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Original Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF ANTI-EPILEPTIC DRUG

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ABSTRACT

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. Clonazepam (CZ) is a benzodiazepine derivative with marked antiepileptic properties. It may be used in the treatment of all types of epilepsy and seizures. Thus the objective of the present study was to formulate and evaluate fast dissolving oral films of clonazepam to overcome the limitation of bioavailability and increase patient's compliance. Oral fast dissolving films prepared by solvent casting method using water and 95% ethanol as solvents and HPMC as film forming polymer. PEG 400 was the selected plasticizers, Superdisintegrants such as croscarmellose sodium (CCS) and sodium starch glycolate (SSG) alone and also in combinations was incorporated to achieve the aim. The prepared films were evaluated for the drug content, weight variation, film thickness, disintegration time, folding endurance, percentage of moisture content and *in vitro* dissolution studies. Among all, the formulation F4 was found to be best formulation which releases 98.78 % of the drug within 15 min and disintegration time is 42 sec. which was significantly high when compared to other formulation. The data obtained from In-vitro release were fitted into the various kinetic models such as Zero Order, Higuchi, First Order and Korsmeyer–Peppas Model in order to determine the mechanism of drug release. When the regression coefficient values compared, it was observed that 'r' values of formulation F4 was maximum i.e 0.974 hence indicating drug release from formulations was found to follow first order drug release kinetics.

Key words: Clonazepam, Fast dissolving oral film, Bioavailability, HPMC, Croscarmellose sodium, Sodium starch glycolate

INTRODUCTION

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages (Liang & Chen, 2001; Borsadia et al., 2003). They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in

the gastrointestinal tract (Klancke, 2003; Parakh and Gothoskar 2003). The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms (Liang and Chen, 2003; Klancke, 2003; Parakh and Gothoskar, 2003). These dosage forms possess certain specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance. United States Food and Drug Administration (USFDA) defined the fast dissolving oral thin films as a thin, flexible, non-friable polymeric film strip containing one or more dispersed/dissolved active pharmaceutical ingredients, which is intended to be placed on the tongue for rapid *in vitro* disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract (Parakh and Gothoskar, 2003]. Clonazepam (CZ) is a benzodiazepine derivative with marked antiepileptic properties. It may be used in the treatment of all types of epilepsy and seizures, practically insoluble in water, half life of about 20 h (Sweetman, 2002). Since epileptic patients have to strictly follow the dosage regimen for preventing sub-therapeutic concentration, FDF will avoid missing out of a dose even during travelling or other situations, where there is no access to water; offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Initial investigations were focused on the development of placebo fast dissolving films with good peelability, appearance and a quick disintegration time. After choosing the components for the placebo film, CZ loaded films were formulated. Although, fast dissolving film is an attractive dosage form for the delivery of CZ. Finally fast dissolving films using HPMC, CCS and SSG were formulated and evaluated.

Materials and Methods

Clonazepam were obtained as pure sample from Torrent Pharma, Ahmedabad as gift samples along with their analytical reports. HPMC K15M, PEG-400, SSG, CCS was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Citric acid, Glycerine was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Preformulation studies

Standardization of CZ by UV-Visible spectrophotometry

Preparation of stock solution: Stock solution 1000µg/ml CZ was prepared in phosphate buffer pH 6.8 solutions. This solution was suitably diluted with buffer solution to obtain a concentration of 15µg/ml. The resultant solution was scanned in the range of 200-400 nm using UV double beam spectrophotometer (Labindia 3000+, Mumbai).

Standard calibration of CZ: From stock solutions of CZ 1 ml was taken and diluted up to 10 ml. from this solution 0.5, 1.0, 1.5, 2.0 and 2.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up

to 10 ml with Phosphate buffer pH 6.8, gives standard drug solution of 5, 10, 15, 20, 25µg/ ml concentration, absorbance was measured at 307nm.

Drug-excipient compatibility study

FTIR spectra of pure drugs, polymers used, and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolutions.

Formulation development of oral film of CZ

Solvent casting technique

Drug (Clonazepam) containing fast dissolving films were fabricated by the solvent casting method (Senthilkumar and Vijaya, 2015). The optimized amount of HPMC was dissolved in 5ml of water and stirrer continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm * 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use.

Formulations were prepared using HPMC K15, PEG-400, SSG and CCS at different drug: polymer ratios. The compositions of the formulations were shown in table 1.

