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RESEARCH ARTICLE

Development and Evaluation of Fast Dissolving Tablets of Quetiapine Fumarate using 3^2 Full Factorial Design

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ABSTRACT

The purpose of this study was to develop Fast Dissolving Tablets of Quetiapine Fumarate. Quetiapine Fumarate is an atypical anti-psychotic drug, used for depressive episodes, acute manic episodes associated with bipolar I disorder at a short time. Initially the inclusion complex between Quetiapine Fumarate and β-Cyclodextrin (β-CD) was prepared by kneading method. FTIR and DSC of Quetiapine Fumarate and it combination with Excipients shows no change in peak of absorbance and melting point. Fast Dissolving Tablets containing Quetiapine Fumarate were prepared by direct compression method using various superdisintegrants like sodium starch glycolate, croscarmellose sodium and crosspovidone in three different concentrations i.e. 4, 6, 8 mg. A 3^2 full factorial design was applied to systematically optimize the drug disintegration time. The concentration of Croscarmellose Sodium (X_1) and concentration of Crospovidone (X_2) were selected as independent variables. The disintegration time (Y_1), wetting time (Y_2) and %CDR (Y_3) were selected as dependent variables. The prepared tablets were evaluated for hardness, friability, disintegration time, wetting time and *In-vitro* drug release. The results indicated that concentration of croscarmellose Sodium (X_1) and concentration of crosspovidone (X_2) significantly affected the disintegration time (Y_1), wetting time (Y_2) and %CDR (Y_3). Regression analysis and numerical optimization were performed to identify the best formulation. Formulation F10 prepared with Croscarmellose Sodium (5 %) & Crospovidone (5 %) was found to be the best formulation with disintegration time 11 sec, wetting time 14 sec and % drug release in 20 min 99.89%.

KEYWORDS

Fast Dissolving Tablet, β-Cyclodextrin, Quetiapine Fumarate, Inclusion complex, Superdisintegrants, 3^2 Full Factorial Design

INTRODUCTION

An oral route of drug administration is the most popular route of administration. It has wide acceptance up to 50-60% of total dosage forms. Also, solid oral delivery system do not require sterile conditions, and therefore, less expensive to manufacture[1].

Fast dissolving tablets (FDTs) rapidly disintegrate in the mouth without chewing upon oral administration and without the need for water, unlike other drug delivery systems and conventional oral solid immediate-release dosage form[2]. FDT dosage forms, also commonly known as fast melt, quick melts, fast disintegrating and orodispersible systems have the unique property of disintegrating the tablet in the mouth in sec. The desired criteria for the FDT they should Have a pleasing mouth feel, Leave minimal or no residue in the mouth after oral administration and not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of sec[3].

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The goal of antipsychotic drug development efforts over the past 10 years has been to develop agents with increased efficacy and safety and fewer of the side effects commonly associated with the older antipsychotic medications. The newer agents, often called atypical antipsychotics, are effective in treating both the positive and negative symptoms of schizophrenia and are associated with fewer neurological- and endocrine-related side effects compared to the older agents. Quetiapine fumarate is the most recently introduced atypical antipsychotic and is indicated for the management of the manifestations of psychotic disorders and schizophrenia[4].

MATERIALS AND METHOD

Quetiapine Fumarate was obtained from Astron Pharmaceutical Pvt. Ltd. betacyclodextrin was procured from West- Coast Pharmaceutical works Ltd. Crosspovidone, Croscarmellose Sodium and Sodium Starch Glycolate was procured from A.M.K. Chemicals. Avicel Ph 101, Mannitol, Magnesium Stearate and Talc was procured from Chemco Chemical Ltd.

Drug and Excipient Compatibility Study

Drug - Excipients Compatibility Study by FT-IR[5]

The FT-IR spectrum of moisture free powdered sample of 1:1 ratio of Quetiapine Fumarate with excipients was recorded on IR spectrophotometer by potassium bromide (KBr) pellet method between wave number of 4000 cm^{-1} to 500 cm^{-1}.

Preparation of Taste Masked Drug-Inclusion Complex[6]

Amounts of the Quetiapine Fumarate and β-CD to give 1:0.5, 1:1 and 1:2 molar ratios were weighed and thoroughly mixed then triturated by addition of few drops of water in mortar and pestle. The slurries were kneaded for 60 min to get paste, and dried at 40^0C. The dried complex was sieved through 80# and stored in airtight container.

Characterization of Taste Masked Inclusion Complex

Fourier Transform Infrared (FTIR) Spectroscopic Analysis[7]

Quetiapine Fumarate, β-CD and Inclusion complex were subjected for FTIR studies. Samples were prepared using KBr disc method and spectra were recorded over the range 4000 cm^{-1} to 500 cm^{-1}. Spectra were analyzed for drug- β-CD interactions and functional groups involved in the complexation process.

Differential Scanning Calorimetry (DSC) Analysis

DSC scans of the powdered samples of drug, β-CD, and kneaded complex were recorded using DSC instrument. The thermal traces were obtained by heating the complex from 40 to 350°C at heating rate of 10 °C under inert nitrogen dynamic atmosphere (100 ml/min) in open aluminum crucibles.

Gustatory Evaluation of Quetiapine Fumarate-β-CD Complex[8]

Each eight healthy human volunteer was given weighed amount of Quetiapine Fumarate-β-CD Complex equivalent to 5mg of Quetiapine Fumarate. Before testing, the volunteers were asked to retain the reference solutions in their mouths for 10sec., and the taste perceived by each volunteer was noted.

In Vitro Taste Evaluation Study[9]

An accurately weighed (8 mg drug equivalent) complex and 10 ml of pH 6.8 phosphate buffer (0.1 M) was taken in series of volumetric flask and stirred at 50 rpm. The stirring was stopped at different time intervals such as 0, 10, 30, 60, and 120 s, dispersion was filtered, and the concentration of quetiapine fumarate in filtered complex was determined. Time for complex to achieve drug concentration corresponding to threshold bitterness in 10 mL phosphate buffer is recorded.

