Research Article

Design and *In-vitro* Evaluation of Fast Dissolving Oral Films of Fluoxetine

Budarapu Divya*, Jeevana Jyothi Bandela
Institute of Pharmaceutical Technology, Sri Padmavathi Mahila Viswavidyalam, Tirupathi (A.P), India.
***Corresponding author's E-mail:** bdivya100@gmail.com

Received: 10-04-2022; **Revised:** 24-06-2022; **Accepted:** 30-06-2022; **Published on:** 15-07-2022.

ABSTRACT

The concept of fast dissolving oral films has become popular as an alternative to fast dissolving tablets. Oral films by reducing the frequency of dosage can provide maximum therapeutic efficacy, enhanced bioavailability and stability. They will also skip the first pass metabolism of drugs. These advantages made this formulation most approved among geriatric and pediatric patients and patients with fear of choking. The present study aimed to develop and evaluate fast dissolving oral films of Fluoxetine HCl by using different film forming polymers like pullulan and PVA by solvent casting method. Six formulations of Fluoxetine HCl were prepared using different ratio's of polymers. The films were evaluated for thickness, weight uniformity, folding endurance, in-vitro disintegration, in-vitro dissolution, FTIR studies, SEM, XRD studies, in-vitro wetting studies, % moisture uptake and drug content. Among all the formulations optimized formulation showed disintegration time within 1min with highest dissolution rate of 97.8% within 12min. Based on the results, it can be concluded that the developed formulation was successful to enhance drug delivery and onset of action.

Keywords: Solvent casting method, Pullulan, PVA, SEM, FTIR.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v75i01.035

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v75i01.035

INTRODUCTION

Oral fast dissolving film (OFDF) is one amongst the new approach to increase patient acceptance by enhancing dissolution. It's novel drug delivery system for the oral delivery of drug. The delivery system consists of very thin oral strip, that once placed on the patient's tongue or on any mucosal tissue, instantly wet by the saliva the film hydrates rapidly and adheres onto the location of application.[1] Oral fast dissolving film outlined as

"Solid dosage forms which disintegrates or dissolves within seconds when placed in the mouth without drinking water or chewing."

In 1970's fast dissolving drug delivery system were developed as an alternative to syrups, tablets and capsules for geriatric and pediatric patients who had difficulty ingesting typical oral solid dosage forms.[2] There are two types of oral fast disintegrating dosage form. They are mouth dissolving tablets and fast dissolving films. Mouth dissolving tablet have been linked with variety of issues including leaves residue in the mouth, causing a feeling of grittiness in the mouth, a fear of choking and trouble in swallowing tablets. To solve the disadvantages of mouth dissolving tablets, a novel drug delivery system was invented which is known as "fast dissolving films''.[3,4]

Fluoxetine is an anti-depressant belongs to the category of selective serotonin reuptake inhibitor[5] (SSRI) mainly used in the treatment of major depression, panic disorder and obsessive-compulsive disorder(OCD). Fluoxetine is sparingly soluble in water but freely soluble in water. It acts by inhibiting reuptake of serotonin in synapse which results in enhanced serotonin availability and neuro transmission.

The aim of the present work is to prepare oral films of Fluoxetine hydrochloride from its solid dispersions which were prepared by using Fluoxetine: PEG 4000 as a polymer in the ratio of 1:4 using solvent evaporation method.

MATERIALS AND METHODS

Pure sample of Fluoxetine was gifted by Strides shasun, Bangalore. Poly ethylene glycol was gifted by Mohini organics, Mumbai. Pullulan polymer was gifted by Kumar organics, Bangalore. All other chemicals and reagents used were of analytical grade.

