Original Article

FORMULATION AND EVALUATION OF CHLOROTHALIDONE LOADED MOUTH DISSOLVING FILM-A BIOAVAILABILITY ENHANCEMENT APPROACH USING MULTILEVEL CATEGORIC DESIGN

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ABSTRACT

Objective: The intension of the present study includes fabrication and optimization of mouth dissolving film loaded with Chlorothalidone by solvent evaporation techniques using two components and their three levels as multilevel Categoric design.

Methods: Major problem associated with the development of film loaded with BCS class II drug is to increase its solubility. Here the Chlorothalidone solubility achieved by co-solvents, such as methanol. After dissolving the drug in co-solvent, this drug solution is poured into an aqueous dispersion of Hydroxypropyl Methylcellulose E5 (HPMC E5) and Polyethylene glycol 400 (PEG 400). The two independent variables selected are factor A (concentration of HPMC E5) and factor B (concentration of PEG 400) was selected on the basis of preliminary trials. The percentage drug release (R1), Disintegration time in sec (R2) and folding endurance (R3) were selected as dependent variables. Here HPMC E5 used as a film former, PEG 400 as plasticizer, mannitol as bulking agent, Sodium starch glycolate as a disintegrating agent, tween 80 as the surfactant, tartaric acid as saliva stimulating agent, sodium saccharin as a sweetener and orange flavour etc. These fabricated films were evaluated for physicochemical properties, disintegration time and *In vitro* drug release study.

Results: The formulation F6 has more favorable responses as per multilevel categoric design is % drug release about 98.95 %, average disintegration time about 24.33 second and folding endurance is 117. Thus formulation F6 was preferred as an optimized formulation.

Conclusion: The present formulation delivers medicament accurately with good therapeutic efficiency by oral administration, this mouth dissolving films having a rapid onset of action than conventional tablet formulations.

Keywords: Mouth dissolving film, Solvent evaporation techniques, Chlorothalidone, HPMC E5, Multilevel categoric designs, Design expert® 12 software etc

INTRODUCTION

Around all drug delivery systems, drug administration by the oral route is being considered more suitable. Various fast disintegrating drug delivery systems developed instead of capsules, tablet and syrups for the patient who having struggled in swallowing. Mouth dissolving film is preferable path to increase patient compliance [1].

Mouth dissolving film becomes a trending drug delivery system because of its various merits. On contact with saliva, it disintegrates within a minute seconds, without the demand of water, making them particularly appropriate for pediatric and geriatric patients. Drug from film directly reaches into systemic circulation, thus it avoids the first-pass effect [2].

Chlorothalidone is a phthalamide derivative of benzene sulphonamide, Thiazide diuretics are preferred pharmacological treatments for uncomplicated hypertension. Chlorothalidone is used in the present study and widely accepted for its excellent antihypertensive as well as anti-diuretic effect. It not only improves blood pressure but also swelling by preventing water absorption from the kidneys through inhibition of the Na^+/Cl^- symporter in the distal convoluted tubule cells in the kidney [3].
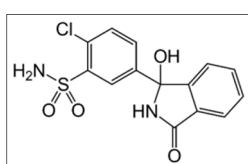

Fig. 1: Chlorthalidone

Multilevel categoric design generates trials that ultimately minimizes cost of an investigation. The outcomes of independent variables were studied on 9 different runs generated by the software. The rational of the present study is to enhance the bioavailability of Chlorothalidone by formulating as mouth dissolving film.

MATERIALS AND METHODS

Materials

Chlorothalidone (Gift sample of Aurobindo Pharma Ltd research Centre II, Hyderabad), HPMC E3, E5 (DOW chemicals), PEG 400 and Tween 80 LR (SDFCL Mumbai), Tartaric acid (Merck Chemicals Ltd., Mumbai), Mannitol (Roguette Freres), Sodium Saccharin, orange flavor (Burgoyne Burbidges and Co, Mumbai, India). All other reagents of analytical grade were used.

Methods

Drug excipients compatibility studies by Infrared spectroscopy (IR)

The IR absorption spectra of the pure drug and their physical mixture with accidents were recorded in the range of 4000-400 cm−1 by using an IR spectrophotometer (PerkinElmer) [4].

