moisture uptake	6.57 ± 0.04	7.01 ± 0.041	7.24 ± 0.016	7.72 ± 0.013	7.31 ± 0.013	7.12 ± 0.008	6.32 ± 0.020

3.7. *In vitro* drug release studies

Results showed that when compared to various tranfersomal formulations, F1 (Formulation containing 10mg of span-80) had the highest cumulative amount of drug release (98.51%) up to 24 hours. When compared to the other formulations, the release rate of Quetiapine from F1 was noticeably higher because of the higher drug content and entrapment efficiency of the formulation.

The maximum release (F1) was also high due to optimum surfactant concentration(10%) because the surfactant molecule binds with the phospholipid bilayer at this concentration, improving drug partitioning and increasing drug release from the vesicles.

Table 9 *In vitro* release profiles of F1- F6

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	11.82	14.21	12.8	14.78	11.3	15.3
2	16.09	22.12	25.85	30.98	29.1	31.78
4	24.12	35.8	37.2	43.8	45.8	50.31
6	32.25	45.61	48.8	58.2	63.8	62.81
8	40.01	66.8	69.7	71.3	70.18	77.8
12	54.24	84.31	80.38	89.4	88.8	85.81
24	98.51	88.45	85.7	92.12	92.3	89.4

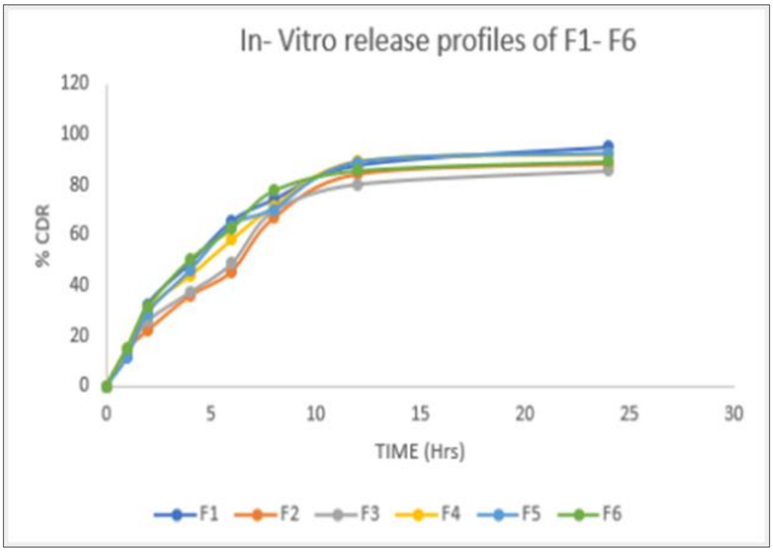


Figure 11 *In vitro* release profiles of F1- F6

Table 10 *In vitro* release profiles of F-7 to F13

Time (hrs)	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0
1	13.31	10.52	16.8	15.41	14.38	14.18	13.81
2	24.8	22.8	23.12	25.82	28.14	25.81	32.12
4	37.45	41.87	39.82	38.78	48.38	41.38	48.47
6	48.12	59.98	51.8	55.31	51.28	61.71	55.51
8	63.87	75.81	68.2	65.8	73.81	72.8	67.27
12	81.17	89.17	88.4	81.45	88.51	85.28	80.74
24	94.31	94.1	93.12	87.1	93.71	90.4	87.41

