IJBPAS, June, 2023, 12(6): 2612-2620

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING FILMS FOR THE DELIVERY OF LORAZEPAM IN THE ORAL CAVITY

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Received 10th July 2022; Revised 15th Aug. 2022; Accepted 5th Oct. 2022; Available online 1st June 2023

https://doi.org/10.31032/IJBPAS/2023/12.6.7180

ABSTRACT

Lorazepam which belongs to Benzodiazepines and is a novel drug used for the treatment of anxiety. The oral films which dissolves easily can mostly absorb in systemic circulation. The present study aimed to formulate and evaluate oral fast dissolving films of lorazepam using HPMC E 50 used as a film-forming polymer, sodium starch glycolate, citric acid used as a saliva stimulating agent, and crospovidone which acts as a super disintegrant in different concentrations. The films were prepared by solvent casting method characterized by Fourier Transform infrared spectroscopy and ultra-violet spectroscopy. The prepared films were evaluated for folding endurance, surface pH, content uniformity, disintegration time, mouth dissolving time, thickness, weight variation, *in vitro,* and *in vivo* studies. *In vitro* release rate of Lorazepam was studied in pH 6.8 phosphate buffer. From in vitro drug release, the optimized formulation F3(HPMC E 50, sodium starch glycolate, citric acid) has given 99.4% drug release than other formulations and a satisfactory disintegration time of 32sec respectively. *In vivo* pharmacokinetic results showed that the Lorazepam film had higher maximum plasma concentrations(C_{max}). In conclusion, the optimized fast dissolving film formulation showed a high absorption rate, rapid onset of action, and improved bioavailability as well as patient compliance. Perhaps the optimized F3 formulation is safe for film application.

Keywords: Fast dissolving films, Lorazepam, sodium starch glycolate, solvent casting method

INTRODUCTION:

Fast dissolving films were first developed in the year of 1970s based on the technology of transdermal patches **[1]**. This is a better option for pediatric patients who have trouble swallowing tablets, capsules, or syrups. Various film-forming agents were evaluated for optimizing the composition of fast dissolving films. Generally, the oral solid dosage form may become very difficult especially in swallowing. So to overcome these problems, a fast-dissolving drug delivery system has been developed which disintegrates or dissolves within one minute when inserted in the mouth without being dipped in saliva. Films enable the drug to deliver to the circulation immediately either through buccal or sublingually. Oral films improve the onset of action, lower the dosing and enhance the bioavailability. Lorazepam is a benzodiazepine it is used for the treatment of anti-anxiety and all types of epilepsy and seizures. Patients with epilepsy must carefully follow dosing schedules, as failure to do, so may result in subtherapeutic drug levels in the systemic circulation, causing seizures to reoccur **[2]**.

MATERIALS AND METHODS

Materials:

Lorazepam was obtained from chandra labs, Hyderabad, India, HPMC E50 and sodium starch glycolate was obtained from Loba Chemie laboratory reagents, Colabo, Mumbai, citric acid was obtained from Thermo fisher scientific India Pvt. Ltd, Powai, Mumbai.

Preparation of fast dissolving films of Lorazepam [3, 4]

Fast dissolving oral films of Lorazepam were prepared by solvent casting method according to the formula given in **Table 1**. Lorazepam, HPMC E 50, crospovidone, sodium starch glycolate, citric acid and crospovidone were accurately weighed. The polymer was dissolved in the required amount of water and kept aside for overnight to get uniform dispersion. Drug, sodium starch glycolate, and citric acid were dissolved in a specific amount of water in another beaker. Then the drug solution was added to a polymeric solution with continuous stirring for up to 1 hr. The resulting solution was degassed to remove air bubbles formed. The bubble-free solution was cast on a film former with 60 to 70°C temperature. The film was removed carefully and observed for any imperfection.