Preliminary trials for choosing a suitable polymer and plasticizer

Preliminary trials of formulation development were carried out using HPMC E3, E5 and sodium alginate etc. as film-forming agent with 2.5 % w/v, 3.0 % w/v and 3.5 % w/v etc. From that sodium, alginate film was easily prone to breaking whereas HPMC E3 shows thin film formation. HPMC E5 has good film-forming property,

satisfied disintegration time and good folding-endurance. In a preliminary feasibility study amount, less than 0.4 % w/v of PEG 400 shows poor flexibility, whereas above 0.8 % w/v shows sticky appearance. So that further formulation development was carried out between 0.4 % w/v to 0.8 % w/v.

Formulation of drug-loaded oral film

Films were prepared as per the formula given in table 1. Solvent casting method was used for the preparation of films using polymers (HPMC E5). Initially, the polymer was weighed accurately and dissolved in half the amount of water and mixed on a magnetic stirrer. The drug was weighed and dissolved in 1 ml of methanol. Tartaric acid and sodium saccharin were both dissolved in the remaining amount of water. This solution was added to the polymeric solution and stirred well using a magnetic stirrer to obtain a homogeneous solution, followed by the addition of PEG 400 as a plasticizer and orange flavor. This solution was allowed to stand for 30 min for de-aeration of the solution. The solution was then cast in a petri dish and kept in a hot air oven for 8-10 h at 50 °C. After

drying, films were removed. Thus the obtained large film was cut into 3 × 3 cm². The film was stored in a butter paper covered with aluminum foil and stored in a desiccator.

Formulation of polymeric mouth dissolving film of chlorothalidone using a multilevel categoric design by design expert® 12 software

In order to optimize the independent variable, factor A (concentration of HPMC E5) and factor B (concentration of PEG 400) was selected for further development. These variables were taken at three different levels, i.e. lower, medium and higher level. Those variables were stipulated on the basis of the preliminary feasibility study earlier to the design of experiments.

The dependent variables or response evaluated were % drug release, disintegration time in second and folding endurance, etc. The total 9 trials were generated by *Design-Expert®12 software;* the experimental data were analyzed using analysis of variance (ANOVA) by fitting responses in the respective run [5].

Table 1: Composition of chlorothalidone loaded mouth dissolving films (F1-F9)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorothalidone	98.38	98.38	98.38	98.38	98.38	98.38	98.38	98.38	98.38
Mannitol	15	15	15	15	15	15	15	15	15
HPMC E5	250	250	250	300	300	300	350	350	350
SSG	10	10	10	10	10	10	10	10	10
PEG 400	40	60	80	40	60	80	40	60	80
Sod. Saccharin	10	10	10	10	10	10	10	10	10
Tartaric acid	10	10	10	10	10	10	10	10	10
Orange flavour	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Water (ml)	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml	9 ml
Methanol	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml

Dose calculation of the amount of drug per batch

Dose of drug per film =12.5 mg

An area of one film = 9 cm²

Area of petri plate = 70.84 cm²

Drug to be added per batch
$$= (\text{Dose of drug per film} \times \text{Area of petri plate}) \div \text{Area of one film}$$

= (12.5 × 70.84)/9 = 98.38 mg.

Standard calibration curve of chlorothalidone

100 mg of Chlorothalidone was dissolved in 10 ml of 6.8 pH phosphate buffer and volume was made up to 100 ml with the 6.8 pH phosphate buffer (1000 µg/ml). 10 ml of the above solution was diluted up to 100 ml with 6.8 pH phosphate buffer (100 µg/ml). Then by serial dilution solutions with concentrations 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml and 30µg/ml were prepared. Absorbance was measured on a Shimadzu 1800 Double Beam Spectrophotometer in the range of 200 to 400 nm. Finally, a spectrum and wavelength of maximum absorption were recorded [6].

Evaluation of chlorothalidone loaded mouth dissolving film

Appearance

Formulated mouth dissolving films were assessed for their appearances either they are transparent or opaque by visual inspection or surface texture was assessed by contact or feel of the film [7].

Weight variation

The individual weight each of 10 films of 3×3 cm²for each formulation on an electronic weighing balance. The average weight was calculated [8].

