

## 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 first-pass 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<sup>2</sup> cm size of film [11-13].

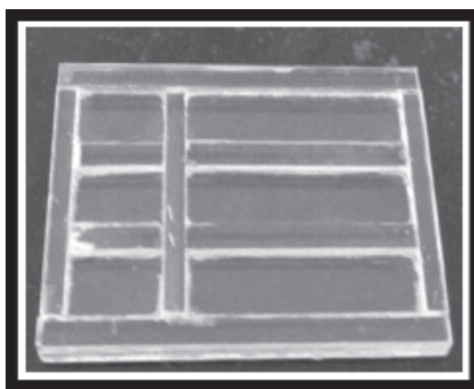


Fig. 1. Mould for casting the films

#### Dose calculation of quetiapine fumarate for mould

- Area of mould is 24 cm<sup>2</sup> (12 cm × 2 cm).
- Area of film is 6 cm<sup>2</sup> (3 cm × 2 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

#### Selection of polymer, its concentration as well as plasticizer and 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	10 ml	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





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  $37 \pm 0.5^\circ\text{C}$  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 amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at  $40^\circ\text{C} / 75\% \text{RH}$  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.

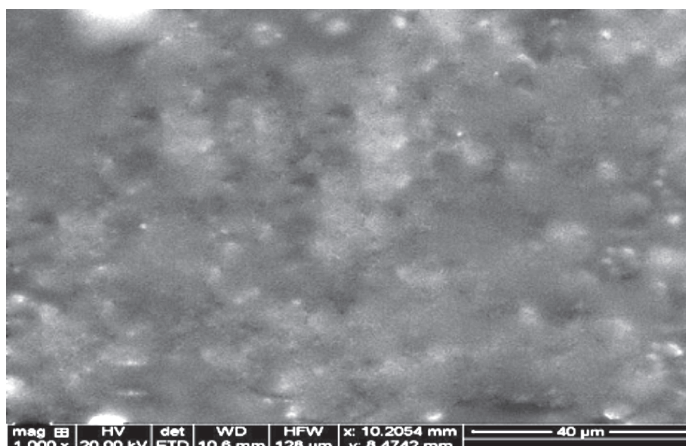


Fig. 2. SEM of film containing quetiapine with PVA polymer

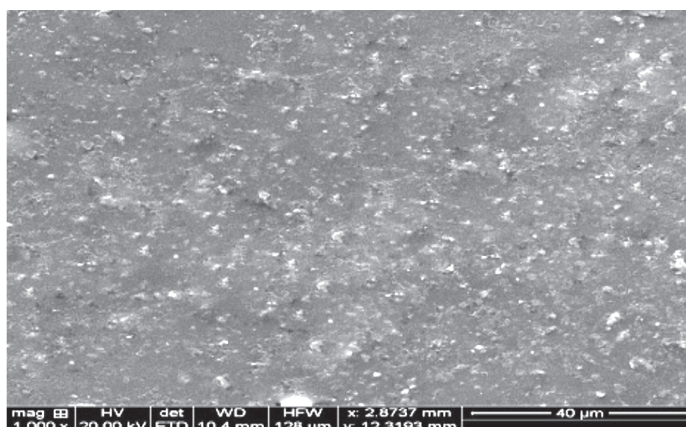


Fig. 3. SEM of film containing quetiapine with HPMC E5 LV polymer

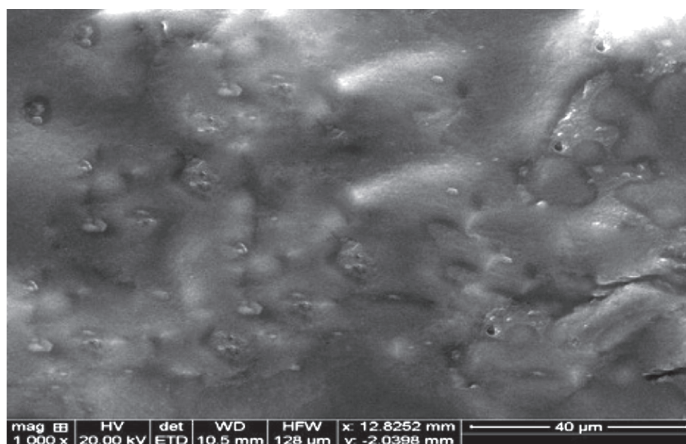


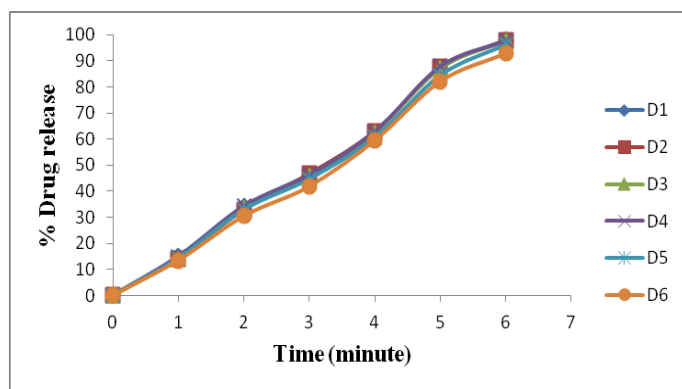
Fig. 4. SEM of film containing quetiapine with PECTIN polymer

#### 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<sub>4</sub> formulation was selected as plasticizer concentration for films.

**Table 8.** Evaluation of fast disintegrating films of quetiapine fumarate

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 ± 0.01	7.33 ± 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 ± 0.57	0.24 ± 0.015	7.33 ± 0.577	49.00 ± 2.081	90 ± 2.00	99.33 ± 0.382	98.53 ± 0.289	94.24
