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Research Article

FORMULATION AND EVALUATION OF HALOPERIDOL-CARRIER LOADED BUCCAL FILM

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A B S T R A C T

The present investigation was performed by formulating buccal film(s) of the typical anti-psychotic drug Haloperidol. The main objective is to enhance the solubility of the drug and provide quick onset of action, improve patient compatibility, convenience by the patient with mental instability, without the problem of swallowing and using water. Haloperidol belongs to BCS class-II with low solubility and high permeability. The solubility of haloperidol is enhanced by solid dispersion method. The complexes were prepare by hot-melt technique using polyethylene glycol in various ratios (1:1, 1:2, 1:3, 1:4). Solubility study of haloperidol was performed in which highest range was observed for 1:3 ratio. The selected inclusion complexes were then utilized for the preparation of film by solvent casting method using HPMC of different grades as film forming agent and PEG-400 as a plasticizer. Six formulae were prepared and evaluated for the *in vitro* dissolution characteristics, *in vitro* disintegration time, and their physico- mechanical properties. The promising film (F2) showed greatest drug dissolution (more than 75% within 15 mins), satisfactory *in vitro* disintegration time (45 sec) and physico-mechanical properties that are suitable for buccal films. The optimized buccal film was observed for stability studies and they were reported to maintain their Physio-mechanical properties after three months of storage at optimum conditions.

INTRODUCTION

Development of new drug delivery systems has been one of the major thrust areas of pharmaceutical research. The goal of any drug delivery system is to provide a therapeutic amount of drug to the actual site in the body to promptly achieve and then maintain the desired concentration. An idea fast dissolving delivery system should have the following properties: high permeability, ease of handling, transportability and administration, no special pacakage material or processing requirements, no water requirement for application, and an acceptable taste. Therefore they are immensely suitable for paediatric and geriatric patients; patients suffering with dysphagia. This novel drug delivery system can also be beneficial for meeting current needs of the industry. Buccal films were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips.

Haloperidol is a first generation typical antipsychotic used in the treatment of schizophrenia and Tourette syndrome, Haloperidol is lipophilic and readily absorbed. Haloperidol inhibits the effects of dopamine and increases its turnover.

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It is believed that haloperidol competitively blocks post-synaptic dopamine (D2) receptors in the brain, eliminating dopamine neurotransmission and leading to the relief of delusions and hallucinations that are commonly associated with psychosis. It acts primarily on the D2-receptors and has some effect on 5-HT2 and α1-receptors, with negligible effects on dopamine D1-receptors. Haloperidol is low soluble- high permeable drug (BCS class II drug). Hence the solubility of Haloperidol is enhanced and the drug release is controlled to increase its absorption and further bioavailability is improved. Therefore Haloperidol is considered a suitable candidate for the design of mucoadhesive drug delivery system with a view to improve its bioavailability.

The prime aim of this research was to develop carrier mediated buccal film of Haloperidol by using polymers like Hydroxy Propyl Methyl Cellulose of different grades in an attempt to improve its bioavailability and consequently solubility.

MATERIALS AND METHODS

Materials

Haloperidol, Hydroxy Propyl Methyl Cellulose (HPMC), Poly ethylene glycol (PEG), citric acid, saccharin, menthol.

Construction of calibration curve for Haloperidol

The calibration curve for Haloperidol was constructed in phosphate buffer solution of pH 6.8±0.5

Preparation of stock solution

Haloperidol (100 mg) was weighed accurately and dissolved in methanol and the volume was made up to 100 mL with the same solvent in a volumetric flask.

Preparation of Phosphate buffer solution pH 7.2±0.5:

Place 50 mL of 0.2M potassium dihydrogen phosphate in a 200 mL in 1000 mL volumetric flask, add 22.4 mL of 0.2M sodium hydroxide and then add water till volume.

