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FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILM CONTAINING QUETIAPINE FUMARATE

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ABSTRACT

The main objective of the study was to formulate and evaluate oral fast dissolving film containing Quetiapine fumarate . Compatibility of Quetiapine fumarate with polymers was confirmed by FT-IR studies. Seven films were evaluated for weight variation and thickness showed satisfactory results. Folding endurance of the films was increased with increase in the concentration of polymer due to increase in the elasticity nature of the polymer. Disintegration time of the films was increased with increase in the concentration of the polymer, as more fluid is required to wet the film in the mouth. The presence of disintegrant showed a considerable effect on the disintegration time of the films. Content uniformity study showed that the drug is uniformly distributed in the film. The accelerated stability studies of the optimized FV formulation indicates that the formulated oral fast dissolving films were unaffected after 3 months storage under accelerated conditions as there were no signs of visually distinguishable changes in appearance, disintegration time and cumulative percentage of drug release.From the present investigation it can be concluded that oral fast dissolving film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

Key Words: Quetiapine fumarate , oral fast dissolving film

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INTRODUCTION

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancement to be made because of their some drawbacks related to Particular class of patients which includes geriatric, pediatric and dysphagic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens. Although solid dosage forms are widely accepted by elders and adolescents, younger children tend to prefer liquid formulations that are easier to swallow.

Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating, and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available. So, Fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention. (ODFT) was already popular amongst the people in the early 2000 year with the introduction and widespread use of Listerine pocket strips, a new launch in the mouthwash range. Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion in near future. However only a few products consisting bitter molecules have been able to be commercialized because of the complexity associated with the ODT. Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing. The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The development of a fast-dissolving film also provides an opportunity for a line extension in the market place, a wide range
of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, anti asthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form (1-5).

Recently Fast dissolving films have gained popularity as dosage forms for the mouth fresheners. Meanwhile pharmaceutical industries have recognized their potential for delivering medicinal products and have launched several products for the OTC market using this technology. The fast dissolving thin film are hardly described and investigated in literature, but seem to be an ideal dosage form for use in young children, especially in geriatric and pediatric patients. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Due to lack of standard methodology for preparation and analysis products existence in the market is limited.

MATERIALS AND METHODS

Preparation of Quetiapine fumarate by Solvent-Casting Method (6-8)

The Oral fast dissolving films were prepared by dissolving strip forming agents and plasticizer in the distilled water, then solution was continuously stirred up to 4 hours on magnetic stirrer and kept for 1 hour to remove all the air bubbles entrapped. Meanwhile, in the separate container remaining water soluble excipients i.e. sweetening agent, flavor and drug were dissolved with constant stirring for 45 min. When the stirring was over both the solutions were mixed together with stirring for another 1 hour on magnetic stirrer. Then the solution was kept stationary for 1 hour to let the foams settle down. The resulting formulation was casted on to a plate of surface area 18 cm^2. It was dried for 24 hours at room temperature. The film was removed from the plate very carefully and observed for any imperfections. Film of area 6 cm^2 (2 X 3) was cut and stored in a butter paper covered with aluminum foil and stored in a dessicator. Composition of various formulations is shown in table-1.

Table-1 Composition of Various Formulations

S.No	Ingredients (mg/film)	Q1	Q2	Q3	Q4	Q5	Q6
1	Quetiapine fumarate	25	25	25	25	25	25
2	SSG	0.5%	1%	1.5%		-	
3	CCS	-	-		0.5%	1%	1.5%
4	HPMC				3%	4%	5%
5	CMC	3%	4%	5%			
6	PEG-400	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
7	Vanillin	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
8	Aspartame	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
Inference		Film not formed	Film formed	Film formed	Film formed	Film formed	Film not formed

Evaluation of Fast Dissolving Oral Films

Weight variation of the film

2 x 3 cm^2 film was cut at five different places in the casted film. The weight of each filmstrip was taken and the weight variation was calculated

Thickness of the film

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film and average was taken and SD was calculated

Folding endurance

The folding endurance is expressed as the number of folds required to break the specimen or develop visible cracks. This gives an indication of brittleness of the film. A small strip of 2×3 square cm was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed.

pH studies

The pH was determined by dissolving a film in 2 ml of distilled water and then the pH of the obtained solution was measured by pH paper.