Preparation of Fast Dissolving Tablets by Direct Compression Technique

Tablet containing 50 mg of quetiapine fumarate was prepared by direct compression method. Drug β-cyclodextrin complex equivalent to 50 mg was taken and pass through the #20. According to the formula, all the ingredients (without magnesium stearate and Talc) were passed through #40 mesh separately. Required quantity of each excipient was weighed accurately and blend was mixed thoroughly. Lubricants i.e. Talc and magnesium stearate were passed through 80# and mixed them to above blend. Powder blend was compressed using 4 mm punch on rotary tablet machine. Then the compressed tablets were evaluated for tablet evaluation tests such as weight variation, hardness, friability, thickness, disintegration time, wetting time, % drug content and *In-vitro* dissolution study.

Evaluation Parameter of Quetiapine Fumarate Fast Dissolving Tablets

Uniformity of Weight

Weigh individually 20 units selected at random or, for single dose preparations in individual containers, the contents of 20 units, and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage.

Hardness[15]

Tablet hardness has been defined as "the force required to break a tablet in a diametric compression test". To perform this test, the tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Hardness of tablet was determined by using a Monsanto tablet hardness tester (Cadmach Machinery Co, Ahmedabad, India).

Friability[15]

Friability of ten tablets from each formulation was determined using the Roche friabilator (Campbell Electronics, Mumbai, India). This device subjects a no of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed.

Table 1: Composition of FDTs of Quetiapine Fumarate

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Quetiapine Fumarate-βCD Complex	148.13	148.13	148.13	148.13	148.13	148.13	148.13	148.13	148.13
Crospovidone	6.6	6.6	6.6	8.8	8.8	8.8	11	11	11
Croscarmellose sodium	6.6	8.8	11	6.6	8.8	11	6.6	8.8	11
Mannitol	60	60	60	60	60	60	60	60	60
Aspartame	6	6	6	6	6	6	6	6	6
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	5	5	5	5	5	5	5	5	5
Avicel PH 101 (MCC)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total Weight (mg/tablet)	310	310	310	310	310	310	310	310	310

(All quantities are expressed in mg)

Friability = $[(W_1-W_2)100]/W_1$

Where, W_1= Weight of tablet before test

W_2 = Weight of tablet after test

Table 2: IP limits for Weight Variation

Average Weight of Tablet	Percentage Deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 or more	5

Disintegration Test[10]

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using water maintained at 37±1ºC as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the water maintained at 37±1ºC. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Wetting Time[11]

A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper & the time required for complete wetting was measured.

Content Uniformity[12]

Six tablets from each formulation were taken randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100ml volumetric flask, containing 0.1 N HCl and mixed thoroughly for few minutes and the volume was made up to 100ml with 0.1 N HCl. The solution was filtered through whatman filter paper and suitably diluted with the same medium and the drug content was estimated from the standard plot by measuring the absorbance at 290 nm using UV-Visible spectrophotometer.

In-vitro Drug Release Study[13]

Dissolution medium: 900 ml of 0.1 N HCl
Temperature: 37 ± 0.5°C
RPM: 50 rpm
Time: 30 min.
Apparatus: USP type II (paddle)

5ml sample aliquots were withdrawn at regular time intervals and were replaced immediately with same volume of fresh buffer medium. Aliquots, following suitable dilutions were assayed spectrophotometrically at λmax 290 nm.

Stability Study[14]

Stability studies of the optimized formulation was carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 25 ± 2°C/ 60 ± 5 % RH and 40 ± 2°C/ 75 ± 5 % RH for time period of 4 weeks.