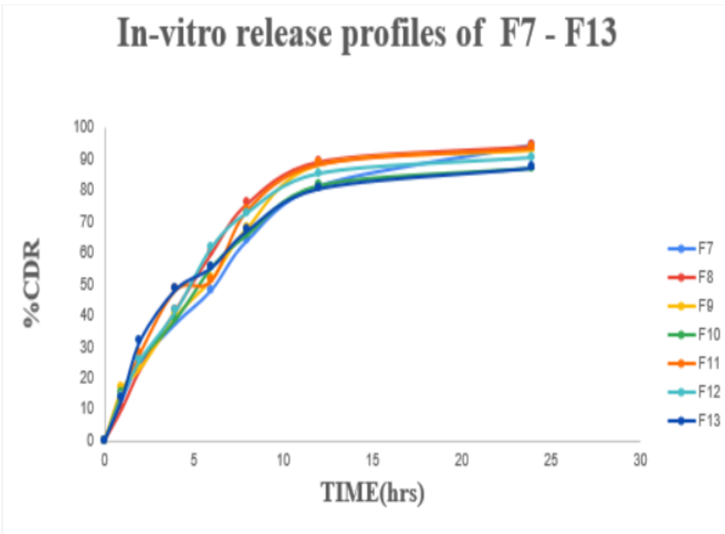


Figure 12 *In vitro* release profiles of F-7 to F13

3.8. Drug release kinetics

Drug Release kinetic study of all formulations (F1 to F13) was studied for different kinetic equations (zero order, first order, Higuchi, and Korsemeyer-peppas equation). Optimized formulation indicates that R^2 for zero order and Higuchi models, formulation (F1) were found to be significant.

According to the Korsmeyer- Peppas model, slope (n) value less than 0.45 indicates the Fickian diffusion. From the results obtained all the formulations (F1) having the slope (n) value between 0.351 and 0.442. This indicates that the formulation follows the release mechanism of Non- Fickian diffusion.

Table 11 Drug release kinetics data for formulation (F1)

Time (hrs)	F1
0	0
1	11.82 ± 0.02
2	16.09 ± 0.016
4	24.12 ± 0.020
6	32.25 ± 0.032
8	40.01 ± 0.026
12	54.24 ± 0.024
24	98.51 ± 0.024

Table 12 Drug release kinetics for formulation (F1)

Parameter	Zero order	First order	Higuchi	Korsemeyer-Peppas
Regression values (R^2)	0.9903	0.5491	0.9455	0.733
Slope	3.893	0.0569	0.048	0.7106
Intercept	6.8547	0.9074	0.5953	0.3022

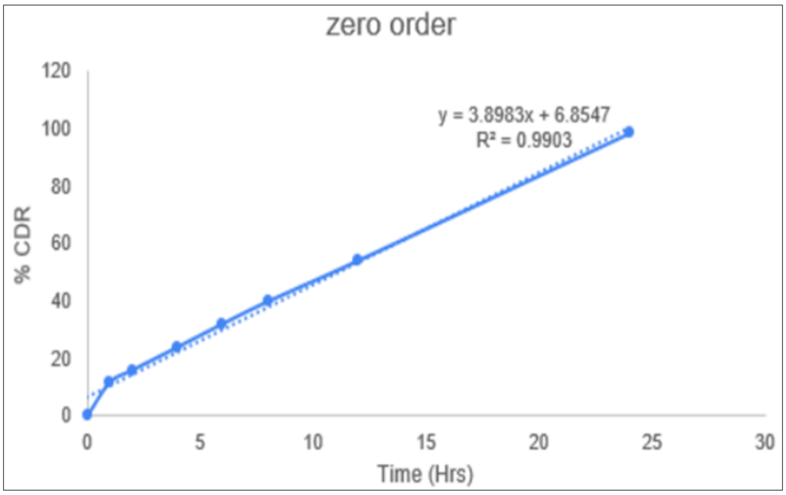


Figure 13 Zero order release kinetics for best formulation (F1)

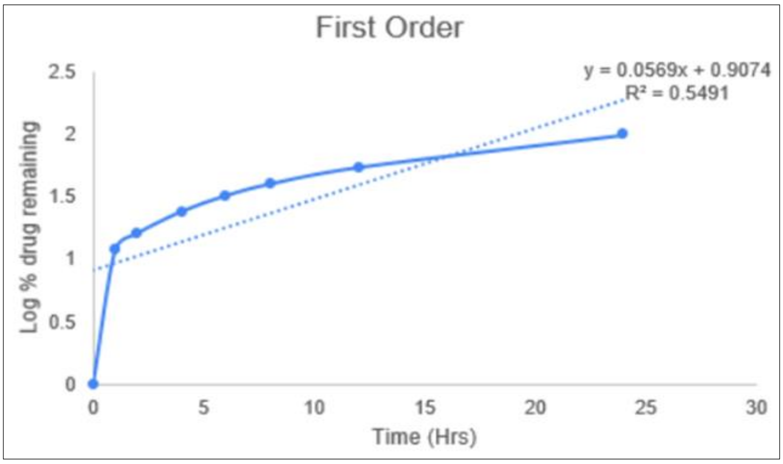


Figure 14 First order release kinetics for best formulation (F1)

