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Design and development of sustained release microspheres of Quetiapine Fumarate using 3^2 full factorial design

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ABSTRACT

The objectives of this investigation were to prepare sustained release microspheres of the anti-psychotic drug, quetiapine fumarate, using ethyl cellulose as the polymer and evaluate it's encapsulation efficiency, release characteristics in vitro; utilizing emulsion solvent evaporation and extraction technique. A 3^2 factorial factorial design was applied to investigate the influence of drug: polymer ratio and average particle size on release characteristics. The drug release was proportional to square root of time, indicating that the drug release from ethyl cellulose microspheres was diffusion controlled. The optimized batch showed no signs of interaction with sustaining the drug release up to 12 h along with identical release behavior to that of marketed sustained release tablet. The sphericity and smoothness of microspheres were also confirmed by scanning electron microscopy study.

Keywords: *Quetiapine fumarate, microspheres, emulsion solvent evaporation, in vitro drug dissolution*

INTRODUCTION

Quetiapine fumarate appears in the list of atypical antipsychotic drugs for the long term treatment of schizophrenia, bipolar I mania and bipolar II depression. The antipsychotic effect of Quetiapine fumarate is mediated through antagonist activity at dopamine and serotonin receptors. [1,2] Quetiapine fumarate has moderate water solubility with extensive metabolism in liver via sulphoxidation route which leads to adult dosage of 300-400 mg/day in 3 or 4 divided dose. It has a mean terminal half life of about 6 hr with peak plasma concentration in 1.5 hr. [3] Hence, Quetiapine fumarate is considered as a very good candidate for sustained drug delivery. As compared to single unit dosage forms multiple unit dosage forms tend to spread more uniformly throughout the gastrointestinal tract (GIT) and avoid the vagaries of gastric emptying. These could results in more reproducible drug absorption and reduced risk of local irritations [4] which ultimately makes multiparticulate systems more advantageous over single unit dosage forms.

In light of these, the present investigation was carried out to formulate sustained release microspheres of Quetiapine fumarate by using ethyl cellulose as one of the widely utilized bio compatible, non-biodegradable encapsulating materials for the sustained release of pharmaceuticals [5] that could provide lower but sustained drug concentration over an extended period of time. Sustained release microspheres were prepared by emulsion solvent evaporation & extraction method. The influence of various processing and formulation factors like stirring speed, drug-to-polymer ratio, external phase saturation condition and volume of processing medium, particle size etc. have been evaluated on encapsulation efficiency and *in vitro* drug dissolution. In the past researchers like Cheu SJ et al., 2001 & Gohel MC et al., 1997 have utilized experimental design as an effective tool in optimization of sustained release microspheres. A 3^2 full factorial design was adopted to evaluate the combined effect of selected independent variables on the percentage of drug dissolved in 60 min (Y_{60}), time for 60% drug dissolution (t_{60}%) and time for 90% drug dissolution (t_{90}%).

MATERIALS AND METHODS

Quetiapine fumarate was generously gifted from Sun Pharmaceuticals Ltd (Mumbai, India). Ethyl cellulose (40–49.5% ethoxy groups, viscosity at 25 °C 30–50 cps) and polyvinyl alcohol (PVA) was purchased from Himedia (Mumbai, India) and Loba chemi (Mumbai, India) respectively. All other chemicals and reagents used were of analytical grade. Double distilled water was used throughout the study.

Preparation of microspheres

Ethyl cellulose microspheres of Quetiapine fumarate were prepared according to emulsion solvent evaporation & extraction method. Ethyl cellulose (1.5 g) and Quetiapine fumarate (1.5 g) were suspended in 20 ml of the combined solvent system consisting of dichloromethane and acetonitrile in 7:3 ratios. The drug suspension was dispersed in the continuous aqueous phase (200 ml) containing 1% polyvinyl alcohol (w/v) at 500 rpm using a magnetic stirrer and the stirring was continued for 2 hr at 25°C to allow complete evaporation of organic solvents. After decantation the microspheres were filtered, washed three times with water and dried in an oven (50°C).

Optimization of processing parameters

Various processing and formulation factors like stirring speed, drug-to-polymer ratio, external phase saturation condition and volume of processing medium, etc. have been optimized on the basis of their impact on average particle size, % yield and % encapsulation efficiency.

