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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF FLUOXETINE HYDROCHLORIDE

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ABSTRACT

Fluoxetine Hydrochloride is an antidepressant belongs to the class of selective serotonin reuptake inhibitor (SSRI). Fluoxetine is a highly soluble drug and the rate of absorption is often controlled by rate of dissolution. The rate of dissolution can be increased by incorporating the drug in a fast dissolving oral film**.** Delivery of drugs via thin film by buccal route has the potential to improve the onset of action, lower the drug dosing, and enhances the efficacy and safety profile of the medicament. Oral fast dissolving films are useful for the pediatric, geriatric patients and also for the patients suffering from diarrhea, acute pain, emesis, allergic attacks, cough, asthma, hypertension, congestive heart failure, migraine, mental disorder, bedridden patients etc, when ultra rapid onset of action is required. Hence the present study was aimed to formulate fast dissolving oral films of Fluoxetine hydrochloride for quick onset of action and efficacy by solvent casting method using HPMC & its polymers (E-15 and E-50) and propylene glycol as a plasticizer. Six film formulations (F1-F6) were prepared and evaluated for their physicochemical parameters like film thickness, weight of the films, surface pH, folding endurance, disintegration time, drug content and *in-vitro* dissolution studies. Among all formulations, formulation F3 (containing HPMC E-15 200mg) disintegrated within 32 sec and was found to release 99.6% of drug within 4 min, which is desirable for faster absorption and rapid onset of action; hence F3 formulation was selected as the best formulation. Different kinetic models were applied to the optimized formulation and observed that formulation (F3) followed first order kinetic model indicating, drug release is concentration dependent.

INTRODUCTION

For the past two decades, there has been enhanced demand for more patient compliance dosage forms. As a result the demand for new technologies has been increased. Among the various delivery routes, oral route is the most preferred route for the delivery of the drug until date due to easy of ingestion, pain avoidance and versatility. But oral drug delivery system still need some advancements to be made because of some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients as they have difficulty in swallowing or chewing and due to fear of chocking solid dosage form. Even with fast dissolving tablets there is a fear of chocking due to its tablet type appearance.

The lower bioavailability of drug/s, long onset time, dysphasia and patient's need turned the manufactures for the formulation of parenteral's and liquid orals, but the liquid orals have the problem of inaccurate dosing and parenteral drug delivery has the problem of patient non-compliance. The pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. To overcome the problems associated with solid, liquid and parenteral dosage forms, a novel dosage form is formulated known as fast dissolving oral films (FDOF's). FDOF's are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of active pharmaceutical ingredients (APIs) by dissolving within minute in oral cavity after coming into contact with saliva and no need of chewing and water for administration. It gives quick absorption and instant bioavailability of drugs due to highly vascular nature and permeability of oral mucosa.

Fluoxetine belongs to the class of selective serotonin reuptake inhibitor (SSRI). It blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on $5HT_{1A}$ auto receptors, which leads to an increase in serotonin levels and enhances the mood of the patients. Fluoxetine is used to treat depression, major depressive disorder, bulimia nervosa (an eating disorder) obsessive-compulsive disorder, panic disorder, and premenstrual dysphoric disorder (PMDD). The bioavailability of Fluoxetine hydrochloride is about 60-80% and having 94-95% of protein binding with a biological half-life of 1-3 days and it's a BCS Class I drug.

MATERIALS AND METHODS

Fluoxetine Hcl obtained as a gift sample from DIVIS LABS, Hyderabad. HPMC purchased from MOLY CHEM, Mumbai, India. HPMC E-15 purchased from LOBA CHEMIE Pvt. Ltd, Mumbai, India. HPMC E-50 purchased from Rolex Chemical Industries, Mumbai, India. Propylene glycol purchased from Kemphasol, Mumbai, India. Sodium saccharine purchased from SD Fine-Chem Ltd, Mumbai, India. Citric acid purchased from FINE CHEM INDUSTRIES, Chennai, India. All other chemicals and reagents used were of A.R. grade.

