Formulation and Evaluation of Fast Dissolving Oral Films of Diazepam

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Abstract

Oral films dissolve rapidly along with drug in mouth and majority of the drug is absorbed through buccal/oral mucosa in to systemic circulation avoiding first pass metabolism. The aim of present investigation was to formulate the Fast dissolving oral films (FDOF) of Diazepam an anti epileptic drug which is normally administered by intramuscular route or as rectal suppository in acute conditions of seizure emergencies. Oral films were prepared by solvent casting method using HPMC E3, E5, and E15 as a film formers and propylene glycol, PEG 400 as plasticizers and evaluated for mechanical properties, disintegration and in vitro dissolution. All formulations showed good mechanical properties and in vitro drug release. The optimized (F4A) Formulation (HPMC E5 and PEG 400) Exhibited drug release of 99.89% in 15 minutes which was significantly high when compared to marketed tablet valium (68.81%).

Introduction

Fast dissolving films for oral administration was a novel approach, for the patients who experience difficulties in swallowing tablets or capsules. Geriatric, pediatric and dysphasic patients associated with many medical conditions face a problem of difficulty in swallowing the solid dosage forms. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets [1]. Oral fast-dissolving drug-delivery systems were developed in the late 1970’s to overcome the problem of difficulty in swallowing solid dosage forms [2]. These systems consist of oral dispersible tablets (ODT) that disintegrate and dissolve quickly in the oral cavity. Oral strips and oral films which rapidly dissolve under the tongue or buccal cavity, could also improve the dissolution of poorly soluble drug.

Epilepsy is a neurological disease characterized by seizures. It is a common chronic neurological disorder which affects 1-3% of population. Treatment of choice in acute conditions of seizures, status epileptics is by administering diazepam rectally before hospitalization and lorazepam by IV route [3]. Administration diazepam as oral films is preferred and convenient route of administration compared to rectal route of administration.

Materials and Methods

Diazepam is a gift sample from Mylan pharmaceuticals inc. Hyd. Pullulan and Hydroxy propyl methyl cellulose E3, E5, E15 and Hydroxy propyl β-cyclodextrin and Glycerin are purchased from SD fine chemicals Mumbai, India. PEG 400, Propylene glycols are of from Merck Ltd, Mumbai, India. Glycerin purchased from S.D fine chem. Ltd, Mumbai, India.

Drug excipient compatibility

Analysis of pure drug, excipient and physical admixtures of the drug with excipient were carried out using DSC. The temperature range room temperature to 200°C.

Preparation of oral films

The oral fast dissolving films of Diazepam (5 mg/film) were prepared by solvent casting technique. Different viscosity grades of HPMC (E3, E5 and E15) as film formers and PEG 400, Propylene glycol were employed as plasticizers in the films.

Method of preparation:
- Required amount of polymer was weighed and dispersed in the solvent mixture of methyl and dichloromethane with the help of cyclo mixer to form a homogenous viscous solution.
- Required quantities of plasticizer and drug were added to the polymer solution and vortexed to get a clear solution.
- Then the solution was degassed in bath sonicator for 5 minutes.
- The bubble free solution was poured in to petriplates and dried under vacuum for about 1 h. Films after drying were removed and cut into the desired size. Formulations were prepared using HPMC E3, E5 and E15 at different drug: polymer ratios (1:4, 1:6, 1:8). Plasticizers PEG 400 and propylene glycol were used at 15% of the dry polymer weight. The compositions of the formulations were shown in table 1.

Evaluation

The formulations were evaluated by the following tests.

Content: Each Film was taken in 100 ml volumetric flask containing phosphate buffer pH 6.8 and sonicated for 20 m and the volume was made up to 100 ml. An aliquot of solution was filtered through 0.22 µ filter and the UV absorbance was measured at 231 nm and the drug concentration was determined, using standard graph obtained between concentrations (1 to 8 µg/ml).

Measurement of mechanical properties: Microprocessor based advanced force gauge tensiometer (DS 2 series) equipped with a 50 kg load cell was used to determine the mechanical properties of OFDFs.

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Film of 60x10 mm² was fixed between two clamps separated by a distance of 3 cm [4]. The lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and percent elongation values were calculated using the following formula.

\[ \text{Tensile strength} = \frac{\text{load at breakage}}{\text{film thickness} \times \text{film width}} \]

\[ \% \text{Elongation} = \frac{\text{increase in length}}{\text{original length}} \times 100 \]

**Folding endurance:** Folding endurance was determined by folding of the strip repeatedly at the same place till the strip breaks [5,6]. Number of times the film is folded without breaking is computed as the folding endurance value.

**Physical appearance and texture analysis of the films:** These parameters were checked simply with visual infection of films and by feel or touch [7].

**In vitro disintegration:** The film of (4.15cm²) size (unit dose) was placed on a petridish containing 10 ml of distilled water [8]. The time required for the film to break was noted as cursive in vitro disintegration time [9].