Preparation of oral films using solid dispersions

Oral films of Fluoxetine hydrochloride solid dispersions were prepared using solvent casting method. The films formulated by using different ratios of polymers like pullulan and polyvinyl alcohol (PVA) were shown in table 1

Table 1: Formulation code of Fluoxetine oral films prepared by using pullulan and PVA polymers

Composition	OF1	OF2	OF3	OF4	OF5	OF6
Fluoxetine solid dispersions (1:4) (mg)	20	20	20	20	20	20
Pullulan (mg)	200	300	400	-	-	-
PVA (mg)	-	-	-	200	300	400
PEG 400 (ml)	0.4	0.4	0.4	0.4	0.4	0.4
Citric acid (mg)	20	20	20	20	20	20
Mannitol (mg)	20	20	20	20	20	20
Water	q. s	q. s	q. s	q. s	q. s	q. s

Method: Solvent casting method[6-8]

Weigh required quantity of polymer and allow it to swell in water and then heat it (if required) to dissolve in one beaker. In another beaker add Fluoxetine solid dispersions and other ingredients dissolve them in smaller portion of water. Both the solutions are combined by using high shear mixer. The solution formed is then casted on petri dish and dried at room temperature for 24h. The formed films were wrapped in butter paper and then in aluminum foil. The films are stored in desiccator. Six formulations were prepared using different polymers like pullulan and poly vinyl alcohol and their compositions were shown in table 1.

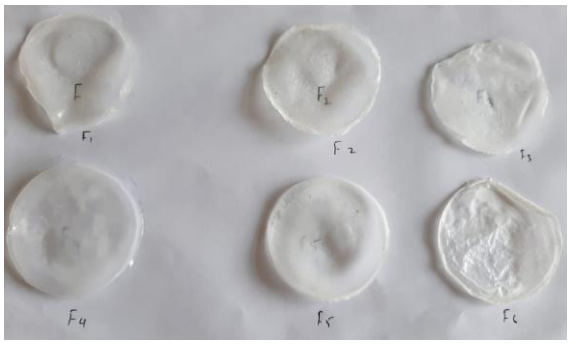

Figure 1: Fast dissolving oral films of different formulations of Fluoxetine HCl

Evaluation of Fluoxetine oral films:[9-12]

Thickness of the film

Thickness of every oral film was determined at 5 different places like corners and center of the film using screw gauge. Average of three values and standard deviation were calculated. Evaluation of thickness of film is important to determine the uniformity which is related directly to the dose accuracy.

Weight uniformity

Three films of 2.5×2.5 cm^2 were taken randomly from each formulation. Films were weighed individually using electronic balance. Mean weight was calculated for every batch.

Folding endurance

Folding endurance can be calculated by folding the film continuously until it breaks. The number of times the film was folded without breaking is considered as folding endurance value.

In-vitro disintegration time

A film of 2.5×2.5 cm^2 was taken and placed in a petridish containing 2ml of distilled water. Time taken by the film to dissolve completely is considered as disintegration time.

Drug content

A film of 2.5×2.5 cm^2 was taken and placed in a 10ml volumetric flask containing 6.8 pH phosphate buffer. This solution is shaken for 1h in mechanical shaker to get a homogenous solution. The solution is then filtered and estimated spectroscopically for drug content at 226nm.

Scanning electron microscopy (SEM)

External and surface morphology of plain drug (Fluoxetine HCl) and optimized oral film formulation can be visualized using scanning electron microscopy (JEOL JSM-IT 500, Japan).

FTIR studies

Fourier transform infra red studies are used to check the chemical interaction in between drug and other polymers or excipients used in the formulation. Oral films are placed on sampler and spectrum was recorded by scanning in 4000-400 cm^{-1} wavelength region using FTIR spectrophotometer.

In-vitro dissolution studies

Dissolution studies were carried in 500ml of 6.8 pH phosphate buffer using USP XXI dissolution apparatus (basket type) (Electro lab, India) maintained at 50rpm with a temperature of 37±0.2^{0}c. A film of 2.5×2.5 cm^2 was taken and placed in a dissolution medium. At specified time interval, 5ml of sample was withdrawn and a similar amount of buffer was added to the dissolution medium to maintain sink condition. Samples withdrawn at 0, 1, 2, 4, 6, 8, 10, 12 and 14min and were assayed for drug release using UV-visible spectrophotometer (Systronics, India) by measuring absorbance at wavelength of 226nm.