Thickness

The average thickness of the mouth dissolving film was determined by using digital Vernier Calliper (Digimatic, Mitutoyo, Japan) with a

least count of 0.01 mm. The thickness was determined at five different places of the film and the average was taken and the standard deviation was calculated [9].

Surface pH

The surface pH was determined by placing one mouth dissolving film in a glass vial, adding 1 ml of distilled water and wait for 30 Sec. The pH value obtained by bringing electrodes of pH meter (Lab, India) in contact with the moistened surface of the film. All measurements were performed in triplicate. It is essential that the strip should have an almost uniform pH value [10].

Folding endurance

It was determined by repeatedly collapsing the film of uniform cross-sectional area and thickness until it breaks. The number of times film was folded without breaking computed as the folding endurance value. This test ensures the tensile strength of the film. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance [11].

Percent elongation

At the point when stress is applied to the film sample stretches and is alluded to as a strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally, the flexibility of the film increases as the plasticizer concentration increases. Percentage elongation was calculated by measuring the increase in the length of the film after tensile strength measurement by using the following formula [12]. At the point when stress is applied to the film sample stretches and is alluded to as a strain.

Percentage Elongation $= [L - L0] \times 100 \div L0$

Where L = Final length

L0 = initial length

Percentage of moisture loss

The percent moisture loss was evaluated by setting the prepared film in desiccators containing anhydrous calcium chloride.

Following three days, the film was taken and reweighed. The percent moisture loss calculated was determined to utilize the following formula [13].

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

Drug content

A film of size 3×3 cm^2 is cut and put in 100 ml of the volumetric flask containing solvent. This is then shaken in a mechanical shaker for 1 hour to get a homogeneous solution and filtered. The drug is determined spectroscopically after appropriate dilution. Chlorthalidone concentrations were assayed spectrophotometrically at 275.8 nm [14].

***In vitro* dissolution study**

The dissolution test was accomplished using to USP type I Basket apparatus (Electrolab Dissolution tester, EDT-08Lx). The dissolution medium was 900 ml of 6.8 pH phosphate buffer, maintained at 37 ± 10 °C and stirred at 75 RPM. Each square cut film sample (3 cm x 3 cm) was placed into the dissolution medium and appropriate aliquots were withdrawn at 3, 6, 9, 12 and 15 minute time intervals and again replaced with the same volume of dissolution media. The sample was filtered through Whatman filter paper for all the batches and analyzed spectrophotometrically at 275.8 nm (Model UV-1800 UV Visible spectrophotometer, Shimadzu, Japan). Sink conditions were maintained during the experiment. The dissolution test was performed in triplicate for each batch [15].

***In-vitro* disintegration study**

The film size to be required for delivering a dose (3×3 cm^2) was placed on a glass Petri dish containing 10 ml of 6.8 pH phosphate buffer. The minimum time required for mouth dissolving film to break was noted as *in vitro* disintegration time [16].

Stability study

The stability study of the optimized formulation was carried out by storage conditions specified by ICH known as ICH guidelines. The single film wrapped in butter paper followed by packing in Aluminium foil and placed in accelerated stability conditions at 40 ± 2 °C and $75 \pm 5\%$ RH for the period of 6 mo. Samples were taken at regular intervals and analyzed for folding endurance, drug content and % drug release [17].

RESULTS AND DISCUSSION

Drug excipients compatibility study by infrared spectroscopy (IR)

IR spectrum of Chlorothalidone and physical mixture with excipients was recorded and it was found in accordance with the reported peaks. It is shown in below fig. (fig. 2 and 3). The IR spectra of Chlorothalidone comply with its chemical structure and show peaks for principal groups. The structural assignments for the characteristic absorption bands are listed in the following table 2**.**

In physical mixtures of Chlorothalidone and excipients, there was neither masking of single characteristic peak nor the existence of an additional peak in drug spectra. The overall correlation in the two spectra was 0.9999. So it was concluded that all excipients were compatible with each other.