RESULTS AND DISCUSSION

Drug - Excipients Compatibility Study by FT-IR

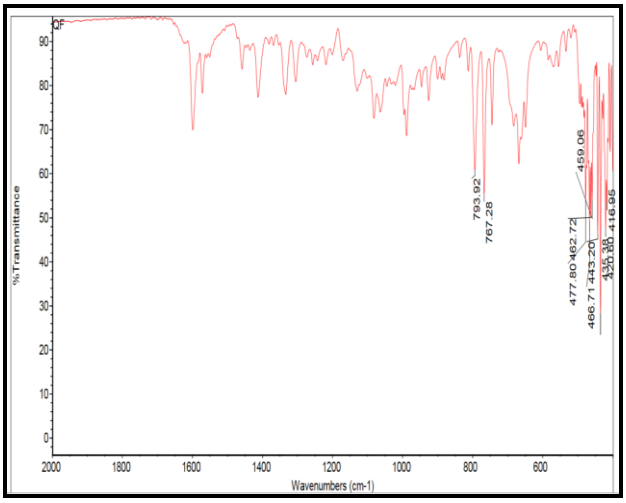

Figure 1: FT-IR Spectra of Quetiapine Fumarate

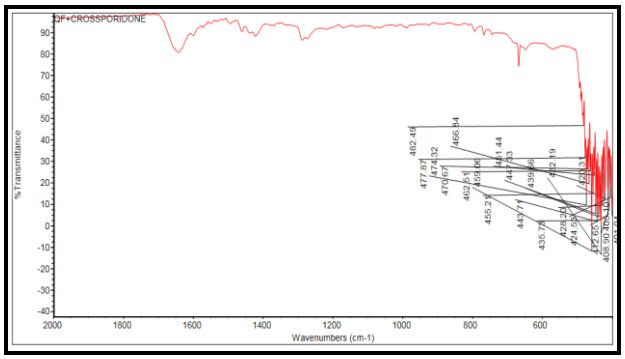

Figure 2: FT-IR Spectra of Drug and Crospovidone mixture

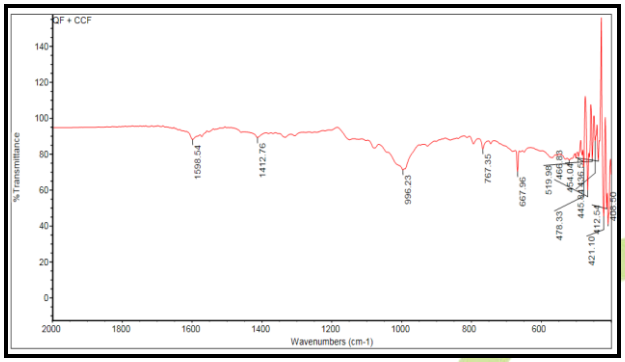

Figure 3: FT-IR Spectra of Drug and Crosscarmellose Sodium mixture

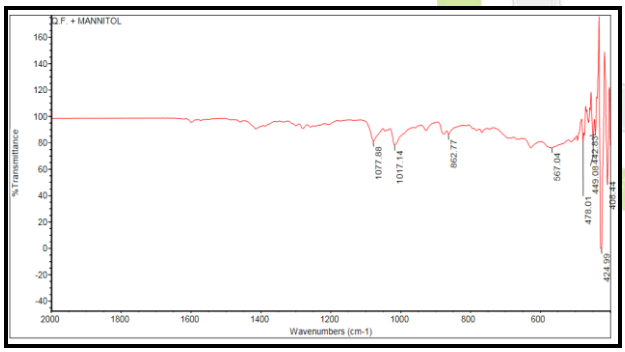

Figure 4: FT-IR Spectra of Drug and Mannitol mixture

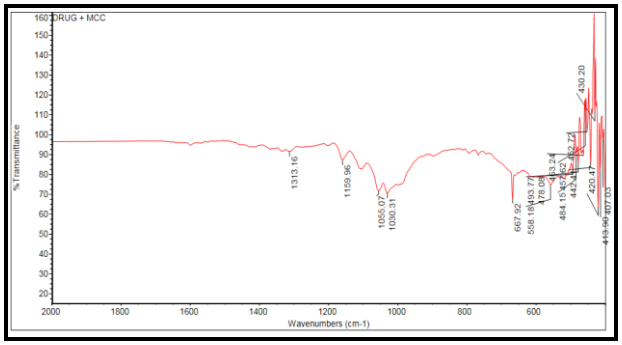

Figure 5: FT-IR Spectra of Drug and Avicel pH 101 mixture

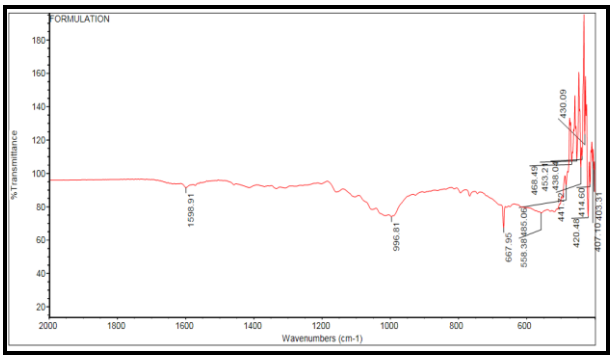

Figure 6: FT-IR Spectra of Mixture of Drug and other excipients

Table 3: Interpretation of Quetiapine Fumarate by FTIR

Observed Peaks	Interpretation
1340 cm^{-1}	-C-H bending
3750 cm^{-1}	-O-H Stretching
3080 cm^{-1}	Ar-H Stretching
2880 cm^{-1}	-C-H Stretch
1600 cm^{-1}	-C-N Stretch
2380 cm^{-1}	-C=C Stretch

Characterization of Taste Masked Inclusion Complex

Characterization of Complex by FT-IR Study

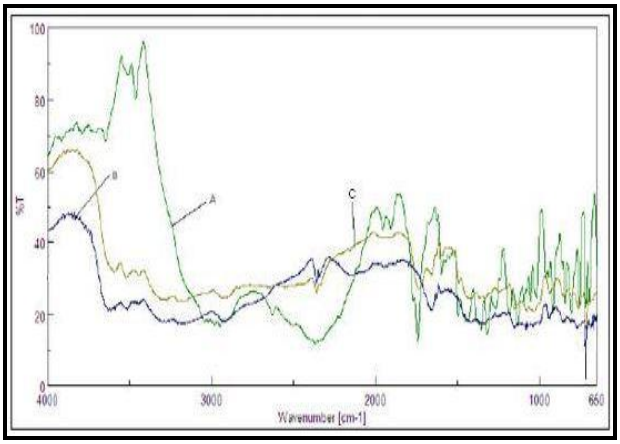

Figure 7: FT-IR Spectra of (A) Quetiapine Fumarate (B) β-Cyclodextrin (C) Drug-β CD Complex

Characterization of Complex by DSC Study

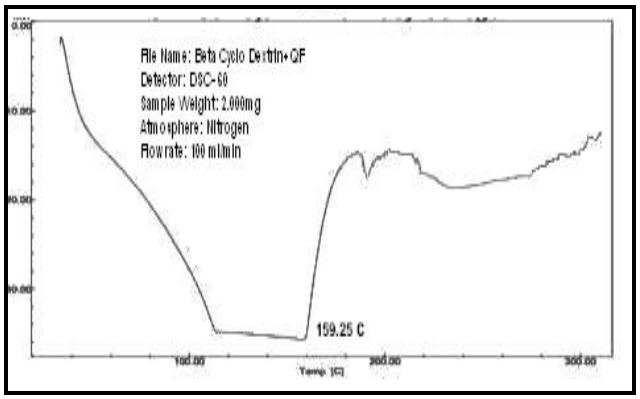

Figure 8: DSC Thermogram of Complex

No intense peak over the melting range of Quetiapine Fumarate was found in the DSC thermogram of inclusion complex, which clearly indicates that the drug was completely embedded in β-CD cavity and confirmation of complexation.

Gustatory Evaluation of Quetiapine Fumarate β- Cyclodextrin Complex

The volunteers did not report any bitterness for DRC throughout the study. Taste evaluation in volunteers confirmed that the taste of Quetiapine Fumarate was masked by complexing with β- Cyclodextrin. The majority of the volunteers found the DRC to be tasteless and agreeable.

