RESEARCH ARTICLE

Formulation Development and Characterization of Pullulan Based Quetiapine Fumarate Oral Films

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ABSTRACT
Quetiapine fumarate is one of the major FDA approved drug in treatment of schizophrenia. Since this drug was having very low bioavailability of 9% and extensive metabolism in liver, it was selected as a suitable drug candidate for our study. This work's objective was to formulate quetiapine fumarate oral films as alternate dosage form to tablets. All the formulations composed of pullulan as film forming agent and glycerine as plasticizer. The experimental runs were generated by central composite design using MINITAB. The concentration of polymer (300-350mg) and plasticizer (40-50 mg) were altered with in the design space limits. Solvent casting method was adopted for casting the films. Studies on the compatibility of drug excipients were conducted by FTIR analysis and also the surface morphology was studied by SEM analysis. All the film shows good mechanical properties. The other evaluation parameters like surface pH, film thickness, disintegration time and uniformity of weight were evaluated and found within the acceptable limits. Drug release kinetic data shows that all the formulations follow first order release kinetics. Finally concludes that the developed films are expected to increase patient acceptance and the method was also easily adoptable in large scale industries.
Keywords: Quetiapine fumarate, oral films, pullulan, glycerine
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INTRODUCTION

The trend toward novel drug delivery methods over the past few decades has significantly raised efforts to give significant effectiveness, safety, and patient acceptance. Since developing novel chemical substances is a difficult, costly, expensive and lengthy, current trends are shifting to develop new delivery methods for already-approved drugs. Oral disintegrating films (ODFs) are one of the most popular medication administration methods in pediatrics and geriatrics. This medication delivery technology offers various benefits over standard fast dissolving tablets, including the ability to be utilized for dysphasic and schizophrenic patients and can be administered without water[1]. The FDA has authorized quetiapine as an adjuvant treatment for major depressive disorder, acute manic episodes and schizophrenia.) The bioavailability of quetiapine fumarate is about 9% and half-life of 6 hours. It is extensively metabolized in liver to form pharmacologically inactive metabolites, so it was selected to prepare as oral disintegrating film[2,3].

MATERIALS AND METHODS

Quetiapine fumarate (QTF) was gift sample from Hetero drugs, Hyderabad, India. Pullulan and glycerine were purchased from Fisher scientific, Mumbai. citric acid, Aspartame, was purchased from Loba chemie Pvt Ltd, Mumbai. lemon oil was procured from Shiva exports India. All the other chemical materials was of pharmaceutical grade or analytical reagent grade.

Determination of λ_{max} of Quetiapine Fumarate

Absorbance maxima was determined by scanning the solutions (100 µg/ml) in pH 6.8 phosphate buffer at wave length range of 200-400 nm on double beam UV- visible spectrophotometer (UV 1800, Shimadzu, Japan)[4].

Construction of Calibration Curve of Quetiapine Fumarate in pH 6.8 Phosphate Buffer

Calibration curve for estimation of quetiapine fumarate was constructed in pH 6.85 phosphate buffer. Stock solution of drug was prepared by weighing and transferring accurately 100 mg drug to a 100 ml flask, little quantity of buffer and shaken well till it gets dissolved, and then adding enough buffer to make the volume to 100ml and kept aside for 30 min. for saturation. A series of different dilutions like 5, 10, 15, 20, 25 and 30 using dilution media. These solutions absorbance was measured at 295nm in UV visible spectrophotometer)

Characterization

Drug- Excipient Compatibility Studies

Studies on the compatibility of drug-excipients were performed with attenuated total Reflectance-FTIR (perkin-Elmer 100). FTIR data was obtained for pure drug and optimized formulations[5].

Development of Quetiapine Fumarate Oral Films by Centred Central Composite Design

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Composition of quetiapine fumarate oral dissolving films was developed by central composite design. The concentration of polymer (pullulan) and the concentration of plasticizer (glycerine) were selected as two independent variables and tensile strength, percent elongation, elastic modulus and the percent drug release at 10 min. were selected as dependent variables.

Based on the preliminary studies, amount of polymer (Pullulan) in between 300 to 350 mg and the concentration of plasticizer (Glycerine) in between 40 to 50 mg was chosen for design space. A total of 13 runs were generated by MINITAB 16. The Table 1 shows the list of various independent variables together with their levels) The details of design and the quantities of independent factors are shown in Table 2.