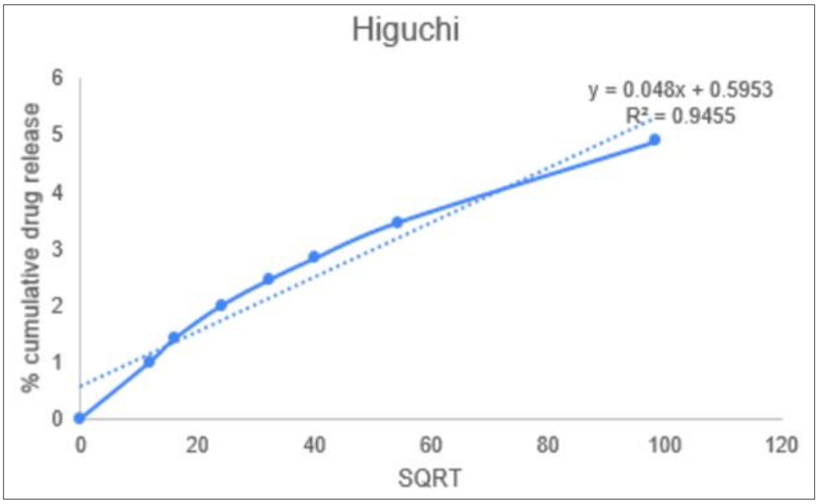


Figure 15 Higuchi release kinetics for best formulation (F1)

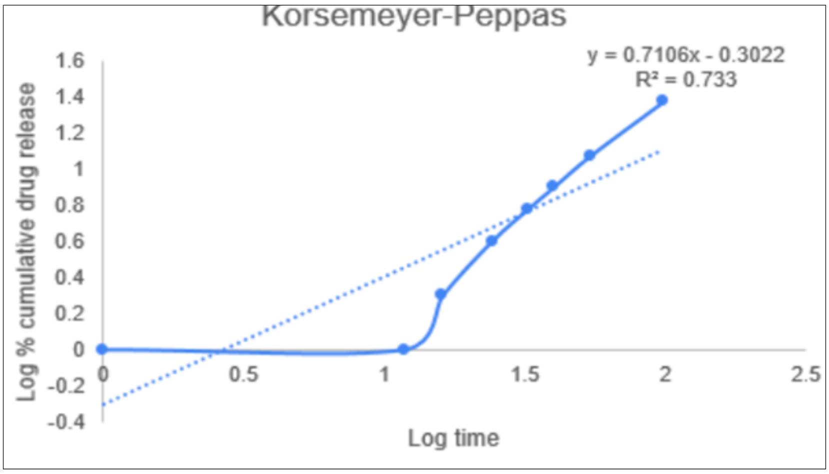


Figure 16 Korsemeyer-Peppas release kinetics for best formulation (F1)

3.9. Stability studies

Stability study was carried out for drug loaded transfersomes at two different temperatures i.e. refrigeration temperature (4.0 ± 0.2 °C) and at room temperature (25-28 °C) for 3 months. Stability studies data revealed that the optimized formulation (F-1) was stable after 3 months of storage at 4.0 ± 0.2 °C while at 25-28 ±2 °C, the formulation was found unstable. Stability of formulation was observed on the basis of % drug remain, average vesicles size and %EE.

Table 13 Characterization of optimized formulation of Transfersomes formulation (F1)

Characteristic	**Time (month)**					
	1 month		**2 month**		**3 month**	
Temperature	4.0 ±0.2 °C	25 ± 2 °C	4.0 ±0.2 °C	25 ± 2 °C	4.0 ±0.2 °C	25 ± 2 °C
Average vesicle size (nm)	160.2	169.3	162.7	172.6	167.7	178.3
% EE	83%	82.3%	81%	79.6%	78.12%	74.2%
Drug content (%)	96.71%	95.2%	92.12%	90.3%	88.3%	86.12%

4. Conclusion

F1 shows the best results among all the formulations. F1 physicochemical characteristics were all found to be satisfactory. Over a 24-hour period, the patch showed controlled release. R^2 value for F1 were found to follow zero order and Higuchi release and according to Korsemeyer-peppas it follows Non- Fickian diffusion.

The results of the study show that Quetiapine Fumarate can be delivered by transdermal patches. The result of the current investigation suggests that the transfersomal patch comprising Quetiapine Fumarate has great promise for effective doses into systemic circulation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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