**Original Article** 

# Design and development of fast disintegrating film of quetiapine fumarate

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# ABSTRACT

The work is to develop, optimize and characterize the fast disintegrating films of quetiapine fumarate by using various natural and synthetic polymers and co-excipients to improve its absorption and bio-availability. After the selection of polymer and plasticizer concentration, the optimize formulation of fast disintegrating film develop by using 3<sup>2</sup> full factorial design. The preliminary batches of film for polymer selection contains quetiapine fumarate as a drug, Poly Vinyl Alcohol (PVA), Hydroxy propyl methyl cellulose E5 LV (HPMC E5 LV), Pectin in different concentration and PEG 400 as plasticizer with other co-excipients. Other preliminary batches of fast disintegrating film for plasticizer selection contains quetiapine fumarate as a drug, HPMC E5 LV as polymer, and PEG 400 as plasticizer in different concentration with other co-excipients. Each formulation was characterised in terms of morphological study, weight variation, thickness, surface pH, tensile strength, folding endurance, % drug content uniformity, % uniform drug distribution, disintegrating time and % drug release. 3<sup>2</sup> full factorial statistical screening designs was used to statistically optimize the formulation batch and evaluate main effects, interaction effects of independent variables on dependent variables. The factorial batches were evaluated on mainly three dependent variables folding endurance (Y1), in-vitro disintegrating time (Y2) and % drug release (Y3) with other parameters. Preliminary batches were evaluated that shows the HPMC E5 LV 300mg polymer gives the best result for film forming polymer and the PEG 400 1.5ml concentration 3<sup>2</sup> full factorial design results on the basis of the contour plot, 3d surface plot, desirability study and overlay study indicates that the independent variables were strongly effected on dependent variables.

# **1. INTRODUCTION**

The most popular oral solid dosage forms are tablets and capsules. Many patients find it difficult to swallow tablets and capsules particularly pediatric and geriatric patients and do not take their medicines as prescribed. Fast disintegrating films are most advance form of solid dosage form due to its flexibility. It improve efficacy of active pharmaceutical ingredients disintegrate in the short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablets. This delivery system consists of the thin film which is kept on tongue or mucosal tissue, which instantly wet by saliva, the film rapidly disintegrate to release the medication for oral mucosal absorption. Fast disintegrating film is prepared using hydrophilic polymer that rapidly disintegrates on the tongue or buccal cavity, delivering the drug to the systemic circulation via buccal mucosa. The fast disintegrating drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability [1-4]. Quetiapine fumarate is the most recently introduced atypical antipsychotic and is indicated for the management of the manifestations of psychotic disorders and schizophrenia. The peak plasma concentration of quetiapine fumarate is reached within 1.5 hr. The bioavailability of quetiapine fumarate is about 9% and half life is 6 hr and is widely distributed throughout the body. About 83% drug binds to plasma proteins. It is extensively metabolised in liver to the sulfoxide metabolite and parent acid metabolite by sulfoxidation and oxidation, both metabolites are pharmacologically inactive leading to lower

bioavailability, so quetiapine fumarate is selected as model drug for fast disintegrating drug delivery to overcome extensive firstpass metabolism [5-8]. The aim of present study was to develop fast disintegrating quetiapine fumarate film by using various natural and synthetic polymers to enhance bioavailability of drug and quick onset of action.

# 2. MATERIAL AND METHOD

Quetiapine Fumarate was obtained as a gift sample from CTX Life Sciences Pvt. Ltd., Surat Gujarat. Hydroxy propyl methyl cellulose E5 LV (HPMC E5 LV), Polyvinyl Alcohol (PVA) and Pectin were purchased from Unimed Pharma Ltd. Ujeti Gujarat. Remaining all the excipients were of analytical grade and purchased from Chemdyes corporation, Rajkot.

# **Experimental Work**

# Solvent casting method

The oral fast disintegrating films are prepared by dissolving film forming agents (polymers), and plasticizer in the distilled water, then solution is continuous stirred up to 4 hr on magnetic stirrer and kept for swelling over night in distilled water. Mean while, in the separate container remaining excipients like saliva stimulating agent. Sweetening agent, surfactant, flavour and drug are dissolved in mixture of water and ethanol solution with constant stirring for 45 min. When the stirring is over both solutions are mixed together with stirring for another 1 h on magnetic stirrer. Then keep the solution stationary for 1 hr to let the foams settle down. To remove the air bubbles sonicate the solution in sonicator. The resulting formulation is casted and is dried to form a film. The film is preferably air-dried then the film is carefully removed and cut in to  $6^2$  cm size of film [11-13].

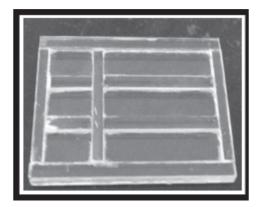


Fig. 1. Mould for casting the films

# Dose calculation of quetiapine fumarate for mould

- > Area of mould is 24 cm<sup>2</sup> (12 cm  $\times$  2 cm).
- Area of film is  $6 \text{ cm}^2$  ( $3 \text{ cm} \times 2 \text{ cm}$ ).
- > Total number of films in each mould 24/6 = 4
- One film contains 25 mg of drug than 4 films containing 100 mg drug
- ≻ So, one mould containing 100 mg drug

# bioavailability, so quetiapine fumarate is selected as model drug *Selection of polymer, its concentration as well as plasticizer and* for fast disintegrating drug delivery to overcome extensive first-*its concentration:*

For selection of various polymers and its concentration various preliminary batches were prepared with following concentration [9]. Four batches were prepared with different concentration of PVA as per Table 1. Four batches were prepared with different concentration of HPMC E5 LV as per Table 2. Four batches were prepared with different concentration of Pectin as per Table 3.