Drug Content uniformity

Drug content uniformity of all eight batches was determined by UV-Spectrophotometric method. For this, each strip at three different places equivalent to 25mg of drug was cut and dissolved in 50ml of 6.8Ph phosphate buffer solution with continuous stirring. This solution was filtered using Whattmann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by U.V.Spectrophotometer and the absorbance was recorded at 242nm. Drug content was calculated by using calibration curve of drug .

Disintegration time

Test was performed using disintegration test apparatus. 2×3 cm^2 film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate equivalent to ten times a minute. Time required by the film, when no traces of film remain above the gauze was noted.

***Invitro* Dissolution studies**

Dissolution study was carried out using USP type I (basket apparatus) with 300 ml of 6.8 pH Phosphate buffer as dissolution medium maintained at 37 $\pm 0.5^0$ C. Medium was stirred at 50 rpm for a period of 30 minutes. Samples were withdrawn at every 1 min interval up to 30 min, replacing the same amount with the fresh medium. Samples were suitable diluted with 6.8 pH and analyzed for drug content at 242 nm. Cumulative percent drug release of Quetiapine fumarate was calculated and plotted against time.

RESULTS AND DISCUSSION

Quetiapine fumarate Fast dissolving oral films were prepared by Solvent-casting method using Natural polymers and PEG-400 as plasticizer. A Successful attempt was made to formulate six formulations of Quetiapine fumarate films by using different Natural polymers. Effect of polymer ratio in formulation development was assessed.

The FT-IR spectrum of the pure drug was found to be similar to the standard spectrum of Quetiapine fumarate. The spectrum of Quetiapine fumarate showed the following functional groups at their frequencies are mentioned. From the FT-IR Spectra of pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristic peaks of drug are present in the combination spectra as well thus indicating the compatibility of the drug with the polymers used.

The weights of the films were found to be in the range of 198mg to 204mg. The results of average weight of all films. The observation by visual inspection of films and by feel or touch, suggests that the films are having smooth surface and they are elegant enough to see. The thicknesses of the films were in the range of to 0.15mm to 0.27mm. Folding endurance of the films was found to be in the range of 97 to106. The surface pHs of all the films were found to be neutral as there was no colour change in the litmus paper. The drug content uniformity is performed by taking three films in each formulation trial and the average drug content was calculated. The results were found to be in the range of 93.4% to 98.2%. The disintegration times of the prepared films were in the range of 2 min to 16 mins.

Quetiapine fumarate FDOF dissolution study was conducted in 6.8pH phosphate buffer solution as this was similar to the pH of simulated salivary fluid. A modified dissolution methodology was followed to simulate the conditions of the oral cavity. The dissolution volume consists of 300ml of 6.8pH phosphate buffer solution at 37±0.5˚C, which was rotated at 50rpm. Quetiapine fumarate FDOF from each formulation was carried out in 6.8 pH phosphate buffer solution for 20min. The data of dissolution studies were summarized in table-2. The dissolution study was conducted for 15 min. The drug release was found to be in the range of 69.3% to 98.7% and the % drug release was maximum. The plots of % cumulative drug release versus time (min) were plotted and depicted as shown in Fig-1, 2. The formulation Q5 showed higher drug release of 97.9% revealing that films made with concentrations of HPMC., 4%w/v and CCS 1% w/v was the optimized formulation as it shows a higher drug release in the dissolution study. As higher dissolution rate aids in faster onset of action, F5 was chosen as the optimized formulation.

Table-2 *In-vitro* dissolution studies

Time in min	Q1	Q2	Q3	Q4	Q5	Q6
2	15.8	12.4	20.3	14.3	36.6	21.8
4	30.8	28.7	35.7	29.8	49.3	37.2
6	44.6	41.1	47.8	42.7	62.8	48.3
8	51.8	48.2	56.3	49.6	73.6	56.6
10	61.1	58.2	65.8	59.5	80.3	66.9
15	72.6	68.3	76.3	70.2	97.9	76.8

