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PREPARATION AND EVALUATION OF EXTENDED-RELEASE MICROSPHERES OF QUETIAPINE FUMARATE

Keyur S. Patel [*1], Sejal A. Madhak [1], Kunal N. Patel [1], Pragna K. Shelat [1] and Deepa R. Patel [2]

K. B. Raval College of Pharmacy [1], Shertha, Gandhinagar - 382423, Gujarat, India.
Kalol Institute of Pharmacy [2], Kalol, Gandhinagar - 382721, Gujarat, India.

Keywords:

Quetiapine fumarate, Eudragit RS100, Eudragit RL100, Microspheres, Sodium Lauryl Sulfate

Correspondence to Author:
Dr. Keyur S. Patel

K. B. Raval College of Pharmacy, Shertha, Gandhinagar - 382423, Gujarat, India.

E-mail: keyur.pharma@gmail.com

ABSTRACT: The objective of present study was to develop extended release microspheres of quetiapine fumarate using Eudragit RS 100 and Eudragit RL100 to reduce the dosing frequency. The quetiapine fumarate-loaded Eudragit microspheres were formulated by a solvent evaporation method. A 3^2 factorial design was employed to study the effect of concentration of sodium lauryl sulfate (SLS) and drug: polymer ratio on percentage yield, percentage entrapment efficiency, particle size, and % *in-vitro* drug release at 10 h. Drug excipients compatibility study by DSC showed no interaction between drug and excipients. The entrapment efficiency was found to be 40.56 ±1.32 % to 72.66 ±2.13 %, and the particle size range was 165±3.51 µm to 243±3.05 µm. *In-vitro* drug release of quetiapine fumarate microspheres showed a sustained release up to 24 h. Concentration of SLS and drug: polymer ratio had significant effect on % yield, % entrapment efficiency, particle size and % *in-vitro* drug release. From all parameters and experimental design evaluation it was concluded that drug release rate decreased with an increase the drug: polymer ratio and a decrease in the amount of SLS. The scanning electron microscopy (SEM) study observed that microspheres were spherical and fairly smooth surfaces. The *in-vitro* release kinetics revealed Korsmeyer - Peppas model is followed, and drug release is by fickian diffusion.

INTRODUCTION: Quetiapine fumarate is a psychotropic substance accepted as a medication to cure schizophrenia, acute mania and acute bipolar depression in adult patients. It is an anti-psychotic agent showing serotonin/dopamine binding ratio, dopamine D2-receptor and 5-HT2-receptor blocking effects and resulting minimal extrapyramidal side effects [1, 2, 3].

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Quetiapine fumarate has mean elimination half life of 6 h and hence there is a need for twice or thrice daily administration. Hence, quetiapine fumarate is considered a very good candidate for extended drug delivery to increase patient compliance and reduce the dosing frequency [4]. Microspheres are the one methods of extended drug delivery system.

Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles [5]. It can also be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level with particle size range of 1-100 µm [6, 7, 8]. Microspheres are one of the multiple unit

dosage forms. Microspheres are a useful approach that significantly prolongs drug effect duration and improves patient compliance [9]. Eudragit are biocompatible copolymers synthesized from acrylic and methacrylic acid esters. Usually, it uses to modify the drug release for delayed-release formulation (Eud L), protecting from an ambient condition or taste masking (Eud E), or as a material for sustained release formulation [10, 11]. They have also been used in the microencapsulation of drugs. Eudragit RL is insoluble but permeable to water and digestive juices, releasing the drug by diffusion. The solvent evaporation method is widely preferred for preparing sustained-release microspheres [12]. This study aimed to prepare eudragit microspheres containing quetiapine fumarate by solvent evaporation method to achieve an extended drug release profile and to study the effect of different formulation variables such as concentration of sodium lauryl sulfate (SLS) and drug: polymer ratio on percentage yield, percentage entrapment efficiency, particle size and its *in-vitro* release behavior.

MATERIALS & METHODS:

Chemicals & Reagents: Quetiapine fumarate was obtained as a gift sample from Torrent Research Center. Eudragit RS 100, Eudragit RL100, and SLS were procured from Yarrow Chem Products. Dichloromethane and methanol were purchased from Astron Chemicals, Ahmadabad.