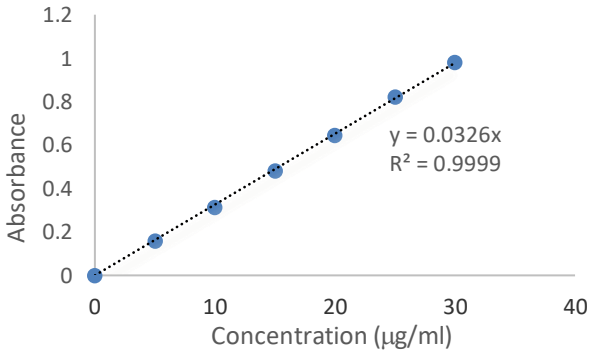

Figure 1: Calibration curve of quetiapine fumarate in pH 6.8 phosphate buffer Drug excipient compatibility studies

Table 1: Design space for central composite design

Independent variable	Level of variation		
	Low	Medium	High
Pullulan (mg)	300	325	350
Glycerine (mg)	40	45	50

Preparation of Oral Films

Composition of quetiapine fumarate oral dissolving films is presented in the Table 3. Initially the polymer was weighed accurately and transferred to beaker containing 5 ml of water and mixed on a magnetic stirrer until the polymer dissolves. Quetiapine fumarate, citric acid and aspartame are dissolved in 5 ml of water in another beaker. This drug solution was then added to the polymer solution with stirring well to obtain a homogenous solution. Now glycerine and lemon oil were added to the above mixture and stirred for one hour at 400 rpm. Allow it to stand for some time to deaeration and finally casted on petri plate. After drying at 50^{0}C for 15 hrs, remove the films with forceps and cut into 2 cm^2 surface area and kept in desiccator until further use.

Evaluation of Films

Evaluation tests like physical appearance, weight variation of films, thickness of film, surface pH of film, uniformity of drug in films, moisture loss, moisture uptake, disintegration time of film, tensile strength, percent elongation, elastic modulus, folding endurance and dissolution were performed on all the films.