 Table 1. Fast disintegrating films of quetiapine fumarate prepared using PVA polymer

Ingredients	A1	A2	A3	A4
Quetiapine Fumarate	183.98 mg	183.98 mg	183.98 mg	183.98 mg
PVA	100 mg	200 mg	300 mg	400 mg
PEG 400	0.3 ml	0.3 ml	0.3 ml	0.3 ml
Aspartame	40 mg	40 mg	40 mg	40 mg
Citric acid	70 mg	70 mg	70 mg	70 mg
Tween 20	50 mg	50 mg	50 mg	50 mg
Raspberry	50 mg	50 mg	50 mg	50 mg
Distilled water	10 ml	10 ml	1 0ml	10 ml

 
 Table 2. Fast disintegrating films of quetiapine fumarate prepared using HPMC E5 LV polymer

Ingredients	A1	A2	A3	A4
Quetiapine Fumarate	183.98 mg	183.98 mg	183.98 mg	183.98 mg
HPMC E5 LV	100 mg	200 mg	300 mg	400 mg
PEG 400	0.3 ml	0.3 ml	0.3 ml	0.3 ml
Aspartame	40 mg	40 mg	40 mg	40 mg
Citric acid	70 mg	70 mg	70 mg	70 mg
Tween 20	50 mg	50 mg	50 mg	50 mg
Raspberry	50 mg	50 mg	50 mg	50 mg
Distilled water	10 ml	10 ml	10 ml	10 ml

 
 Table 3. Fast disintegrating films of quetiapine fumarate prepared using pectin polymer

Ingredients	C1	C2	C3	C4
Quetiapine Fumarate	183.98 mg	183.98 mg	183.98 mg	183.98 mg
Pectin	100 mg	200 mg	300 mg	400 mg
PEG 400	0.3 ml	0.3 ml	0.3 ml	0.3 ml
Aspartame	40mg	40mg	40mg	40mg
Citric acid	70 mg	70 mg	70 mg	70 mg
Tween 20	50mg	50mg	50mg	50mg
Raspberry	50mg	50mg	50mg	50mg
Distilled water	10ml	10ml	10ml	10ml

For selection of plasticizer the six batches from D1 to D6 were shown in Table 4.

# Optimization of factors for development of fast disintegrating film of quetiapine fumarate by using 3<sup>2</sup> full factorial design:

It is desirable to develop acceptable pharmaceutical formulation in shortest possible time using minimum raw material. It may be difficult to develop an ideal formulation using this technique since the joint effects of independent variables are not considered. It was therefore essential to understand the complexity of pharmaceutical formulation using established statistical tools such as factorial design. In addition to art of formulation, this technique was effective method of indicating the relative significance of a number of variables and their interactions. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The number of experiments required for the studies is dependent on the number of independent variables selected. The response is measure for each trial.

 $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \acute{\epsilon}$ 

Where, Y is the dependent variable. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1 X2) show response changes when two factors are simultaneously changed. A  $3^2$  randomized full factorial design was utilized in present study. In this design the two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The concentration of plasticizer PEG 400 (X1) and the concentration of polymer HPMC E5 LV (X2) were selected as independent variables. The folding endurance (Y1), disintegrating time (Y2) and in-vitro drug release (Y3) were selected as dependent variables. Matrix design of optimization is shown in Tables 5 and 6.

- > 3<sup>2</sup> Full factorial design.
- ▶ 2 factor as Independent variable
  - ✓ Plasticizer (PEG 400)
  - ✓ Polymer (HPMC E5 LV)
- > 3 level (-1, 0, +1)

- Dependant variable
  - ✓ Folding endurance
  - ✓ Disintegrating time
  - ✓ In-vitro drug release
- Check different polymer and plasticizer's concentration effect on film batch.

<b>Table 5.</b> 3 <sup>2</sup>	full Factorial Design Layout for PEG 400 (X1) and	
	HPMC E5 LV $(X_2)$	

Batch no	Independent variables					
	(X <sub>1</sub> )	(X <sub>2</sub> )				
F <sub>1</sub>	-1	-1				
F <sub>2</sub>	0	-1				
F <sub>3</sub>	+1	-1				
$F_4$	-1	0				
F <sub>5</sub>	0	0				
F <sub>6</sub>	+1	0				
F <sub>7</sub>	-1	+1				
F <sub>8</sub>	0	+1				
F9	+1	+1				

 Table 6. Optimization of fast disintegrating films of quetiapine fumarate

	Concentration of independent variable								
Level	Concentration of PEG 400 (ml)	Concentration of HPMC E5 LV (mg)							
- 1	1.0	250							
0	1.5	300							
+1	2.0	350							

# Design and development of fast disintegrating film of quetiapine fumarate by using $3^2$ full factorial design:

Fast disintegrating film containing quetiapine fumarate and polymer HPMC E5 LV was prepared by solvent casting method. The formulation codes and their respective concentrations are given in Table 7. An aqueous solution of polymer HPMC E5 LV

Ingredients	D1	D2	D3	D4	D5	D6
Quetiapine Fumarate	183.98 mg					
HPMC E5 LV	300 mg					
PEG 400	0.6 ml	0.9 ml	1.2 ml	1.5 ml	1.8 ml	2.1 ml
Aspartame	40 mg					
Citric acid	70 mg					
Tween 20	50 mg					
Raspberry	50 mg					
Distilled water	10 ml					