Optimization of the selected independent variable by *design-expert®12 software*

In a preliminary feasibility study, films were prepared with different polymers like HPMC (E3, E5) and sodium alginate. Finally, from these trials made and results obtained, HPMC E5 and PEG 400 were selected with different levels for further formulation development. The polymer HPMC E5 and plasticizer PEG 400 were taken at three different level, i.e. lower, medium and higher level. Thus, total 9 trails were obtained by *Design-Expert®12 software* and the dependent variables or response evaluated were % drug release in 15 min, disintegration time (second) and folding endurance (number of folds) are shown in table 3.
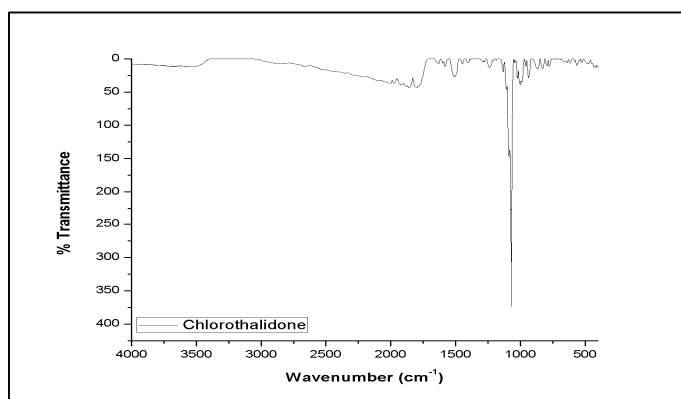

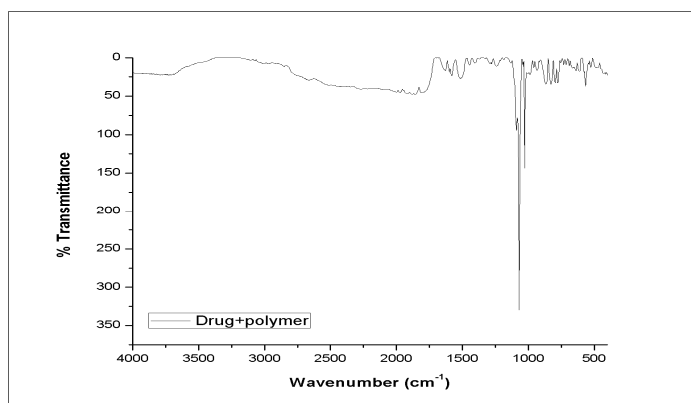**Fig. 2: IR spectrum of pure chlorthalidone**

Fig. 3: IR Spectrum of chlorothalidone and excipients

Table 2: Infrared spectral assignment for chlorothalidone

S. No.	Functional group	Reported frequency (cm^{-1})	Frequency for drug (cm^{-1})	Frequency physical mixture of drug and excipients (cm^{-1})
1	C=O (S)	1630-1980	1828.59	1828.28
2	Primary NH (S)	3100-3500	3361.92	3361.92
3	SO2 (S)	1000-1100	1039.63	1037.34
4	OH (S)	3200-3400	3255.84	3253.55

Table 3: Optimization parameters of chlorothalidone loaded mouth dissolving films