Table 5: Scale of bitterness value

Scale	Bitterness Value
0	Tasteless
1	Very Slightly bitter
2	Slightly bitter
3	Slightly to moderately bitter

In-Vitro Evaluation of Bitter Taste

Table 6: Time for attainment of threshold bitterness concentration *in vitro* (n = 5)

Stirring Time (sec)	Concentration (µg/ml)
0	1.12 ± 0.42
5	1.35 ± 0.21
10	1.58 ± 0.36
30	1.97 ± 0.25
60	3.14 ±0.74
120	5.48 ± 0.32

Table 4: Bitterness Evaluation of DRC by Panel of 8 Volunteers

Volunteer No.	Bitterness Level after					
1	0 sec.	5 sec.	10 sec.	15 sec.	20 sec.	30 sec.
2	2	1	0	0	1	0
3	1	0	1	1	0	0
4	0	2	0	0	0	0
5	0	0	0	0	0	0
6	1	1	0	1	0	0
7	2	0	0	0	1	0
8	1	0	1	0	0	0

The time for this threshold bitterness concentration to be achieved in buffer of salivary pH showed that the drug is not released in saliva to attain threshold bitterness concentrations thereby masking the bitter taste satisfactorily.

Evaluation Factorial Design Batches

In a full factorial design, all the factors are studied in all the possible combinations, as it is considered to be most efficient in estimating the influence of individual variables (main effects) and their interactions, using minimum experimentation. Hence, 3^2 Factorial design (FD), was chosen for the current formulation optimization study.

Pre Compression Evaluation of Batches F1 to F9

The powder blend for all nine formulations were evaluated for bulk density which ranged from 0.53 to 0.59 g/ml, tapped density which ranged from 0.65 to 0.78 g/ml, Carr's index ranged from 18.93 to 25.14%, Hausner's ratio ranged from 1.22 to 1.35 and angle of repose ranged from 27.15 to 32.45.

All these results had indicated that, the power blend possess good flow ability and compressibility properties.

Hence, tablets were prepared using direct compression method.

Table 7: Pre compression Evaluation of Batches F1 to F9

Batch	Angle of repose (^{0})	bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's Index (%)
F1	29.22±0.90	0.55±0.032	0.74±0.025	1.34±0.012	23.60±0.542
F2	30.15±0.43	0.58±0.025	0.78±0.036	1.35±0.007	25.14±0.538
F3	32.45±0.07	0.59±0.031	0.77±0.022	1.34±0.002	23.64±0.258
F4	30.57±0.52	0.54±0.011	0.75±0.001	1.32±0.002	20.14±0.768
F5	27.15±0.16	0.58±0.019	0.72±0.001	1.28±0.021	21.25±0.125
F6	29.03±0.43	0.53±0.025	0.68±0.022	1.25±0.011	20.38±0.228
F7	28.55±0.23	0.55±0.036	0.69±0.024	1.31±0.009	21.22±0.981
F8	31.44±0.07	0.58±0.047	0.68±0.005	1.19±0.007	20.45±0.326
F9	28.32±0.68	0.54±0.016	0.65±0.015	1.22±0.025	18.93±0.112

All values are expressed as mean ± Standard Deviation, n=3.

Post Compression Evaluation of Batches F1 to F9

Table 8: Post Compression Evaluation of Batches F1 to F9

Test	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation (n=20)	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**
%Drug content (n=3)	95.45± 1.3	96.7±2 .47	97.5±1 .35	96.4±1 .05	96.62± 1.66	96.08± 1.35	97.2± 1.06	98.4±1.1 5	98.8±1 .56
Friability (%) (n=6)	0.26±0. 02	0.72±0 .01	0.86±0 .01	0.57±0 .025	0.42±0 .035	0.93±0 .029	0.54± 0.011	0.37±0.0 28	0.49±0 .025
Hardness (Kg/cm^2) (n=3)	4.2± 0.2	4.3± 0.15	4.1± 0.50	4.5± 0.25	4.2± 0.51	4.1± 0.2	4.0± 0.42	4.3± 0.20	4.0± 0.3
Disintegration time *(Sec) (n=3)	21.3±0. 57	19.7±0 .57	18.3±1 .15	20.3±1 .05	19.2±0 .35	17.3±0 .55	14.7± 1.52	13.2±0.5 7	11.5±0 .55
Wetting time *(sec) (n=3)	23.3±0. 20	20.8±0 .52	19.1±0 .55	22.4±0 .53	20.5±0 .15	18.5±0 .57	16.3± 0.52	15.6±0.5 7	14.5±0 .57

All the batches were evaluated for various physical parameters before proceeding further. Table 4 includes the values (mean ± SD) of weight variation, hardness, friability, disintegration time, wetting time, % drug content of 9 batches prepared using different combinations of functional excipients. All the batches passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. Hardness of tablets was in range between 4.0 ± 0.3 to 4.5 ± 0.25 kg/cm^2. Friability was in range between 0.26 ± 0.02 to 0.86 ± 0.01 %. Disintegration Time was in the range between 11.5 ± 0.55 to 21.3 ± 0.57. Wetting time was in the range between 14.5 ± 0.57 to 23.3 ± 0.20. Thus, all the physical parameters of the manually compressed tablets were quite within control. Friability values were less than 1% in all cases shows good mechanical strength at the time of handling and transports.