Table 4. Fast disintegrating films of quetiapine fumarate prepared using different concentration of plasticizer

was prepared by dissolving with distilled water in nine separate containers with continuous stirring. These solutions were kept for swelling over night in distilled water. In the other nine separate containers calculated amount of quetiapine fumarate (drug) 183.98mg was dissolved in distilled water with other excipients like saliva stimulating agent, sweetening agent, surfactant, and flavour with constant stirring for 45 min. when the stirring is over both solutions mixed together. In this nine containers polyethylene glycol 400 (PEG 400) as a plasticizer in different concentration were added according the Table 7 concentration. The solutions were kept for another 1 hr stirring on magnetic stirrer, then keep the solution stationary for 1 hr to let the foams settle down. Sonicate the solution for remove the air bubble in sonicator. The resulting formulations were casted and dried to form a film. The films formulated batches F<sub>1</sub>, F<sub>2</sub>, F<sub>3</sub>, F<sub>4</sub>, F<sub>5</sub>, F<sub>6</sub>, F<sub>7</sub>, F<sub>8</sub>, F<sub>9</sub> were preferably air-dried then the films is carefully removed, cut in to 6 cm<sup>2</sup> size of film and evaluated. A 3<sup>2</sup> randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The concentration of PEG 400 (X1) and the concentration of HPMC E5 LV (X2) were selected as independent variables. The folding endurance  $(y_1)$ , disintegrating time  $(y_2)$  and in-vitro drug release  $(y_3)$  were selected as dependent variables [14].

### Evaluation of fast disintegrating films [15-19]

**Morphology Study:** Morphology of the prepared film was observed under a scanning electron microscope (SEM) (Model QUANTA-200 FEI Neitherland). The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at definite magnification.

*Weight Variations:* Weight variation is measured by the individually weighting randomly selected 3 films. The average weight should not differ significantly from weight of the film.

*Thickness:* The thickness of film is determined by micrometer screw gauge at 3 different points of the film.

*Surface pH:* Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min.

*Tensile Strength:* Tensile strength of film is determined by applying the maximum stress to a point till the oral film breaks. It is calculated by the applied load at rupture divided by the cross section area of the oral film.

Tensile strength =  $\frac{\text{Load at break}}{\text{Strip break} \times \text{Strip Width}}$ 

**Folding endurance:** The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately  $3 \times 2$  cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

**Drug content uniformity study of film:** The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 6 cm<sup>2</sup> diameter were cut from three different places from the one Petridish. Each patch was placed in 100 ml volumetric flask and dissolved in 6.8 pH phosphate buffer solution, make the volume up to 100 ml in the volumetric flask and 1 ml is taken and diluted with water up to 10 ml. The absorbance of the solution was measured at 254.76 nm using UV/visible spectrophotometer. The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

*Uniform drug distribution in film:* The films were tested for uniform drug distribution by UV- Spectrophotometric method. Films of 6 cm<sup>2</sup> diameter were cut from three different portions from the single film. Each part of the film was placed in 100 ml volumetric flask and dissolved in 6.8 pH phosphate buffer solution, make the volume up to 100 ml in the volumetric flask and 1 ml is taken and diluted with water up to 10 ml. The absorbance of the solution was measured at 254.76 nm using UV/visible spectrophotometer. The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

*In-vitro disintegration time: In-vitro* disintegration time was determined visually in a glass petridish containing 10ml distilled water. The disintegration time was taken when the film starts to break or disintegrates and also time was noted at which the film disintegrates completely.

*In-vitro Dissolution Study: In-vitro* dissolution of quetiapine fumarate film was studied in USP dissolution test apparatus,

Table 7. The formulation codes and their respective concentrations of fast disintegrating films of quetiapine fumarate

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Q.F (Drug) (mg)	183.98	183.98	183.98	183.98	183.98	183.98	183.98	183.98	183.98
PEG 400 (ml)	1.0	1.5	2.0	1.0	1.5	2.0	1.0	1.5	2.0
HPMC E5 LV (mg)	250	250	250	300	300	300	350	350	350
Aspartame (mg)	40	40	40	40	40	40	40	40	40
Citric acid (mg)	70	70	70	70	70	70	70	70	70
Tween 20 (mg)	50	50	50	50	50	50	50	50	50
Raspberry (mg)	50	50	50	50	50	50	50	50	50
Distilled water (ml)	10	10	10	10	10	10	10	10	10

900 ml 6.8 pH phosphate buffer solutions was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at  $37\pm0.5^{\circ}$ C throughout the experiment. One film was used in each test. Samples of dissolution medium (5 ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 254.76 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.

*Stability Studies:* The selected formulation was packed in ambercolored bottles, which were tightly plugged with cotton and capped. They were then stored at 40°C / 75% RH for 1 month and evaluated for their physical appearance, in vitro disintegrating time, drug content uniformity and drug release study at specified intervals of time [20].

# **3. RESULTS AND DISCUSSION**

The preliminary batches of fast disintegrating films were evaluated by different parameter like morphological study, weight variation, disintegration time, surface pH, folding endurance, thickness, drug content uniformity, % uniform drug distribution and in-vitro drug release study.

Morphology of the prepared films was observed under a scanning electron microscope (SEM). The scanning electron photomicrograph of the films at 1000 X magnification showed that, the prepared film containing quetiapine fumarate with HPMC E5 LV polymer was clear, colourless, smooth surface with some little pores and without any scratches then other formulated batches of film with PVA and pectin polymer.

The various evaluation tests were performed according to the above procedure and results of all the parameters were shown in Table 8.

# **Observation**

So, taking consideration in all the aspects i.e. Weight of films, thickness, surface pH, disintegrating time, folding endurance, % drug content uniformity, % uniform drug distribution, % drug release. The HPMC E5 LV, B<sub>3</sub> formulation was selected as a polymer and its concentration for film.