X-ray diffraction studies

In this study optimised formulations were analysed at an angle of 2Θ over a range of 0-5^0 with a scan rate of 2^0/min. Powder X-ray patterns of optimised formulation (OF3)

were recorded and compared with the X-ray pattern of Fluoxetine pure drug.

% moisture loss[13-15]

A film strip of 2.5 × 2.5 cm^2 was taken and placed in a desiccator containing fused anhydrous calcium chloride after weighing for 3 days. After 3 days the film strip was taken out from desiccator and weighed again to determine the loss of moisture.

% Moisture loss = Initial weight – Final weight / Initial weight × 100

In-vitro wetting time[13]

In this study 6ml of 0.1% amaranth dye solution was prepared and placed in a petriplate containing circular tissue paper. A film strip of 2.5 × 2.5 cm^2 was taken and placed in a petri dish containing circular paper. The time within which the dye appear on the surface is considered as wetting time.

RESULTS AND DISCUSSION

Thickness of the film

Concentration of polymer used plays an important role in the thickness of the film. Thickness of every oral film was measured using screw guage at different places and the thickness varies between 0.30mm to 0.38mm shown in table 2.

Weight uniformity

Weight variation values of the films range in between 137-190mg, which clearly indicates that the weight of the film depends on polymer concentration. Increase in polymer concentration enhances the weight of the oral film.

Folding endurance

Brittleness of the film can be determined by repeatedly folding the film until it breaks. The folding endurance of all the films were in the range of 84-189. Among the 6 formulations, films formulated with PVA as a polymer showed high folding endurance compared with pullulan. Higher values of folding endurance suggests that the films are strong to withstand handling.

In-vitro disintegration time

In-vitro disintegration time for all the oral films varies from 27-56 sec. It was observed that, with the increase in the polymer concentration disintegration time of the films increased. Higher the concentration of polymer thicker the gel formed upon contact with medium, prolonging the disintegration time. Among all the films, films formulated with pullulan polymer showed less disintegration time.

Table 2: Evaluation Data of Fluoxetine Oral Films

Formulation	Physical appearance	Thickness (mm)	Folding endurance	Weight variation (mg)	Disintegration (seconds)
OF1	Thin, sticky	0.30 ± 0.05	84.66±1.69	144 ±0.5	27.66 ± 1.52
OF2	Thin, sticky	0.32 ± 0.005	89.33±1.247	163.58 ±1.01	33 ± 2.00
OF3	Thin, non-sticky	0.36 ± 0.015	95.33±2.00	190 ±2.5	39.33 ± 2.51
OF4	Thin, slightly sticky	0.33 ± 0.05	135±1.632	137.4 ±0.85	38.33 ± 4.16
OF5	Thin, slightly sticky,	0.35 ± 0.05	153±1.632	158.5 ±0.81	44.66 ± 2.51
OF6	Thick, non-sticky	0.38 ± 0.015	189±2.00	188.23 ±1.25	56 ± 1.5

Drug content

Drug content varies between all the films. According to USP requirement, criteria for drug uniformity should be 85%-115% of the label claim. All the six formulations showed % drug content from 95.28%- 96.49% which clearly indicates uniformity of drug throughout the area of film as shown in table 3.

Table 3: Drug uniformity data of Fluoxetine oral films

Formulation code	% Drug content
OF1	96.3% ± 0.2081
OF2	95.9% ± 1.527
OF3	96.49% ± 0.378
OF4	95.63% ± 0.351
OF5	95.8% ± 0.251
OF6	95.28% ± 0.2

Scanning electron microscopy (SEM)

Scanning electron microscope (JEOL JSM-IT500, Japan) was used to observe the surface morphology of the film. The film sample was placed in the sample holder and photomicrographs of OF3 and OF6 were taken at different magnification as shown in fig 2-3.