In vitro Drug Release Study of Batches F1 to F9

Table 9: Cumulative % Drug Release of Batches F1 to F9

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	68.5 ± 1.25	58.56 ± 2.05	70.2 ± 2.12	49.2 ± 1.25	59.2 ± 2.12	69.4 ± 2.31	60.6 ± 2.87	75.29 ± 2.14	82.02 ± 1.65
2	75.2 ± 2.59	72.63 ± 2.35	79.7 ± 2.35	62.4 ± 2.69	67.6 ± 1.96	82.7 ± 1.44	68.4 ± 1.12	82.23 ± 2.31	88.55 ± 2.33
4	81.4 ± 2.63	78.23 ± 1.32	86.8 ± 3.15	85.6 ± 2.56	91.3 ± 2.58	94.9 ± 2.75	77.4 ± 2.81	89.12 ± 1.25	91.23 ± 2.54
6	85.2 ± 2.74	83.23 ± 2.95	92.3 ± 2.41	89.4 ± 2.14	92.3 ± 3.21	95.7 ± 2.47	86.5 ± 1.25	94.56 ± 2.48	94.56 ± 1.98
8	88.6 ± 3.45	87.58 ± 3.24	94.6 ± 2.50	91.9 ± 3.11	94.1 ± 2.20	96.3 ± 2.03	90.5 ± 2.34	95.23 ± 1.85	96.12 ± 1.67
10	90.5 ± 2.98	91.56 ± 2.17	95.3 ± 2.69	92.2 ± 2.87	95.1 ± 2.96	96.9 ± 2.49	93.7 ± 2.86	96.54 ± 2.37	98.25 ± 2.55
12	91.4 ± 2.71	93.02 ± 2.85	96.3± 3.16	93.8 ± 2.10	95.2 ± 3.31	97.1 ± 1.32	95.5 ± 2.54	97.2 ± 2.96	98.82± 2.34
14	92.4 ± 2.11	94.32 ± 3.14	96.9 ± 2.85	94.1 ± 3.16	95.4 ± 2.49	97.4 ± 2.55	96.1 ± 2.65	97.8 ± 3.11	99.12 ± 2.41
16	92.9 ± 2.47	95.3 ± 2.65	97.2 ± 2.71	94.4 ± 2.45	96.6 ± 3.09	97.8 ± 3071	96.6 ± 2.12	98.2 ± 2.17	99.65 ± 3.09
20	93.2 ± 3.02	95.6 ± 2.31	97.5 ± 2.69	94.3 ± 3.01	96.4 ± 2.66	98.1 ± 2.65	96.8 ± 3.14	98.5 ± 2.45	99.89 ± 3.22

All values are expressed as mean ± Standard Deviation, n=3

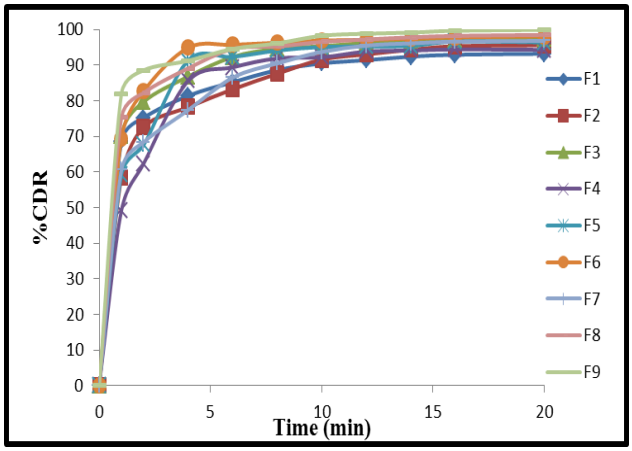

Figure 9: Cumulative % Drug Release of Batches F1 to F9

The comparative % cumulative drug release study of F1 to F9 batches were shown in Figure 8 to 10. From above all nine batches, F9 batch prepared with CP 5% and CCS 5% which contain highest % drug release 99.89%. From graph it was concluded that as the concentration of superdisintegrant increases, % drug release was also increased. Combination of two disintegrates also improves dissolution rate as compared to individual superdisintegrant.

Statistical Analysis

The experimental runs with independent variables and corresponding responses for the 9

formulations are represented. The dependent variable was disintegration time (Y_1), Wetting time (Y_2), and %CDR (Y_3). Based on the 3^2 factorial design, the factor combinations resulted in different concentration of superdisintegrants.

DOE Analysis and Model Selection

Various models, such as linear, 2FI, quadratic and cubic, were fitted to the data for dependent response simultaneously using Design Expert software.

These three responses are suggested to be analyzed using quadratic model. since all the criteria of closest adjusted R-squared and predicted R-squared value lowest PRESS value and significant p-value are satisfied.

Evaluation of Response by Analysis of Variance (ANOVA)

ANOVA was carried out for design batches using the response (Y_1, Y_2 and Y_3) and independent variable (X_1 and X_2).

Table 10: Results of Effect of Independent Variables on Responses

Batch Code	Independent Variables		Dependent Variables		
	X_1	X_2	Y_1	Y_2	Y_3
F1	3	3	21.3	23.3	93.2
F2	4	3	19.7	20.8	95.6
F3	5	3	18.3	19.1	97.5
F4	3	4	20.3	22.4	94.3
F5	4	4	19.2	20.5	96.4
F6	5	4	17.3	18.5	98.1
F7	3	5	14.7	16.3	96.8
F8	4	5	13.2	15.6	98.5
F9	5	5	11.5	14.5	99.8
X_1 = Conc. of Crosscarmellose Sodium (%) X_2 = Conc. of Crospovidone (%)			Y_1 = Disintegration Time (sec) Y_2 = Wetting Time (sec) Y_3 = %CDR (%)		

Table 11: DOE Analysis and Selection of Model

Model Type	Y1				Y2				Y3				Remark
	P-value	Adj. R^2	Predicted R^2	Press	P-value	Adj. R^2	Predicted R^2	Press	P-value	Adj. R^2	Predicted R^2	Press	
Linear	0.0024	0.8204	0.7284	25.14	0.0036	0.7948	0.6622	25.30	0.0001	0.9511	0.9143	3.03	-
2FI	0.9519	0.7847	0.5071	45.63	0.4367	0.7846	0.5161	36.25	0.2193	0.9579	0.9287	2.52	-
Quadratic	0.0006	0.9975	0.9921	0.73	0.0079	0.9858	0.9355	4.83	0.0006	0.9995	0.9977	0.081	Suggested
Cubic	0.9001	0.9939	0.8600	12.96	0.1581	0.9989	0.9757	1.82	0.0204	1.0000	1.0000	5.06	Aliased