# *Evaluation of preliminary batches to select the concentration of plasticizer*

The preliminary batches of fast disintegrating films for selection concentration of plasticizer were formulated using HPMC E5 LV as a polymer with different concentration of PEG 400 as a plasticizer. These preliminary batches were evaluated for selection of best plasticizer concentration for fast disintegrating film. These preliminary batches of fast disintegrating films for selection concentration of plasticizer were evaluated by different parameter like morphological study, weight variation, disintegration time, surface pH, folding endurance, thickness, drug content uniformity, % uniform drug distribution and in-vitro drug release study. Results for the same are tabulated in the Table 8.

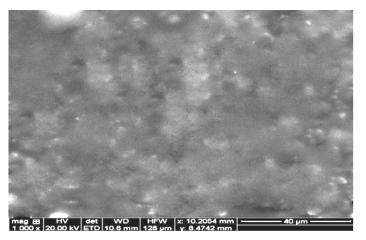


Fig. 2. SEM of film containing quetiapine with PVA polymer

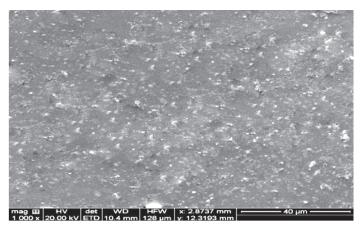


Fig. 3. SEM of film containing quetiapine with HPMC E5 LV polymer

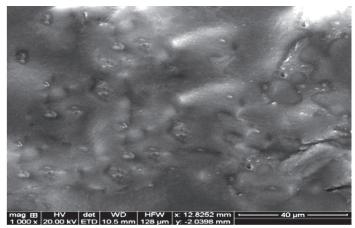


Fig. 4. SEM of film containing quetiapine with PECTIN polymer

### **Observation**

So, taking consideration in all the aspects i.e. Weight uniformity, thickness, surface pH, disintegrating time, folding endurance, % drug content uniformity, % drug release. The  $D_4$  formulation was selected as plasticizer concentration for films.

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Formulation Code	Avg. Weight (mg) ± SD, n = 3	Avg. Thickness (mm) ± SD, n = 3	Avg. Surface pH ± SD, n = 3	Avg. In Vitro Disintegration Time (sec) ± SD, n = 3	Avg. Folding Endurance ± SD, n = 3	Avg. Drug Content uniformity (%) ± SD, n = 3	Avg. uniform Drug Distribution (%) ± SD, n = 3	% Drug release (In 6 min.)
A <sub>1</sub>	86.33 ± 1.527	$0.22 \pm 0.01$	$7.33 \pm 0.577$	46.00 ± 1.527	86 ± 1.732	98.42 ± 0.289	97.42 ± 0.289	92.49
A <sub>2</sub>	$100.66 \pm 0.57$	$0.24 \pm 0.015$	$7.33 \pm 0.577$	$49.00 \pm 2.081$	90 ± 2.00	99.33 ± 0.382	98.53 ± 0.289	94.24
A <sub>3</sub>	$113.00 \pm 1.00$	$0.24\pm0.05$	$6.66\pm0.577$	$55.00 \pm 1.00$	99 ± 1.732	$99.33 \pm 0.289$	$96.33 \pm 0.382$	90.01
$A_4$	$132.33 \pm 1.53$	$0.27\pm0.01$	$6.66 \pm 0.577$	$59.66 \pm 2.081$	75 ± 3.00	$100.7 \pm 0.382$	$94.67 \pm 0.500$	87.04
$B_1$	88.66 ± 1.527	$0.10\pm0.005$	$6.33 \pm 0.577$	$25.66 \pm 1.154$	$135 \pm 2.00$	$99.75 \pm 0.500$	$98.50 \pm 0.289$	94.16
B <sub>2</sub>	$102.33 \pm 0.58$	$0.13 \pm 0.015$	$6.00 \pm 0.00$	$28.00 \pm 2.00$	$149 \pm 1.00$	99.33 ± 0.144	$99.50 \pm 0.144$	96.20
B <sub>3</sub>	$116.66 \pm 0.58$	$0.14 \pm 0.01$	$6.00\pm0.00$	28.33 ± 1.527	161 ± 1.732	$99.92 \pm 0.144$	99.75 ± 0.144	97.12
$B_4$	$134.33 \pm 2.52$	$0.18 \pm 0.057$	$6.33 \pm 0.577$	$36.66 \pm 0.577$	$136 \pm 2.645$	98.5 ± 0.433	$97.25 \pm 0.289$	92.91
C1	$91.00 \pm 2.645$	$0.19 \pm 0.0057$	$6.66 \pm 0.577$	$52.00 \pm 2.00$	$114 \pm 2.00$	$98.67 \pm 0.382$	$96.05 \pm 0.433$	88.35
C <sub>2</sub>	$109.66 \pm 1.53$	$0.20 \pm 0.0057$	$7.00\pm0.00$	58.33 ± 1.15	$126 \pm 1.732$	$99.50 \pm 0.433$	$96.75 \pm 0.500$	90.62
C <sub>3</sub>	$121.67 \pm 1.00$	$0.22 \pm 0.011$	$7.33 \pm 0.577$	$69.00 \pm 1.00$	$102 \pm 1.00$	$103.0 \pm 0.250$	$94.25 \pm 0.834$	89.85
$C_4$	$138.66 \pm 0.58$	$0.23 \pm 0.012$	$7.66 \pm 0.577$	74.33 ± 2.561	71 ± 2.645	97.33 ± 0.382	92.05 ± 2.197	82.92
D1	$116.79 \pm 0.113$	$0.13 \pm 0.0058$	$6.00 \pm 0.00$	$28.67 \pm 0.577$	$193 \pm 3.46$	99.75 ± 0.50	99.25 ± 0.289	98.07
D <sub>2</sub>	$116.99 \pm 0.017$	$0.14 \pm 0.0058$	$6.33 \pm 0.577$	31.33 ± 0.577	232 ± 1.73	98.42 ± 0.29	99.25 ± 0.289	97.98
D3	$117.06 \pm 0.038$	$0.16 \pm 0.0058$	$6.67 \pm 0.577$	34.67 ± 1.155	273 ± 3.46	99.92 ± 0.29	99.25 ± 0.144	97.91
$D_4$	$117.13 \pm 0.012$	$0.17 \pm 0.0058$	$6.67 \pm 0.577$	37.67 ± 0.577	300.67 ± 1.53	99.92 ± 0.14	99.75 ± 0.144	97.87
D <sub>5</sub>	$117.26 \pm 0.021$	$0.19 \pm 0.0058$	$6.33 \pm 0.577$	50.67 ± 1.528	319.67 ± 0.58	$102.7 \pm 1.30$	98.75 ± 0.289	96.17
D <sub>6</sub>	$117.38 \pm 0.010$	0.21 ± 0.010	$6.00 \pm 0.00$	60.33 ± 3.215	328.67 ± 0.58	99.41 ± 0.38	98.50 ± 0.291	92.81