Experimental design

A 3^2 full factorial design was employed to systematically study joint influence of the effect of independent variables such as ratio of drug: polymer (X_1) and particle size of microspheres (X_2) on the dependent variables like percentage of drug dissolved in 60 min (Y_{60}), time for 60% drug dissolution (t_{60}) and time for 90% drug dissolution (t_{90}). In this design, two factors are evaluated, each at three levels, and experimental trials are performed at all 9 possible combinations. A statistical model incorporating interactive and polynomial terms is used to evaluate the response.

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Where, Y_i is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_i is the estimated coefficient for the factor X_i. The main effects ($X_1$and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. [6] The composition of the factorial design batches MS1 to MS9 are shown in Table 1.

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Table 1 Composition of 3^2 Factorial Design Batches *

Batch	Variable Levels in Coded Form X_1	X_2	Y_{60} (%)± SD	t_{60}(min) ± SD	t_{90}(min) ± SD
MS1	-1	-1	27.04 ± 2.5	4.03 ± 1.6	5.29 ± 0.9
MS2	-1	0	17.15 ± 1.8	4.48 ± 1.9	6.12 ± 1.3
MS3	-1	1	15.03 ± 1.3	5.45 ± 2.1	9 .00± 2.5
MS4	0	-1	19.25 ± 2.1	6.00 ± 1.2	10.20 ± 3.7
MS5	0	0	15.21 ± 1.5	7.50 ± 1.9	14.00 ± 3.9
MS6	0	1	11.25 ± 1.1	8.00 ± 2.7	17.00± 3.2
MS7	1	-1	16.04 ± 2.7	8.50 ± 3.5	15.13 ± 2.8
MS8	1	0	12.10 ± 1.9	12.05 ± 4.7	16.67 ± 4.7
MS9	1	1	6.71 ± 0.8	15.00 ± 5.2	22.00 ± 3.9

Codedvalues	**Actual values** X_1	X_2	
-1	1:1		150-180 µm (Microspheres pass from 85 # sieve and retained on 100# sieve)
0	1:2		180-250 µm (Microspheres pass from 60 # sieve and retained on 85# sieve)
1	1:3		250-355 µm (Microspheres pass from 44 # sieve and retained on 60# sieve)

**X_1 = drug: polymer ratio and X_2 = Particle size of microspheres in µm, Y_{60} (%) = drug dissolved in 60 min, t_{60} (min) = time required for 60% drug dissolution and t_{90} (min) = time for 90% drug dissolution*

Determination of drug loading, encapsulation efficiency and yield of microspheres Accurately weighed amount of drug loaded microspheres have been extracted with 10 ml of methanol. The amount of drug was analyzed by double beam UV visible spectrophotometer at 233 nm after filtration and suitable dilution. All the readings were carried out in triplicate.

Drug loading was determined by the following equation:

$$\% \text{ Drug loading} = \frac{\text{Wt.of drug}}{\text{Wt.of Microspheres}} \text{ X } 100 \quad (2)$$

Encapsulation efficiency was determined by the following equation:

$$\text{Encapsulation efficiency } (\%) = \frac{\text{Calculated drug content}}{\text{Theoritical drug content}} \text{ X } 100 \quad (3)$$

Yield of the produced microspheres was calculated for each batch by dividing the whole weight of product (M) by the total expected weight of drug and polymer (M_0): [7]

$$\% \text{ Yield} = \frac{M}{Mo} \quad (4)$$

Determination of the physicochemical properties of microspheres

Fourier transforms infrared spectroscopy (FT-IR) studies
FTIR spectra of pure drug, ethyl cellulose blank microspheres and drug loaded ethyl cellulose microspheres were taken by using KBr pellet technique and recorded on Perkin Elmer-2000 infrared spectrophotometer. The scanning was performed at moderate speed between 4000-650cm^{-1}. [8]

Scanning electron microscopy (SEM) studies
The samples for the SEM analysis were prepared by sprinkling the microspheres on one side of a double adhesive stub. The stub was then coated with gold (Fine coat, Ion sputter, JFC-1 100). The samples analysed were drug loaded microspheres, its surface view of and microspheres collected after dissolution study. [8]