Table 12: ANOVA for Response Surface Quadratic Model for Y_1

Source	Sum of Square	DF	Mean Square	F Value	P Value Prob > F
Model	92.49	5	18.50	632.19	0.0001
X_1	14.11	1	14.11	482.13	0.0002
X_2	66.00	1	66.00	2255.75	0.0001
X_1X_2	0.010	1	0.010	0.34	0.5999
X_1^2	0.036	1	0.036	1.22	0.3508
X_2^2	12.33	1	12.33	421.54	0.0003
Residual	0.088	3	0.029		
Cor Total	92.58	8	-	-	-

Table 13: Summary of Response Y_1

Std. Dev.	0.17	**R-Squared**	0.9991
Mean	17.28	**Adj R-Squared**	0.9975
C.V.%	0.99	**Pred R-Squared**	0.9921
PRESS	0.73	**Adeq Precision**	69.452

The Model F-value of 632.19 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_1, X_2, $X_2$2 are significant model terms.

Summary of response Y_1 is given in Table 13. The "Pred R-Squared" of 0.9921 is in reasonable agreement the "Adj R-Squared of 0.9975. "Adeq Precision" measures the signal to noise ratio. The ratio of 69.452 indicates an adequate signal. This model can be used to navigate the design space.

The equation generated from the coefficient of the estimates in terms of coded factors is:

$$Y1= 19.02 - 1.53\ X_1 - 3.32\ X_2 - 0.050\ X_1X_2 - 0.13\ X_1^2 - 2.48\ X_2^2$$

Response Surface Plots for Disintegration Time

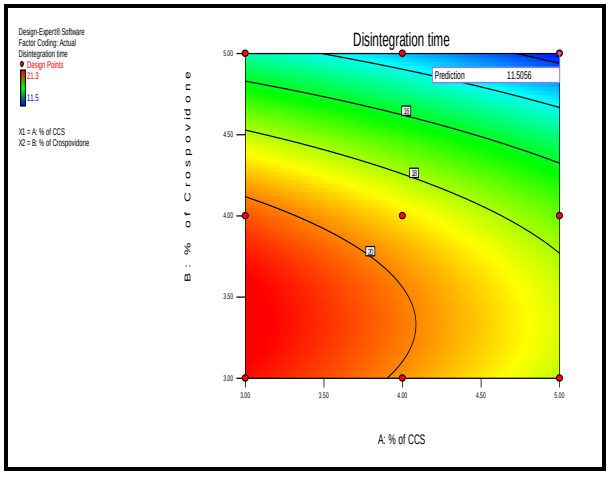

Figure 10: 2D Contour Curve showing effect of Croscarmellose Sodium (X_1) and Crosspovidone (X_2) on Disintegration Time (Y_1)

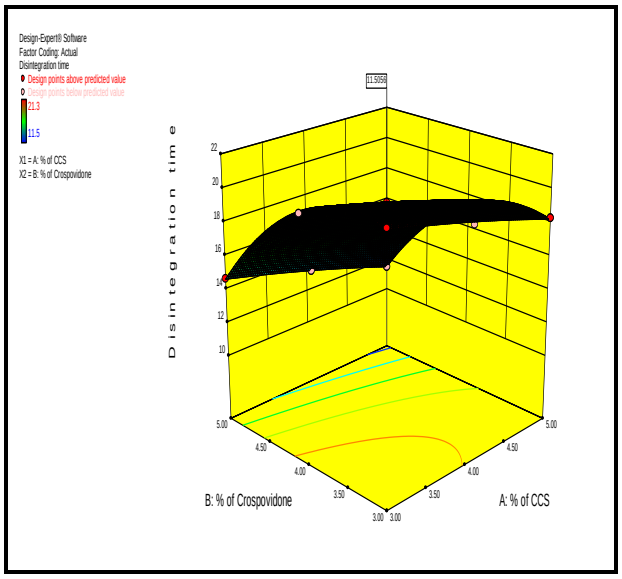

Figure 11: 3D Graph showing effect of Croscarmellose Sodium (X_1) and Crosspovidone (X_2) on Disintegration Time (Y_1)

From the 3D surface plot, it can be observed that disintegration time is strongly dependent on concentration of croscarmellose sodium (X_1) and crospovidone (X_2). This contour plot shows the effect of concentration of croscarmellose sodium (X_1) and concentration of crospovidone on disintegration time (Y_1). As concentration of X_1 and X_2 increases, the value of response Y_1 decreases. Analysis of Variance (ANOVA) for wetting time (Y_2) is given in the table.

The Model F-value of 111.75 implies the model is significant. There is only a 0.13% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case X_1, X_2, X_1X_2 and X_2^2 are significant model terms.

Table 14: ANOVA for Response Surface Quadratic Model for Y_2

Source	SS	DF	MS	F Value	P Value Prob > F
Model	74.50	5	14.90	111.75	0.0013
X_1	16.34	1	16.34	122.51	0.0016
X_2	47.04	1	47.04	352.80	0.0003
X_1X_2	1.44	1	1.44	10.80	0.0462
X_1^2	5.000	1	5.000	0.037	0.8588
X_2^2	9.68	1	9.68	72.60	0.0034
Residual	0.40	3	0.13		
Cor Total	74.90	8	-	-	-

Table 15: Summary of Response Y_2

Std. Dev.	0.37	**R-Squared**	0.9947
Mean	19.0	**Adj R-Squared**	0.9858
C.V.%	1.92	**Pred R-Squared**	0.9355
PRESS	4.83	**Adeq Precision**	29.852

Summary of response Y_2 is given in Table 15. The "Pred R-Squared" of 0.9355 is in reasonable agreement the "Adj R-Squared of 0.9858. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 29.852 indicates an adequate signal. This model can be used to navigate the design space.