Preparation of working standard solutions

From the stock solution, 0.5, 1, 1.5, 2, 3, 3.5 mL were pipette out and the volume was made up to 100 mL with phosphate buffer solution of pH 6.8±0.5 to produce concentrations of 5, 10, 15, 20, 25, 30, 35µg/ml respectively. A scan was performed in order to determine the λ_{max} and the absorbance of diluted solution was measured at the λ_{max} obtained using spectrophotometer against blank buffer solution of pH 6.8±0.5 as the blank. The λ_{max} was found to occur at 247 nm. The results are tabulated in (Table 1)

A calibration curve (Figure 1) was constructed by plotting the absorbance against the concentration of haloperidol. A regression equation was derived from the plot, which was used for the estimation of Haloperidol in phosphate buffer solution of pH 6.8±0.5

The method obeyed Beer's law in concentration range of 5-50µg/mL and is suitable for the estimation of Haloperidol from different sample solutions. The correlation coefficient value (r) was found to be 0.996 indicating a positive correlation between the concentration of haloperidol and the corresponding absorbance values. The regression line describes the relation between the concentration and absorbance was as follows.

Y= 0.021X + 0.027
Where, Y is the absorbance at 247nm and
X is the concentration of haloperidol in µg/mL

Table 1 Data for standard haloperidol plot

Concentration	Absorbance
0	0
5	0.165
10	0.2445
15	0.354
20	0.4555
25	0.5719
30	0.6628
35	0.7796

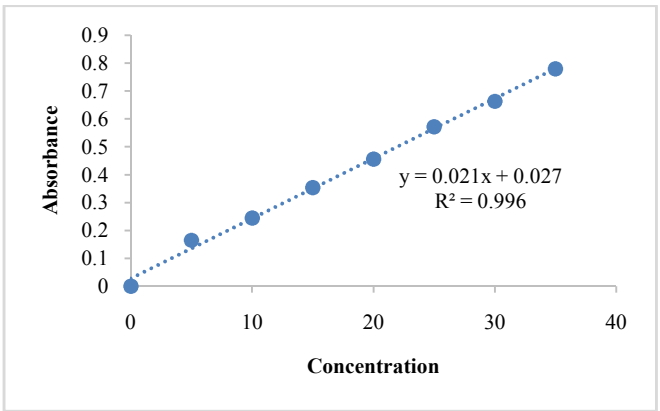

Figure 1 Calibration plot of Haloperidol

Drug-Excipient compatibility study

FTIR spectra of pure drug, polymers used, and excipients were recorded using FTIR Bruker alpha system with spectrum opus 6.5 software Spectrophotometer to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with all excipients in a glass mortar with pestle and FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm^{-1} using 20 scans with $4cm^{-1}$ resolution.

Preparation of inclusion complexes

Haloperidol-polyethylene glycol 6000/4000 inclusion complexes by hot melt technique in different ratios (1:1, 1:2, 1:3, 1:4). Prepared products were obtained by dissolving the drug in ethanol. Then the required moles of polyethylene glycol was placed in a china dish and is melted and then the drug was added and triturated till they both get mixed well. Then it was placed in ice bath and cooled immediately with vigorous stirring. The dried powder is scrapped from the china dish and pulverized and passed through sieve no.10 stored in an air tight container till use.

Formulation of Haloperidol buccal films: (table 2- composition of haloperidol buccal film)

A series of buccal films composed of different proportions and combinations of hydroxy propyl methyl cellulose K100M, K15M, K4M was mixed with 10 mL of water. Saccharine was added in 5 mL of water and to this citric acid was added and mixed with the above prepared polymer mixture. The drug complex mixture was added in 5 mL of methanol and this was finally added to the polymer mixture and 2 mL of PEG400 was added and mixed well till the contents become uniform.

Two drops of glycerin was applied to the petri dish whose area was known so that film does not stick to it at the time of removal. The above prepared solution was poured into the glycerin applied petri dish and was made sure that the solution was uniformly spread. Then the petri dish was placed in a hot air oven for 24 hours at 50˚C. After 24hours the film was removed and was cut into dimensions of 2×2 and assessed.