A <sub>3</sub>	113.00 ± 1.00	0.24 ± 0.05	6.66 ± 0.577	55.00 ± 1.00	99 ± 1.732	99.33 ± 0.289	96.33 ± 0.382	90.01
A <sub>4</sub>	132.33 ± 1.53	0.27 ± 0.01	6.66 ± 0.577	59.66 ± 2.081	75 ± 3.00	100.7 ± 0.382	94.67 ± 0.500	87.04
B <sub>1</sub>	88.66 ± 1.527	0.10 ± 0.005	6.33 ± 0.577	25.66 ± 1.154	135 ± 2.00	99.75 ± 0.500	98.50 ± 0.289	94.16
B <sub>2</sub>	102.33 ± 0.58	0.13 ± 0.015	6.00 ± 0.00	28.00 ± 2.00	149 ± 1.00	99.33 ± 0.144	99.50 ± 0.144	96.20
B <sub>3</sub>	116.66 ± 0.58	0.14 ± 0.01	6.00 ± 0.00	28.33 ± 1.527	161 ± 1.732	99.92 ± 0.144	99.75 ± 0.144	97.12
B <sub>4</sub>	134.33 ± 2.52	0.18 ± 0.057	6.33 ± 0.577	36.66 ± 0.577	136 ± 2.645	98.5 ± 0.433	97.25 ± 0.289	92.91
C <sub>1</sub>	91.00 ± 2.645	0.19 ± 0.0057	6.66 ± 0.577	52.00 ± 2.00	114 ± 2.00	98.67 ± 0.382	96.05 ± 0.433	88.35
C <sub>2</sub>	109.66 ± 1.53	0.20 ± 0.0057	7.00 ± 0.00	58.33 ± 1.15	126 ± 1.732	99.50 ± 0.433	96.75 ± 0.500	90.62
C <sub>3</sub>	121.67 ± 1.00	0.22 ± 0.011	7.33 ± 0.577	69.00 ± 1.00	102 ± 1.00	103.0 ± 0.250	94.25 ± 0.834	89.85
C <sub>4</sub>	138.66 ± 0.58	0.23 ± 0.012	7.66 ± 0.577	74.33 ± 2.561	71 ± 2.645	97.33 ± 0.382	92.05 ± 2.197	82.92
D <sub>1</sub>	116.79 ± 0.113	0.13 ± 0.0058	6.00 ± 0.00	28.67 ± 0.577	193 ± 3.46	99.75 ± 0.50	99.25 ± 0.289	98.07
D <sub>2</sub>	116.99 ± 0.017	0.14 ± 0.0058	6.33 ± 0.577	31.33 ± 0.577	232 ± 1.73	98.42 ± 0.29	99.25 ± 0.289	97.98
D <sub>3</sub>	117.06 ± 0.038	0.16 ± 0.0058	6.67 ± 0.577	34.67 ± 1.155	273 ± 3.46	99.92 ± 0.29	99.25 ± 0.144	97.91
D <sub>4</sub>	117.13 ± 0.012	0.17 ± 0.0058	6.67 ± 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 ± 0.021	0.19 ± 0.0058	6.33 ± 0.577	50.67 ± 1.528	319.67 ± 0.58	102.7 ± 1.30	98.75 ± 0.289	96.17
D <sub>6</sub>	117.38 ± 0.010	0.21 ± 0.010	6.00 ± 0.00	60.33 ± 3.215	328.67 ± 0.58	99.41 ± 0.38	98.50 ± 0.291	92.81