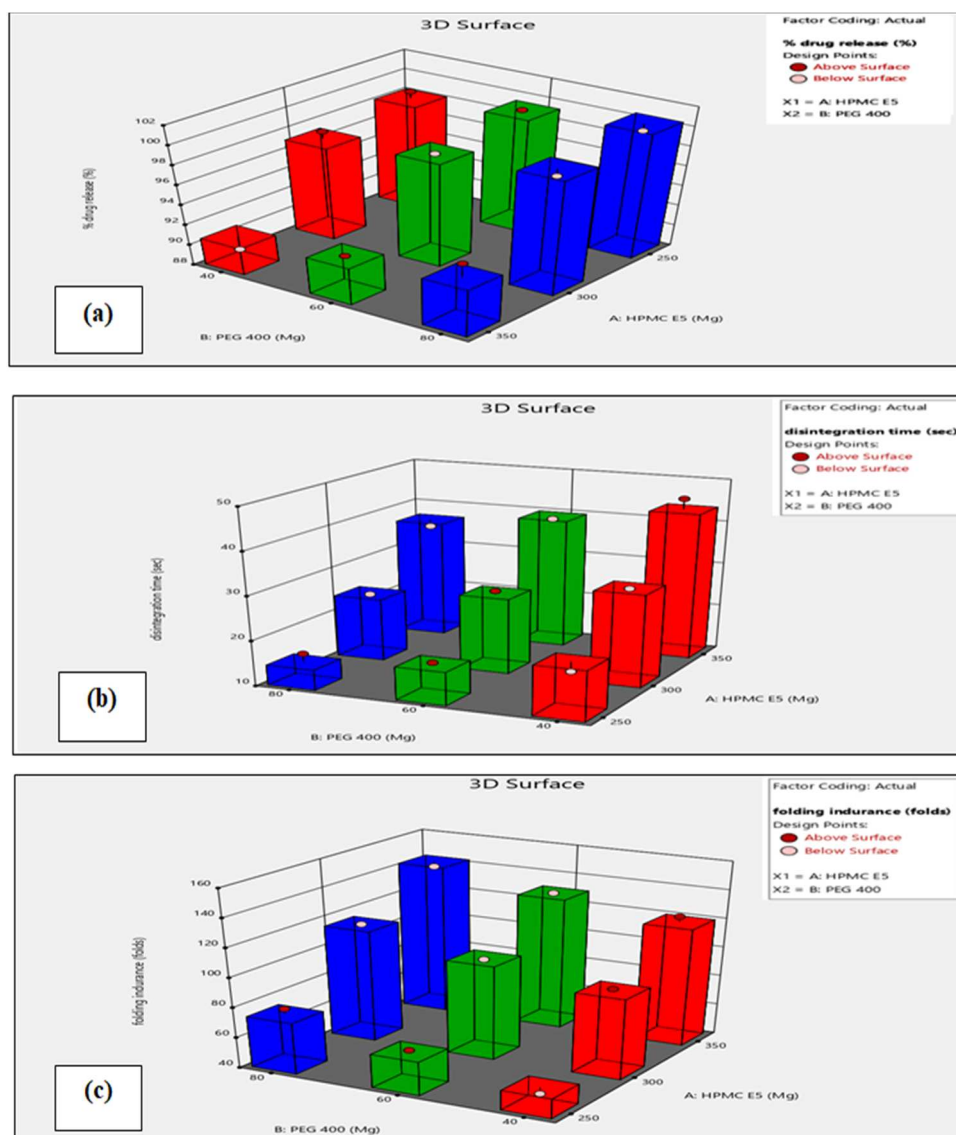| Run	Independent variables		Dependent variables		
	Factor 1 HPMC E5 (mg)	Factor 2 PEG 400 (mg)	% Drug release in 15 Min	Disintegration time (Sec)	Folding endurance (Folds)
F1	250	40	99.12	19.22	49
F2	250	60	99.56	17.87	64
F3	250	80	99.93	16.62	79
F4	300	40	98.17	31.12	96
F5	300	60	98.48	27.84	104
F6	300	80	98.95	24.33	117
F7	350	40	89.46	46.16	125
F8	350	60	91.87	39.41	131
F9	350	80	94.26	35.45	140

Fig. 4: 3 D surface plots (a-c) showing the effect of the selected independent variable on dependent variable viz. % Drug release (R1), disintegration time (R2) and folding endurance (R3)

Table 4: ANOVA for chlorothalidone mouth dissolving film from multilevel categoric design

Source	d. f.	Sum square	Mean square	F value	P value
% Drug release in 15 Min (Response 1)					
A-HPMC E5	2	104.38	52.19	39.01	0.0024
B-PEG 400	2	6.81	3.40	2.54	0.1938
Model	4	111.18	27.80	20.77	0.0061
Disintegration time Sec (Response 2)					
A-HPMC E5	2	758.80	379.40	87.40	0.0005
B-PEG 400	2	67.73	33.86	7.80	0.0416
Model	4	826.52	206.63	47.60	0.0013
Folding endurance (Response 3)					
A-HPMC E5	2	7053.56	3526.78	238.65	0.0001
B-PEG 400	2	729.56	364.78	24.68	0.0056
Model	4	7783.11	1945.78	131.67	0.0002

Numerical optimization

Table 5: Constraints for selected independent variables

Name	Goal	Lower limit	Upper limit	Lower weight	Upper weight	Importance
A: HPMC E5	is in range	250	350	1	1	3
B: PEG 400	is in range	40	80	1	1	3
Dissolution in 15 Min	Maximize	89.46	99.93	1	1	5
Disintegration time (Sec)	Minimize	16.62	46.16	1	1	5
Folding endurance (Folds)	Maximize	49	140	1	1	5