Particle size & size distribution
The average particle size of microspheres was calculated by optical microscopy. An average of 100 microspheres was taken for the study of particle size and size distribution. [9]

***In vitro* drug release study**
The *in vitro* release studies of drug loaded microspheres were carried out using USP I dissolution rate apparatus (Basket type, 200rpm, 37± 0.5ºC) in two stages. In first stage of 5 hr, 900 ml of 0.05 M sodium citrate and 0.09 N sodium hydroxide (pH 4.7-4.9) was used as dissolution media. While for the 2nd stage additional 100 ml of 0.05 M sodium phosphate, 0.46 N sodium phosphate and 0.46 N sodium hydroxide was added to the media which was prepared for 1st stage (pH 6.4-6.8). At pre-set time intervals, 5 ml aliquots are withdrawn and replaced by an equal volume of fresh dissolution medium. After suitable dilution, the samples were analyzed spectrophotometrically, at 246 nm for 1st stage & at 249 nm for 2nd stage. After total drug release, the intact microspheres were collected and observed under scanning electron micro scope.

RESULTS AND DISCUSSIONS

Quetiapine Fumarate due to its hydrophilicity is likely to preferentially partition out into the aqueous medium, leading to low entrapment efficiency, when encapsulated using the aqueous phase as the processing medium. Depending on the processing conditions, as much as 90% of the drug was partitioned out into the outer processing medium. In order to increase the encapsulation efficiency of Quetiapine fumarate microspheres, the processing medium was previously saturated by the drug itself which ultimately retard the drug leaching into processing medium.

Preparation of microspheres
In this study an external phase was aqueous polyvinyl alcohol (1%) solution saturated with drug itself to retard drug leaching from microspheres. The internal phase (Dichloromethane: Acetone in 7:3 ratio) was selected on the basis of preliminary trials. Both the solvents of internal phase were removed by a combination of extraction and evaporation. During formation of microspheres, acetone was extracted by aqueous polyvinyl alcohol solution as it is water immiscible and dichloromethane was evaporated during stirring.[10] After emulsification of internal phase into external phase, it was stirred for 2 hr using a magnetic stirrer, during this phase it is assumed that the droplet sizes were allowed to stabilize while dichloromethane and acetone were escaped, making emulsion droplets free from solvents. Polyvinyl alcohol was used to stabilize the emulsification process.

Optimization
The process parameters such as volume of internal phase (20 ml), processing temperature (25 °C), concentration of polyvinyl alcohol as stabilizer (1%), ratio of solvent system of the organic phase (Dichloromethane: Acetone in 7:3 ratio) were selected on the basis of preliminary experimental trials and were kept constant for optimization of sustained release microspheres.

Table 2: Results of optimization of process parameters on the properties of microspheres*

Experimental variables	Range	Av. Particle size (µm) ± SD	% Yield	Entrapment) efficiency (%
Drug-to-polymer ratio	1:1	187 ± 17	71.57	22.60
	1:2	222 ± 21	72.34	52.17
	1:3	242 ± 14	82.08	75.56
Volume of processing medium	100 ml	284 ± 24	69.83	19.67
	200 ml	224 ± 36	70.21	35.78
	300 ml	200 ± 19	72.17	40.34
Stirring speed	300 rpm	327 ± 31	69.71	21.45
	500 rpm	250 ± 27	74.42	40.78
	700 rpm	285 ± 35	78.7	47.89
External phase saturation condition	Without saturation	269 ± 16	50.00	10.76
	Saturation at room temperature	292 ± 34	53.33	38.95
	Saturation at 60-70 °C	327 ± 21	67.42	44.16

**Volume of internal phase – 20 ml, Ratio of solvents in organic solvent system – Dichloromethane: Acetone in 7:3 ratios, Concentration of Stabilizer (polyvinyl alcohol) - 1%,Processing temperature – 25 °C*

The results of Table 2 indicates that there was a pronounced impact of parameters like drug: polymer ratio, volume of processing medium, stirring speed and saturation level of external phase on various properties of microspheres such as average particle size, % drug entrapment, % yield etc.