Table 8. Evaluation of fast disintegrating films of quetiapine fumarate

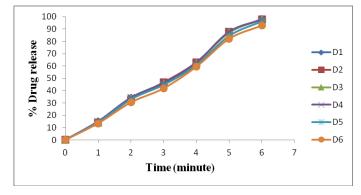


Fig. 5. In-vitro drug release profile of formulations  $D_1$ ,  $D_2$ ,  $D_3$ ,  $D_4$ ,  $D_5$ ,  $D_6$ 

# Design and development of fast disintegrating film of quetiapine fumarate by using 3<sup>2</sup> full factorial design:

 $3^2$  full factorial design has often been applied to optimize the formulation. In this design two factors were evaluated, each at three levels and experimental trials were carried out at all nine possible combinations. The concentration of PEG 400 (X<sub>1</sub>) and the concentration of HPMC E5 LV (X<sub>2</sub>) were selected as independent variables. The folding endurance (Y<sub>1</sub>), disintegrating time (Y<sub>2</sub>) and

 Table 9. Optimization of fast disintegrating films of quetiapine

 fumarate using 3<sup>2</sup> full factorial design

Formulation Code	Avg. Folding Endurance $\pm$ SD, n = 3 (Y <sub>1</sub> )	Avg. Disintegrating time (second) $\pm$ SD, n = 3 (Y <sub>2</sub> )	% Drug release (In 6 min.) (Y <sub>3</sub> )
$F_1$	$168 \pm 1.00$	$24.67 \pm 2.516$	99.14 ± 1.74
F <sub>2</sub>	$201 \pm 2.00$	28.33 ± 1.527	98.76 ± 2.96
F <sub>3</sub>	$249 \pm 2.645$	$32.67 \pm 2.081$	98.02 ± 2.34
F <sub>4</sub>	$263 \pm 1.732$	$34.00 \pm 0.577$	97.99 ± 1.86
F <sub>5</sub>	$300 \pm 1.00$	$37.33 \pm 0.577$	$97.87 \pm 0.96$
F <sub>6</sub>	334 ± 1.732	$43.67 \pm 1.527$	$96.25 \pm 0.58$
F <sub>7</sub>	$349\pm2.00$	$57.00 \pm 1.00$	95.40 ± 3.04
F <sub>8</sub>	374 ± 2.645	$68.07 \pm 1.15$	94.43 ± 2.34
F9	$393 \pm 3.00$	81.33 ± 3.215	93.79 ± 1.86

In-vitro drug release  $(Y_3)$  were selected as dependent variables. The polynomial equations can be used to draw conclusions. Results for experimental design batches are shown in Table 9.

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Time (min)	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	$F_4$	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>	F <sub>8</sub>	F9
0	0	0	0	0	0	0	0	0	0
1	$17.12 \pm 2.96$	$16.13 \pm 2.15$	$16.02 \pm 0.89$	$15.46 \pm 1.65$	$14.78 \pm 1.25$	$14.14 \pm 0.87$	$13.05 \pm 1.48$	$12.47 \pm 1.86$	$11.14 \pm 3.04$
2	35.96 ± 3.05	35.29 ± 2.65	35.14 ± 2.65	34.82 ± 1.99	34.30 ± 1.79	33.90 ± 2.58	$34.02 \pm 2.67$	32.47 ± 1.68	$31.96 \pm 1.73$
3	$49.27 \pm 2.08$	$48.48 \pm 1.96$	48.39 ± 2.48	47.13 ± 2.11	$46.23 \pm 2.43$	$45.32 \pm 2.64$	$44.70 \pm 3.04$	43.94 ± 2.51	$42.74\pm2.64$
4	67.59 ± 2.39	65.96 ± 2.61	65.38 ± 2.91	$63.87 \pm 2.67$	$62.90 \pm 1.95$	61.89 ± 1.78	61.42 ± 1.41	59.92 ± 2.64	$58.25 \pm 2.77$
5	93.06 ± 1.42	91.82 ± 3.05	91.09 ± 2.96	89.68 ± 2.81	87.97 ± 2.64	86.67 ± 1.73	86.10 ± 3.47	84.39 ± 0.58	$82.28 \pm 2.47$
6	99.14 ± 1.74	98.76 ± 2.96	98.02 ± 2.34	97.99 ± 1.86	$97.87 \pm 0.96$	96.25 ± 0.58	95.40 ± 3.04	94.43 ± 2.34	$93.79 \pm 1.86$

Table 10. In-vitro drug release (% drug release) of fast disintegrating films of quetiapine fumarate

\*all results are shown in mean  $\pm$  S.D, n=3.