Table 2 Composition of Haloperidol buccal film

Ingredients	F1	F2	F3	F4	F5	F6
Haloperidol-carrier PEG6000	1:3	1:3	1:3	1:3	1:3	1:3
HPMC K 100M (mg)	200	250	-	-	-	-
HPMC K 15M (mg)	-	-	250	300	-	-
HPMC K 4M (mg)	-	-	-	-	250	350
PEG400 (mL)	2	2	2	2	2	2
Citric acid(mg)	15	15	15	15	15	15
Saccharine(mg)	10	10	10	10	10	10
Menthol(mg)	5	5	5	5	5	5
Water (mL)	20	20	20	20	20	20

Evaluation of haloperidol buccal films:

Haloperidol buccal films were evaluated for uniformity of weight (schimadzu electronic balance, Japan), thickness of film(Dial guage. model: K17, accuracy 0.001mm, Baker Precision Measuring Instruments, China), surface pH, weight variation, thickness, folding endurance, drug content, moisture uptake, moisture content, *invitro* release study.

Uniformity of weight

Each film was individually weighed on analytical balance (Shimadzu Electronic Balance, Japan) and average weight of three films was found. A large difference in weight denoted the non-uniform distribution of drug in the film.

Thickness

The thickness of different films was measured using a calibrated dial guage (Baker Precision Measuring Instrument, China) with an accuracy of 0.0001 mm. Thickness was measured by placing each film between the anvil and the presser foot of the digital guage in 5 different locations and the average thickness was calculated.

Folding endurance

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

Drug content

The drug content in the buccal patches were determined by dissolving 1 cm^2 patch in 100 mL phosphate buffer saline (pH 6.8) and shaken vigorously for 24 hr at room temperature. These solutions were filtered through Whatman filter paper (No.42). After proper dilution, the samples were analyzed by UV-Vis spectrophotometer at 247 nm against blank.

Moisture content and moisture absorption

The buccal patches were weighed accurately and kept in desiccator containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using formula:

$$\text{Moisture content (\%)} = \frac{initialweight - Finalweight}{initialweight} \times 100$$

The buccal patches were weighed accurately and placed in the dessicator containing 100 ml of saturated solution of aluminium chloride, which maintains 76% and 86% relative humidity (RH). After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

$$\text{Moisture absorption (\%)} = \frac{Finalweight - Initialweight}{Initialweight} \times 100$$

In vitro dissolution studies

Release of Haloperidol from the buccal film was studied in Phosphate buffer of pH 6.8 (900 ml) for 30mins using USP II Dissolution apparatus with a rotating paddle stirrer at 50 rpm and 37 ± 0.5ºC. Samples of dissolution fluid were withdrawn through a pipette at different time intervals and were assayed at 247nm for Haloperidol content using a UV/Visible spectrophotometer.

In vitro drug release kinetic studies

The mechanism of drug release from the formulations during the dissolution in pH 6.8.

Phosphate buffer was determined using

- First order
- Zero order

Zero Order Model

The model describes the systems where the drug release rate is independent of the concentration.

$C=k_o t$

Where k_o is zero order rate constant expressed in units of concentration/time.

C is the amount of drug released at time t.

A graph of cumulative %drug released Vs time would yield a straight line with a slope equal to k_o and the intercept at the origin of the axes.

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal system, as well as matrix tablets with low dosage forms, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First Order Model

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behaviour generally follows the following first order equation:

$\text{Log } C = \text{Log } C_o - kt/2.303$

Where C is the amount of drug dissolved at time t,

C_o is the amount of drug dissolved at t=0 and

K is the first order rate constant.

A graph of log cumulative of %drug remaining vs time yields a straight line.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way, that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

RESULTS AND DISCUSSION

Solubility studies

The solubility values of Haloperidol, Haloperidol/ PEG4000 & Haloperidol/ PEG6000 inclusion complexes are shown in (Table 3). Each of the two preparation methods could increase the solubility of Haloperidol but to a different extent. Hot melt extrusion method produced a considerable enhancement of solubility of Haloperidol in PEG6000 and PEG4000.Within the same preparation method, it was found that Haloperidol solubility was comparatively higher in PEG6000 than in PEG4000.

In all the cases it was observed that solubility was gradually increase until 1:3 ratio either it is of PEG6000 or 4000 of different polymers, indicating further no need of solubility enhancer for drug solubilisation.