Table 6: Different solutions for 9 combinations

Number	HPMC E5	PEG 400	Dissolution in 15 min	Disintegration time	Folding endurance	Desirability	
1	300	80	99.602	24.561	117.111	0.809	Selected
2	300	60	98.526	27.468	104.778	0.695	
3	250	80	100.606	14.701	75.444	0.662	
4	300	40	97.472	31.261	95.111	0.580	
5	250	60	99.529	17.608	63.111	0.524	
6	350	80	92.932	37.138	143.444	0.466	
7	350	60	91.856	40.044	131.111	0.350	
8	250	40	98.476	21.0401	53.444	0.328	
9	350	40	90.802	43.838	121.444	0.200	

Table 7: Regression analysis of response R1, R2 and R3

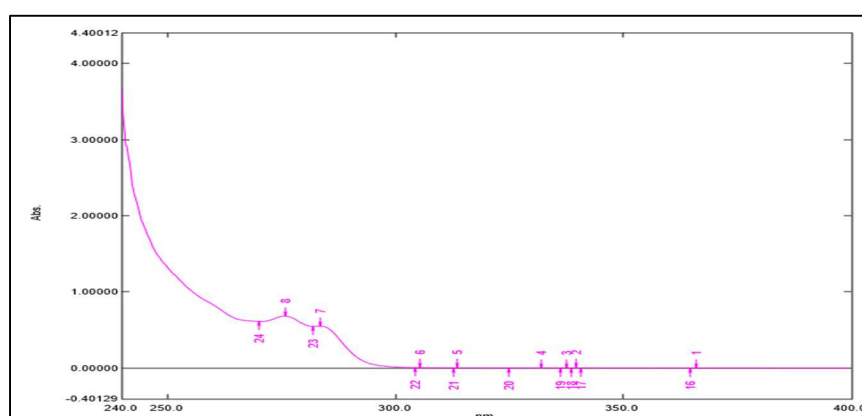| Factorial model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
R1 % Drug release in 15 min	0.9541	0.9082	0.7675	1.16	1.20
R2 Disintegration time (sec)	0.9794	0.9588	0.8958	2.08	7.27
R3 folding endurance (folds)	0.9925	0.9849	0.9618	3.84	3.82

Fig. 5: UV spectrum of chlorthalidone

Determination of λ max

A concentration of 30 μg/ml was prepared from standard Chlorothalidone solution and scanned by a UV-visible spectrophotometer in the range of 200-400 nm using 6.8 pH phosphate buffer as blank then the maximum wavelength (λ-max) was determined (fig. 5).

Standard calibration curve of chlorthalidone in 6.8 pH phosphate buffer

Chlorthalidone showed maximum absorption at wavelength 275.8 nm in 6.8 pH phosphate buffer. A standard curve was plotted by taking absorption of diluted stock solutions (5, 10, 15, 20, 25 and 30 μg/ml) at wavelength 275.8 nm [18].

Table 8: Standard calibration curve of chlorothalidone in 6.8 pH phosphate buffer

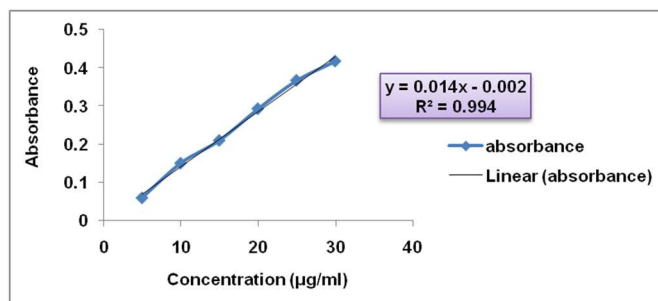| S. No.	Concentration (µg/ml)	Absorbance at 275.8 nm
1	5	0.0598
2	10	0.1507
3	15	0.2102
4	20	0.2931
5	25	0.3675
6	30	0.4178

Fig. 6: Calibration curve of chlorothalidone in 6.8 pH phosphate buffer

Preparation and physical characterization of chlorothalidone mouth dissolving film

Preliminary feasibility trails were prepared with different polymers like HPMC (E3, E5) and sodium alginate. Finally, from these trials made and results obtained, HPMC E5 and PEG 400 were selected with different levels for further formulation development.