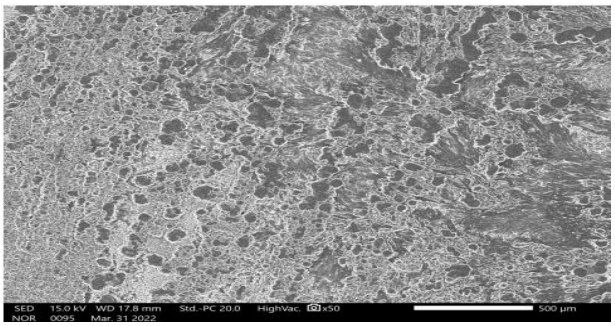

Figure 2: SEM image of OF3 (Fluoxetine+pullulan) oral film

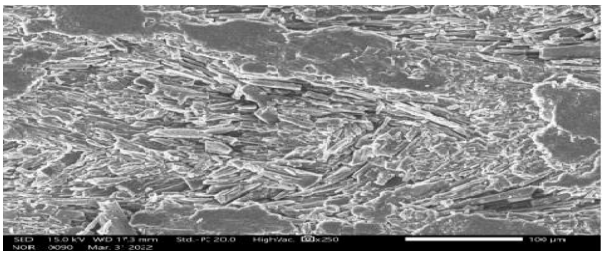

Figure 3: SEM image of OF6 (Fluoxetine+PVA) oral film

FTIR studies

FTIR spectrophotometer was used to establish physicochemical compatibility of drug and polymers. FTIR studies were conducted for selected formulations of Fluoxetine prepared with film forming polymers like pullulan and PVA. The spectrum peak points of pure Fluoxetine HCl and formulations were similar clearly indicating that there is no compatibility between drug and polymer as shown in fig 4-5.

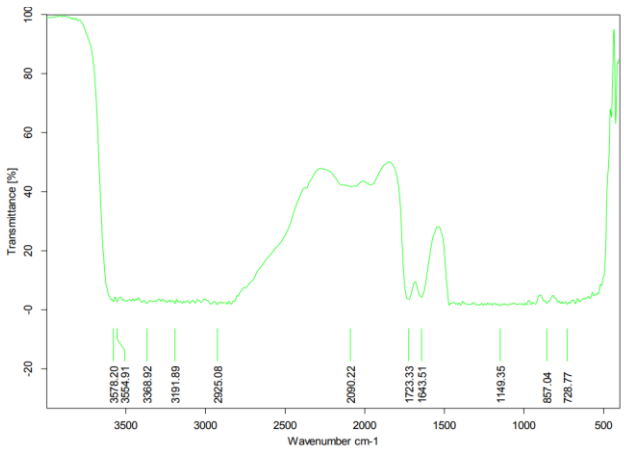

Figure 4: FTIR graph of (Fluoxetine + pullulan) oral film

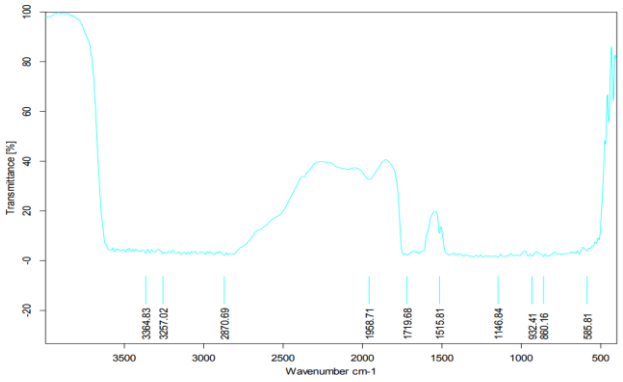

Figure 5: FTIR graph of (Fluoxetine + PVA) oral film

***In-vitro* dissolution studies**

Dissolution studies were conducted for all the formulations using USP type I apparatus (Basket) in 6.8 pH phosphate buffer as dissolution medium. The in-vitro release data of oral films were shown in table 4, fig 6. From the release data, it was observed that formulation OF1 to OF3 containing pullulan as polymer showed drug release from 95.07% to 97.08% in 12 min whereas OF4 to OF6 formulations containing PVA as polymer showed drug release from 95.46% to 97.04% in 14 min.

