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Research Article

Design, Development and Characterization of Fast Dissolving Oral Film of Clonazepam

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ABSTRACT

The present study proposed to prepare fast dissolving oral film containing clonazepam for the treatment of epilepsy. HPMC E15 and PEG 400 were used as film forming agent and plasticizer, respectively. Solvent casting method was used to prepare Clonazepam loaded fast dissolving oral films. The prepared films were characterized for weight variation, thickness, percent elongation, tensile strength, folding endurance, moisture content, content uniformity, surface pH and swelling index. The DSC and FTIR Spectra revealed that drug was compatible with the polymer. The prepared oral films were opaque in nature having good folding endurance. Shows the rapid release of drug in oral cavity. Drug release by diffusion (93.44 %) and by dissolution (98.32%) after 5 minute. All nine batches are rapid release of drug after film contact with saliva.

INTRODUCTION

According to US FDA, fast dissolving oral film is a sort of thin, flexible and non-friable polymeric film containing one or more dispersed active pharmaceutical ingredients. Fast dissolving oral film is intended to be kept in the buccal region for rapid disintegration or dissolution in the saliva before swallowing for drug delivery into the gastrointestinal tract [1].

In the last few decades, fast dissolving oral film has drawn much attention of researchers because of its distinct advantages over the other fast dissolving dosage forms. Fast dissolving oral film can be readily wetted and dissolved by saliva quickly without drinking water or chewing, allowing pediatric, geriatric or bedridden patients who have troubles in swallowing medicine [2, 3].

Fast dissolving oral film as a buccal drug delivery system, can enhance bioavailability by avoiding first-pass metabolism as well; as a result, patients can absorb drugs very fast through the rich vasculature of buccal region. For some special medicines which are vulnerable in gastrointestinal tract environment or have stomach irritation, it is also a good choice [4-7].

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Epilepsy is the most common chronic brain disease and affects people of all ages. Nearly 50 million people around the world have epilepsy, which makes it one of the most common neurological diseases worldwide. Around 80% of people having epilepsy live in countries with lower and middle-income. It is characterized by recurrent seizures, which are short episodes of involuntary movement that may involve one part of the body (partial) or the whole body (generalized) and are sometime accompanied by loss of consciousness, control of bowel or bladder function [8].

Clonazepam (CNZ), a chlorinated derivative of nitrazepam, is an anticonvulsant benzodiazepine widely used in the treatment of epilepsy. It is also effective in the management of some types of neuralgia [9].

It is also used in mycoclonus and associated abnormal movements, also for the treatment of panic disorders [10].

Moreover, it has recently been shown its efficacy also in the therapy of the burning mouth syndrome (BMS), pathology characterized by a painful burning sensation and/or other dysesthesias of the oral mucosa [11].

The present study intended to prepare fast dissolving oral film containing clonazepam for the treatment of epilepsy.

MATERIALS AND METHODS

Materials

Clonazepam was procured from Torrent Pharmaceuticals Ltd, Mumbai. HPMC E15, PEG 400 and Citric acid were obtained from Loba Chemicals, Mumbai. All other chemicals were of analytical grade and used as obtained.

Preparation of Fast Dissolving Oral Film

Weight accurate amount of polymer (HPMC E15) and socked in 10mL water for overnight. Required quantity of Clonazepam is dissolved in 10mL of water. Put in citric acid, mannitol and flavour and stirred for 45 minutes. Add the drug solution to the polymer solution with constant stirring. Finally, PEG 400 was introduced as a plasticizer and stirred it for 45 minutes. Sonicate the mixture for 15 minutes to remove the air bubbles. The clear homogenous solution obtained was casted on the petri dish (area, 63.58 cm^2), previously lubricated with glycerol. Then the films were cut in to size of 2×2 cm^2 containing 1 mg of clonazepam. The prepared films were stored at room temperature.