Table 1 Formulation of clonazepam oral fast dissolving films

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6
Clonazepam	6	6	6	6	6	6
HPMC	200	400	600	200	400	600
PEG-400	150	150	150	150	150	150
SSG	100	200	300	-	-	-
CCS	-	-	-	100	200	300
Citric acid	20	20	20	20	20	20
Glycerine	-	-	-	-	-	-
DM water qs to (ml)	-	-	-	-	-	-

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 0.5 mg of drug.
- 12 no. of films contains mg of drug? = 0.5×12 = 6mg
- The amount of drug added in each plate was approximately equal to 6mg.

Evaluation

The formulations were evaluated by the following tests (Nagar et al., 2012).

Physical appearance and texture analysis of the films

These parameters were checked simply with visual infection of films and by feel or touch.

Thickness:

Randomly 10 films were selected and thickness was measured using vernier calliper at three different places.

Weight variation

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 307 nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work. The film of (4.15cm2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

In vitro dissolution study

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved CZ was determined using UV-Visible spectrophotometer at 307 nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40±2ºC temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature.

Results and Discussion

Solubility of CZ was slightly soluble in water, ethanol and methanol, soluble in 0.1N HCl and 6.8 pH phosphate buffers. The melting point of CZ was 238-240ºC and λ_{max} of CZ was found 307 nm by using U.V. spectrophotometer (Labindia-3000+). The calibration curve of CZ was found to be linear in the concentration range of 5-25µg/ml at

307 nm. The general appearance, assay, weight variation and thickness of all the films were within acceptable limits table 2. The results for tensile strength, folding endurance, disintegrating time and % of moisture were shown in table 3. Tensile strength value of optimized formulation (F4) was 1.236±0.045 kg/cm^2 and folding endurance was 145± 8.55. The formulations containing CCS were showing good results compared to SSG. The assay values of all the formulations were ranging from 97.65 to 99.05 %. The disintegration time was ranging between 42 to more than 73 sec. The final formulation shows better drug release (98.78%) compared to other formulation within 15 m (Table 4). The cumulative percentage (%) drug release profile and the assay of the F4 formulation films indicates that the drug remains stable under the ASC without any significant change in its release profile and the drug content. 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.

Table 2 Result of general appearance, thickness, weight variation and % assay

F. code	General Appearance	Thickness in µm	Weight(mg) Mean ± S.D	% Assay
F1	Translucent	45±5	88±1	98.89±0.13
F2	Translucent	48±3	93±4	97.65±0.22
F3	Translucent	52±1	95±3	98.85±0.31
F4	Translucent	42±4	85±6	99.05±0.25
F5	Translucent	44±2	90±5	98.98±0.15
F6	Translucent	49±3	93±3	98.78±0.13

Table 3 Result of folding endurance, disintegrating time, tensile strength &% of moisture content

F. code	Folding endurance (Times)	Disintegrating time (Sec)	Tensile strength in kg/cm^2	% of moisture content
F1	125± 9.87	69±4	1.105±0.056	2.45±0.111
F2	135± 4.56	73±6	1.241±0.045	2.22±0.101
F3	132± 6.45	65±7	1.265±0.012	1.98±0.142
F4	145± 8.55	42±6	1.236±0.045	1.45±0.156
F5	165± 7.67	55±4	1.165±0.065	2.23±0.136
F6	147± 5.29	63±5	1.145±0.045	2.65±0.145

Table 4 Results of *In-Vitro* release study of optimized formulation F4

S. No.	Time (Min.)	Cum % Drug release
1.	1	22.45
2.	2	45.65
3.	5	75.65
4.	10	89.98
5.	15	98.78

Conclusion

From present study it can be concluded that oral fast dissolving films are superior in drug release. The films prepared by HPMC and PEG 400 had shown good mechanical strength, drug release, disintegration time and stability. F4 formulation is considered as the best according to the obtained results with less disintegrating time and complete drug release in 15 min. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. As the concentration of CCS was increased, both the disintegration and the drug release rates increased. The disintegration and release rates were found to be faster for films prepared with lowest concentration of HPMC along with maximum concentration of superdisintegrants. CZ 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. Stability studies indicated F4 was stable for 90 days. Hence, there is a lot of scope for future *in vivo* studies.

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