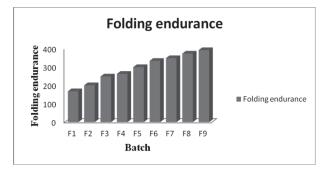


Fig. 6. Folding endurance data of factorial design batches

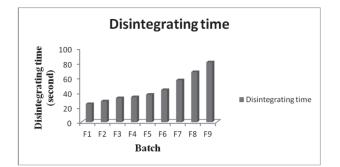


Fig. 7. Disintegrating time data of factorial design batches

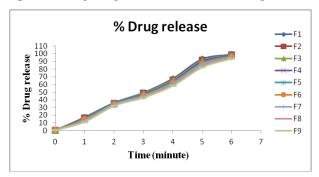


Fig. 8. % Drug release data of factorial design batches

### Response 1: Folding endurance $(Y_1)$

The polynomial equations can be used to draw conclusions after considering magnitude of coefficients and mathematical sign it conveys either positive or negative. For folding endurance  $(Y_1)$  both variables  $X_1$  (concentration of PEG 400) (p= 0.0002) and  $X_2$  (concentration of HPMC E5 LV) (p= <0.0001) were found to be significant as p values were less than 0.05.

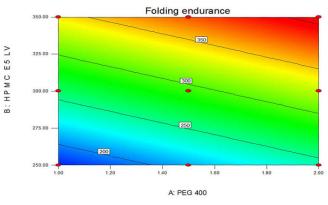
Polynomial equation:

 $\begin{array}{l} Y_1 = 298.33 + 32.67 \; X_1 + 83.00 \; X_2 - 9.25 \; X_1 \; X_2 + 1.00 \; X_1{}^2 \\ - \; 10.00 \; X_2{}^2 \end{array}$ 

Table 11. ANOVA for  $Y_1$ 

	DF*	SS*	MS*	F	p value
Regression	2	47736.67	23868.33	234.26	< 0.0001
Residual	6	611.33	101.89	-	-
Total	8	48348.00	-	-	-

\*DF: degree of freedom, SS: sum of squares, MS: means of squares



**Fig 9.** Contour plot for Y<sub>1</sub> (folding endurance)

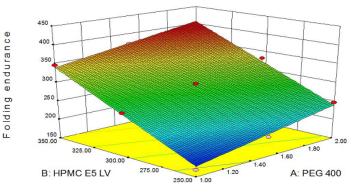


Fig. 10. Surface plot for Y<sub>1</sub> (folding endurance)

The ANOVA results, contour plot and 3d surface plot for the folding endurance showed the strong effect of the two independent variables (concentration of PEG 400, X<sub>1</sub> and concentration of HPMC E5 LV, X<sub>2</sub>). Polynomial equation of the folding endurance indicated that the both amount of plasticizer and polymer have positive effect on folding endurance. Folding endurance of the films was found to increase with increase in the amount of PEG 400 and concentration of HPMC E5 LV. It was observed that folding endurance varies from 168  $\pm$  1.0 to 393  $\pm$  3.0 for all the formulations. Folding endurance of the formulation F<sub>9</sub> was maximum than other formulations. Maximum amount of plasticizer PEG 400 and maximum amount of polymer HPMC E5 LV in F<sub>9</sub> may be the reason for maximum folding endurance.

# Response 2: Disintegrating time (Y<sub>2</sub>)

The polynomial equations can be used to draw conclusions after considering magnitude of coefficients and mathematical sign it conveys either positive or negative. For disintegrating time (Y<sub>2</sub>) both variables  $X_1$  (concentration of PEG 400) (p= 0.0044) and  $X_2$  (concentration of HPMC E5 LV) (p= 0.0002) were found to be significant as p values were less than 0.05.

Polynomial equation:

 $Y_2 = 37.68 + 7.00 X_1 + 20.12 X_2 + 4.08 X_1 X_2 + 0.98 X_1^2 + 10.35 X_2^2$ **Disintegrating time** 350.00 HPMC E5 LV 50 325.00 300.00 B 30 275.00 250.00 1.20 1.40 1.80 1.00 1.60 A: PEG 400

Fig. 11. Contour plot for Y<sub>2</sub> (disintegrating time)

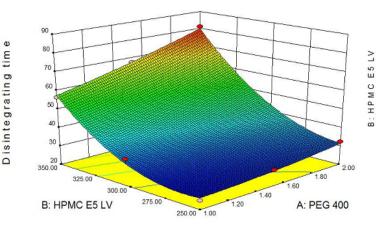


Fig. 12. Surface plot for Y<sub>2</sub> (disintegrating time)

Table	12.	ANOVA	for	$Y_2$
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	DF*	SS*	MS*	F	p value
Regression	5	3005.91	601.18	124.15	0.0011
Residual	3	14.53	4.84	-	-
Total	8	3020.44	-	-	-

\*DF: degree of freedom, SS: sum of squares, MS: means of squares

The ANOVA results, contour plot and 3d surface plot for the disintegrating time showed the strong effect of the two independent variables (concentration of PEG 400, X<sub>1</sub> and concentration of HPMC E5 LV, X<sub>2</sub>). Polynomial equation of the disintegrating time indicated that the both amount of plasticizer and polymer have positive effect on disintegrating time. Disintegrating time of the films was found to increase with increase in the amount of PEG 400 and concentration of HPMC E5 LV. It was observed that disintegrating time varies from 24.67 ± 2.516 to  $81.33 \pm 3.215$  for all the formulations. Disintegrating time of the formulation F<sub>9</sub> was maximum than other formulations. Maximum amount of plasticizer PEG 400 and maximum amount of polymer HPMC E5 LV in F<sub>9</sub> may be the reason for maximum folding endurance.