**In vitro dissolution:** Drug release from OFDFs was studied by using dissolution test apparatus. OFDFs of desired formulation were placed in the vessels of dissolution apparatus. Samples were collected at time intervals of 2, 5, 10, 15, 20, 25, 30, 40 and 60 m, replenished with equal volume of the blank solution. The samples were filtered immediately and analyzed for the drug concentration and percentage of drug dissolved or released. The release studies were performed on 3 films and mean values were taken [10-12].

**Stability Studies and Visual Inspection**

The drug-excipient compatibility study was performed by subjecting the drug: excipient mixture (1:1) ratio to 40°C temperature and 75 % RH. The samples at weekly intervals were analysed for drug content and by DSC. For a 

Period of 3 months.

These studies were conducted manually by visual inspection. The films were visually inspected for the and by hands for the appearance and texture (feel).

**Results and Discussion**

**Drug excipient compatibility studies**

The DSC thermo grams of the pure drug and drug: HPMC E5 mixture were shown in Figure1 sharp peak at 131.9°C and good compatibility with polymers. These study concluded that no excipient incompatibility.

**Evaluation of oral fast dissolving films**

**Thickness, weight variation and assay:** The assay, weight variation and thickness of all the films were within acceptable limits. The results for content, Tensile strength, elongation, folding endurance and drug release were shown in table 2.

**Mechanical properties of diazepam oral fast dissolving films:** Tensile strength value of optimized formulation (F4A) 2.1 ± 0.10Kg/m² and percent elongation 6.67 ± 0.62.

**Folding endurance:** The folding endurance of the optimized oral fast dissolving formulation (F4 A) 122.35 ± 6.45. The formulations containing PEG 400 were showing good results compared to propylene glycol and the formulations containing HPMC E5 (F4–F6) were showing better results compared to HPMCE3 and HPMC E15 [13,14]. The folding endurance of formulation with PEG 400 as plasticizer were higher compared to propylene glycol formulations (Table 3).

**Physical appearance and texture analysis:** These studies were conducted manually by visual inspection. This study the films made contained PEG 400 were shown good physical appearance and texture when compared with the films formulated by using propylene glycol.

**Assay, in vitro disintegration time:** The assay values of all the formulations were ranging from 97.69 to 99.72 %. The disintegration time was ranging between 41 to more than 4 minutes and results shown in table 4.

**In vitro release studies of prepared formulations:** The final formulation shows better drug release (99.89%) compared to the marketed tablet valium (roche) (68.81%) within 15 m (Figure 2).

**Stability studies:** DSC thermo gram of optimized formulation after accelerated stress conditions were given in the figure compared to the ASC without any significant change in its release profile and the drug content.
Table 2: Formulation parameters.