Evaluation of films

Appearance

In preliminary trails, film from sodium alginate shows brittle nature, whereas HPMC E3 shows thin film-forming ability. Finally, the film prepared with HPMC E5 showed good film-forming property. Mouth dissolving films were visually evaluated, all films F1 to F9 shows good transparency, homogeneity and smooth appearance. All the formulations showed no change in the properties at the end of 6 the month time period [19].
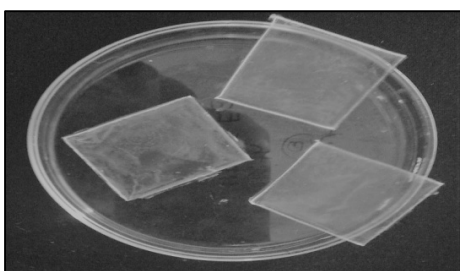

Fig. 7: Photograph of optimized formulation (F6) of mouth dissolving film

Wt. variation

The weight of mouth dissolving film was determined by using digital weighing balance and the average weight of all film (F1 to F9) was found to be in the range of 55-73 mg. Some films shows less than 5% variation in the weight, maybe due to lack of flat surface in petri plate or slant surface of hot air oven. Form a result, it was observed that the increase in polymer–plasticizer ratio weight of films also increased [8].

Thickness

The thickness of the mouth dissolving films was measured using digital Vernier caliper and the average thickness of all Fast dissolving film was found in between 0.153–0.349 mm (n=3). All films show a standard deviation of average thickness in the range 0-5 % that may be due to good positioning during the solvent evaporation process [20].

Surface pH

The surface pH was noted by pH meter near the surface of the fast-dissolving film and allowing equilibrating for 30 Sec and the surface pH of all fast dissolving film was found to in between 6.59-6.89 pH (n=3). All batches show pH towards a neutral range, which is evidence for the absence of oral mucosal irritation [10].

Folding endurance

The average folding endurance of all Fast dissolving films was ranging from 49-140. It was observed that folding endurance increases with increasing plasticizer concentration [11].

Percentage elongation

The average % elongation for formulation F1 to F9 was found in the range of 10.79±0.32 % to 19.23±0.68 %. Percentage elongation was decreased with increasing polymer concentration [12].

Percentage of moisture loss

The percentage of moisture loss of formulations F1 to F9 was estimated. The average % moisture loss found in the range of 1.471±0.008 % to 1.974±0.004 %. All formulation shows moisture within the limits that is evidence for the stability of the film against microbial growth [13].

Drug content

The percentage of drug content for all trails F1 to F9 was obtained in the range of 98.21±0.27 % to 99.87±0.20 %. All films having drug content within the limits, therefore it can be concluded that mouth dissolving film will deliver an accurate dose of medicament [15].

***In vitro* dissolution study**

In vitro dissolution investigation of Chlorothalidone loaded mouth dissolving film was carried out in pH 6.8 phosphate buffer solution (shown in fig. 8). Drug release from F1 to F9 was more than 90 % within 15 min. It was observed that the drug release is slower with increasing polymer concentration [21].

***In-vitro* disintegration study**

Mouth dissolving film with dimension 3 x 3 cm^2 size taken and disintegration time observed visually. Average disintegration times of three fast dissolving films were calculated. Disintegration time ranges from 16-46 seconds, which indicates the disintegration time of film obtained within a minute. As polymer concentration increases disintegration time also increases, but PEG 400 minimizes disintegration time [16].