Table 3 Solubility values of Haloperidol/Polyethelene glycol inclusion complexes

Code	Haloperidol/Polyethyleneglycol	Solubility, mg/mL
Hal	Hal No PEG	0.7±0.12
HP4000(1:1)	Hal: PEG4000 (1.0 :1.0)	1.66±0.78
HP4000(1:2)	Hal: PEG4000 (1.0 :2.0)	2.02±0.26
HP4000(1:3)	Hal: PEG4000 (1.0 :3.0)	2.74±0.34
HP4000(1:4)	Hal: PEG4000 (1.0 :4.0)	2.70±0.09
HP6000(1:1)	Hal: PEG6000 (1.0 :1.0)	1.69±0.63
HP6000(1:2)	Hal: PEG6000 (1.0 :2.0)	2.19±0.37
HP6000(1:3)	Hal: PE6000 (1.0 :3.0)	2.79±0.07
HP6000(1:4)	Hal: PEG6000 (1.0 :4.0)	2.73±0.08

Drug-Excipient compatibility study

The drug-excipient compatibility studies were conducted with different ratios of drug: excipient admixture at 40 ± 2ºC and 75± 5% RH for one month and the samples were observed. The samples were then analysed by FT-IR spectroscopy for any interactions. The FT-IR spectrum of Haloperidol was shown in (figure 2). The drug showed prominent peaks at 1407.90cm^{-1}, 1109.61cm^{-1} due to C-F stretch and at 1680.89 cm^{-1} ,1900.61 cm^{-1} due to C=O stretching, 1363.15cm^{-1},1595.72due to N-H bending. The spectrum of the drug-excipient admixtures and the final formulation are shown in (figure 3). All the characteristic peaks discussed above appeared unchanged in the spectra of the Drug-Excipient mixtures. This indicated the absence of any interactions for the drug with the excipients used.

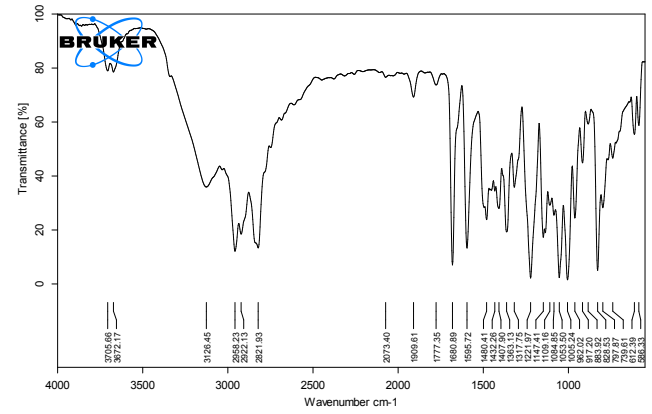

Figure 2 FTIR spectrum of Haloperidol (Pure drug)

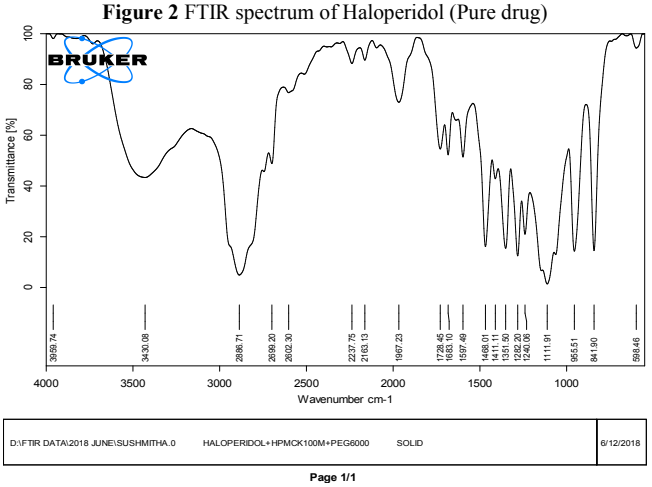

Figure 3 FTIR spectrum of final formulation (dry powder)

In vitro dissolution of inclusion complexes

The mean dissolution profiles of haloperidol and haloperidol inclusion complexes produced using two different grades of poly ethylene glycol (PEG4000 and PEG 6000) are presented. The dissolution of haloperidol was below 40%, while the dissolution of haloperidol along with PEG 6000 was more than 70% at 15 mins. The results showed that formation of inclusion complex with PEG improved haloperidol dissolution.