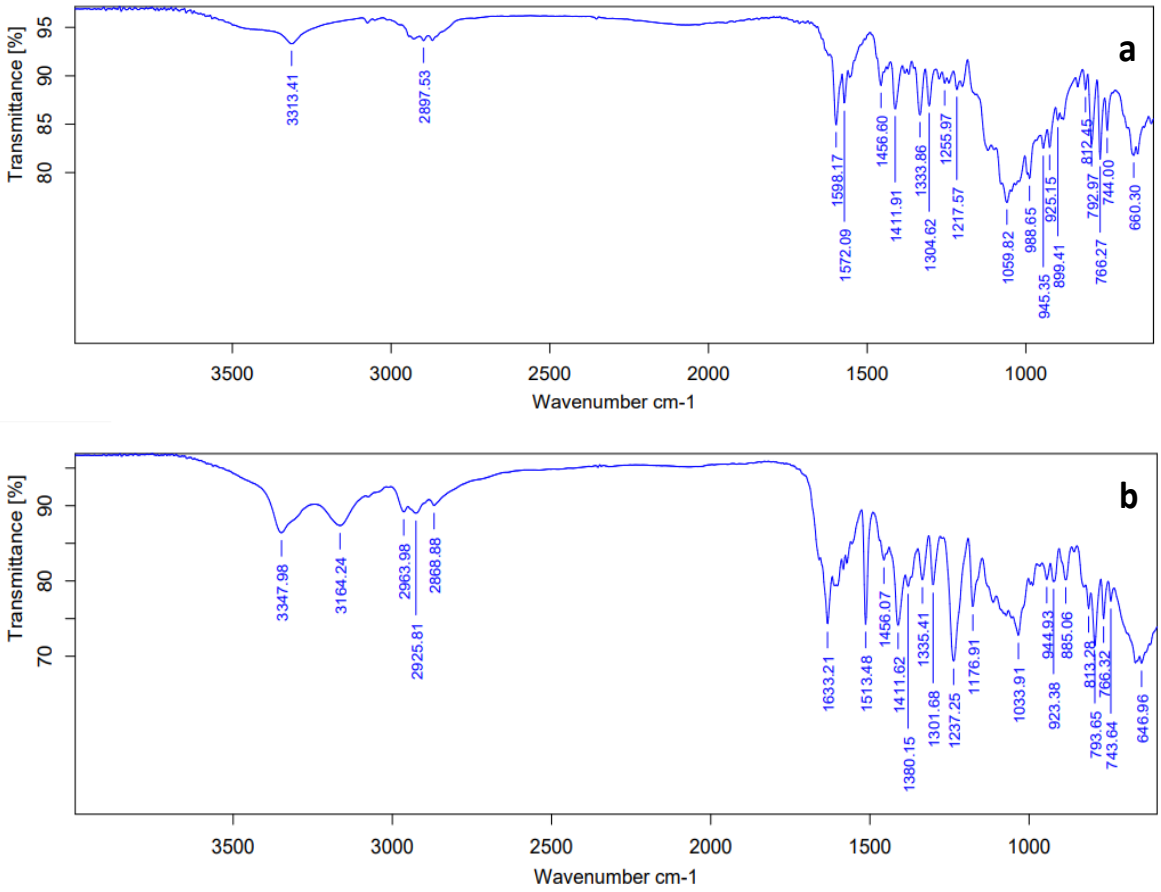

Figure 2: FTIR spectra of a) Quetiapine fumarate b) Quetiapine fumarate Film

Surface Properties

The surface characters like surface texture, transparency and appearance were examined physically and reported.

Weight Variation

Weight 10 films of 2X2 cm area was measured on balance.

Thickness

The thickness of film was determined at four corners and center point) using calibrated digital micrometer (Model: OCNEDMIC-25; Korea) and then mean average (n = 3) is calculated[6].

Surface pH

A digital pH meter (Make: Systronics, Model:335, Ahmedabad) was used to measure the pH of oral film. Oral film has to be placed in petri plate and hydrated with water and its pH to be measured[7].

Uniformity of Drug Content

A 2 cm^2 films (n=10) was carefully placed in 100 ml volumetric flask and it was filled with pH 6.8 phosphate buffer and shaked till it dissolves to form a solution. Filter the solution and drug content was measured spectroscopically at 295 nm.

Table 2: Central composite design for the formulated films containing different concentrations of pullulan and glycerin for quetiapine fumarate oral film

Formulation code	Std Order	Point Type	Blocks	Pullulan (mg)	Glycerine (mg)
CDQ01	1	1	1	300	40
CDQ02	2	1	1	350	40
CDQ03	3	1	1	300	50
CDQ04	4	1	1	350	50
CDQ05	5	-1	1	300	45
CDQ06	6	-1	1	350	45
CDQ07	7	-1	1	325	40
CDQ08	8	-1	1	325	50
CDQ09	9	0	1	325	45
CDQ10	10	0	1	325	45
CDQ11	11	0	1	325	45
CDQ12	12	0	1	325	45
CDQ13	13	0	1	325	45

Disintegration Time

The disintegration time depends upon the composition of the film and generally it ranges from 5 to 60 sec for films. A film was put in a petri plate

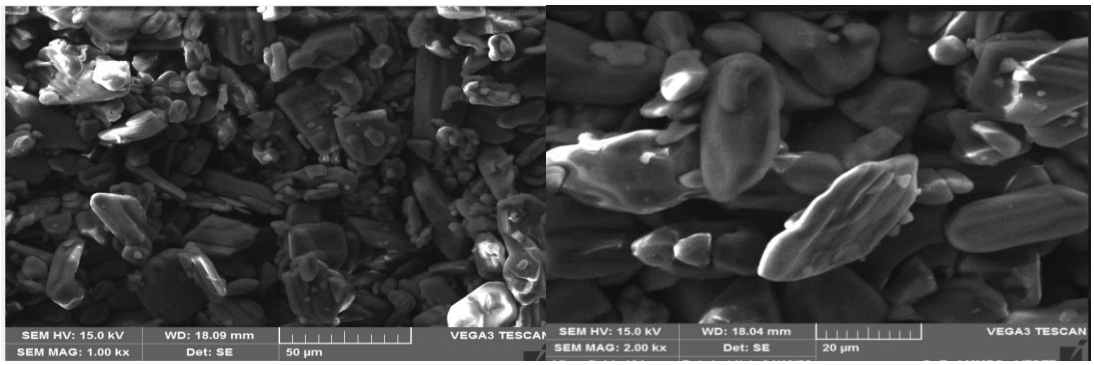

Figure 3: SEM image of pure drug (Quetiapine fumarate)