Table 1: Composition for fast disoslving films of Lorazepam

S. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Lorazepam	4	4	4	4	4	4	4	4
2	HPMC E50 LV	5	5	5	5	5	5	5	5
3	Sodium starch glycolate	2	3	4	-	-	-	-	-
4	Guar gum	-	-	-	0.4	0.7	-	-	-
5	Crospovidone	-	-	-	-	-	2	3	4
6	Citric acid	2	2	2	2	2	2	2	2
7	Vanillin	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8	Water	qs	qs	qs	qs	qs	qs	qs	qs

Evaluation of fast dissolving films:

Drug and polymer compatibility studies [5, 6, 7]

Compatibility studies were carried out by using FTIR and Differential Scanning Calorimetry (DSC)

Content uniformity [8, 9, 10]

The prepared films were cut into the required size ($2\times2cm^2$) and taken into a 100ml volumetric flask containing 6.8 pH phosphate buffer. The solution was sonicated for 20min and the solution was filtered and then UV absorbance was measured at 230nm against blank **[11, 12]**. By using a standard graph the concentration of the solution was measured.

Uniformity of film thickness [13, 14, 15]

The film thickness was measured by using a screw gauge at 5 different spots. This helps to determine the thickness uniformity of oral fast dissolving films which directly relates to the accuracy of the dose **[16]**.

Weight variation [17, 18]

The films were cut into five different pieces in the cast film. The weight of each film was taken and the weight variation is calculated.

Folding endurance [19, 20]

This gives the information regarding the physical ability as well as the flexibility of the films. The number of folds on the same crease, required to produce a crack of the film was noted as the value of folding endurance **[21, 22]**

Surface pH [23, 24]

The film was cut into ($2\times2cm^2$) and was placed in a dish and moistened with 1ml of distilled water and kept aside for 1min. The prepared film's surface pH was measured by using a pH meter.

Mouth dissolving time [25, 26]

The mouth dissolving time was estimated by placing the film manually into a beaker containing 50ml of 6.8 pH phosphate buffer, the time required by the film to dissolve was noted.

Disintegration [27]

Disintegration tests were performed by placing the film 2×2 cm^2 in the glass petri dish containing 10ml of water with stirring at every 10 sec time interval. The required

time for the film to disintegration time was recorded.

Dissolution [28]

The release rate of Lorazepam oral fast dissolving films was determined by the dissolution test apparatus. The dissolution test was performed by using 300ml 6.8 pH Phosphate buffer at 37±5°C. 5ml solution was collected from the dissolution apparatus at a definite time interval and added 5ml of fresh dissolution medium. The absorbance for the filtered solution was measured at 230nm.

Stability studies [29]

The optimized formulation F3 was packed in a butter paper covered with aluminium foil and was isothermally strained to examine the stability under accelerated temperatures and relative humidity conditions during a 6 months period . Test samples were withdrawn for 1st, 3rd and 6th month and were subjected to various tests like disinintegration time, and cumulative percentage of drug release. The results are shown in the **Table 4**.

***In vivo* pharmacokinetic parameters [30]**

In vivo pharmacokinetic studies were carried out to determine the parameters from F3 optimized formulation. The study protocol were approved by IAEC of the institution. The rabbits with an average body weight of 2.25kg were divided into 3 groups each consisting of 6 rabbits. Animals were maintained at room temperature 26°C, 45% RH for 12 hrs alternate light and dark with 100% fresh air. The rabbits were fasted overnight before administration and animals were anaesthesized and positioned on the table. The formulated film F3 was administered to the animal through inner side wall of the oral cavity.

Blood samples for the pharmacokinetic analysis were withdrawn at different time intervals 0, 0.25, 0.50, 1.00, 1.50, 2.00, 4.00, 6.00, 8.00 and 24 hrs after dosing. Collected blood samples were centrifuged for 10min at 3000 rpm at room temperature.