Methods:

Drug and Excipient Compatibility Study by Differential Scanning Calorimetry (DSC): The DSC study was carried out using DSC-60 (Shimadzu Corporation, Japan). The samples were heated in sealed aluminum pans under airflow (30 ml/min) at a scanning rate of 10°C/min from 50 to 300°C. An empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples [13].

Preparation of Microspheres: Eudragit RS 100 and Eudragit RL100 were dissolved in 20 ml Dichloromethane: methanol mixture (1:1). 400 mg drug was dispersed in an above polymer solution. Above drug-polymer solution was added dropwise with the help of syringe into 100 ml SLS solutions and continuously stirred using a mechanical stirrer for 2 h at 1500 rpm until the organic solvent evaporated. The prepared microspheres were filtered by using a vacuum filter. The collected microspheres were dried at room temperature [14, 15].

Experimental Design: In this design, 2 factors were evaluated at 3 levels, and experimental trials were performed using all possible 9 combinations. In this present study, the concentration of SLS (X_1) and drug: polymer ratio (X_2) were selected as independent variables.

The % yield, % entrapment efficiency, particle size, and % *in-vitro* drug release at 10 h were selected as dependent variables. A statistical model incorporating interactive and polynomial terms was used to evaluate the response.

$$Y = b0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Where Y is the dependent variable, b_0 is the arithmetic mean response, and b_1 and b_2 are the estimated coefficient for the factor X_1 and X_2, respectively. The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value.

TABLE 1: VARIABLES IN 3^2 FACTORIAL DESIGN

Independent Variables	Level		
	-1	0	+1
X_1: Concentration of SLS (%)	0.2 %	0.4 %	0.6 %
X_2: Drug: polymer ratio	1:2 (400 mg: 800 mg)	1:3 (400 mg:1200 mg)	1:4 (400 mg: 1600 mg)
Dependent variables: Y_1: Percentage yield Y_2: Percentage entrapment efficiency Y_3: Particle size Y4: % drug release at 10 h			

TABLE 2: FORMULATION OF MICROSPHERES

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	400	400	400	400	400	400	400	400	400
Eudragit RS 100 (mg)	400	400	400	600	600	600	800	800	800
Eudragit RL100 (mg)	400	400	400	600	600	600	800	800	800
Concentration SLS (%)	0.2	0.4	0.6	0.2	0.4	0.6	0.2	0.4	0.6

The interaction term (X_1X_2) shows how the responses change when two factors are changed simultaneously. The polynomial terms (X_1^2, X_2^2) are included to investigate nonlinearity [13] **Table 1 & 2**.

Evaluation of Microspheres:

Percentage Yield: The yield of microspheres was calculated from the amount of microspheres obtained divided by the total amount of non-volatile components.

Practical yield of microspheres after drying / Total weight of drug + Polymer × 100

Percentage Entrapment Efficiency: 25mg of microspheres were crushed in mortar pastel, dispersed in 50 ml 0.1N HCl solution, and then sonicated for 10 min by sonicator. Then this dispersion was allowed to rotate in an incubator for 24 h and permitted to pass through Whatman filter paper. A UV spectrophotometer assayed the net content of the drug after suitable dilution at λmax 289 nm [1].

% Entrapment efficiency = Practical drug content / Theoretical drug content × 100

Particle size Analysis: A compound microscope performed a particle size analysis of drug-loaded eudragit microspheres by optical microscopy using a compound microscope [16]. A small amount of dry microspheres was suspended in purified water (5 ml). A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing eudragit microspheres was mounted on the stage of the microscope and the diameter of at least 300 particles was measured using a calibrated ocular micrometer.

***In-vitro* Drug Release:** *In-vitro* drug release studies for the prepared microspheres were conducted for a period of 24 h using USP rotating paddle apparatus (Electrolab Dissolution Tester (USP) TDT- 08L) at 37±0.5°C and 100 rpm. The in vitro drug release study was performed in 900 ml 0.1 N HCL pH 1.2 for 2 h and 900 ml phosphate buffer pH 6.8 for 3 to 24 h. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration the sample solutions were analyzed at 289 nm for quetiapine fumarate by a UV-Visible spectrophotometer [1].