Drug and Excipients Compatibility Study by FTIR Spectroscopy

The compatibility of drug and excipients is an important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. FT-IR Spectroscopy of pure drug (Fluoxetine Hcl), HPMC E-15(200mg) and its formulations were carried out on Bruker FT-IR 16000 model to investigate any possible interaction between the drug and the utilized polymers. The samples were finely grounded and a spectrum was scanned in the wavelength range of 400 and 4000 cm^{-1} using Bruker FT-IR spectrophotometer. The compatibility of drug in the formulation was confirmed by comparing FTIR spectra of pure drug with FTIR spectra of its formulation.

FORMULATION OF FAST DISSOLVING BUCCAL FILMS[4-7]

The mouth dissolving films of Fluoxetine Hcl were prepared by solvent casting technique using HPMC, HPMC E15, HPMC E50 as film forming polymers and Propylene glycol as a plasticizer. Citric acid is used as saliva stimulating agent and sodium saccharin as sweetening agent.

Weighed quantity of drug was dissolved in required volume of water in a beaker and the selected concentrations of polymers were added to another beaker followed by dissolving with sufficient amount of water. Then both the solutions were mixed together. Initially stirring was carried out at low RPM and later at higher speed. The required quantity of plasticizer was added drop wise. The solution was poured into a Petridish (area of 64 cm^2) and a inverted funnel was placed over the pertidish and allowed to dry overnight at room temperature. The films were removed carefully which contains 160mg of drug and an area of 4 cm^2 was punched out so that each strip contains 10mg of the drug. The dried film were wrapped in butter paper then covered with aluminum foil and kept in desiccators until further use.

Fig 1: Oral strips containing 10mg of drug Formulation of Fluoxetine Hcl fast dissolving oral films

EVALUATION PARAMETERS

The prepared films were evaluated for following tests:

1. Visual inspection:

Properties such as homogeneity, color, transparency and surface of the oral films were evaluated for all the prepared oral films.

2. Weight variation[8]:

2 × 2 cm^2 film was cut at three different places in the cast film. The weight of each film strip was taken on electronic balance and then the average weight was calculated.

3. Film thickness[9-11]

The thickness of the film was measured by using vernier calipers and it should be evaluated at five different locations (four corners and one at center) and average values were calculated.

4. Folding endurance[12-13]: Folding endurance gives the brittleness of a film. The film (2 × 2 cm^2) is repeatedly folded at the same place until it breaks. The number of times the film is folded without breaking or without any visible crack is the calculated folding endurance value and average values were calculated.

5. Surface pH[14-16]

The surface pH of fast dissolving film was determined in order to find out the possible *in-vivo* side effects if any. Commercially available pH strips were used for this purpose. The film to be tested was placed in a petridish and was slightly wetted with water. The pH was measured with pH strip in contact with the surface of the oral film. The average of three determinations for each formulation was calculated.

6. Disintegration time[17]

The disintegration time was measured using modified disintegration method. For this purpose, a petridish was filled with 10 ml of water and the film was carefully put in the center of pertridish. The time for the film to completely disintegrate in to fine particles was noted. The experiment was performed in triplicate and average values were calculated.

7. Drug content[18-23]

Drug content of all films was determined by UV-Spectrophotometric method. For this 2x2 cm^2 strip was dissolved in 100 ml of phosphate buffer (6.8) and the solution was stirred for 1 hr on a magnetic stirrer. The solution was filtered and absorbance was recorded at 264 nm and drug content was calculated for all the film formulations.

8. *In-vitro* dissolution studies[24-26]

The *in-vitro* dissolution study was performed by using USP basket (Type I) apparatus. The studies were carried out at 37±0.5°C with stirring speed of 50 rpm in 300 ml of pH 6.8 phosphate buffer as dissolution medium. 5 ml of samples were withdrawn at predetermined time intervals of 0, 1, 2, 4, 6, 8, 10 and 12 minutes and the sink conditions were maintained by replacing with the same volume of buffer solution. The samples were collected and the absorbance was determined at 264 nm using UV-visible spectrophotometer.