### Response 3: % Drug release (Y<sub>3</sub>)

The polynomial equations can be used to draw conclusions after considering magnitude of coefficients and mathematical sign it conveys either positive or negative. For % drug release in 6 minute (Y<sub>3</sub>), both variables X<sub>1</sub> (concentration of PEG 400) (p= 0.0147) and X<sub>2</sub> (concentration of HPMC E5 LV) (p= 0.0001) were found to be significant as p values were less than 0.05.

Polynomial equation:

 $Y_3 = 97.54 - 0.75 X_1 - 2.05 X_2 - 0.12 X_1 X_2 - 0.25 X_1^2 - 0.78 X_2^2$ 

	DF	SS	MS	F	p value
Regression	2	28.55	14.27	49.26	0.0002
Residual	6	1.74	0.29	-	-
Total	8	30.28	-	-	-

Table 13. ANOVA for Y<sub>3</sub>

DF: degree of freedom, SS: sum of squares, MS: means of squares

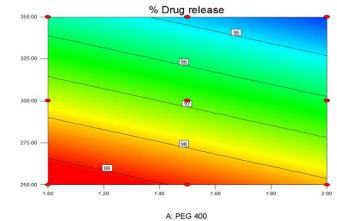


Fig. 13. Contour plot for Y<sub>3</sub> (% drug release in 6 minute)

HPMC

8

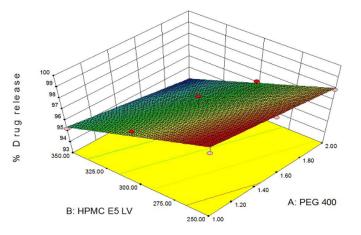


Fig. 14. Surface plot for Y<sub>3</sub> (% drug release in 6 minute)

The ANOVA results, contour plot and 3d surface plot for the % drug release (in 6 minute) showed the strong effect of the two independent variables (concentration of PEG 400,  $X_1$  and concentration of HPMC E5 LV,  $X_2$ ). Polynomial equation of the % drug release indicated that the both amount of plasticizer and polymer have negative effect on % drug release. % drug release of the films was found to decrease with increase in the amount of PEG 400 and concentration of HPMC E5 LV. It was observed that % drug release varies from 99.14 ± 1.74 to 93.79 ± 1.86 for all the formulations. % drug release of the formulation  $F_1$  was maximum than other formulations. Minimum amount of plasticizer PEG 400 and minimum amount of polymer HPMC E5 LV in  $F_1$  may be the reason for maximum % drug release.

Formulation picture presenting factorial experimental design batches of fast disintegrating film of quetiapine fumarate.

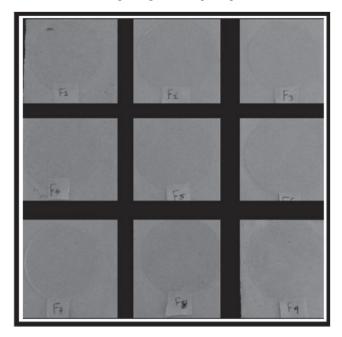
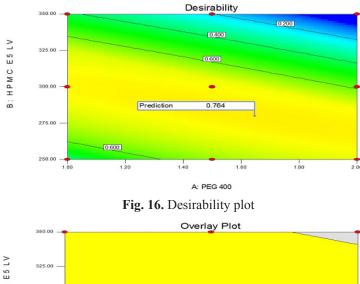


Fig. 15. Factorial experimental design batches F<sub>1</sub> to F<sub>9</sub>

# Evaluation of factorial design batches:



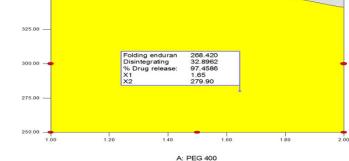


Fig. 17. Overlay plot

Desirability study and overlay study showed that prediction is 0.764 when 1.65 ml PEG 400 plasticizer and 279.90 mg HPMC E5 LV polymer are used.

**Batch Selection:** From desirability study, overlay study and other evaluation of factorial design batches observation, the formulation  $F_5$  was selected as the optimized batch having 1.5 ml PEG 400 plasticizer and 300 mg HPMC E5 LV polymer which gives the best result of folding endurance, drug disintegrating time, % drug release, tensile strength and drug content uniformity.

**Stability studies of optimized batch:** Stability study was done to see the effect of temperature and humidity on fast disintegrating film of quetiapine fumarate. Fast disintegrating film was evaluated periodically (1 months) for appearance, weight variation, thickness, surface pH, folding endurance, disintegrating time, tensile strength, % drug content uniformity, % uniform drug distribution and % drug release. The results of the stability study for the optimized batch is given in Table 15 and 16. Stability studies were carried out at 40°C / 75% RH for the selected for selected for the period of 1 month.

The results in Table 18 and Table 19 clearly prove that after the stability study, formulation F5 doesn't show significant difference for appearance, thickness, surface pH, folding endurance, disintegrating time, tensile strength, % drug content uniformity, % uniform drug distribution and % drug release study. This result indicates that all the excipients used are compatible and stable.