***In-vitro* Release Kinetics:** The drug release data of sustained-release microspheres was fitted to kinetics models, *i.e.*, zero-order, first-order, Higuchi and Korsmeyer- Peppas to find out drug release pattern and mechanism.

Surface Morphology: Morphological characterization of the microspheres was carried out by using scanning electron microscopy. Using double-sided carbon tape, a monolayer of dry microspheres was mounted on an aluminum slab. Using a sputter coater, the sample was coated with a 10 nm thick gold film. Coated samples were examined using an electron acceleration voltage of 10 KV.

RESULTS & DISCUSSIONS:

Drug Excipient Compatibility Study by DSC: DSC of the quetiapine fumarate **Fig. 1** and quetiapine fumarate + Eudragit RS100 + Eudragit RL100 mixtures **Fig. 2** show an endothermic peak at 177.37 °C and 175.36°C, respectively. There was no change in the melting endotherm of the drug and drug-polymers mixture. So, it was concluded that drugs and polymers were compatible.

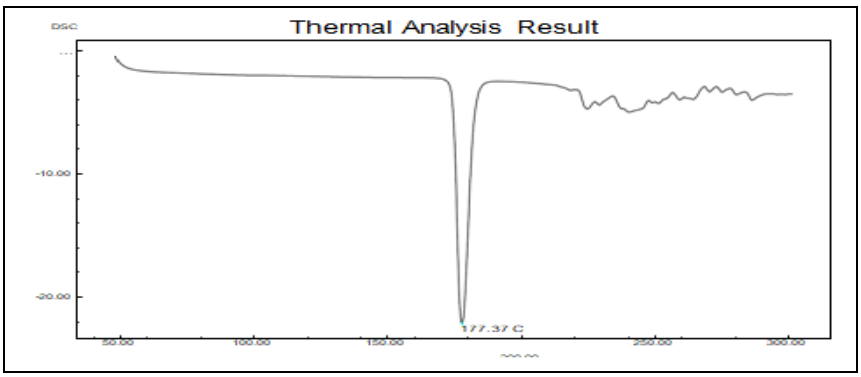

FIG. 1: DSC STUDY OF QUETIAPINE FUMARATE

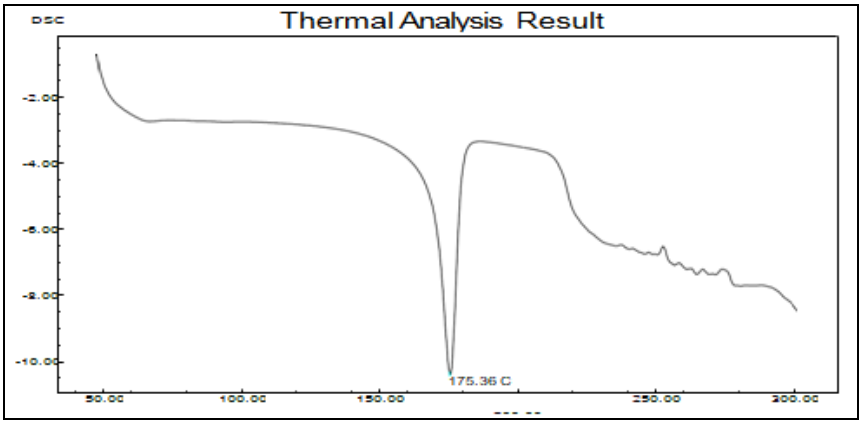

FIG. 2: DSC STUDY OF QUETIAPINE FUMARATE + EUDRAGIT RS100+ EUDRAGIT RL100

Result of Batches of Quetiapine Fumarate Microspheres: Results of quetiapine fumarate microspheres are shown in **Table 3**.