Effect of various parameters on average particle size
The drug-to-polymer ratio appears to influence the particle size distribution of microspheres. When the drug-to-polymer ratio was increased from 1:1 to 1:3, the proportion of larger particles formed was high, because the viscosity of the internal phase was increased with increase of the drug-to-polymer ratio. When the volume of the processing medium was increased from 100 to to 300 ml, mean particle size of microspheres were decreased (Table 2). This might be due to as volume of processing medium was increased, the emulsion droplets can be moved freely in the medium and they had less chance to collide with each other there by

yielding small and uniform microspheres. When the stirring speed was decreased from 500 to 300 rpm, the mean particle size of the microspheres was increased and they were large and aggregated. When the speed was increased from 500 to 750 rpm, the size of the microspheres was uniform. The change in the saturation condition affected the mean particle size of the microspheres, as shown in Table 2. As the saturation level was increased, more amount of drug was required to saturate the external phase.

Effect of various parameters on % Entrapment efficiency % Yield

The yield and entrapment efficiency of drug loaded microspheres of different drug: polymer ratios are shown in Table 2. Entrapment efficiency of the drug was dependent on its solubility in the solvents and processing medium and also depends on the physicochemical properties of the drug and polymer. In case of microspheres as the drug to polymer ratio increases the % entrapment efficiency also increases. This may be because of higher probability of entrapment of the drug by surrounding polymer matrix which acts as a barrier to drug and may lead to restrict the movement of the drug to the external phase.

Experimental design

Preliminary investigations of the process parameters revealed that factors drug: polymer ratio (X_1) and Particle size (X_2) highly influenced the rate of *in vitro* dissolution and hence they were used for further systematic studies. The Y_{60}, t_{60} and t_{90} for 9 batches (MS1 to MS9) showed a wide variation of 6.71 to 27.04 %, 5.29 to 22 min and 4.03 to 15 min respectively (Table 1). The data clearly indicates that X_1 and X_2 strongly influence the selected responses (Y_{60}, t_{60} and t_{90}). The fitted polynomial equations (full and reduced model) relating the response Y_{60} to the transformed factors are shown in Table 1. The polynomial equations can be used to draw conclusions after considering magnitude of coefficients and mathematical sign it carries either positive or negative.

Table 3 Summary of Results of Regression Analysis*

Coefficients for Y_{60}	b_0	b_1	b_2	b_{12}†	b_{11} †	b_{22}†
FM	14.5256	-4.06167	-4.8900	0.6700	0.4412	1.0667
RM	15.5312	-4.06167	-4.8900	——	——	——
Coefficients for t_{60}	b_0	b_1	b_2	b_{12}†	b_{11} †	b_{22}†
FM	7.2866	3.5982	1.6532	1.2703	1.0852	-0.1798
RM	7.8901	3.5982	1.6532	——	——	——
Coefficients for t_{90}	b_0	b_1	b_2	b_{12}†	b_{11} †	b_{22}†
FM	13.1733	5.5650	2.8967	0.7900	-1.3650	0.8400
RM	12.8233	5.5650	2.8967	——	——	——

**FM indicates full model; RM, reduced model. †Response is insignificant at P = 0.05.*

The coefficients b_1 and b_2 were found to be significant as P was less than 0.05 and thus, were retained in the reduced model. Similarly, for t_{60} and t_{90} fitted polynomial equations (full and reduced model) were generated. (Table 3)

Table 4 Calculations for Testing the Model in Portions*

Regression	DF	SS	for Y_{60} MS	R^2	F_{cal} = 0.4257, F_{table} = 9.28 DF = (3,3)
FM	5	246.92	49.38	0.9592	
RM	2	242.46	121.23	0.9412	
Error					
FM	3	10.51	3.50		
RM	6	14.98	2.50		
Regression	DF	SS	for t_{60} MS	R^2	F_{cal} = 5.9, F_{table} = 9.28 DF = (3,3)
FM	5	102.95	20.59	0.9858	
RM	2	94.08	47.04	0.9008	
Error					
FM	3	1.49	0.50		
RM	6	10.36	1.73		
Regression	DF	SS	for t_{90} MS	R^2	F_{cal} = 2.992, F_{table} = 9.28 DF = (3,3)
FM	5	243.79	48.76	0.9896	
RM	2	236.16	118.08	0.9586	
Error					
FM	3	2.55	0.85		
RM	6	10.18	1.70		