**Fig. 5.** In-vitro drug release profile of formulations D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, D<sub>5</sub>, D<sub>6</sub>

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

3<sup>2</sup> 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

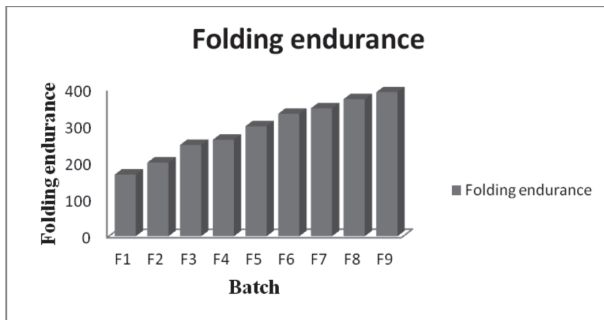
Formulation Code	Avg. Folding Endurance ± SD, n = 3 (Y <sub>1</sub> )	Avg. Disintegrating time (second) ± SD, n = 3 (Y <sub>2</sub> )	% Drug release (In 6 min.) (Y <sub>3</sub> )
F <sub>1</sub>	168 ± 1.00	24.67 ± 2.516	99.14 ± 1.74
F <sub>2</sub>	201 ± 2.00	28.33 ± 1.527	98.76 ± 2.96
F <sub>3</sub>	249 ± 2.645	32.67 ± 2.081	98.02 ± 2.34
F <sub>4</sub>	263 ± 1.732	34.00 ± 0.577	97.99 ± 1.86
F <sub>5</sub>	300 ± 1.00	37.33 ± 0.577	97.87 ± 0.96
F <sub>6</sub>	334 ± 1.732	43.67 ± 1.527	96.25 ± 0.58
F <sub>7</sub>	349 ± 2.00	57.00 ± 1.00	95.40 ± 3.04
F <sub>8</sub>	374 ± 2.645	68.07 ± 1.15	94.43 ± 2.34
F <sub>9</sub>	393 ± 3.00	81.33 ± 3.215	93.79 ± 1.86

In-vitro drug release (Y<sub>3</sub>) were selected as dependent variables. The polynomial equations can be used to draw conclusions. Results for experimental design batches are shown in Table 9.

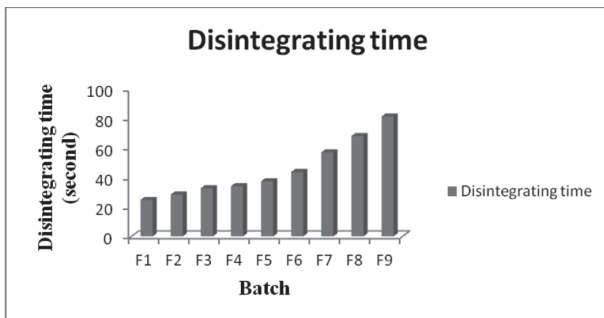
**Table 10.** *In-vitro* drug release (% drug release) of fast disintegrating films of quetiapine fumarate