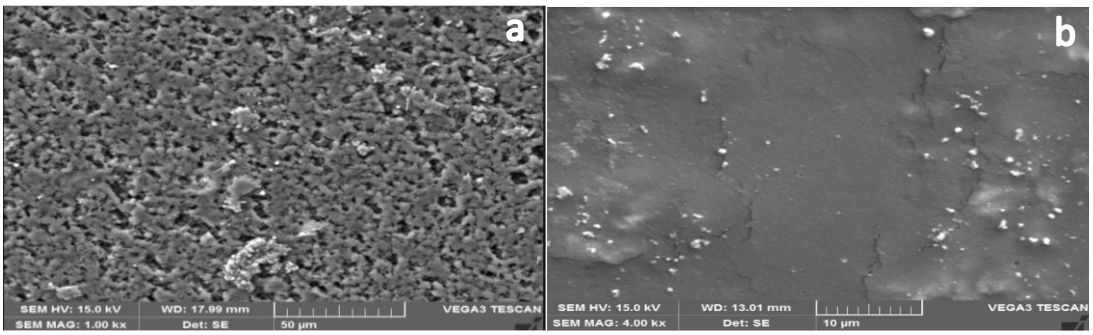

Figure 4: SEM image of a) Quetiapine fumarate placebo film (Pullulan) b) Optimized formulation

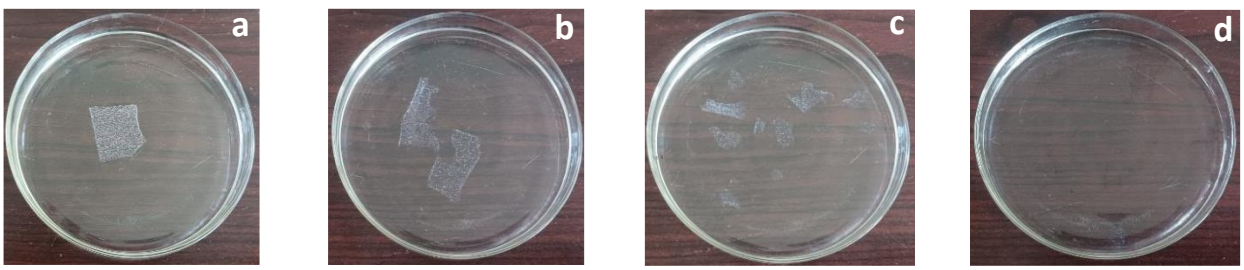

Figure 5: Disintegration pattern of QTF ODF at different stages a) initial b) after 10 sec c) after 30 sec d) after complete disintegration (CDQ01)

Table 3: Composition of Quetiapine oral disintegrating film

S. No.	Ingredients	Quantity (for 10 films of $2cm^2$)
1	Quetiapine fumarate	250 mg
2	Pullulan	300-350 mg
3	Glycerine	40-50 mg
4	Citric acid	60 mg
5	Aspartame	90 mg
6	Lemon oil	Q.S.
7	Distilled water	Q.S to 10 ml

comprising 15 ml of distilled water and disintegration time was noted[8].

Moisture Loss and Moisture Uptake

The pre weighed film is placed in desiccator containing anhydrous $CaCl_2$ for three days. After three days, films were reweighed and the weight difference between original and final weights was used to determine moisture loss percentage as below.)

$$Moisture\ loss = \left[\frac{(\ Initial\ wt. - Final\ wt.)}{Initial\ wt.}\right] X\ 100$$

For moisture uptake determination the initial weight of the film was noted down. These films were kept at room temperature for one week with 75% RH. After one week the films were reweighed and moisture uptake was determined as below[9].

$$Moisture\ uptake = \left[\frac{(\ Final\ wt. - Initial\ wt.)}{Initial\ wt.}\right] X\ 100$$

Tensile Strength

ODFs are fixed between clamps at 2 cm distance and the force or load which causes the breaking of the ODFs load require to cut the film was calculated with following equation[10] .

$$Tensile\ strength = \left[\frac{Load\ at\ failure}{(Strip\ thickness\ X\ strip\ width)}\right] X\ 100$$

Percent Elongation

Table 4: Absorbance vs. concentration of Quetiapine fumarate

Concentration (µg/ml)	Absorbance (mean ± s.d, n=3)
0	-
5	0.161±0.004
10	0.315±0.002
15	0.482±0.003
20	0.647±0.004
25	0.822±0.004
30	0.983±0.007