TABLE 3: RESULT OF BATCHES OF QUETIAPINE FUMARATE MICROSPHERES

Batch No	Independent variables		Dependent variables			
	X1	X2	% yield	% entrapment efficiency	Particle size (µm)	% *in-vitro* drug release at 10 h
F1	-1	-1	65.6 ± 1.38	48.12 ±3.2	182±4.65	93.36± 1.40
F2	0	-1	53.9± 1.69	43.23 ±2.3	173±3.32	95.15±1.23
F3	+1	-1	53.9± 1.69	40.56 ±1.32	165±3.51	98.67±1.54
F4	-1	0	75.9 ± 1.73	58.46 ±1.16	222±4.68	80.24± 1.35
F5	0	0	72.4 ± 1.28	56.18±3.12	214±4.70	81.27± 1.23
F6	+1	0	69.4 ± 1.40	52.12 ±2.17	210±3.60	84.79± 1.40
F7	-1	+1	83.48±2.10	72.66 ±2.13	243±3.05	77.35 ±1.24
F8	0	+1	82.16 ± 2.29	69.55 ±2.07	239±2.31	79.91± 1.0
F9	+1	+1	80.13 ±1.90	65.48 ±2.39	224±3.51	81.7±1. 35

*Values are expressed as mean ± SD (n=3)

Percentage Yield: The % yield in Eudragit microspheres was found between 53.9±1.69 to 83.48±2.10. Here p-value of X_1 and X_2 was less than 0.05, so the concentration of SLS and drug: polymer had a significant effect on % yield. Above equation (2) show that concentration of SLS and drug: polymer ratio had a negative and positive effect on % yield, respectively. So it was concluded that as the concentration of SLS increased, the % yield decreased and the amount of polymer increased, the % yield increased.

TABLE 4: STATISTICAL ANALYSIS OF % YIELD

Source	Sum of square	Degree of freedom (df)	Mean square	F value	p value	Significant Terms (p value < 0.05)
Model (Quadratic)	879.15	5	175.83	749.05	<0.0001	+
X_1 –Concentration of SLS	77.40	1	77.40	329.73	<0.0001	+
X_2 – Drug: polymer ratio	772.25	1	772.25	3289.86	<0.0001	+
$X_1 X_2$	17.43	1	17.43	74.26	<0.0001	+
X_1^2	0.48	1	0.48	2.05	0.1950	-
X_2^2	11.63	1	11.63	49.55	0.0002	+
Residual	1.64	7	0.23			
Core Total	880.79	12				

$$\% \text{ Yield} = +72.35 - 3.59 * X_1 + 11.34 * X_2 + 2.09 * X_1 X_2 + 0.42 * X_1^2 - 2.05 X_2^2 \quad \text{----------(2)}$$

Percentage Entrapment Efficiency: The entrapment efficiency in Eudragit microspheres was found between 40.56 ±1.32 to 72.66 ±2.13 %. Here p-value of X_1 and X_2 was less than 0.05, so the concentration of SLS and drug: polymer ratio had a significant effect on % entrapment efficiency. Effect of concentration of SLS: Increasing the concentration of SLS from 0.2% to 0.6 % results in

a significant decrease in the entrapment efficiency in eudragit microspheres. This could be attributed to the fact that, at a low concentration of surfactant, the surface of the microspheres is smooth and intact. Increasing surfactant concentration results in microspheres with brittle surfaces, which may lead to a drug loss on washing microspheres [14, 17].

Effect of the drug: polymer ratio: The Entrapment Efficiency of quetiapine fumarate microspheres in Batch F1, F4 & F7 were found to be 48.12 ±3.2, 58.46 ±1.16, and 72.66 ±2.13, respectively. So, it was concluded that entrapment efficiency increased with an increase in drug: polymer ratio.