Table 4 Drug release data of Haloperidol (pure drug) and haloperidol-carrier prepared by hot-melt technique

Time (min)	Cumulative percent drug release (%) of Polyethyleneglycol 6000				
	Hal	HP6000 1:1	HP6000 1:2	HP6000 1:3	HP6000 1:4
0	0	0	0	0	0
5	2.80	36.67	37.30	37.35	36.87
10	10.93	45.92	55.71	59.06	59.03
15	18.14	65.87	67.73	68.51	68.28
20	21.44	71.29	72.57	77.40	76.92
30	24.86	78.43	79.21	83.89	82.92
45	27.94	70.08	75.07	79.06	79.45
60	38.23	69.23	74.56	78.09	78.02

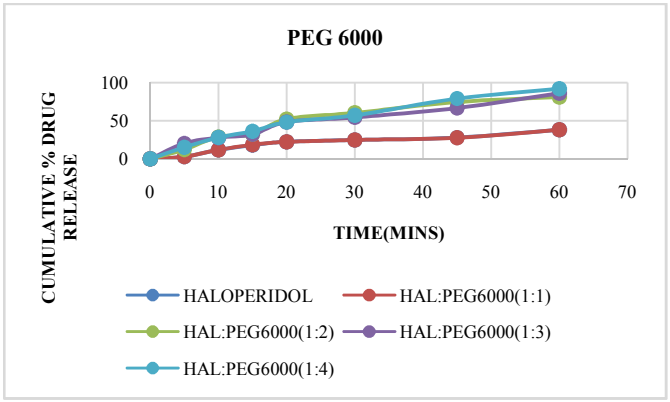

Figure 5 Dissolution profiles of Haloperidol, Hal-PEG6000

Invitro drug release of prepared formulation

The prepared six formulations are subjected to *invitro* dissolution in dissolution apparatus USP paddle type. The samples are withdrawn at every five minutes intervals till half an hour. Then they are analyzed by UV spectroscope at 247nm. The values are tabulated in (table 5) and graph plotted between time and percentage drug release (figure 6) shows 50% drug release at 15 mins. Among all the formulations F2 shows the maximum drug release.

Table 5 Drug release profiles of haloperidol from haloperidol - PEG complex loaded buccal films

Time (hr)	Cumulative percent drug release (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	26.89±0.01	23.76±0.52	27.98±0.65	27.97±0.23	26.45±0.12	25.89±0.01
10	46.56±0.23	51.23±0.43	46.09±1.22	44.23±0.93	47.14±0.45	43.56±0.23
15	70.91±0.98	74.22±0.24	68.91±0.32	67.92±0.08	69.56±0.65	62.91±0.98
20	81.23±0.12	85.32±1.12	72.34±0.65	79.87±0.93	76.54±1.22	78.23±0.12
25	93.86±0.13	90.65±1.43	85.45±0.98	83.56±0.76	87.45±1.54	82.56±0.23
30	96.51±1.23	98.62±1.47	95.63±0.23	94.89±0.98	97.01±0.34	96.13±0.78

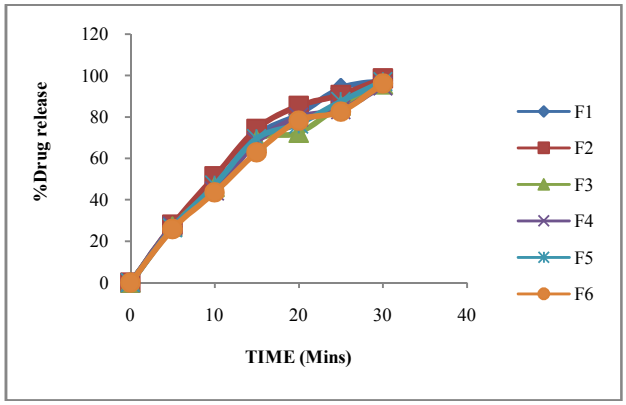

Figure 6 Dissolution profile of haloperidol from Haloperidol-carrier loaded buccal films