RESULTS & DISCUSSION

FTIR studies were performed to detect the possible molecular interactions between drug and utilized polymers. FTIR spectra were showed in **figure 2 & 3**. The comparison between FTIR spectrum of physical mixture of drug with excipients and pure drug (Fluoxetine) revealed that there was no appreciable change in position and intensity of peak with respect to IR spectrum of pure Fluoxetine Hcl, which indicates there was no interaction between drug and utilized polymers.

Table 1: Composition of Fluoxetine Hcl Oral Films

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Fluoxetine Hcl	160	160	160	160	160	160
HPMC	200	300	_	_	_	_
HPMC-E 15	_	_	200	300	_	_
HPMC-E 50	_	_	_	_	200	300
Propylene glycol (1%w/w)	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid	10	10	10	10	10	10
Sodium saccharin	10	10	10	10	10	10
Water	q.s	q.s	q.s	q.s	q.s	q.s

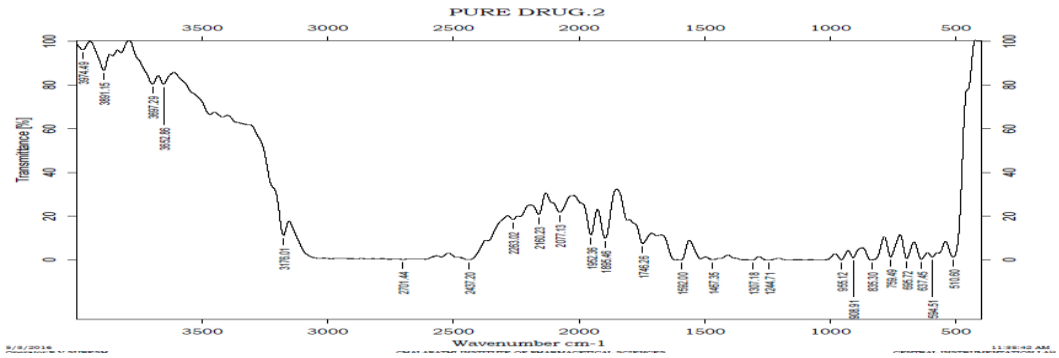

Figure 2: FT-IR spectrum of pure drug

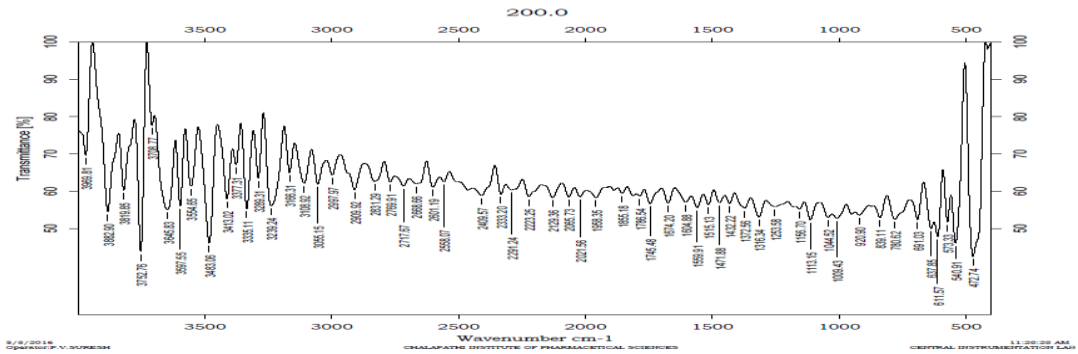

Figure 3: FT-IR spectrum of HPMC E-15 Optimized film

Table 2: Physical Characterization of Fast Dissolving Oral Films

formulation code	film thickness (mm) (n=3)	weight of the films (mg) (n=3)	folding endur-ance of the films (%) (n=3)	surface p^{h} (n=3)	disintegration time (sec) (n=3)	Content uniformity (%) (n=3)
F1	0.2±0.02	25.33±0.1	266.66±4.16	6.63±0.15	96	98.0±1.00
F2	0.25±0.02	32.33±0.2	297.33±2.51	6.66±0.15	108	99.0±1.00
F3	0.2±0.02	25.66±0.1	117.66±2.51	6.30±0.10	32	100.3±1.15
F4	0.25±0.02	32.33±0.2	134.66±4.50	6.50±0.20	40	97.6±0.57
F5	0.2±0.02	25.66±0.1	158.00±2.0	6.63±0.15	54	98.3±1.15
F6	0.25±0.02	33.00±0.2	174.33±2.08	6.43±0.15	63	100.6±1.52

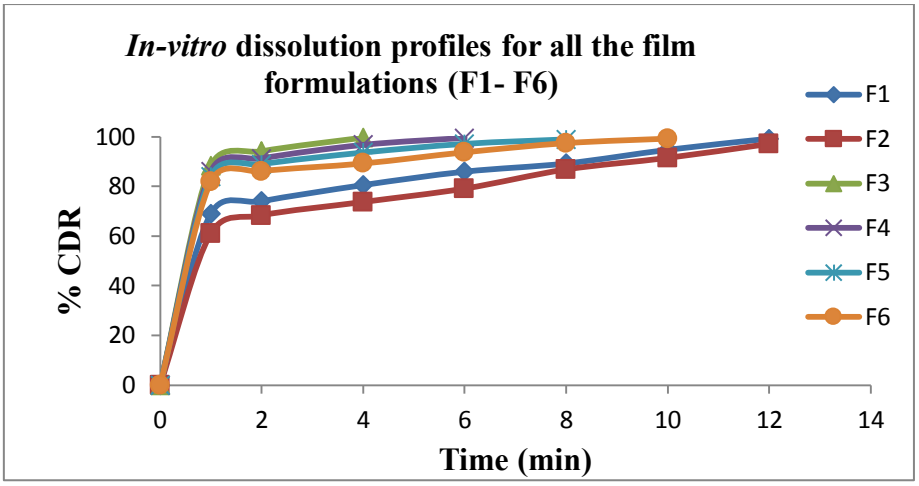

Figure 4: *In-vitro* dissolution profiles for all the film formulations (F1- F6)

EVALUATION