TABLE 5: STATISTICAL ANALYSIS OF % ENTRAPMENT EFFICIENCY

Source	Sum of square	Degree of freedom (df)	Mean square	F value	p-value	Significant terms
Model (Linear)	1031.16	2	515.58	1300.26	<0.0001	+
X_1 –Concentration of SLS	74.06	1	74.06	186.78	<0.0001	+
X_2 – Drug: polymer ratio	957.10	1	957.10	2413.75	<0.0001	+
Residual	3.97	10				
Core Total	1035.13	12				

% Entrapment efficiency = $+25.37359-17.56*X_1+0.0315*X_2$ ----------(3)

Particle size Analysis: The particle size range in quitapine microspheres was found in a range of between 165±3.51 µm to 243±3.05 µm as shown in **Table 3**. Here p value of X_1 and X_2 was less than 0.05, so the concentration of SLS and drug: polymer ratio had a significant effect on mean particle size. Effect of concentration of SLS: Increasing the amount of surfactant from 0.2% to 0.6 % resulted in a significant decrease ($P<0.05$) in the mean diameter of microspheres. This can be attributed to the lower concentration of emulsifier may not be sufficient to cover the droplets of emulsion, resulting in coalescence, leading to an increase in microspheres aggregation and fusion of the formed droplets [14, 18]. Effect of the drug: polymer ratio: The data obtained showed that the mean particle size increased significantly as the drug: polymer ratio varied from 1:2 to 1:4. At a lower concentration of Eudragit (800 mg), the mean particle size of microspheres observed was 182±4.65µm. At medium concentration (1200 mg), the mean particle size was observed to be 222±4.68µm. At a higher concentration (1600 mg), the mean particle size was observed 243±3.05 µm. Due to higher viscous disperse being poured into the dispersion medium, bigger droplets were formed and the mean particle size of microspheres was increased [19, 20]. The mean particle size of microspheres was significantly increased when a high drug: polymer ratio was used.

TABLE 6: STATISTICAL ANALYSIS OF MEAN PARTICLE SIZE

Source	Sum of square	Degree of freedom (df)	Mean square	F value	p value	Significant Terms (p value<0.05)
Model (Quadratic)	6489.73	5	1297.95	239.31	<0.0001	+
X_1 –Concentration of SLS	384.00	1	384.00	70.80	<0.0001	+
X_2 – Drug: polymer ratio	5766.00	1	5766.00	1063.12	<0.0001	+
$X_1 X_2$	1.00	1	1.00	0.18	0.6805	_
X_1^2	0.082	1	0.082	0.015	0.9055	_
X_2^2	285.80	1	285.80	52.69	0.0002	_
Residual	37.97	7	5.42			
Core Total	6527.69	12				

Mean particle size = $+214.62-8.00* X_1+31.00* X_2-0.50* X_1* X_2-0.17* X_1^2-10.17*X_2^2$----------(4)

***In-vitro* Drug Release:** Here p-Value of X_1 and X_2 was Less than 0.05, So the Concentration of SLS and Drug: polymer ratio had a significant effect on % drug release at 10 h. Above equation (5) showed that concentration of SLS and drug: polymer ratio had negative and positive effects on % cumulative drug release, respectively, So it was concluded that as the concentration of SLS increased, the % cumulative drug release increased, and drug: polymer ratio increased, the % cumulative drug release decreased. The *in-vitro* release of quetiapine fumarate from Eudragit microspheres exhibited biphasic release, initially a fast release due to fast dissolution of drug molecules attached

to the surface of the microspheres followed by a slower release **Fig. 3.** Effect of Concentration of SLS: The *in-vitro* release studies reveal that drug release is increased as the surfactant concentration increases at a constant drug: polymer ratio as shown in **Fig. 3**. This is due to the increase the wet ability of the drug in dissolution media [14, 21]. Effect of Drug: Polymer Ratio: The results indicated that quetiapine fumarate release from Eudragit microspheres was decreased as the drug: polymer ratio was increased. Due to increased polymer concentration, the matrix wall of microspheres became thicker, and the formation of a thicker matrix wall led to slower drug release of drugs [21-23]. The results of the present study are by **Fig. 5** (*i.e.*, At 10 h for F1, F4 and F7 are 93.36± 1.40 %, 80.24± 1.35, and 77.35 ±1.24, respectively in the case of 0.2 % of SLS) indicating a decrease in drug release with an increase in Eudragit concentration.

