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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 dissolves under the tongue or buccal cavity, could also improve the dissolution of poorly soluble drug.

Epilepsy is a neurological disease characterized by seizers. It is a common chronic neurological disorder which affects 1-3% of population. Treatment of choice in acute conditions of seizers, 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 Hydroxyl 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, excepient and physical admixtures of the drug with excepient 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 methanol 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 5minuts.
- 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.

Thickness: Randomly 10 films were selected and thickness was measured using a digital screw gauge, (Digimatic outside micrometer, Mitutoyo, Japan). The individual film was placed between two anvils of the screw gauge and sliding knob was rotated until the film was fitted. The digital reading displayed was noted.

Weight variation: 20 films were randomly selected from each formulation and the average weight variations were determined.

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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Formulation Code	Diazepam mg	HPMC E3 mg	HPMC E5 mg	HPMC E15 mg	PEG 400 mg	PG mg
F1A	75	300	_	_	45	_
F1B	75	300	_	_	_	45
F2A	75	450	_	_	67.5	_
F2B	75	450	_	_	_	67.5
F3A	75	600	_	_	90	_
F3B	75	600	_	_	_	90
F4A	75	_	300	_	45	_
F4B	75	_	300	_	_	45
F5A	75	_	450	_	67.5	_
F5B	75	_	450	_	_	67.5
F6A	75	_	600	_	90	_
F6B	75	_	600	_	_	90
F7A	75	_	_	300	45	_
F7B	75	_	_	300	_	45
F8A	75	_	_	450	67.5	_
F8B	75	_	_	450	_	67.5
F9A	75	_	_	600	90	_
F9B	75	_	_	600	_	90
All formulations with suffix A indicate the plasticizer PEG 400 and B indicates propylene glycol.						

Table 1: Formulation of Diazepam oral fast dissolving films.

Film of 60x10 mm^2 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.

Tensile strength = load at breakage/film thickness × film width

% Elongation = increase in length ×100/original length

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 (4.15cm^2) 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 calculated the 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-excepient compatibility study was performed by subjecting the drug: excepient 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

131.97°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/mm^2 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]. T he 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 of 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 that of the initially obtained DSC thermo grams of pure diazepam drug.

DSC thermograms of F4A after 45 days

The DSC of the optimized formulation after subjecting to accelerated for 45 days has been constructed and compared with that of the DSC thermograms. The characteristic peak of the diazepam was well retained in optimized formulation without any significant change after being subjected to the accelerated stress conditions for 45 days. Drug release profiles of the stability sample at 40 ± 2°C/75 ± 5% RH [15,16] (Figure 3).

The cumulative percentage (%) drug release profile and the assay of the F4 A formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content.