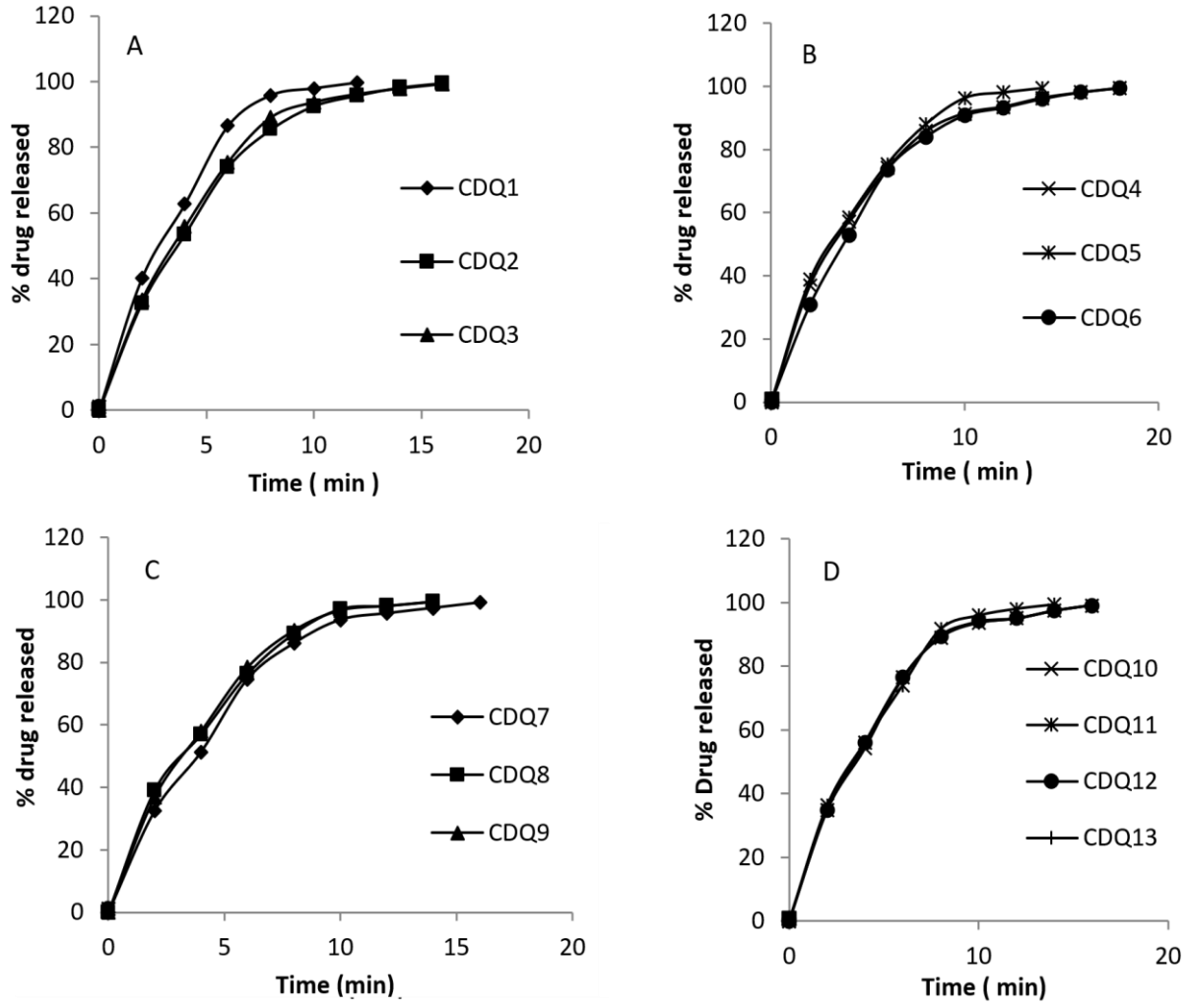

Figure 6: Cumulative drug release profile of all formulations (CDQ01 -CDQ13)

Percentdongation is determined by calculating the ratio of ultimate length and initial length of the film with the application of stress before the point of breakage. Then percent elongation was calculated with following equation[11].

$$Percent\ elongation = \left[\frac{Increase\ in\ length\ at\ break\ point}{Original\ length}\right] X\ 100$$

Elastic Modulus (Young's Modulus)

It is a measurement of stiffness of the films against the applied force up to the elastic limit. It was determined by measuring the applied force over the film to cause stiffness of the film using the following formula[12].

$$Young's\ modulus = \left[\frac{Slope}{(Strip\ thickness\ X\ Cross\ head\ speed)}\right] X\ 100$$

Folding Endurance

Folding endurance is one of the mechanical properties of the film, can be determined by folding the film repeatedly at one place until it ruptured[13].