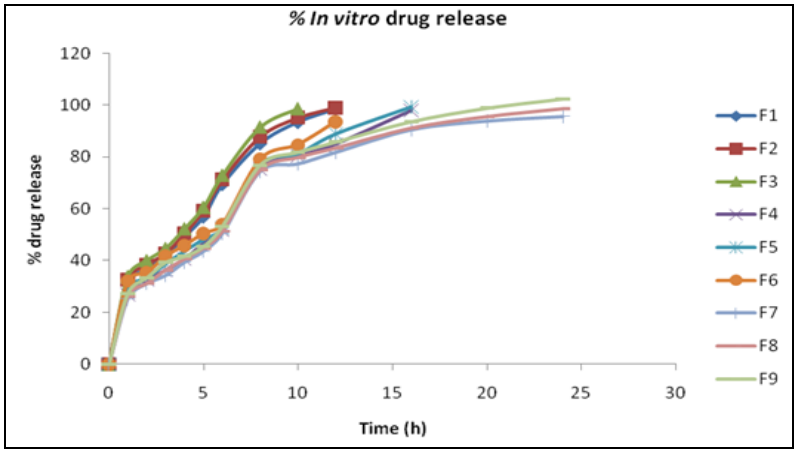

FIG. 3: *IN-VITRO* DRUG RELEASE DATA OF QUETIAPINE FUMARATE MICROSPHERE BATCHES

TABLE 7: STATISTICAL ANALYSIS OF % *IN-VITRO* DRUG RELEASE AT 10 H

Source	Sum of square	Degree of freedom (df)	Mean square	F value	p value	Significant terms (p value<0.0)
Model (Quadratic)	541.82	5	108.36	609.99	<0.0001	+
X_1 –Concentration of SLS	33.65	1	33.65	189.44	<0.0001	+
X_2 – Drug: polymer ratio	387.53	1	387.53	2181.44	<0.0001	+
$X_1 X_2$	0.23	1	0.23	1.30	0.2922	-
X_1^2	1.59	1	1.59	8.98	0.0201	-
X_2^2	92.11	1	92.11	518.47	<0.0001	+
Residual	1.24	7	0.18			
Core Total	543.06	12				

% drug release at 10 h = 81.41+2.37* X_1-8.04* X_2-0.24* X_1* X_2+0.76* X_1^2+5.77* X_2^2 ------(5)

Optimized Batch Selection:

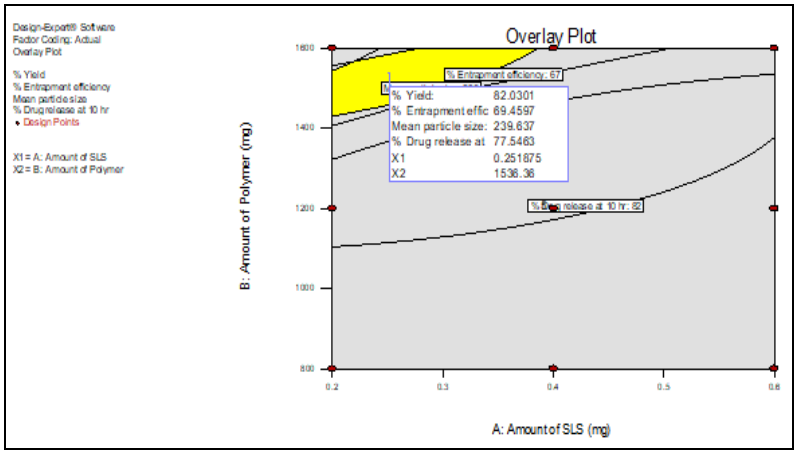

FIG. 4: OVERLAY PLOT OF OPTIMIZED BATCH

Evaluation of optimized batch (F0): Fig. 4 shows the yellow area was the optimized area, and batch F0 fell in the yellow region.