**DF indicates degree of freedom; SS, sum of squares; MS, mean of squares; R^2, regression coefficient; FM, full model; RM, reduced model*

Table 4 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficients for Y_{60}, t_{60} and t_{90} indicate a good fit. The critical values of F for all the three responses were at a =0.05 which was equal to 9.28 (df = 3, 3). Since the calculated value [F = 0.4257 (Y_{60}), 5.91 (t_{60}), 2.99 (t_{90})] was less than critical value (F = 9.28) hence, it may be concluded that the interaction term b_{12} and the nonlinearity terms b_{11} and b_{22} does not contribute significantly to predict Y_{60}, t_{60} and t_{90} and hence can be omitted from the full model. The change in Y_{60}, t_{60} and t_{90} as a function of X_1 and X_2 is depicted in the form of response surface plot (Figure 1 (a), (b), (c) respectively) based on full factorial design.

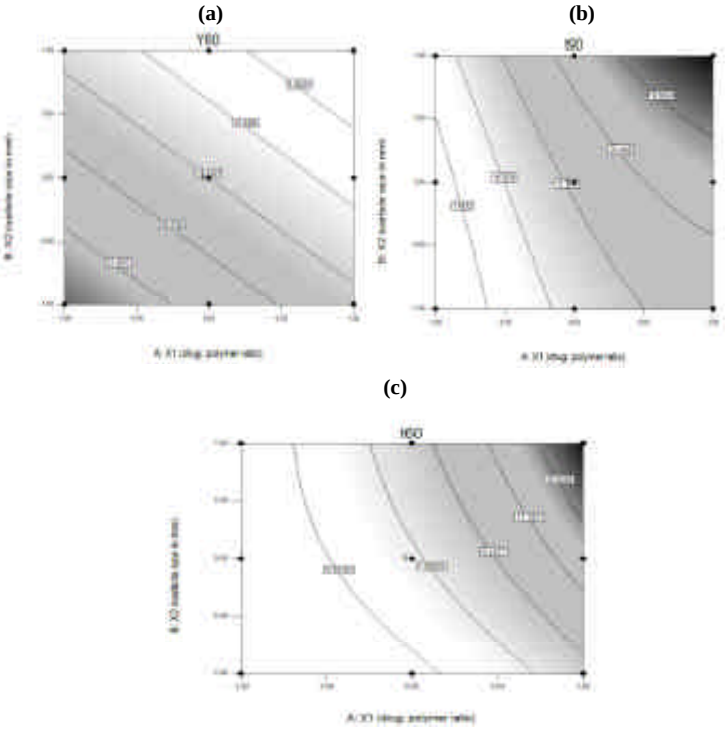

Figure 1 Counter plot of drug dissolved in 60 min (Y_{60}) (a), Counter plot of time for 60% drug dissolution (t_{60}) (b), Counter plot of time for 90% drug dissolution (t_{90}) (c)

The data of all the 9 batches of factorial design were used to generate interpolated values using Design Expert 7® software. Low levels of both X_1 and X_2 were found to be favorable for obtaining faster dissolution. Multiple linear regression analysis (Table 3) revealed that coefficient b_1 is positive and b_2 is negative. This indicates as drug: polymer ratio (X_1) was increased Y_{60} decreases. This decrease in dissolution profile might be attributed to a retardation of drug particles at higher polymer concentration, resulting in a slower dissolution profile at 60 min. Similarly in case of particle size of microspheres (X_2) as it increases the Y_{60} decreases. This might be due to the smaller surface area provided for dissolution by the larger particle size as compared to the microspheres having smaller particle size. Similarly for t_{60} and t_{90} as drug: polymer ratio (X_1) increases more amount of time requires for 60% and 90% drug release and hence both increases. While as the particle size of microspheres (X_2) increases both t_{60} and t_{90} increases which might be due to the faster dissolution provided by smaller size microspheres having larger effective surface area for dissolution (Table 1). A Checkpoint batch MS10 was prepared at X_1 = -0.14 and X_2 = -0.48 levels, respectively. The theoretical Y_{60}, t_{60} and t_{90} of batch MS10 were 18.34 %, 6.186 min and 11.72 min, respectively. The experimental values are 18.77%, 6.5 min and 12.2 min (Table 1), which are in good agreement with theoretical values. Batch MS4 may be considered as a promising formulation for sustained release microspheres of Quetiapine fumarate on the basis of its ability to sustain drug release up to 12 hr with almost 20% drug release in 1st hr. Hence, this batch was further selected for physical characterization. The dissolution profiles of optimized formulation (1:1 ratio, particle size 150-180 µm, Batch MS4) and pure drug are shown in Figure 2. It is also observed from the dissolution profile of optimized formulation that the total quantity of the drug present in the microspheres gets dissolved within 12 hr. The sustained release microspheres of best batch MS4 was evaluated for physical characterization viz FTIR and SEM.