Table 1: Formulations of clonazepam loaded fast dissolving oral film

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clonazepam (mg)	15.89	15.89	15.89	15.89	15.89	15.89	15.89	15.89	15.89
HPMC (mg)	150	200	250	150	200	250	150	200	250
PEG400(ml)	10	10	10	20	20	20	30	30	30
Tween 80 (ml)	0.2	0.2	0.2	02	0.2	0.2	0.2	0.2	0.2
Mannitol(mg)	60	60	60	60	60	60	60	60	60
Citric acid(mg)	50	50	50	50	50	50	50	50	50
Lemon oil (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol (ml)	1	1	1	1	1	1	1	1	1
Water(ml)	20	20	20	20	20	20	20	20	20

Weight Variation of the Film

2×2 cm^2 film was cut at five different places in the caste film. The weight of each film/strip was taken on digital analytical balance and the weight variation was calculated [12] and the results are given in the Table 2.

Thickness of the Film

The thickness of the polymer films was measured by using screw gauge. The thickness of each film at 3 different areas was determined and standard deviation was calculated [13].

Tensile Strength

Film strip of dimension 2x2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. To prevent the film from being cut by the grooves of the clamp a cardboard was attached on the surface of the clamp via a double sided tape. For measurement, the strips were pulled at the bottom clamp by adding weights in the pan until film breaks, when the films break the force was measured [13, 14]. Tensile strength was calculated by using following formula:

$$\text{Tensile strength (kg/mm2)} = \frac{\text{Force at Break}}{\text{Initial cross sectional area of the film}}$$

Percent Elongation

Upon exerting stress on a film, the specimen stretches which is referred as strain. Strain can be defined as change in the length of film divided by its original / initial length of the film specimen. Percent elongation is associated quantitatively to the amount of plasticizer which is used in film formulation. Increased plasticizer concentration in the film usually results in enhanced elongation of strip. It is determined by the following formula [15]:

$$\text{Percentage elongation} = \frac{\text{Change in length}}{\text{Initial length}} \times 100$$

Folding Endurance

This parameter was determined by folding one film at the same place repeatedly till it breaks. The value of folding endurance can be obtained by the number of times the film could be folded at the same place without breaking / cracking it [13, 16].

Moisture Content

The prepared films are weighed individually and kept in a desiccator containing calcium chloride for 24 h at room temperature. The films are to be weighed again and again after specific intervals, until they show a constant weight. The percent

moisture content is calculated by using following formula [17].

$$\% \text{ Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Surface pH

The film to be tested was placed in a Petri dish and moistened with 0.5 ml of distilled water then kept for 1 h. The pH was noted down after bringing the electrode of the pH meter in contact with the surface of the formulation prepared and allowing equilibrium for 1.0 min [13, 14].

Content Uniformity

Films of 2x2 cm^2 were cut and placed in 100 ml volumetric flask and dissolved in phosphate buffer with pH 6.8, volume was made up to 100 ml with same buffer. Solution was suitably diluted. The absorbance of the solution was measured at 273 nm [13].

Swelling Index

The studies of swelling index of the film are conducted in simulated salivary fluid. The film sample is weighed and placed in a pre-weighed stainless steel wire sieve. The mesh containing the film was submerged in 50 ml of simulated salivary medium contained in a mortar. Increase in weight of the film is determined at every interval until a constant weight is observed. The degree of swelling is calculated using the formula [18]:

$$\text{Swelling index (SI)} = \frac{Wt - W0}{W0}$$

Where,

SI = swelling index,

Wt. = weight of the film at time "t", and

o = weight of the film at t = 0

***In Vitro* Disintegration Time**

The film of (2x2 cm^2) size (unit dose) was placed on a petridish containing 2 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time [13].