TABLE 8: RESULT OF EVALUATION PARAMETERS OF OPTIMIZED BATCH (F0)

Parameters	Result
% yield	81.50 ± 2.23
% Entrapment efficiency	71.23 ± 2.14
Particle size (µm)	235 ±2.68
In vitro drug release at 10 h	78.67 ±1.79

*Values are expressed as mean ± SD (n=3)

% *In-vitro* Drug Release Data of Optimized Batch (F0):

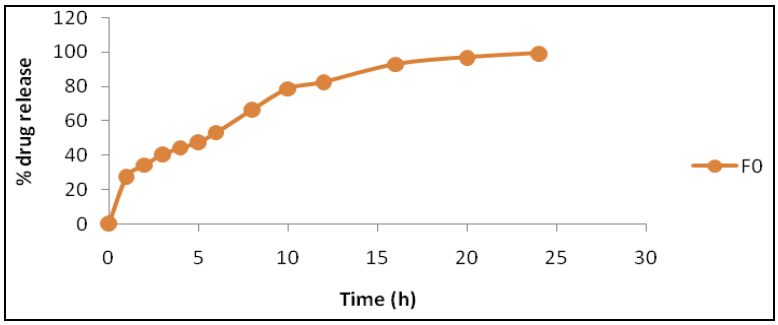

FIG. 5: *IN-VITRO* DRUG RELEASE OF OPTIMIZED BATCH (F0)

***In-vitro* Release Kinetic Studies of Optimized Batch:** The release kinetic of the formulation was checked by fitting the release data to various kinetic models which is shown in **Tabel 9**. The release was best fitted to the Korsmeyer-Peppas model. Here, n value was 0.4484, so the release mechanism was Fickian diffusion-based [24]. Surface Morphology of an optimized batch of microspheres was carried out by SEM studies. From **Fig. 6**, it was observed that the shape of microspheres seems to be spherical with fairly smooth surface.

TABLE 9: *IN-VITRO* RELEASE KINETIC STUDIES OF OPTIMIZED BATCH

Batch	Zero-order	First order	Higuchi	Korsmeyer-Peppas model	
	R^2	R^2	R^2	R^2	n
Optimized batch (F0)	0.9106	0.8301	0.9710	0.9781	0.4484

Surface Morphology:

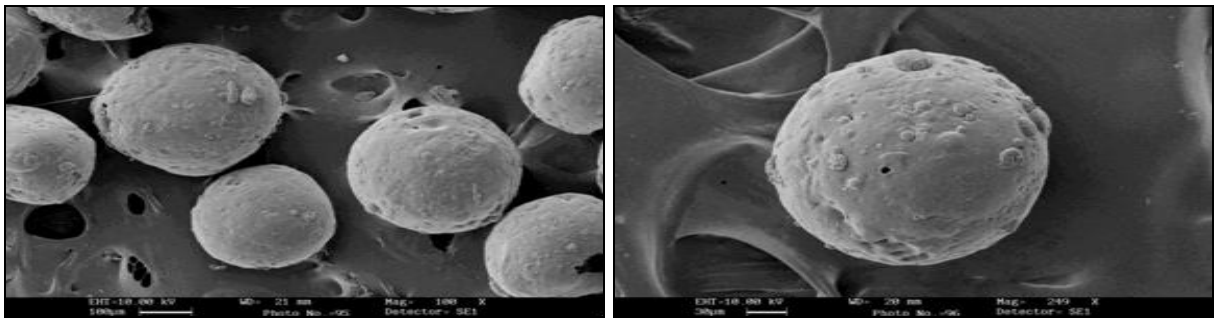

FIG. 6: SEM ANALYSIS OF QUETIAPINE FUMARATE MICROSPHERES

CONCLUSION: Quetiapine fumarate microspheres were prepared successfully by solvent evaporation method and provided a extended-release up to 24 h. The concentration of SLS and drug: polymer ratio significantly affected various parameters like percentage yield, percentage entrapment efficiency, particle size, and % *in-vitro* drug release. It was found that increasing the drug: polymer ratio resulted in an increased Percentage yield, entrapment efficiency, and particle size. Here % the drug release rate was decreased with increasing the polymer concentration and decreasing concentration of SLS. The optimized batch (F0) showed the drug release at 78.67% at 10 h and 99.34 at 24 h. The SEM study observed that microspheres were spherical

and had fairly smooth surfaces. The release pattern quetiapine fumarate fit the Korsmeyer- Peppas model indicating Fickian diffusion. This also suggests that extended released microspheres of quetiapine fumarate can be a good alternative to conventional therapy and reduce the dosing frequency.

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CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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