Fast dissolving oral films (F1-F6) containing Fluoxetine Hcl were prepared by solvent casting method by using HPMC & its polymers (E-15 and E-50) and propylene glycol as a plasticizer and all the formulations were evaluated for their physicochemical parameters like film thickness, weight of the films, surface pH, folding endurance, disintegration time, drug content and *in-vitro* dissolution studies. The results for all the evaluation tests were shown in **table 2**.

Visual inspection

All the films prepared were found to be flexible, smooth, non-sticky, homogenous, light yellow colored and transparent with no visible particulate matter.

Weight variation

The values obtained for weight variation were in the range of 25-33 mg, which revealed that the weight of the films varied with polymer concentration and an increase in polymer concentration resulted in increase in weight of the film, but the increase was marginal.

Thickness measurements

Thickness of mouth dissolving film depends on the concentration of polymer. Thickness of all mouth dissolving films was measured with vernier calipers and the thickness was found to vary between 0.2 to 0.25mm with very low standard deviation value. A very low standard deviation value indicating that the method used for the formulation of films gives films of uniform thickness and hence dosage accuracy in each film can be ensured. The results indicating that as the concentration of polymer increases, thickness of fast dissolving film increases.

Folding endurance

Folding endurance gives an indication about brittleness of the film. The folding endurance of the prepared films was found to be ranged from 115 to 300. Among all the formulations, F2 formulation showed higher folding endurance of 300. From the results it was concluded that as the concentration of polymer increases, folding endurance of fast dissolving films also increases.

Surface pH study:

The surface pH of the films was found between 6.2-6.8. The surface pH of all the formulations were close to the neutral pH, which indicated that films may have less potential to irritate the oral mucosa, and hence, more acceptable by the patients.