Time (min)	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>
0	0	0	0	0	0	0	0	0	0
1	17.12 ± 2.96	16.13 ± 2.15	16.02 ± 0.89	15.46 ± 1.65	14.78 ± 1.25	14.14 ± 0.87	13.05 ± 1.48	12.47 ± 1.86	11.14 ± 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 ± 2.67	32.47 ± 1.68	31.96 ± 1.73
3	49.27 ± 2.08	48.48 ± 1.96	48.39 ± 2.48	47.13 ± 2.11	46.23 ± 2.43	45.32 ± 2.64	44.70 ± 3.04	43.94 ± 2.51	42.74 ± 2.64
4	67.59 ± 2.39	65.96 ± 2.61	65.38 ± 2.91	63.87 ± 2.67	62.90 ± 1.95	61.89 ± 1.78	61.42 ± 1.41	59.92 ± 2.64	58.25 ± 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 ± 2.47
6	99.14 ± 1.74	98.76 ± 2.96	98.02 ± 2.34	97.99 ± 1.86	97.87 ± 0.96	96.25 ± 0.58	95.40 ± 3.04	94.43 ± 2.34	93.79 ± 1.86

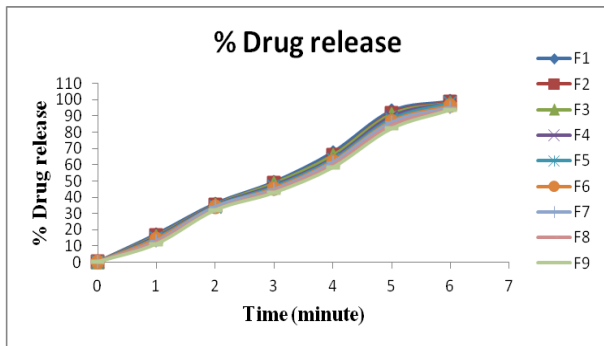
\*all results are shown in mean ± S.D, n=3.



**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<sub>1</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 folding endurance (Y<sub>1</sub>)

both variables X<sub>1</sub> (concentration of PEG 400) (p= 0.0002) 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.

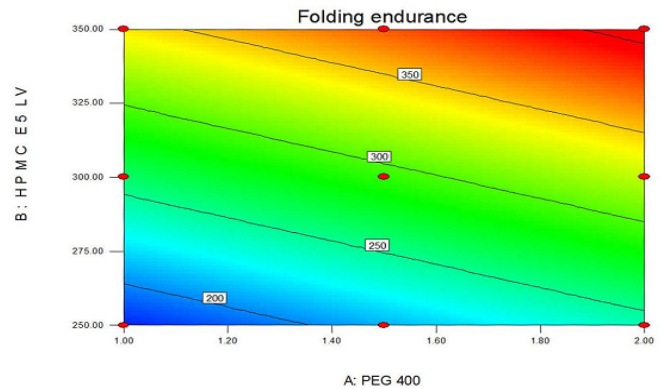
Polynomial equation:

$$Y_1 = 298.33 + 32.67 X_1 + 83.00 X_2 - 9.25 X_1 X_2 + 1.00 X_1^2 - 10.00 X_2^2$$

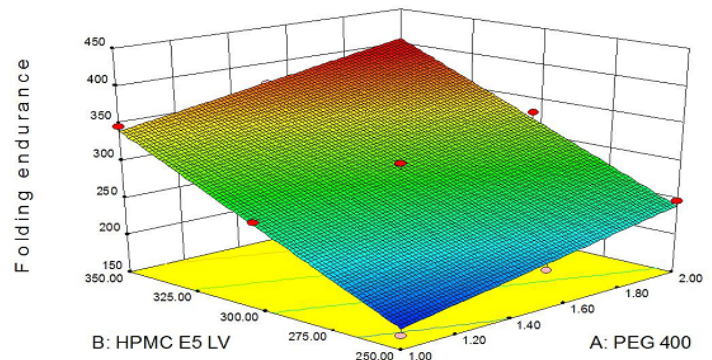
**Table 11.** ANOVA for Y<sub>1</sub>

	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)