| Formulation code | Thickness(mm) Mean ± S.D | weight(mg) Mean ± S.D | Tensile strength (Kg/mm²) Mean ± S.D | Percent elongation Mean ± S.D | Folding endurance Mean ± S.D | Assay (%) Mean ± S.D | Disintegration time (sec) Mean ± S.D |
|------------------|---------------------------|------------------------|--------------------------------------|-------------------------------|-------------------------------|---------------------|-------------------------------------|
| F1A              | 0.243 ± 0.012             | 28.21 ± 0.56           | 0.606 ± 0.61                         | 1.92 ± 0.84                   | 99.33 ± 7.67                  | 99.46 ± 0.15       | 41 ± 0.93                           |
| F1B              | 0.254 ± 0.024             | 29.40 ± 0.67           | 0.628 ± 0.59                         | 1.99 ± 0.67                   | 98.41 ± 5.88                  | 97.69 ± 0.39       | 42 ± 1.26                           |
| F2A              | 0.283 ± 0.017             | 40.33 ± 0.61           | 0.670 ± 0.635                        | 2.29 ± 0.78                   | 95.66 ± 6.23                  | 98.74 ± 0.32       | 45 ± 1.29                           |
| F2B              | 0.286 ± 0.021             | 42.07 ± 0.49           | 0.732 ± 0.66                         | 2.24 ± 0.57                   | 93.66 ± 8.12                  | 99.09 ± 0.47       | 43 ± 0.78                           |
| F3A              | 0.290 ± 0.022             | 54.86 ± 0.59           | 0.810 ± 0.51                         | 2.74 ± 0.69                   | 103.33 ± 9.87                 | 99.15 ± 0.41       | 48 ± 0.98                           |
| F3B              | 0.300 ± 0.014             | 53.38 ± 0.51           | 0.760 ± 0.72                         | 2.4 ± 0.59                    | 105.25 ± 4.56                 | 98.94 ± 0.59       | 49 ± 1.98                           |
| F4A              | 0.290 ± 0.019             | 30.33 ± 0.44           | 2.1 ± 0.10                           | 6.67 ± 0.62                   | 122.35 ± 6.45                 | 99.31 ± 0.15       | 43 ± 2.12                           |
| F4B              | 0.297 ± 0.014             | 31.80 ± 0.59           | 1.98 ± 0.16                          | 6.34 ± 0.81                   | 120.66 ± 5.29                 | 99.20 ± 0.23       | 45 ± 0.87                           |
| F5A              | 0.309 ± 0.019             | 43.41 ± 0.62           | 2.18 ± 0.11                          | 6.1 ± 0.93                    | 128.66 ± 5.87                 | 99.05 ± 0.32       | 50 ± 0.98                           |
| F5 B             | 0.312 ± 0.023             | 44.77 ± 0.53           | 2.05 ± 0.46                          | 6.06 ± 0.87                   | 125.66 ± 7.55                 | 99.05 ± 0.23       | 52 ± 1.78                           |
| F6 A             | 0.318 ± 0.026             | 51.41 ± 0.51           | 2.19 ± 0.71                          | 6.5 ± 0.53                    | 111.02 ± 8.55                 | 98.74 ± 0.23       | 58 ± 1.87                           |
| F6 B             | 0.320 ± 0.018             | 52.10 ± 0.61           | 2.07 ± 0.62                          | 5.94 ± 0.88                   | 110.2 ± 9.45                  | 99.10 ± 0.39       | 59 ± 1.98                           |
| F7 A             | 0.310 ± 0.022             | 28.67 ± 0.66           | 2.34 ± 0.25                          | 4.35 ± 0.66                   | 114.33 ± 8.33                 | 99.52 ± 0.63       | 87 ± 0.97                           |
| F7 B             | 0.311 ± 0.016             | 29.00 ± 0.48           | 2.35 ± 0.46                          | 4.29 ± 0.67                   | 112.33 ± 5.88                 | 99.72 ± 0.23       | 88 ± 0.81                           |
| F8 A             | 0.524 ± 0.019             | 39.72 ± 0.49           | 2.48 ± 0.87                          | 3.9 ± 0.91                    | 117.33 ± 8.23                 | 99.28 ± 0.39       | 120 ± 1.67                          |
| F8 B             | 0.527 ± 0.020             | 40.92 ± 0.51           | 2.43 ± 0.15                          | 3.21 ± 0.21                   | 101.21 ± 6.21                 | 99.09 ± 0.21       | 121 ± 0.92                          |
| F9 A             | 0.630 ± 0.025             | 51.12 ± 0.21           | 2.54 ± 0.35                          | 2.89 ± 0.45                   | 105.12 ± 8.10                 | 99.04 ± 0.26       | 240 ± 1.62                          |
| F9 B             | 0.632 ± 0.010             | 53.01 ± 0.34           | 2.49 ± 0.15                          | 2.21 ± 0.24                   | 103.40 ± 5.12                 | 99.06 ± 0.50       | 230 ± 1.22                          |

Data represents Mean ± Standard deviation, n=3

![Figure 1: DSC thermo grams of a) Diazepam pure drug and b) Diazepam pure drug, HPMC E5 mixture in a ratio of 1:1.](image-url)
Discussion

Evaluation properties

Tensile strength: The tensile strength of formulation made of higher viscosity grade i.e HPMC E15 is competitively high (2.54 kg/m²) when compared to formulation E3 (0.7 kg/m²) [17].

Percent elongation: The percent elongation of formulation made of HPMC E5 was greatest i.e. 5.94 to 6.67 compared to HPMC E3 (2.74) and HPMC E15 (4.35).

Folding endurance: The folding endurance value of the films prepared with HPMC E3 of ratios 1:4, 1:6 and 1:8 were ranged from 98.33 to 105.35. The folding endurance value of the films prepared with HPMC E5 of ratios 1:4, 1:6 and 1:8 were ranged from 122.35 to 128.66. The folding endurance value of the films prepared with HPMC E15 of ratios 1:4, 1:6 and 1:8 were ranged from 101.21 to 117.37. In the formulations as polymer concentration increases folding endurance values were also increased [18-21].

Disintegration time: The disintegration time ranged between 41± 1.26 to 128 ± 0.75 seconds. Disintegration time of the films was increase in polymer content, F1A and F4A formulations was quickly disintegrated that is in 41 and 43 sec respectively.

% In vitro dissolution: Formulation F4A with 1:4 ratio of HPMC E5 plasticizer PEG 400 was showed a disintegration time of 43 sec and exhibited good physical and mechanical properties such as tensile strength (2.1 ± 0.10 Kg/mm²) and percent elongation (6.67 ± 0.62) and it shown a cumulative percentage drug release of 99.78% within 15 min [22-24].
Stability studies
From the stability studies it was clearly observed that the drug showed good stability after subjecting to accelerated stress conditions and the polymers shown significantly compatibility with the drug.

Conclusion
From present investigation it can be concluded that oral fast dissolving films are superior in drug release when compared to marketed valium (Roche) tablets of diazepam. The films prepared by HPMC E5 and PEG 400 had shown good mechanical strength, drug release, disintegration time and stability. Diazepam administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for general population by providing faster release and better patient compliance.

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