The equation generated from the coefficient of the estimates in terms of coded factors is:

$$Y2= 20.43 -1.65\ X_1 - 2.80\ X_2 + 0.60\ X_1X_2 + 0.050\ X_1^2 - 2.20\ X_2^2$$

Response Surface Plot for Wetting Time

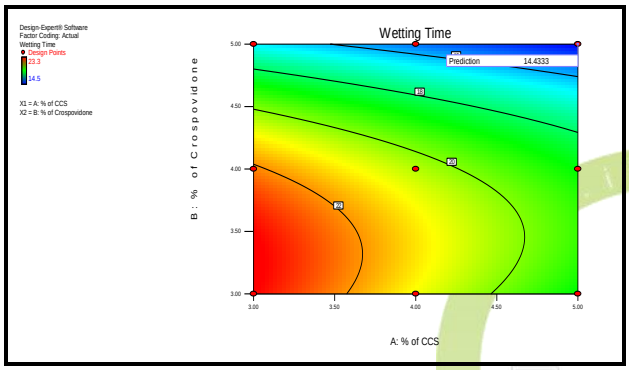

Figure 12: 2D Contour Curve showing effect of Croscarmellose Sodium (X_1) and Crosspovidone (X_2) on Wetting Time (Y_2)

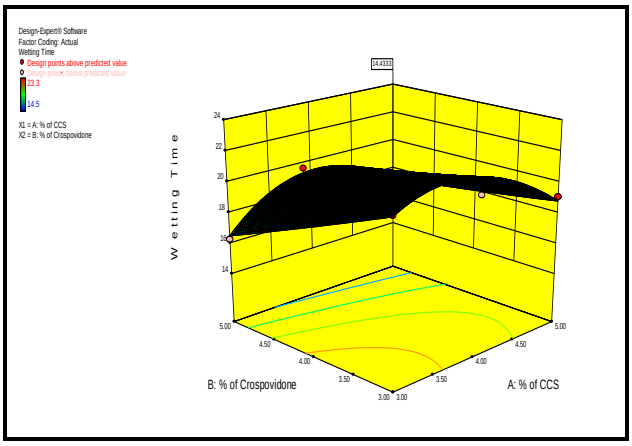

Figure 13: 3D Graph showing effect of Croscarmellose Sodium (X_1) and Crosspovidone (X_2) on Wetting Time (Y_2)

From the 3D surface plot, it can be observed that wetting time is strongly dependent on concentration of croscarmellose sodium (X_1) and crospovidone (X_2). This contour plot shows the effect of concentration of croscarmellose sodium (X_1) and concentration of crospovidone on wetting time (Y_2). As concentration of X_1 and X_2 increases, the value of response Y_2 decreases.

Analysis of Variance (ANOVA) for % CDR (Y_3) is given in the table.

Table 16: ANOVA for Response Surface Quadratic Model for Y_3

Source	SS	DF	MS	F Value	P Value Prob > F
Model	35.33	5	7.07	3170.40	0.0001
X_1	20.87	1	20.87	9363.90	0.0001
X_2	13.17	1	13.17	5910.17	0.0001
X_1X_2	0.37	1	0.37	164.23	0.0010
X_1^2	0.081	1	0.081	36.50	0.0091
X_2^2	0.84	1	0.84	377.20	0.0003
Residual	6.686	3	2.229		
Cor Total	74.90	8	-	-	-

The Model F-value of 3170.40 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_1, X_2, X_1X_2, X_1^2 and X_2^2 are significant model terms.

Table 17: Summary of Response Y_3

Std. Dev.	0.047	**R-Squared**	0.9998
Mean	96.70	**Adj R-Squared**	0.9995
C.V.%	0.049	**Pred R-Squared**	0.9977
PRESS	0.081	**Adeq Precision**	173.645

Summary of response Y_3 is given in Table 17. The "Pred R-Squared" of 0.9977 is in reasonable agreement with the "Adj R-Squared" of 0.9995. "Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 173.645 indicates an adequate signal. This model can be used to navigate the design space.
The equation generated from the coefficient of the estimates in terms of coded factors is:

$$Y3= 96.40 + 1.87\ X_1 + 1.48\ X_2 - 0.30\ X_1X_2 + 0.20\ X_1^2 + 0.65\ X_2^2$$

Response Surface Plot for % CDR

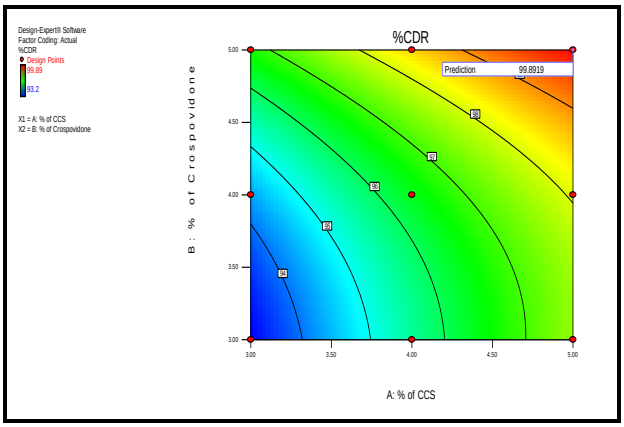

Figure 14: 2D Contour Curve showing effect of Croscarmellose Sodium (X_1) and Crosspovidone (X_2) on %CDR (Y_3)

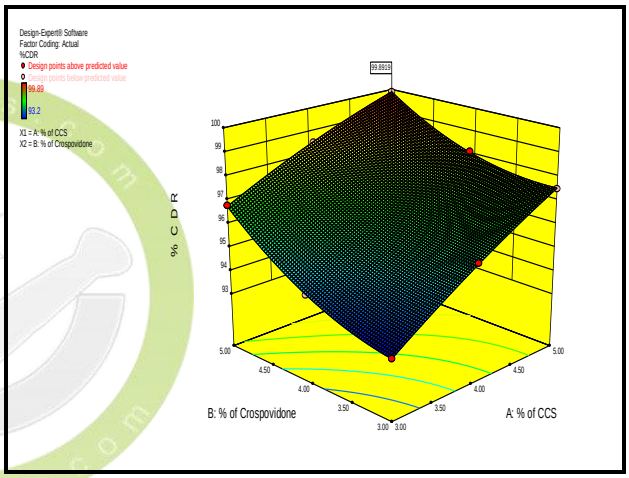

Figure 15: 3D Graph showing effect of Croscarmellose Sodium (X_1) and Crosspovidone (X_2) on %CDR (Y_3)