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Formulation Code	Avg. Weight (mg) ± SD, n=3	Avg. Thickness (mm) ± SD, n = 3	Avg. Surface pH ± SD, n = 3	Avg. Tensile strength (N/cm <sup>2</sup> ) ± SD, n = 3	Avg. Drug Content uniformity (%) ± SD, n = 3	Avg. uniform Drug Distribution (%) ± SD, n = 3
F <sub>1</sub>	$109.08 \pm 0.040$	$0.13 \pm 0.0058$	$6.00 \pm 0.00$	$1.231 \pm 0.145$	$98.67 \pm 0.144$	98.75 ± 0.289
F <sub>2</sub>	$109.52 \pm 0.023$	$0.14 \pm 0.0058$	$6.33 \pm 0.577$	$1.584 \pm 0.172$	99.50 ± 0.433	98.75 ± 0.289
F <sub>3</sub>	$109.88 \pm 0.015$	$0.15 \pm 0.0058$	$6.33 \pm 0.577$	$2.057 \pm 0.058$	97.33 ± 0.382	98.50 ± 0.144
F <sub>4</sub>	$117.07 \pm 0.017$	$0.16 \pm 0.00$	$6.67 \pm 0.577$	$2.180 \pm 0.065$	$99.92 \pm 0.289$	99.75 ± 0.289
F <sub>5</sub>	$117.22 \pm 0.012$	$0.17 \pm 0.0058$	$6.67 \pm 0.577$	$2.381 \pm 0.042$	$99.92 \pm 0.144$	99.75 ± 0.144
F <sub>6</sub>	$117.55 \pm 0.025$	$0.17 \pm 0.00$	$7.00 \pm 0.00$	$2.875 \pm 0.058$	$98.67 \pm 0.382$	99.25 ± 0.289
F <sub>7</sub>	$124.32 \pm 0.025$	0.19 ± 0.0058	$6.67 \pm 0.577$	$2.512 \pm 0.316$	$100.0 \pm 0.00$	98.75 ± 0.443
F <sub>8</sub>	$126.05 \pm 0.023$	0.20 ± 0.0058	$7.00 \pm 0.00$	$2.639 \pm 0.307$	98.67 ± 0.382	97.75 ± 0.144
F9	$127.00 \pm 0.030$	$0.21 \pm 0.00$	$7.00 \pm 0.00$	$3.093 \pm 0.177$	$103.0 \pm 0.250$	97.25 ± 0.289

Table 14. Evaluation parameters of factorial design batches

Table 15. Stability data of F5 formulation at accelerated (40±2°C & 75±5% RH) conditions

Initial	After 1 month	
Colorless, Transparant, Smooth surface	Colorless, Transparant, Smooth surface	
$117.22 \pm 0.012 \text{ mg}$	$117.21 \pm 0.025 \text{ mg}$	
$0.17 \pm 0.0058 \text{ mm}$	$0.17 \pm 0.0058 \text{ mm}$	
$6.67 \pm 0.577$	$6.67 \pm 0.577$	
$300 \pm 1.00$	$298 \pm 2.00$	
$37.33 \pm 0.577$ sec.	$36.01 \pm 1.15$ sec.	
$2.381 \pm 0.042 \text{ N/cm}^2$	$2.298 \pm 0.0577 \text{ N/cm}^2$	
99.92 ± 0.144 %	99.90 ± 0.144 %	
99.75 ± 0.144 %	98.99 ± 0.289 %	
	Smooth surface $117.22 \pm 0.012 \text{ mg}$ $0.17 \pm 0.0058 \text{ mm}$ $6.67 \pm 0.577$ $300 \pm 1.00$ $37.33 \pm 0.577 \text{ sec.}$ $2.381 \pm 0.042 \text{ N/cm}^2$ $99.92 \pm 0.144 \%$	

 $<sup>(</sup>n=3, Mean \pm S.D.)$ 

Table 16. In-vitro drug release study of fast disintegrating film of quetiapine fumarate

Time (minute)	Initial	After 1 month
0	0 %	0 %
1	14.78 %	14.54 %
2	34.30 %	34.00 %
3	46.23 %	46.20 %
4	62.90 %	61.89 %
5	87.97 %	87.69 %
6	97.87 %	97.52 %

# 4. CONCLUSION

To select best polymer for the preparation of fast disintegrating film of quetiapine fumarate, various batches of films were prepared by using different concentration of polyvinyl alcohol (PVA), Hydroxypropyl methyl cellulose E5 LV (HPMC E5 LV), and pectin. These fast disintegrating films were evaluated for morphology study, weight variation, thickness, surface pH, tensile strength, folding endurance, % drug content uniformity, % uniform drug distribution and in-vitro drug release study. Among 12 batches of fast disintegrating films of quetiapine fumarate, formulation  $A_3$  - HPMC E5 LV 300mg polymer was selected on the basis of evaluated parameter. To select best plasticizer for the preparation of fast disintegrating film of quetiapine fumarate, various batches of films were prepared by using different concentration of polyethylene glycol 400 (PEG 400). These fast disintegrating films were evaluated for morphology study, weight variation, thickness, surface pH, tensile strength, folding endurance, % drug content uniformity, % uniform drug distribution and in-vitro drug release study. Among 6 batches of fast disintegrating films of quetiapine fumarate, formulation  $D_4$  - HPMC E5 LV 300mg polymer and PEG 4001.5ml plasticizer was selected on the basis of evaluated parameter. The optimized formulation, fast disintegrating film of quetiapine fumarate was successfully prepared using  $3^2$  full factorial design with different combination of  $F_5$  formulation was found to have good folding endurance, disintegrating time, % drug release and other evaluated parameters. The optimized formulation  $F_5$  was found to be stable for 1 month under accelerated stability condition.

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