Dissolution

Dissolution study is performed on USP dissolution testing apparatus- paddle type (Model: DISSO2000, Make: Labindia, India) set at 37 – 0.50c and 50 rpm for 20 minutes with 300 ml of pH 6.8 phosphate buffer. Dissolution study is performed by placing the film attached with the metal wire to prevent the floating of the film. Each film 25 mg of drug containing (2cm^2 film containing equivalent of 25 mg of drug) was placed in dissolution apparatus. Two ml of sample was collected at 0,2,4,6,8,10,12,14,16,18,20 minutes and fresh medium was replaced to maintain sink conditions. Collected sample was filtered, diluted appropriately and analysed. The dissolution kinetics was calculated with PCP Disso software.)

Surface Morphology

Surface morphological study of pure drug quetiapine

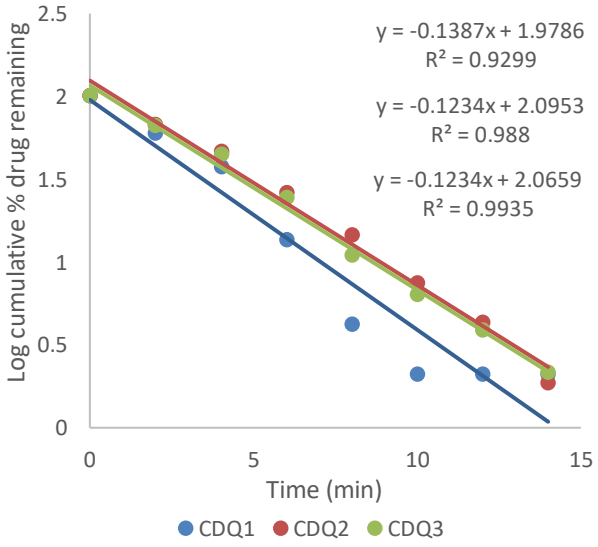

Figure 7: First order plots of films (CDQ01 – CDQ03)

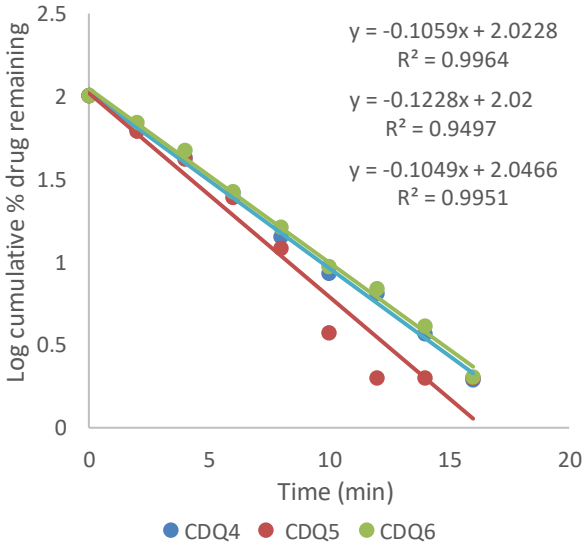

Figure 8: First order plots of films (CDQ04 – CDQ06)

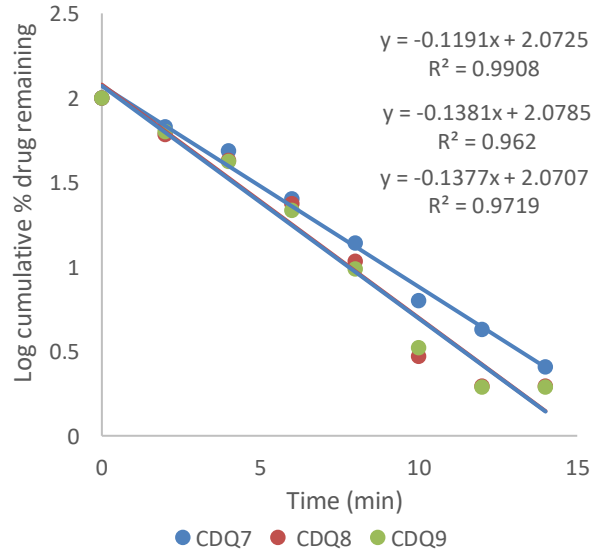

Figure 9: First order plots of films (CDQ07 – CDQ09)