FTIR Spectroscopy

FTIR spectra are usually recorded in the middle infrared [4000 cm-1 to 650 cm-1] with a resolution of 4 cm-1 in the absorbance mode for 8 to 128 scans at room temperature. The samples for FTIR analysis are prepared by grinding the dry blended powders with powdered KBr, often in the ratio of 1:5 [Sample: KBr] and then compressed to form discs. Spectra are sometimes measured using a denudated triglycerine sulphate detector [DTGS] with a specific detectivity of 1 x 109 cmHz1/2 w-1 or on films using an attenuated total refraction [ATR] method in an IR spectrometer. Diffuse Reflectance Infrared Fourier-Transform [DRIFT] spectroscopic analysis is also applied [19].

Differential Scanning Calorimetry

Differential scanning calorimetry allow the fast assessment of possible incompatibilities, as it shows changes in the appearance, shift of melting endotherms and exotherms, and variations in corresponding enthalpies of reaction. The differential scanning calorimetric, thermograms of pure drug clonazepam and optimized fast dissolving oral film formulation were recorded on the thermal analyzer of equipped with an intercooler. The thermal analysis was performed at a heating rate of 10°C/min over temperature range of 30°C to 275°C in a nitrogen atmosphere [20].

***In Vitro* Dissolution Studies**

Dissolution studies were carried out by using USP type I (basket apparatus) with 300ml of Phosphate buffer having pH 6.8, as dissolution medium maintained at 37±0.5°C. For a period of 20 minutes medium was stirred at 50 rpm. Samples were withdrawn at definite interval of time, replacing the same amount with the fresh medium. Samples were suitable diluted with pH 6.8 and analyzed for drug content at 273 nm [13].

***Ex-Vivo* Drug Diffusion Studies**

Ex-vivo permeation studies were carried out through porcine oral mucosa of sheep (ventral surface of tongue) using the Franz diffusion cell of an internal diameter of 2.5 cm. The oral mucosa was excised and trimmed evenly from the sides, washed in isotonic phosphate buffer of pH 6.8 and used immediately. Before mounting, the membrane was strengthened to extract the soluble elements. The mucosa was installed between the rooms of the recipient and the receptor. The receptor compartment was filled with 15 ml of pH 7.4 isotonic phosphate buffer held at 37±0.2°C and preserved hydrodynamics using a magnetic stirrer. One film of dimension 2 cm 2 cm was placed in donor compartment. 1 ml phosphate buffer of pH 6.8 was loaded in the donation room. From receptor compartment 1 ml samples were withdrawn at specified intervals of time which was then replaced with 1 ml of pH 6.8 phosphate buffer. The percentage of clonazepam permeated was determined by using

UV Visible spectrophotometer at λ max of 273 nm [21].

Analysis of the Clonazepam Release Kinetics from the Fast Dissolving Oral Film

The release data of the fast dissolving oral films were modelled using different kinetic equations with a view to determine their mechanisms and kinetics of drug release. Zero order, First order, Korsmeyer - Peppas model, Higuchi model and Hixson Crowell model are the different kinetic equations.

RESULTS AND DISCUSSION

Clonazepam loaded fast dissolving oral films were successfully prepared by solvent casting method. All films were found opaque in nature upon visual appearance.

Weight Variation of the Film

Weight of the film was found to be in the range of 37.8 mg to 38.6 mg. Variation in the weight of each film was due to variation in concentration of excipient in each film. As there is increase in concentration of polymer; increase in weight of film (Table 2).

Thickness of the Film

The thickness of all films was found to be in range of 0.10 mm to 0.41 mm. The difference in the thickness of film was due to concentration of excipient which used in formulation (Table 2).

Tensile Strength

The tensile strength of all batches was found in the range of 1.80 to 4.40N/m^2. The difference in tensile strength is due to the concentration of polymer which having film forming property (Table 2).