Fourier transforms infrared spectroscopy (FT-IR) studies

FTIR spectra of pure drug (a), ethyl cellulose blank microspheres (b) and drug loaded ethyl cellulose microspheres (c) has showed no signs of interaction which makes the selected excipients compatible with quetiapine fumarate.

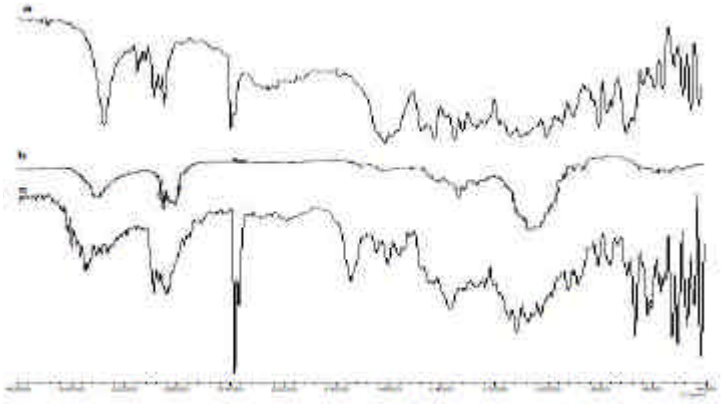

Figure 2: FTIR spectra of (a) Batch MS4, (b) Ethyl cellulose blank microspheres, (c) Quetiapine fumarate loaded ethyl cellulose microspheres

Scanning electron microscopy (SEM) studies

As shown in SEM photographs (Figure 3 (a)), the microspheres were spherical and porous. The surface of the microspheres was rough and revealed the presence of pores in the drug loaded microspheres. The study of drug loaded microspheres showed the presence of drug particles on the surface, which was responsible for the initial burst release of the drug during dissolution (Figure 3 (b)). Surface study of the micro spheres after dissolution showed bigger pores, suggesting that the drug was released through pores and the mechanism of drug release may be diffusion sustained.

(a) (b)

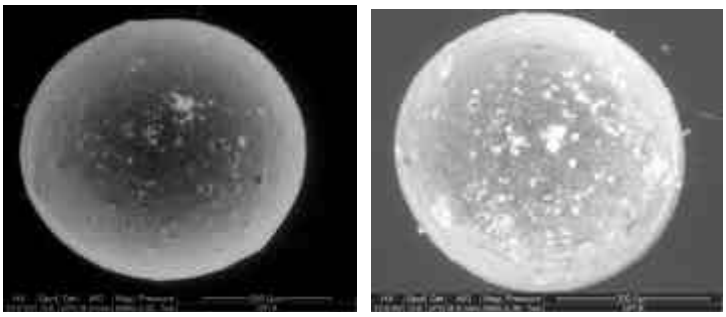

Figure 3: SEM of Batch MS4 (a) before and (b) after *in vitro* drug dissolution

***In vitro* drug release**

The in vitro release of Quetiapine from ethyl cellulose microspheres was biphasic with the initial burst effect, which was varied from 18–52% depending on the drug-to-polymer ratio. The initial burst effect was due to the presence of drug particles on the surface of the microspheres, which was revealed by SEM studies. The initial burst effect may be attributed as a desired effect to ensure initial high plasma concentrations of drug to elicit pharmacological activity (Figure 4).