The pharmacokinetic analysis: [30]

The pharmacokinetic parameters, peak plasma concentrations(C_{max}) and time to reach peak concentrations were directly attained from concentration time data. In this study, AUC_{0-t} refers to the AUC from 0 to 24hrs. $AUC_{0-\infty}$ refers to AUC from time at zero hours to infinity.

AUC_{0-t} was calculated by using the formula

$$AUC_{0-t} = [C_{last}/K]$$

Where, C_{last} is the concentrations in µg/ml at the last time point

K is the elimination rate constant

Various pharmacokinetic parameters like area under the curve[AUC], elimination half life[$t_{1/2}$], C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were calculated. All the values were expressed as mean±SD as shown in the **Table 5**.

RESULTS AND DISCUSSION:

Drug polymer compatibility studies:

Analysis of pure drug and physical mixture of excipients was done by using FTIR pellet press method with KBr and obtained graphs were observed for spectra wavelengths.

As it can be seen in **Figure 1**. the intense band present for lorazepam is centered at 1017cm^{-1} and it can be related to be presence of carbonyl group(C=O) and less intense band located at 1101 cm^{-1} could be associated in the plane of C-H bending vibrations of benzene ring interacts with various ring CC vibrations.

Physical charcterization of fast dissolving films

The physical characterization of formulated films prepared by solvent casting technique and the results are mentioned in the **Table 2**. for various parameters like thickness, weight variation, folding endurance, mouth dissolving time, disintegration time, drug content uniformity, *in vitro* dissolution and *invivo* pharmacokinetics **[30]**.

Weight variation varies from 41.06±0.51 to 51.96±0.41mg, if polymer concentration increases folding endurance, disintegration time, and thickness of film also increases. The optimized formulation F3 shows 32 sec(disintegration time), folding endurance was found to be 130±8.14, the drug content for the optimized F3 formulation was found to be 99.4%, surface pH of all the films was uniform and within a range. *In vitro* disolution test was carried out by using USP type 1 basket to study the release of drug from prepared films as shown in the **Table 3**.

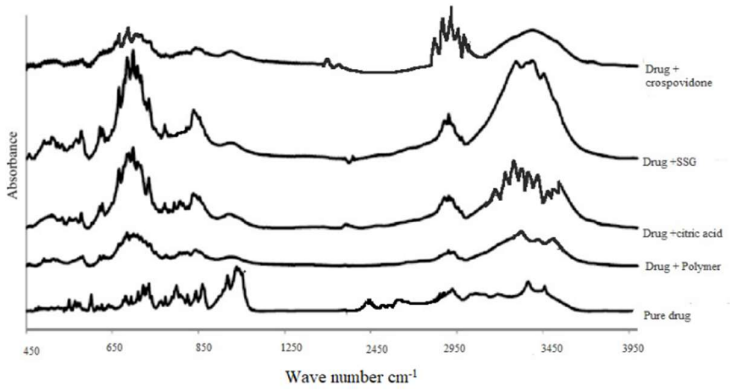

Figure 1: FTIR spectra in KBr disc of Lorazepam and excipients used in the study

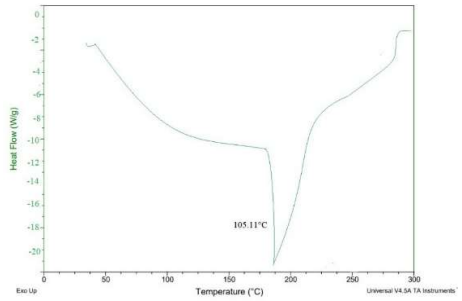

Figure 2: Showing DSC thermogram of Lorazepam:

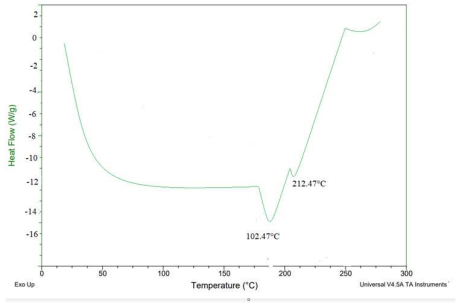

Figure 3: DSC thermogram of Lorazepam + SSG

Table 2: Evaluated table of Fast Dissolving Films

S. No	Formulation	Thickness (mm)	Weight variation (mg)	Mouth dissolving time(sec)	Disintegration time(sec)	Drug Content(%)	Folding endurance
1	F1	0.1±0.02	41.06±0.51	53.6±1.52	46±2	97.6%	121±2.15
2	F2	0.16±0.01	52.75±0.56	64.56±3.04	52.5±2	98.5%	124±3.60
3	F3	0.18/±0.04	42.8±0.6	48±2	32.34±1	99.4%	130±8.14
4	F4	0.22±0.025	54.14±0.84	54.32±3.06	42.33±1.13	95.2%	113±11.01
5	F5	0.21±0.01	41.4±0.44	40.56±3.02	40.34±3.05	97.2%	95±6.23
6	F6	0.23±0.01	51.2±0.62	53.65±3.22	46.32±1.51	96.7%	110±6.04
7	F7	0.26±0.01	40.5±0.30	58.66±4.04	48±1	94.5%	122±2.08
8	F8	0.28±0.014	51.96±0.41	65.45±2.08	57.32±0.56	96%	114±4.13

Table 3: Cumulative % drug release of fast dissolving films

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
1	30	35.3	38.5	25	22.8	32	38.7	28
2	49.6	48.4	42	38.9	34.9	44.6	45.8	43.8
3	85.6	67.2	69.7	45.6	40.2	53.3	61.2	77.6
4	92.3	82.8	87.4	53.7	56.2	65.5	83.6	87.5
5	93.5	92.6	91.6	66.8	60.8	70.5	90.5	92.3
6	93.7	93.5	92.8	78.5	78.5	83.4	92.2	93.5
7	94.4	94.3	94.5	82.7	87.6	94.3	93.6	94.3
8	95.5.	95.5	95	91.2	91.6	95.7	94.2	95.6
9	96.2	96.3	95.8	93.6	92.6	96.9	95.8	96.8
10	97.8	97.5	98.3	95.2	94.6	97.3	96.2	97.5

Table 4: Stability studies

Parameters	1st month	3rd month	6th month
Thickness(mm)	0.15±0.02	0.18±0.04	0.20±0.07
Drug content(%)	99.5±0.09	98.3±0.07	97.6±0.02
%weight variation	Pass	Pass	Pass
Disintegration time(sec)	33.3	32.5	30.3
Folding endurance	128±0.32	127±0.30	125±0.28
Dissolution %	98.5	97.2	97.0
%drug release	99.92	97.95	97.25

Table 5: *In vivo* pharmacokinetic parameters

S.No	Parameters	Oral fast-dissolving films (mean±SD)
1	C_{max}(ng/ml)	12.72±3.8
2	AUC_{0-t}(ng hr/ml)	82.02±18.5
3	$AUC_{0-\infty}$(ng hr/ml)	85.69±14.8
4	T_{max}(hr)	0.4±0.5
5	$t_{1/2}$(hrs)	1.425±0.17

CONCLUSION:

The fast dissolving films of Lorazepam were prepared by using different concentration of film forming polymers by solvent casting method which is simple and effective. The prepared film showed satisfactory results. Films were found to be stable at accelerated stability conditions. Amongst 8 formulations prepared, the film prepared using 5 mg of HPMC E 50 which acts as a film forming agent, 4mg of sodium starch glycolate showed the highest dissolution rate was selected as optimized formulation. Accelerated stability studies for optimized formulation showed that was stable for the period of 6 months. Therefore present study on orodispersible film containing Lorazepam is considered useful for anti anxiety which can improve patient compliance.

ACKNOWLEDGEMENTS:

I am sincerely thankful to the Department of pharmaceutics, Chalapathi institute of pharmaceutical sciences, Lam, Guntur for providing the facilities to complete this research work.

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