Table 18: Checkpoint batches with predicted and measured DT, WT and %CDR

Batch code	**X_1**	**X_2**	**Disintegration Time (Y_1)**		**Wetting Time (Y_2)**		**% CDR (Y_3)**	
			Measured	**Predicted**	**Measured**	**Predicted**	**Measured**	**Predicted**
F10	0.5	0.5	15.93	15.53	17.81	17.45	98.11	98.59
F11	0	-0.5	20.06	20.87	20.98	20.36	95.82	96.14
F12	1	0	17.36	17.60	18.83	18.21	98.07	99.47

From the 3D surface plot, it can be observed that the percentage drug release is equally dependent on concentration of croscarmellose sodium (X_1) and crospovidone (X_2). This contour plot shows the effect of concentration of croscarmellose sodium (X_1) and concentration of crospovidone (X_2) on %CDR (Y_3). As concentration of X_1 and X_2 increases, the value of response Y_3 increases.

Check Point Analysis

Three check point batches were prepared and evaluated for disintegration time, wetting time and % CDR as shown in Table.

Result indicated that the measured values matches well with expected values. When measured DT, WT and %CDR values were compared with predicted DT, WT and %CDR values, the differences were found to be not significant. Thus, it can concluded that the obtained mathematical equation is valid for predicting % CDR.

Optimization of Formulation

Optimization of Statistical Model by Overlay Plot

From overlay plot of responses, optimized formulation was selected as checkpoint to validate RSM. The tablets were formulated using chosen optimal composition & evaluated for DT, WT and % CDR.

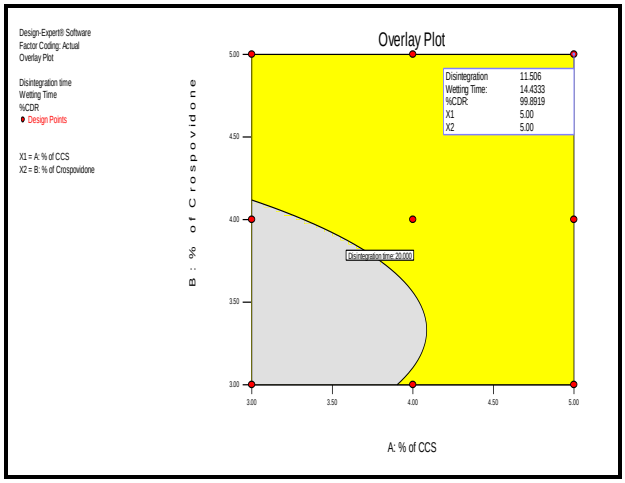

Figure 16: Optimization of Statistical Model by Overlay Plot

Stability Study of Optimized Batch

Optimized batch was put on stability as below mention condition.

Temperature Condition: 25°C/60% RH and 40°C/75% RH

Table 19: Stability Study of Optimized Formulation (F10) carried out at 25 ± 2°C/ 60 ± 5 % RH

No. of Weeks	Disintegration Time (Sec)	Wetting Time (Sec)	% Drug Content	% CDR
0	11 ± 0.65	14 ± 0.40	99.12 ±1.21	99.89 ± 1.23
1	11 ± 0.90	14 ± 0.77	99.02 ± 1.68	99.65 ± 2.05
2	12 ± 0.48	15 ± 0.32	98.87 ± 1.32	99.10 ± 1.96
3	12 ± 0.91	16 ± 0.12	98.55 ± 1.74	98.62 ± 1.26
4	13 ± 0.69	16 ± 0.84	98.24 ± 1.29	98.27 ± 1.98

All values are expressed as mean ± standard deviation, n=3

Table 20: Stability Study of Optimized Formulation (F10) carried out at 40 ± 2°C/ 75 ± 5 % RH

No. of Weeks	Disintegration Time (Sec)	Wetting Time (Sec)	% Drug Content	% CDR
0	11 ± 0.65	14 ± 0.40	99.12 ±1.21	99.89 ± 1.23
1	12 ± 0.89	15 ± 0.76	98.83 ± 1.32	99.22 ± 2.12
2	12 ± 0.07	16 ± 0.95	98.21 ± 1.69	98.77 ± 1.69
3	13 ± 0.22	16 ± 0.11	97.91 ± 1.15	97.50 ± 1.84
4	14 ± 0.67	17 ± 0.69	97.38 ± 1.19	96.43 ± 2.25

All values are expressed as mean ± standard deviation, n=3

Stability study of FDT of Quetiapine Fumarate was carried out for 4 weeks at specified condition. All data are mentioned in Table 19 & 20. The stability studies of the optimized formulation of FDT revealed that no significant changes in the physical parameters, disintegration time, % drug content and % drug release when stored at temperature and humidity conditions of $25^oC \pm 2^oC/60 \pm 5$ % RH and $40 \pm 2^oC/ 75 \pm 5$ % RH. So, it proves the good stability of the optimized batch.

CONCLUSION

In this study Fast Dissolving tablet of Quetiapine Fumarate was prepared by direct compression method using croscarmellose sodium, crospovidone and sodium starch glycolate as superdisintegrant. Taste masking of Quetiapine Fumarate was achieved by β-Cyclodextrin. The batch F10 formulated with 5% of Crospovidone and 5% of Croscarmellose Sodium had shown minimum disintegration time and wetting time 11 and 14 sec respectively. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release etc. were evaluated for these formulations. The optimized batch F10 had shown better dissolution profile with maximum drug being released at all-time intervals when compared to other batches. Based on these results batch F10 was found to be the most promising formulation. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 1 month which revealed the stability of the formulations.

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