Table 2: Weight variation, thickness and tensile strength of clonazepam oral film

Formulation code	Weight Variation (mg)	Thickness (mm)	Tensile Strength (N/m2)
F1	18.56	0.18	4.00
F2	22.53	0.22	4.11
F3	19.21	0.20	3.25
F4	20.21	0.23	3.40
F5	24.74	0.22	3.58
F6	21.25	0.25	2.80
F7	24.33	0.27	2.46
F8	26.45	0.24	2.20
F9	26.80	0.29	1.91

Percent Elongation

The percent elongation of all batches was found in range 100 to 120 % the equal concentration of plasticizers in percent elongation due to the equal elongation in all batches (Table 3).

Folding Endurance

After folding the film 30 times at same point still it will not shows any break or crack, the folding endurance was found in the range of 20 to 30. The folding endurance of film was due to PEG 400 which was used as plasticizer, as concentration of PEG 400 increased folding endurance of film also increased which imparts better flexibility and plasticity to films (Table 3).

Moisture Content

The moisture content of all batches was found to be in range of 2.29 to 3.70 %. The moisture contents are calculated by formula of moisture content (Table 3).

Table 3: Percent elongation, folding endurance and moisture content of clonazepam oral film

Formulation Code	Percent Elongation (%)	Folding Endurance (%)	Moisture Content (%)
F1	120	20	2.66
F2	130	26	3.43
F3	115	28	2.36
F4	115	30	3.36
F5	130	25	2.25
F6	135	28	3.79
F7	130	28	3.86
F8	135	29	2.63
F9	140	32	3.43

Surface pH

The surface pH of all the batches was found to be in the range of 6.3 to 6.7. The surface pH is calculated using digital pH meter and pH ranges were similar to the saliva pH (Table 4).

Content Uniformity

Determination of drug content was found to be in the range of 89.32 % to 95.83 %. On the basis of drug content *in vitro* dissolution studies were carried out (Table 4).

Swelling Index

The swelling index of formulated oral film was found in the range of 0.50 to 38 %. The swelling index of are calculated by using swelling index formula (Table 4).

In Vitro Disintegration Time

The disintegration study of all batches was found to be in a range of 2.1 min to 2.7 min. The difference in disintegration time of film was due to the concentration of disintegrant used. As there is increase in the concentration of HPMC E15, there is also increase in the disintegration time (Table 4).

Table 4: Surface pH, drug content, swelling index and disintegration time of clonazepam oral film

Formulation code	Surface pH	Drug content (%)	Swelling index (%)	Disintegration Time (Sec)
F1	6.4	90.69	0.91	76
F2	6.7	93.02	1.22	82
F3	6.3	96.51	1.00	69
F4	6.6	91.86	0.96	90
F5	6.5	94.18	0.96	95
F6	6.8	93.02	1.06	98
F7	6.4	95.34	1.07	103
F8	6.3	93.02	0.93	107
F9	6.8	97.67	0.93	116

FTIR Spectroscopy

The FTIR spectrum of pure clonazepam, shown in Fig. 1, an absorption band was observed, peaks of aldehyde 2925.48 cm-1 (CH Stretch), Alcoholic group like OH shown in 3293.82cm-1, structure in aromatic compound observed 1699.94 cm-1 (C = C stretch), structure containing ester group confirmed by peak 1743.33 cm-1 (C = O stretch) and 3495.35 cm-1 (NH Stretch) shows primary amine in structure. This information is described by the help of Fig. 6.6 and sample is combination of API and HPMCs polymer.

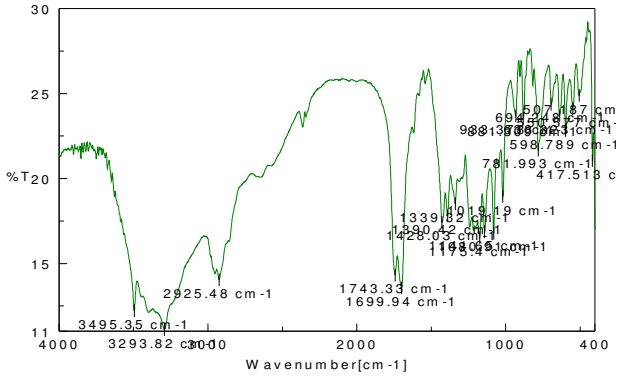

Figure 1: IR spectrum of formulation

Differential Scanning Calorimetry

DSC thermograms of pure drug and clonazepam-loaded fast dissolving oral film are shown in Fig. 2a. The endothermic peak of clonazepam at 238°C is reflected in clonazepam-loaded fast dissolving oral film (Fig. 2b) proving that drug and polymer are compatible to each other.