Table 4: *In-Vitro* release data of different formulations of Fluoxetine oral films

Formulation code	% Drug release
OF1	95.07% ± 0.2
OF2	95.53% ± 0.1
OF3	97.8% ± 0.2
OF5	95.46% ± 0.1
OF6	96.06% ± 0.208
OF7	97.04% ± 0.264

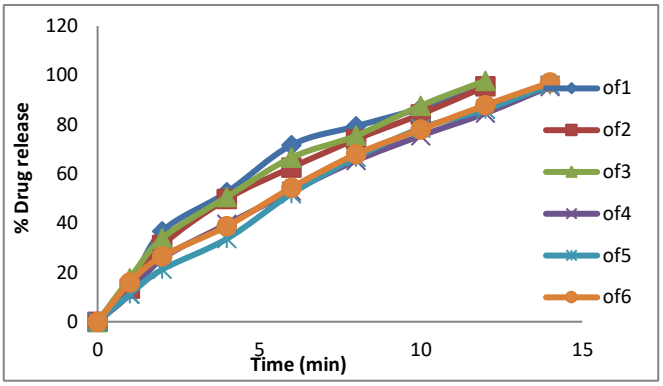

Figure 6: *In-Vitro* drug release of different formulations of Fluoxetine oral films

X-ray diffraction studies

Reduction in the intensity of peaks and peak heights are observed at 13.87, 14.52, 16.43, 20.27, 21.95, 24.26 indicating decrease in crystallinity of drug. Absence of peaks of Fluoxetine pure drug in oral films, presence of new diffraction peaks in oral films may be related to change of crystallinity of drug to amorphous nature as shown in below figures.

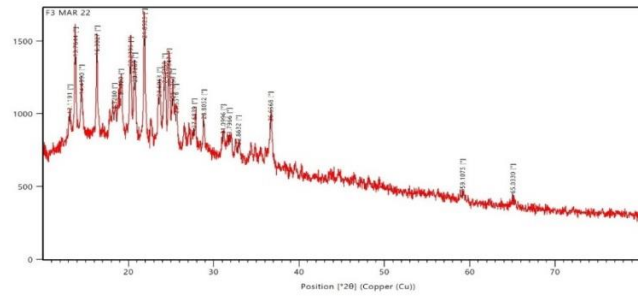

Figure 7: X-Ray diffraction pattern of OF3 oral film of Fluoxetine

% Moisture loss

The physical stability and integrity of oral films can be measured by conducting percent moisture loss studies. From the results obtained, it was clear that the percent moisture loss of all the formulations ranges in between 1.01 ± 0.02 to 2.63±0.02 clearly indicating increase in moisture loss with increase in polymer as shown in the table 5.

Table 5: % Moisture loss of different formulations of Fluoxetine oral films

Formulation code	% Moisture loss
OF1	1.38±0.01
OF2	1.57±0.03
OF3	2.63±0.02
OF4	1.01±0.02
OF5	1.32±0.05
OF6	2.11±0.01

***In-vitro* wetting time**

Wetting time varies between all the films. Decrease in wetting time was observed with the increase in the concentration of polymer. Wetting time was evaluated to estimate disintegration behaviour of films. Wetting time of all six formulations were showed in table 6.

Table 6: *In-vitro* wetting time data of Fluoxetine oral films

Formulation code	Wetting time(seconds)
OF1	24
OF2	21
OF3	19
OF4	35
OF5	32
OF6	28

CONCLUSION

The conclusions are as follows

1. The thickness of all the films varies between 0.30mm to 0.38mm.
2. Weight variation of films from OF1 to OF6 range in between 137-190mg showing increase in the weight of the oral film with increase in polymer concentration.
3. Folding endurance of oral films were in the range of 84- 189. Films formulated with PVA as polymer showed high folding endurance compared with pullulan.
4. *In-vitro* disintegration time varies between 27- 56sec. Films formed with PVA showed high disintegration time.
5. From the % drug content, uniform distribution of drug throughout the film area was cleared.
6. From SEM images, surface morphology of oral films was observed.
7. FTIR studies proved no chemical interaction between drug and polymer.
8. *In-vitro* dissolution studies cleared OF3 showed 97.8% in 12min.
9. From X-ray diffraction studies, reduction in crystallinity of pure drug was observed.
10. Percent moisture loss indicated increase in moisture loss with increase in polymer concentration.
11. From *in-vitro* wetting studies, with the increase in concentration of polymer decrease in wetting time was observed.

