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 ratios 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 1 min with highest dissolution rate of 97.8% within 12 min. 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.

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 the 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 (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

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.

Evaluation of Fluoxetine oral films:

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 cm² 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 cm² 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 cm² 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°C. A film of 2.5×2.5 cm² 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° with a scan rate of 2°/min. Powder X-ray patterns of optimised formulation (OF3)
were recorded and compared with the X-ray pattern of Fluoxetine pure drug.

% moisture loss\textsuperscript{13-15}

A film strip of 2.5 × 2.5 cm\textsuperscript{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\textsuperscript{13}

In this study 6ml of 0.1% amaranth dye solution was prepared and placed in a petri plate containing circular tissue paper. A film strip of 2.5 × 2.5 cm\textsuperscript{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 variation (mg) | Weight (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.
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.

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.

| Formulation code | % Drug release   |
|------------------|------------------|
| OF1              | 95.07% ± 0.2     |
| OF2              | 95.53% ± 0.1     |
| OF3              | 97.8% ± 0.2      |
| OF4              | 95.46% ± 0.1     |
| OF5              | 96.06% ± 0.208   |
| OF6              | 97.04% ± 0.264   |

% 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.

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