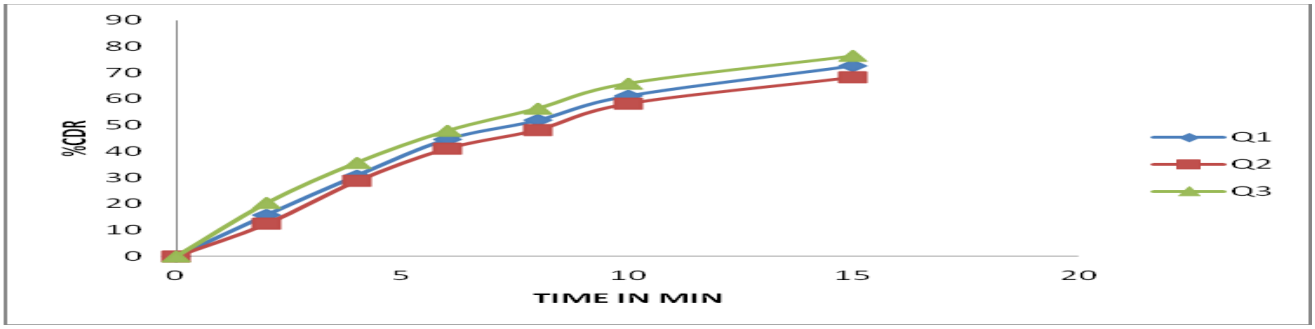

Fig-1 *Invitro* drug release data of formulations Q1-Q3

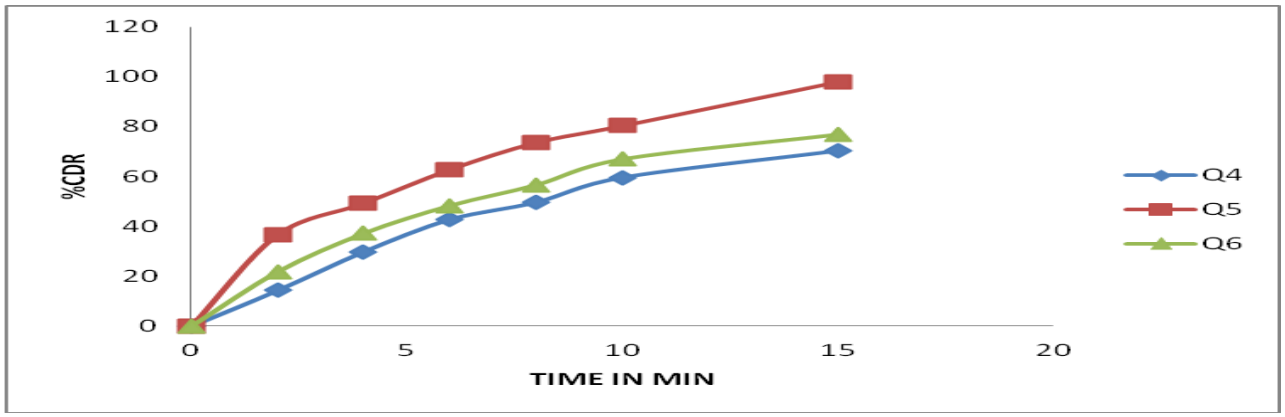

Fig-*2 Invitro* drug release data of formulations Q4-Q6

For analyzing the mechanism of the drug release kinetics of the dosage form, the data obtained were fitted to various kinetic equations of Zero order, First order, Higuchi model and Korsmeyer - Peppas model. The regression coefficient is calculated. The data of regression coefficient of different kinetic models were summarized in table-3.

Table-3 Regression data

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	5.990733945	-0.10398717	25.41912993	-1.108335473
Intercept	18.70853211	2.107477161	0.11052700	2.19941021
R 2	0.894345402	0.915457878	0.99938311	0.695285328

CONCLUSION

Present study reveals that all the Seven formulated films showed satisfactory film parameters. It can be concluded that, Oral fast dissolving film-containing Quetiapine fumarate can be prepared by solvent casting method. 3% w/v of HPMC and 1% CCS (FV) film exhibited required folding endurance and disintegration time. The drug release was about 98.7 % in 15min. The accelerated stability studies of the optimized FV formulation indicates that the formulated oral fast dissolving films were unaffected after 3 months storage under accelerated conditions as there were no signs of visually distinguishable changes in appearance, disintegration time and cumulative percentage of drug release. From the present investigation it can be concluded that oral fast dissolving film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

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