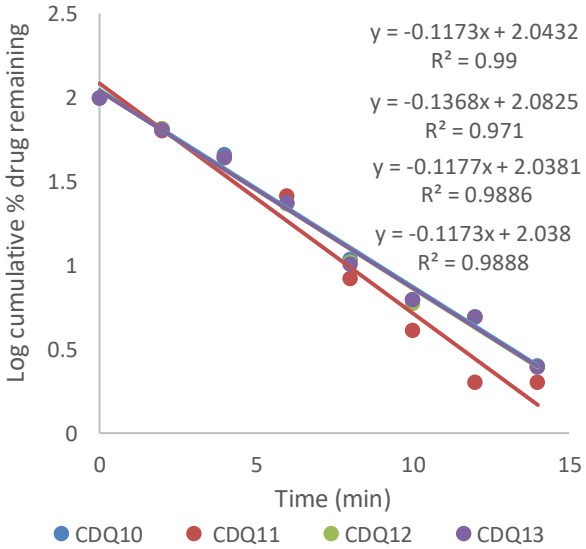

Figure 10: First order plots of films (CDQ10 – CDQ13)

Table 5: Physical characteristics for Quetiapine fumarate ODF

F. code	Surface texture	Trans-parency	Thickness [a] (mm)	Weight [b] (mg)	Surface pH [a]	Drug content [b] (%)	D.T [c] (Sec)	Moisture loss[d] (%)	Moisture uptake [d] (%)
CDQ01	Smooth	NT	0.189 ± 0.07	91.24 ± 1.51	6.62 ± 0.41	99.98 ± 1.09	53 ± 1	5.490 ± 1.06	5.326 ± 1.02
CDQ02	Smooth	NT	0.218 ± 0.04	98.30 ± 2.11	6.51 ± 0.35	98.85 ± 0.35	65 ± 2	4.760 ± 0.59	5.67 ± 1.62
CDQ03	Smooth	NT	0.199 ± 0.06	94.12 ± 1.26	6.37 ± 0.46	99.69 ± 0.58	55 ± 2	3.521 ± 0.63	6.33 ± 3.68
CDQ04	Smooth	NT	0.224 ± 0.04	99.21 ± 1.41	6.42 ± 0.40	99.55 ± 0.21	68 ± 3	6.703 ± 1.48	5.253 ± 3.11
CDQ05	Smooth	NT	0.195 ± 0.05	91.13 ± 1.15	6.45 ± 0.43	99.14 ± 0.46	54 ± 3	5.36 ± 2.88	4.516 ± 0.79
CDQ06	Smooth	NT	0.221 ± 0.04	96.66 ± 1.52	6.43 ± 0.17	99.30 ± 0.17	67 ± 3	6.220 ± 2.15	4.94 ± 0.59
CDQ07	Smooth	NT	0.208 ± 0.05	95.33 ± 1.52	6.97 ± 0.20	98.78 ± 0.40	58 ± 2	4.88 ± 1.23	6.29 ± 1.05
CDQ08	Smooth	NT	0.214 ± 0.05	96.66 ± 1.52	6.54 ± 0.24	100.1 ± 0.73	62 ± 2	5.831 ± 1.26	5.913 ± 2.03
CDQ09	Smooth	NT	0.217 ± 0.04	95.24 ± 1.12	6.54 ± 0.31	99.56 ± 0.09	60 ± 1	4.133 ± 1.76	5.216 ± 1.08
CDQ10	Smooth	NT	0.211 ± 0.03	95.66 ± 0.57	6.62 ± 0.24	99.69 ± 0.14	59 ± 2	5.956 ± 2.22	5.136 ± 1.02
CDQ11	Smooth	NT	0.215 ± 0.04	94.66 ± 0.57	6.77 ± 0.20	98.90 ± 0.68	60 ± 1	5.240 ± 0.90	4.59 ± 0.62
CDQ12	Smooth	NT	0.214 ± 0.05	95.66 ± 0.57	6.43 ± 0.36	99.43 ± 0.19	61 ± 1	5.916 ± 1.32	4.95 ± 0.64
CDQ13	Smooth	NT	0.215 ± 0.04	94.21 ± 0.61	6.69 ± 0.30	99.53 ± 0.17	60 ± 1	5.880 ± 1.58	5.596 ± 1.65

NT- Non transparent; a : mean ± s.d, (n = 3); b : mean ± s.d, (n = 10); c : mean ± No. of seconds (n = 5); d : mean ± s.d, (n = 5)