Acknowledgement: I wish to thank Prof Dr. B. Jeevana Jyothi madam, for her guidance who made this work possible. Her guidance and advice supported me in all the stages of conducting and writing my research work.

REFERENCES

1. Abhishek Meher, Nachiket S. Dighe, “An overview of fast dissolving oral film”, Journal of Drug Delivery and Therapeutics, 2019; 9(4-s): 822-825. DOI: https://doi.org/10.22270/jddt.v9i4-s.3428
2. Nagaraju T, Gowthami R, Rajasekhar M, Sandeep S, Mallesham M, Sathish D, Shravan Kumar Y, “Comprehensive review on oral disintegrating films”, Curr Drug Deliv, 2013; 10(1): 96-108. doi: 10.2174/1567201811310010016.
3. Bhupinder Bhyan, Sarita Jangra, Mandeep Kaur, Harmanpreet singh, “Orally fast dissolving films: Innovations in formulation and technology”, International Journal of Pharmaceutical Sciences Review and Research, 2011; 9(2): 50-57.
4. Priyanka Gupta, Amrita Bisht, Raghavendra Rao. N.G, “Fast dissolving oral films: A comprehensive review”, WJPMR, 2019; 5(7): 116-127.
5. Himani, Garg Rajeev, “Oral dissolving films: A review,” IAJPS, 2018; 5(10): 10315-10326. Doi: http://doi.org/10.5281/zenodo.1466025
6. Seeta devi. A, Naga jyothi. P, Charan raju. P,Kiran kumar. P et al., ”Formulation and evaluation of fast dissolving oral films of Fluoxetine hydrochloride”, J Global Trends Pharm Sci 2016;7(3):3394-3400.
7. Usha kiran reddy T, Sunil kumar reddy K, Manogna K, Thyagaraju K, “A Detailed review on fast dissolving oral films”, IAJPR, 2018; 8(6):1315-1326.
8. Arun Arya, Amrish Chandra,” Fast dissolving oral films: An innovative drug delivery system and dosage form”, International journal of ChemTech Research, 2010; 2(1): 576-583.
9. Shimoda H, Taniguchi K, Nishimura M, Matsuura K, Tsukioka T, “Preparation of fast dissolving oral thin film containing dexamethasone: a possible application to antiemesis during cancer chemotherapy”, Eur J Pharm Biopharm, 2009; 73(3): 361-5.
10. Dixit RP, Puthli SP, “Oral strip technology: Overview and future potential”, Journal of control release, 2009; 139(2): 94-107.
11. Mukesh Gohel, Madhabhai Patel, Avani Amin, Ruchi Agrawal, “Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique”, APS PharmSciTech, 2004; 5(3): 10-15.

12. Rama Krishna K," Formulation and In-vitro evaluation of Loratidine fast dissolving films," IAJPS, 2014; 1(4): 275-283.

13. Sharma Pravin Kumar, Sharma Pankaj Kumar, Darwhekar Gajanan N, Shrivastava Birendra," An overview about novel fast dissolving oral films", International Journal of Drug Regulatory Affairs, 2018; 6(1): 1-7. Doi https://doi.org/10.22270/ijdra.v6i1.220

14. Rajni Bala, Shailesh Sharma, IKGPTU, "Formulation optimization and evaluation of Fast dissolving film of aprepitant by using design of experiment," Bulletin of faculty of pharmacy, 2018, Cairo university 2018;56: 159-168. DOI:10.1016/j.bfopcu.2018.04.002

15. Syed Naiem Raza, Aabid Husain Kar, Taha Umair Wanii and Nisar Ahmad Khan," Formulation and evaluation of mouth dissolving films of Losartan potassium using 3^2factorial design," IJPSR, 2019; 10(3): 1402-1411.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.