Table 9: Formulation result from trails batches

Run	Weight (mg) (n=3)	Thickness (mm) (n=3)	Surface pH (n=3)	% Elongation (n=3)	% Moisture loss (n=3)	Drug content (%) (n=3)
F1	55.12±0.076	0.153±0.017	6.81±0.88	18.81±0.74	1.794±0.001	98.97±0.59
F2	57.56±0.054	0.162±0.027	6.84±0.54	19.23±0.68	1.974±0.004	99.29±0.84
F3	59.98±0.015	0.164±0.012	6.89±0.15	18.13±0.41	1.663±0.001	99.72±0.27
F4	61.41±0.044	0.241±0.021	6.78±0.24	14.27±0.33	1.659±0.007	99.17±0.88
F5	63.87±0.037	0.249±0.014	6.92±0.37	16.89±0.87	1.513±0.004	99.22±0.56
F6	66.61±0.043	0.253±0.03	6.96±0.66	14.72±0.57	1.669±0.003	98.21±0.27
F7	67.76±0.028	0.327±0.082	6.59±0.69	11.67±0.92	1.539±0.002	99.10±0.81
F8	70.31±0.092	0.349±0.038	6.66±0.52	10.79±0.32	1.471±0.008	99.19±0.66
F9	72.84±0.019	0.339±0.043	6.81±0.13	13.07±0.63	1.739±0.007	99.87±0.20

*All data are given in mean±SD

Table 10: *In vitro* drug release profiles of mouth dissolving film

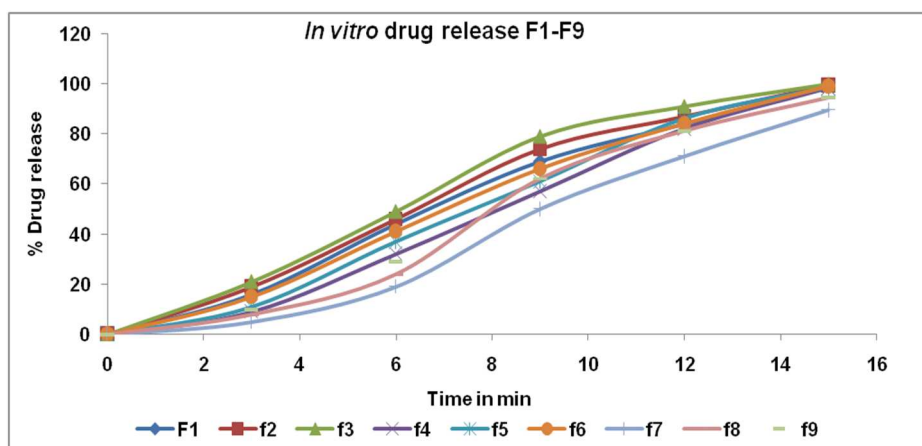| Batches	% Drug release				
	3 Min	6 Min	9 Min	12 Min	15 Min
F1	16.12	44.23	69.27	84.64	99.12
F2	19.74	46.32	74.11	87.45	99.56
F3	21.46	49.22	79.41	91.37	99.93
F4	9.45	32.04	57.41	82.66	98.17
F5	11.25	37.44	61.23	86.74	98.48
F6	15.12	41.16	66.87	84.43	98.95
F7	5.46	19	50.41	71.22	89.46
F8	8.22	24	54.44	77.54	91.87
F9	10.49	29	62.96	81.41	94.26

Fig. 8: Comparison of *in vitro* dissolution profile between F1 to F9

Table 12: Accelerated stability study of optimized trail F6

Parameter for study	The maintained temperature at 40±2 °C and relative humidity (RH) at 75%±5% RH			
	Initial	After1 mo	After 3 mo	After 6 mo
% Drug release	98.95	98.91	98.82	98.49
Drug content (%) (n=3)	98.21±0.27	98.71±0.41	98.11±0.87	98.49±0.62
Folding endurance	117	121	114	116

*Data are given in mean±SD, n=3

Stability study

Optimized formulation (F6) do not show changes in appearance, folding endurance, drug content and *In-vitro* % drug release after placing in the Accelerated Stability Studies. Hence the formulation (F6) was indicated to be stable [17].

CONCLUSION

Mouth dissolving films of Chlorothalidone were fabricated with HPMC E5 and PEG 400 by using the solvent evaporation technique.

All formulation shows a good drug release profile, drug content, folding endurance, disintegration time, pH and % elongation etc.

Among that formulation, F6 shows better drug release, disintegration time, folding endurance and found to be a good stable at accelerated stability condition specified by ICH.

So that F6 batch considered as optimized formulation. Hence mouth dissolving film of Chlorothalidone was found to be suitable for the management of edema and hypertension.

AUTHORS CONTRIBUTIONS

The authors of this research article share an equal contribution in all steps up to the approval of the final version.

CONFLICT OF INTERESTS

Authors have none conflict of interest

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