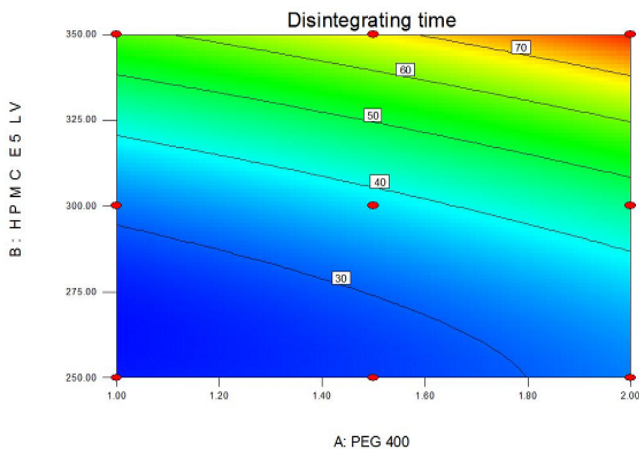
The ANOVA results, contour plot and 3d surface plot for the folding endurance showed the strong effect of the two independent variables (concentration of PEG 400,  $X_1$  and concentration of HPMC E5 LV,  $X_2$ ). Polynomial equation of the folding endurance indicated that the both amount of plasticizer 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  $F_9$  was maximum than other formulations. Maximum amount of plasticizer PEG 400 and maximum amount of polymer HPMC E5 LV in  $F_9$  may be the reason for maximum folding endurance.

**Response 2: Disintegrating time ( $Y_2$ )**

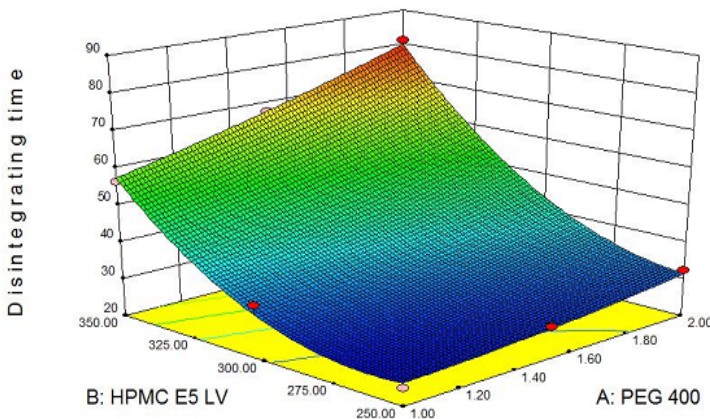
The polynomial equations can be used to draw conclusions after considering magnitude of coefficients and mathematical sign it conveys either positive or negative. For disintegrating time ( $Y_2$ ) both variables  $X_1$  (concentration of PEG 400) ( $p= 0.0044$ ) and  $X_2$  (concentration of HPMC E5 LV) ( $p= 0.0002$ ) were found to be significant as p values were less than 0.05.

Polynomial equation:

$$Y_2 = 37.68 + 7.00 X_1 + 20.12 X_2 + 4.08 X_1 X_2 + 0.98 X_1^2 + 10.35 X_2^2$$



**Fig. 11.** Contour plot for  $Y_2$  (disintegrating time)



**Fig. 12.** Surface plot for  $Y_2$  (disintegrating time)

**Table 12.** ANOVA for  $Y_2$

	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,  $X_1$  and concentration of HPMC E5 LV,  $X_2$ ). 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  $24.67 \pm 2.516$  to  $81.33 \pm 3.215$  for all the formulations. Disintegrating time of the formulation  $F_9$  was maximum than other formulations. Maximum amount of plasticizer PEG 400 and maximum amount of polymer HPMC E5 LV in  $F_9$  may be the reason for maximum folding endurance.

**Response 3: % Drug release ( $Y_3$ )**

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 ( $Y_3$ ), both variables  $X_1$  (concentration of PEG 400) ( $p= 0.0147$ ) and  $X_2$  (concentration of HPMC E5 LV) ( $p= 0.0001$ ) were found to be significant as p values were less than 0.05.

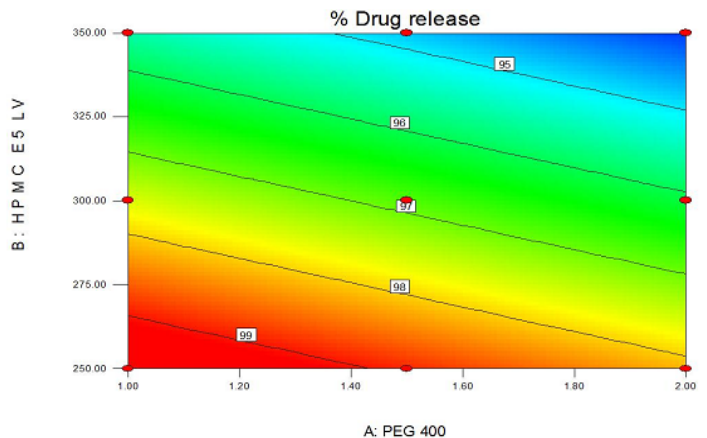
Polynomial equation:

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

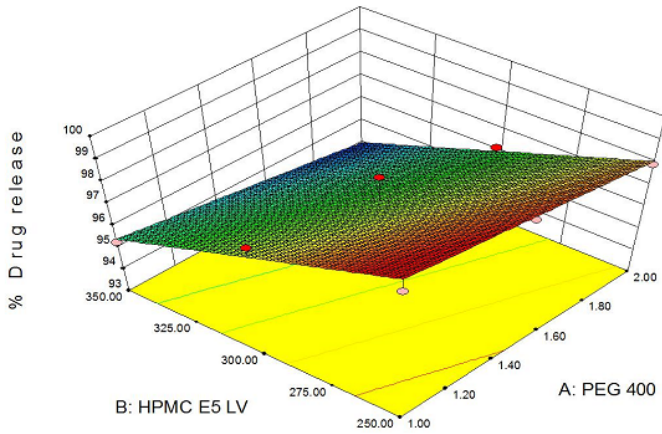
**Table 13.** ANOVA for  $Y_3$

	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	-	-	-

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



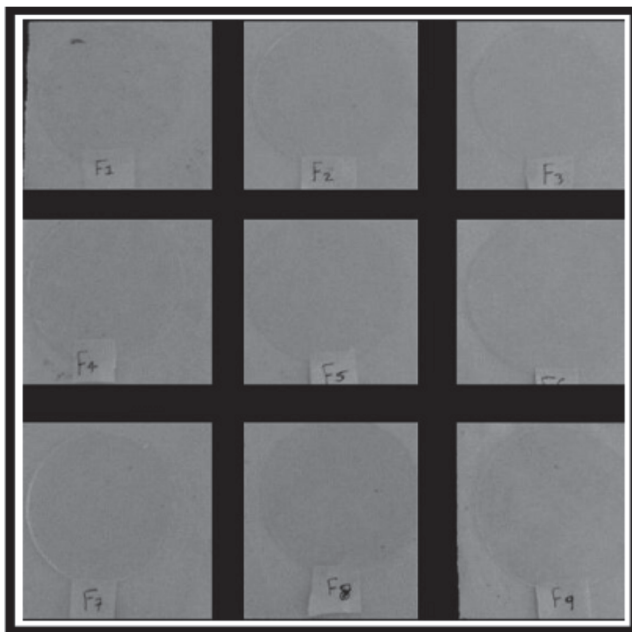
**Fig. 13.** Contour plot for  $Y_3$  (% drug release in 6 minute)



**Fig. 14.** Surface plot for  $Y_3$  (% drug release in 6 minute)

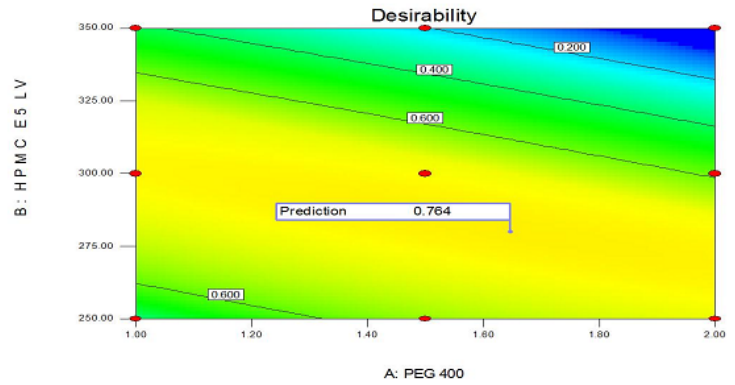
The ANOVA results, contour plot and 3d surface plot for the % drug release (in 6 minute) showed the strong effect of the two independent variables (concentration of PEG 400,  $X_1$  and concentration of HPMC E5 LV,  $X_2$ ). Polynomial equation of the % drug release indicated that the both amount of 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  $99.14 \pm 1.74$  to  $93.79 \pm 1.86$  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.