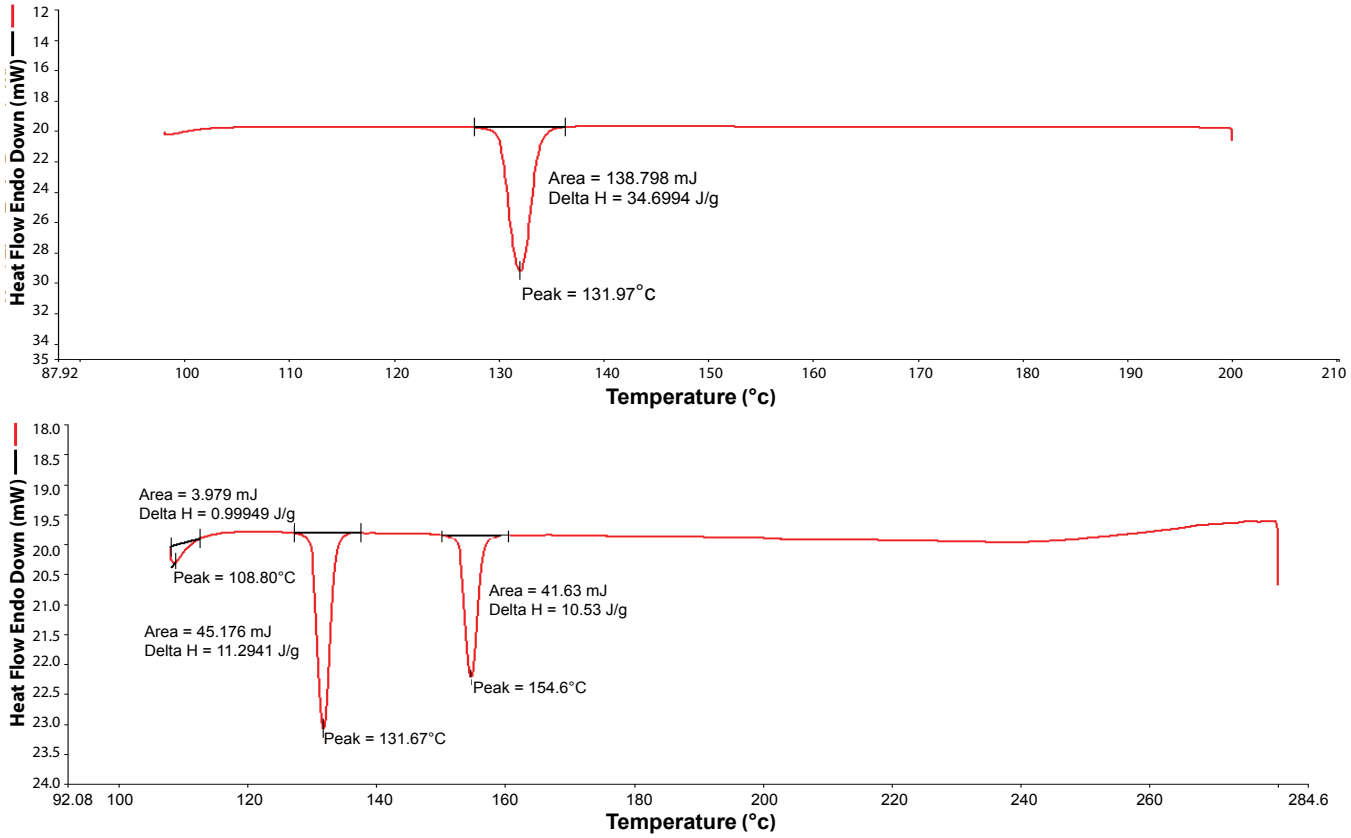

Figure 1: DSC thermo grams of a) Diazepam pure drug and b) Diazepam pure drug, HPMC E5 mixture in a ratio of 1:1.

Formulation code	Thickness(mm) Mean ± S.D	weight(mg) Mean ± S.D	Tensile strength (Kg/mm²) Mean ± SD	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 ± 0.82	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	99.26 ± 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							

Table 2: Evaluation parameters.

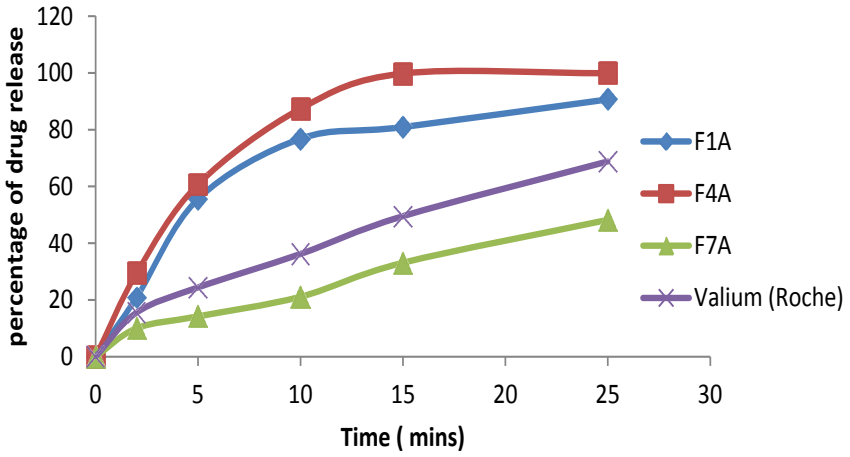

Figure 2: *In vitro* drug release profile of F1 A, F4 A, F7A and Valium (Roche) 5mg marketed tablet.

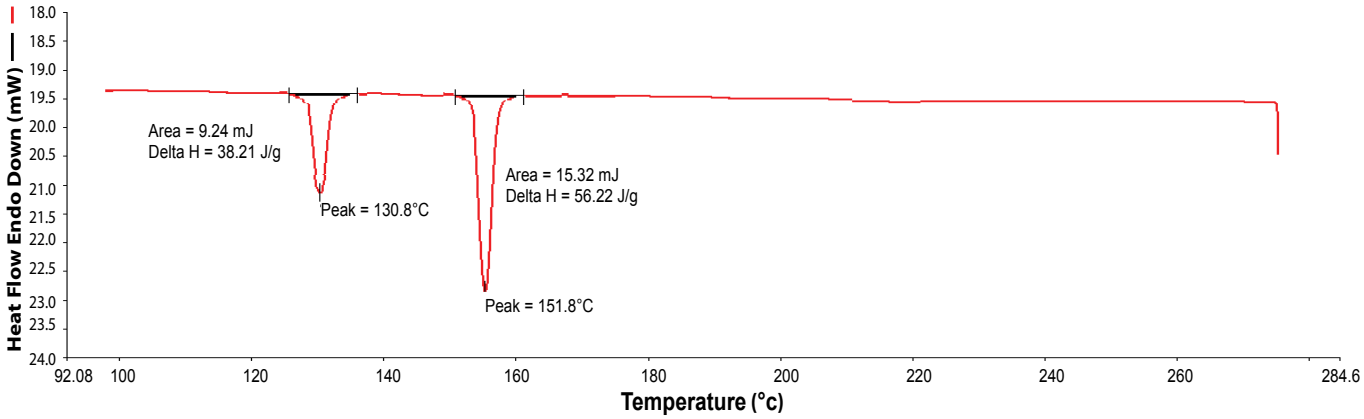

Figure 3: DSC thermograms of a) diazepam, b) Physical mixture of Drug + HPMC E5 c) F4 formulation (drug + HPMC E5).

Time (min)	Initial (F4 A) Mean ± SD	After 30 days	After 45 days
0	0	0	0
2	29.45 ± 2.12	27.21 ± 1.98	24.32 ± 2.91
5	60.74 ± 2.21	57.11 ± 3.12	58.61 ± 1.66
10	87.38 ± 2.10	82.33 ± 2.41	85.78 ± 2.64
15	99.78 ± 1.47	99.01 ± 2.18	99.25 ± 2.28

Table 3: Drug release profiles of the stability sample at 40 ± 2°C/75 ± 5% RH.

Time	Assay (% mean ± SD)	Release at 15 m
Initial	99.51 ± 1.49	99.78 ± 1.47
After 30 days	98.92 ± 1.78	99.01 ± 2.18
After 45 days	98.24 ± 1.44	99.25 ± 2.28

Table 4: Assay of the ASC subjected F4A formulation film.

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/mg) when compared to formulation E3 (0.7 kg/m^2) [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 to105.35. 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 with1:4 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/mm^2) 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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