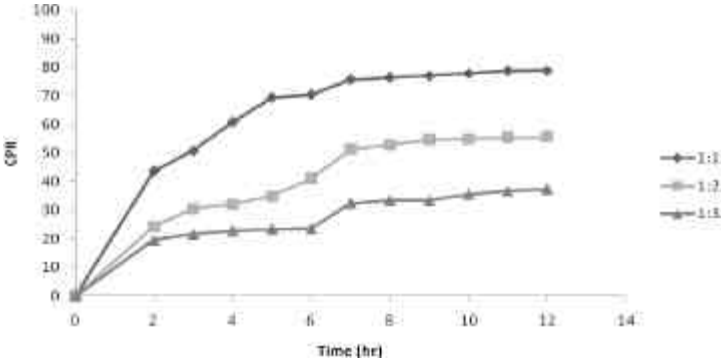

Figure 4: Effect of drug: polymer ratio on *in vitro* drug dissolution

The effect of retardation on the release rate depends on the drug-to-polymer ratio. As the concentration of ethyl cellulose increased with respect to drug concentration, the release rate was decreased which may be attributed to the slower rate of diffusion of dissolution medium into the microspheres due to increased thickness of the polymer matrix. After the total drug release, the microspheres were intact and were collected and observed under a scanning electron microscope for the surface changes occurred after dissolution. The effect of particle size on the drug release was also studied, by using microspheres of different size fractions of 150-180 µm, 180-250 µm and 250-355 µm, as shown in Figure 5. The release profile was in line with the general hypothesis of the effect of the particle size on dissolution. As the particle size decreased, the drug release was fast because of more available surface area.

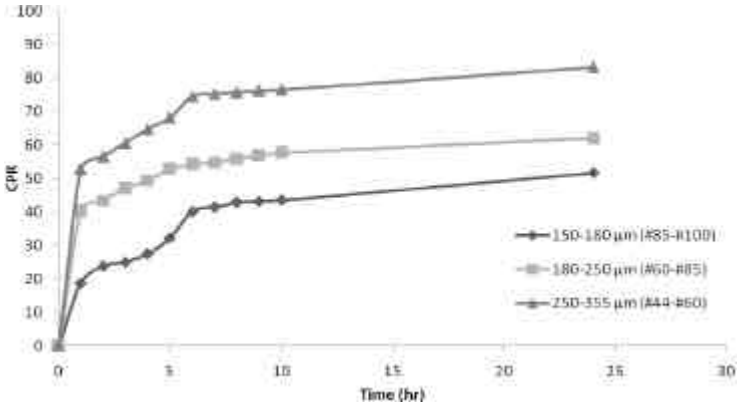

Figure 5: Effect of particle size on *in vitro* drug dissolution

Moreover the dissolution profile of marketed sustained release tablet (Quitin SR 50) was also compared with optimized batch MS4 of microspheres. As seen from Figure 6 both formulations exhibits almost identical release behavior up to 12 hr.

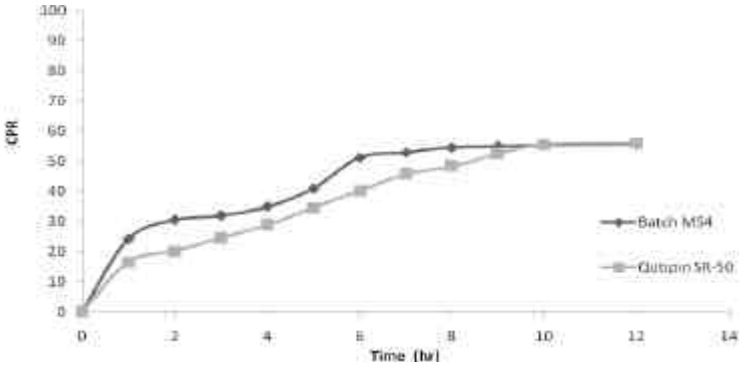

Figure 6: Comparison of *in vitro* dissolution profile of batch MS4 and marketed SR tablet – Quitin SR 50 of quetiapine fumarate

CONCLUSION

It can be concluded from the present investigation that quetiapine fumarate, a highly water soluble drug can be formulated as sustained release microspheres using ethyl cellulose as carrier. Further *in vivo* studies are required in order to analyze the impact of various parameters on behavior of the sustained release formulation inside the oral cavity.

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