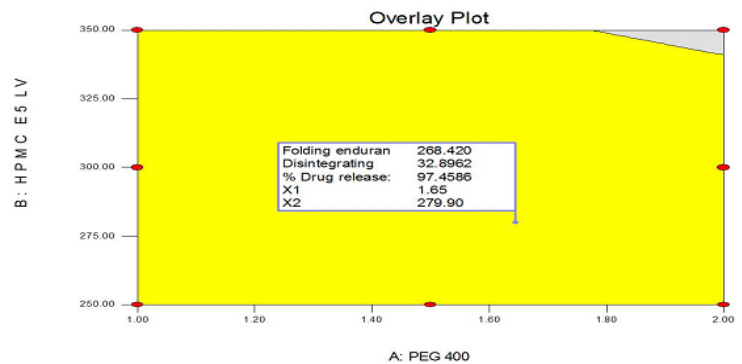


**Fig. 15.** Factorial experimental design batches  $F_1$  to  $F_9$

**Evaluation of factorial design batches:**



**Fig. 16.** Desirability plot



**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  $40^\circ\text{C} / 75\% \text{RH}$  for the selected for selected formulation for the period of 1 month.

The results in Table 18 and Table 19 clearly prove that after the stability study, formulation  $F_5$  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.

**Table 14.** Evaluation parameters of factorial design batches

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 ± 0.040	0.13 ± 0.0058	6.00 ± 0.00	1.231 ± 0.145	98.67 ± 0.144	98.75 ± 0.289
F <sub>2</sub>	109.52 ± 0.023	0.14 ± 0.0058	6.33 ± 0.577	1.584 ± 0.172	99.50 ± 0.433	98.75 ± 0.289
F <sub>3</sub>	109.88 ± 0.015	0.15 ± 0.0058	6.33 ± 0.577	2.057 ± 0.058	97.33 ± 0.382	98.50 ± 0.144
F <sub>4</sub>	117.07 ± 0.017	0.16 ± 0.00	6.67 ± 0.577	2.180 ± 0.065	99.92 ± 0.289	99.75 ± 0.289
F <sub>5</sub>	117.22 ± 0.012	0.17 ± 0.0058	6.67 ± 0.577	2.381 ± 0.042	99.92 ± 0.144	99.75 ± 0.144
F <sub>6</sub>	117.55 ± 0.025	0.17 ± 0.00	7.00 ± 0.00	2.875 ± 0.058	98.67 ± 0.382	99.25 ± 0.289
F <sub>7</sub>	124.32 ± 0.025	0.19 ± 0.0058	6.67 ± 0.577	2.512 ± 0.316	100.0 ± 0.00	98.75 ± 0.443
F <sub>8</sub>	126.05 ± 0.023	0.20 ± 0.0058	7.00 ± 0.00	2.639 ± 0.307	98.67 ± 0.382	97.75 ± 0.144
F <sub>9</sub>	127.00 ± 0.030	0.21 ± 0.00	7.00 ± 0.00	3.093 ± 0.177	103.0 ± 0.250	97.25 ± 0.289

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

	Initial	After 1 month
Appearance	Colorless, Transparent, Smooth surface	Colorless, Transparent, Smooth surface
Weight variation	117.22 ± 0.012 mg	117.21 ± 0.025 mg
Thickness	0.17 ± 0.0058 mm	0.17 ± 0.0058 mm
Surface pH	6.67 ± 0.577	6.67 ± 0.577
Folding endurance	300 ± 1.00	298 ± 2.00
Disintegration time	37.33 ± 0.577 sec.	36.01 ± 1.15 sec.
Tensile strength	2.381 ± 0.042 N/cm <sup>2</sup>	2.298 ± 0.0577 N/cm <sup>2</sup>
% Drug content uniformity	99.92 ± 0.144 %	99.90 ± 0.144 %
% uniform drug distribution	99.75 ± 0.144 %	98.99 ± 0.289 %

(n=3, Mean ± 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<sub>3</sub> - 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<sub>4</sub> - 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<sup>2</sup> full factorial design with different combination of F<sub>5</sub> formulation was found to have good folding endurance, disintegrating time, % drug release and other evaluated parameters. The optimized formulation F<sub>5</sub> was found to be stable for 1 month under accelerated stability condition.

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