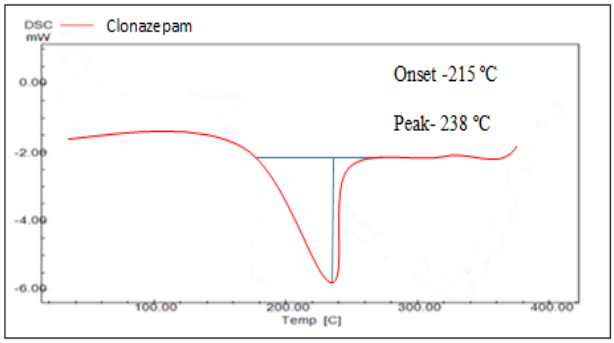

Figure 2a: DSC Thermogrram of Clonazepam

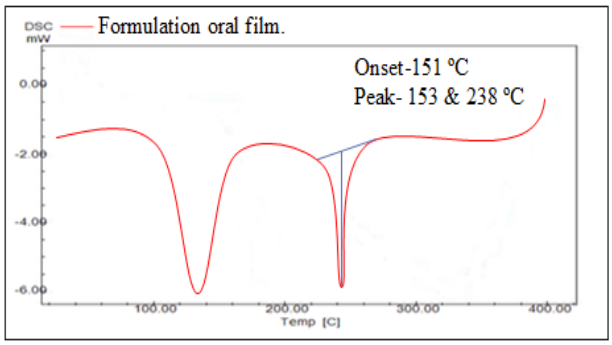

Figure 2b: DSC Thermogram of Formulation

In Vitro Dissolution Studies

After the dissolution study it observed that the drug release in up to 5 minute, it might be due to presence of HPMC and sodium starch glycolate which absorbed the surrounding fluid and release the drug. From the drug release studies of formulation F1 to F9, the drug release was found to be between 88.50 to 99.18 % at the end of 5 minute. The drug release profile for these formulations was shown in Fig. 3.

Ex-Vivo Drug Diffusion Studies

Diffusion study of batches F1 to F9 were carried out, which shows drug release in the range of 77.07 to 94.46 % the drug release extended up to 5 min, it might be due to the presence of HPMC and sodium starch glycolate which absorbed the surrounding fluid, swelled, dissolve and diffuse the drug (Fig. 4).

Analysis of the Clonazepam Release Kinetics from the Fast Dissolving Oral Film

Table 5 lists the values from applying the release data to different kinetic models. The formulation F9 was best explained by first order, as the plot showed the highest linearity (r^2 = 0.9863).