Table 6: Mechanical properties for QTF ODFs

Formulation code	Mechanical properties			
	Tensile strength* (gm/cm^2)	% Elongation*	Elastic modulus* (kg/m^2)	Folding endurance*
CDQ01	12.85 ± 0.35	32.50 ± 0.53	12.60 ± 0.38	124.6 ± 1.15
CDQ02	21.65 ± 0.36	34.88 ± 0.19	18.70 ± 0.35	119.6 ± 1.52
CDQ03	13.46 ± 0.44	40.72 ± 0.43	15.38 ± 0.41	134.3 ± 1.52
CDQ04	23.38 ± 0.55	39.13 ± 0.59	14.59 ± 0.40	128 ± 1.00
CDQ05	12.79 ± 0.29	36.35 ± 0.78	10.72 ± 0.46	129.6 ± 3.05
CDQ06	23.89 ± 0.33	37.64 ± 0.14	16.47 ± 0.32	124.3 ± 0.57
CDQ07	13.31 ± 0.44	35.40 ± 0.53	11.44 ± 0.47	121 ± 3.00
CDQ08	15.36 ± 0.40	42.10 ± 0.50	13.32 ± 0.25	130.6 ± 2.30
CDQ09	18.29 ± 0.35	45.34 ± 0.41	12.59 ± 0.30	127 ±.64
CDQ10	17.83 ± 0.32	47.37 ± 0.27	14.54 ± 0.42	125.6 ± 2.51
CDQ11	18.38 ± 0.43	48.41 ± 0.21	15.33 ± 0.26	125.6 ± 1.52
CDQ12	18.32 ± 0.52	47.30 ± 0.32	15.38 ± 0.42	126.6 ± 2.08
CDQ13	17.34 ± 0.70	47.67 ± 0.33	14.42 ± 0.21	128 ± 2.00

* All results are shown as mean = s.d, n = 3.

fumarate and its optimized film formulation was conducted with scanning electron microscope at voltage of 0.5-30kv[14].

RESULTS AND DISCUSSIONS

Standard Calibration Curve

The values of absorbance against concentration are given in Table 4 and standard graph of QTF was shown in Figure 1 respectively. This method shows linearity in 5-30 µl / ml concentration range in pH 6.8 phosphate buffer. A good positive correlation was observed with a 0.999 correlation coefficient value. The equation between concentration and absorbance was given by y = 0.0326x. The FTIR of drug and optimized formulation are shown in Figure 2. The peak at 2897.53 cm^{-1} represents O-H stretching, a sharp peak at 1304.62 cm^{-1} was due to C-N stretching vibration and a broad peak at 1059.82 cm^{-1} represents C-O stretch. The same characteristic bands were observed in the film composition indicating that there was no physical incompatibility in between the ingredients used to develop the films.

Evaluation of Quetiapine Fumarate Films

Surface Morphology of Film

The SEM images of drug (QTF) and optimized ODF was shown in Figure 3 and Figure 4. The SEM images of pure API shows that the drug was in crystalline state, where as in SEM of optimized film formulation conforms the conversion of crystalline form to amorphous nature. The results of all evaluation parameters were presented in Table 5 and Table 6. All experimental batches were clear, non-transparent, non-sticky with a smooth surface in physical appearance. Other parameters like weight was in range of 91-99 mg, folding endurance was in range 119-134, percent moisture loss was in range of 3.521-6.70%, thickness was in range of 0.189-0.224 mm, pH in range of 6.37-6.96, drug content was in range of 98.78-100.1%, in vitro DT was in range of 53-68 seconds, tensile strength in range of 12.80-23.90 gm/cm^2, elastic modulus values in range of 10.72-18.70 kg/m^2 and percent elongation values in range of 32.50-48.41%. The Figure 5 shows the disintegration stages of QTF ODFs. The results of all evaluated parameters of experimental batches were within acceptable range. The dissolution data obtained for quetiapine films were presented as cumulative percent drug release graphs in Figure.6. All the formulations follow first order release and the graphs are shown in Figure 7 to Figure 10. All the formulations show more than 90% of drug released within

5 minutes.

CONCLUSION

In the present study, we made an attempt to develop quetiapine fumarate oral films as alternate dosage form to tablets. The preparation method was a simple solvent casting technique, that can be easily adopted in prototype industries. The developed films overall shown good results in all evaluation parameters. The compatibility studies between drug and film composition indicates no significant interaction effect. Finally, we conclude that the scope of the project to be extended further to optimize the formulation composition.

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