Disintegration time

It was observed that *in-vitro* disintegration time varies from 32-108sec. *In-vitro* disintegration time of the films was found to be increased with increasing the concentration of the polymer, because high concentration of poly-

mer resulted in a thicker gel upon contact with the medium, resulting in longer disintegration time. From all the formulations, F3 formulation showed less disintegration time.

Drug uniformity

Drug content in all the films was found to be between 97 to 102%. As per USP requirements, the films were found to meet the criteria for content uniformity 85- 115 % of the label claim. It was observed that no significant difference in the drug content among all the films, which indicates that the drug was dispersed uniformly throughout the 4 cm^2 area of the film.

***In-vitro* release studies**

In-vitro dissolution studies were conducted for all oral film formulations (F1-F6) by using USP type I (Basket) apparatus in simulated salivary fluid i.e., phosphate buffer of pH 6.8 to check the effect of type of polymer and its concentration on drug release. The *in-v*itro drug release data for all the oral films were shown in **figure 4**. From the dissolution profiles it could be concluded that formulation F1 containing HPMC (200mg) released the drug 99.2% at 12min time point due to more viscous nature of the polymer. Formulation F2 containing HPMC (300mg) released 97.1% of drug at 12min due to high retarding nature of the polymer which is due to increase in concentration of polymer than in formulation F1.Formulation F3 containing HPMC-E 15 (200mg) released 99.6% of drug at 4min time point due to less retarding nature of the polymer when compared to formulation F1 and F2. Formulations F4 containing HPMC-E15 (300mg) released 99.5% of drug at 6min time point due to increase in concentration of polymer when compared to F3, which resulted in slightly increase in viscosity of polymer.Formulation F5 containing HPMC-E50 (200mg) released 98.9% of drug at 8min time point due to increase in viscosity of polymeric solution than formulation F4.Formulation F6 containing HPMC-E50 (300mg) released 99.2% of drug at 10min time point due to still slightly increase in viscosity of polymeric solution than in formulation F5 but less viscous when compared to formulation F1 and F2.Among the six formulations, formulation F3 (containing HPMC E-15 200mg) was found to release 99.6% of drug within 4 min, which is desirable for faster absorption and rapid onset of action. Hence, F3 formulation was selected as the best formulation among six. From the results, it was also confirmed that as the molecular weight and viscosity of polymer increases, the drug release decreases and as the concentration of polymer increases, the drug release was found to decrease. In the present study, HPMC E-15 has less molecular weight and viscosity than HPMC E-50 and HPMC. Hence, the drug release from the films made with HPMC E-15 was found to be faster than from films made with HPMC E-50 and HPMC. The drug release from different polymers was found to be in the following order.

HPMC E-15>HPMC E-50> HPMC

RELEASE KINETICS

The release kinetics for all formulations can be explained by comparing the correlation coefficients values for their Zero order and First order regression equations. The data has shown that correlation coefficient (R^2) values for First order plots were higher than that of Zero order plots. Thus the Fluoxetine Hcl film formulations were found to follow first order release kinetics; indicates the drug release is concentration dependent.

CONCLUSION

Fast dissolving films of Fluoxetine Hcl were prepared by solvent casting method using HPMC & its polymers (E-15 and E-50) and propylene glycol as a plasticizer. The formulated films were evaluated for their physicochemical parameters like thickness and weight of the films, surface pH, folding endurance, disintegration time, drug content, *in-vitro* release study. Among the six formulations prepared, formulation F3 (containing HPMC E-15 200mg) was found to release 99.6% of drug within 4 min, which is desirable for faster absorption and rapid onset of action. From the results, it was also confirmed that the molecular weight and viscosity of polymer increases drug release decreases and as the concentration of polymer increases drug release was found to decrease. In the present study, HPMC E-15 has less molecular weight and viscosity than HPMC E-50 and HPMC. Hence, the drug release from the films made with HPMC E-15 was found to be faster than from films made with HPMC E-50 and HPMC.

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