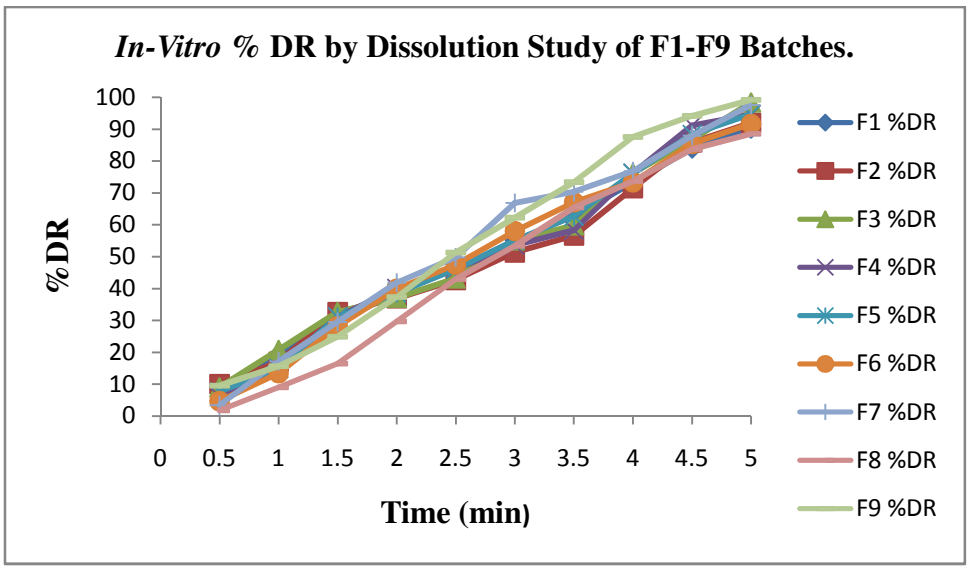

Figure 3: *In-Vitro* % DR by Dissolution Study of F1-F9 Batches.

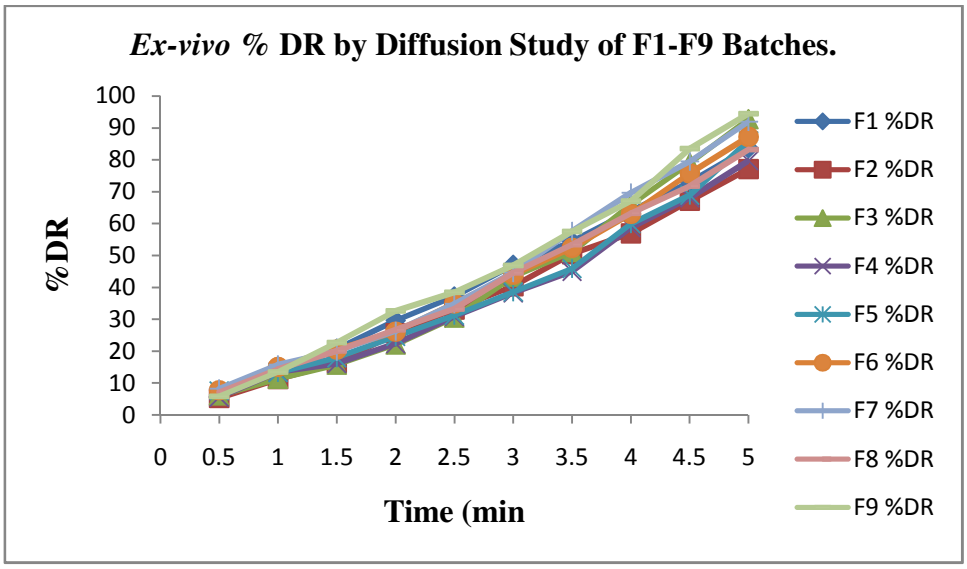

Figure 4: *Ex-Vivo* % DR by Diffusion Study of F1-F9 Batches.

Table 5: Kinetics models of *in-vitro* drug release of clonazepam oral films

Formulation Code	Regression coefficient (R^2)				
F9	Zero order	First order	Korsmeyer- pappas model	Higuchi model	Hixon Crowell model
	0.8534	0.9863	0.9625	0.9452	0.7871

CONCLUSION

HPMC E-15 was found use full to prepare fast dissolving oral films of Clonazepam. Film properties are affected by amount of the film forming polymer. The *in-vitro* dissolution time was very less in formulations F3, F7 and F9. Results obtained from *ex vivo* permeation study shows that formulations F3, F7 and F9 were found to be the best formulation. Therefore finally we conclude that mouth dissolving films of Clonazepam of HPMC E15 can meet the ideal requirements for fast release intra-oral devices. It can be a good alternative to bypass the widespread hepatic first pass metabolism and also increase the bioavailability.

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