Evaluation parameters of buccal films

The film evaluation (Table 6) indicates that the weight variation of these formulated buccal films varied between 2.02±0.03 to 2.73±1.02. The thickness of these films varied between 0.21±0.12 to 0.27±0.83 mm, the thinnest formulation F1 and F2. The thickest formulation F6 folding endurance was measured manually. The highest folding endurance was observed in case of F1 (123) and the lowest in the case of F6 (98). The range of folding endurance system ensured flexibility of these formulated buccal films. The drug content (%) in all formulations varied between the ranges 94.89±0.98 to 98.62±1.47, this indicates that the drug dispersed uniformly throughout the polymeric film.

The moisture content (%) study was done for 3 days. The percentage of moisture content (%) is varied between 2.05±0.33 to 2.98±0.24, in most cases the moisture uptake content was found to increase with increasing concentration of polymers that are more hydrophilic in nature. The low moisture content in the formulation is highly appreciable to protect from the microbial contamination and bulkiness of the films. A low moisture content in the formulations helps them to remain stable from being a completely dried and brittle film.

Table 6 Physicochemical evaluation of haloperidol-carrrier loaded buccal films

Formulations	Weight variation* (g)	Thickness* (mm)	Folding endurance	Drug content* (%)	Moisture content (%)	Moisture uptake %
F1	2.02±0.03	0.51±0.12	90±0.23	98.02±0.16	2.05±0.33	2.04±6.03
F2	2.08±0.13	0.53±0.63	96±0.73	99.19±0.43	2.06±0.08	2.07±0.08
F3	2.07±0.18	0.55±0.83	84±0.63	99.23±0.23	2.83±0.11	2.12±0.78
F4	2.10±0.53	0.53±0.93	82±0.43	99.45±0.24	2.11±0.03	2.19±0.67
F5	2.07±0.98	0.54±1.22	85±0.09	98.43±0.45	2.76±0.03	2.13±1.23
F6	2.87±1.02	0.55±0.09	87±0.67	98.06±0.03	2.98±0.24	2.27±0.91

In vitro release kinetics

In order to predict and correlate the release behavior of Haloperidol from different films, it is necessary to fit into a mathematical model. The in vitro drug release data from buccal films were evaluated kinetically using various mathematical models like zero order and first order (figure 7) by observing the regression coefficient values the drug release from the dosage form follows zero order independent of the concentration.

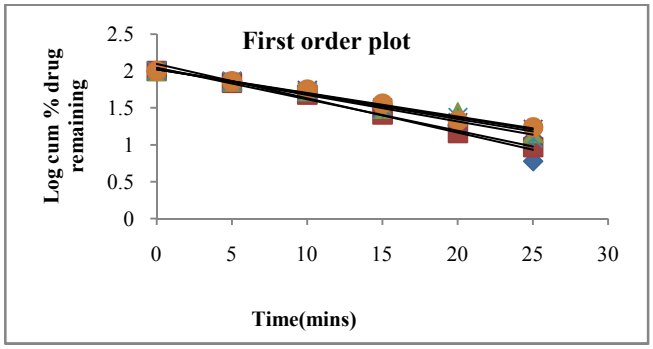

Figure 7 First order plot of prepared haloperidol-carrier loaded buccal films

Stability studies

Stability studies were conducted for the best formulation F2 as per ICH guidelines for a period of 3 months and the result were shown in (Table 7). The results indicate that there was no significant changes in physical appearance, folding endurance, moisture uptake. However, there is a slight variation in the in vitro drug release. It was concluded that the films were stable during the study period.

Table 7 Stability studies of the best formulation (F2)

Sampling time	Physical appearance	Folding endurance	Moisture uptake	*In vitro* drug release
Initial	Transparent	98	3.26	98.68
After 1 month	Transparent	98	3.20	97.72
After 2 month	Transparent	98	2.91	97.23
After 3 month	Transparent	98	2.89	96.91

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