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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF LISINOPRIL USING NATURAL DISINTEGRANTS

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ABSTRACT

The formulation and evaluation of a fast-dissolving oral film of Lisinopril, a vital medication for hypertension treatment, were investigated in this study. A comprehensive preformulation study was conducted to characterize Lisinopril's physical and chemical properties, including organoleptic properties, solubility profile, infrared spectrum, loss on drying, melting point, and moisture content. Additionally, a calibration curve was established to quantify Lisinopril concentration accurately. Subsequently, various natural disintegrants were explored to optimize the formulation, considering parameters such as general appearance, thickness, weight, folding endurance, disintegrating time, tensile strength, moisture content, and assay. Among the formulations evaluated, F7 emerged as the optimized formulation, composed of Lisinopril, HPMC K4, HPMC K15, PEG-400, Xanthan gum, Mannitol, Citric acid, and DM water. The in-vitro release kinetics of formulation F7 revealed a diffusion-controlled release mechanism, with the Higuchi model providing the best fit. The study highlights the successful development of an optimized oral film formulation of Lisinopril, offering rapid drug dissolution and potential clinical benefits in hypertension management.

Keywords: Lisinopril, fast-dissolving oral film, natural disintegrants, optimization, in-vitro release kinetics.

INTRODUCTION

The pharmaceutical industry continues to innovate dosage forms to enhance patient compliance and therapeutic efficacy. Among these innovations, fast dissolving oral films (FDOFs) have gained prominence due to their convenience, rapid onset of action, and suitability for patients with swallowing difficulties [1]. FDOFs are thin, flexible films that disintegrate almost instantly in the oral cavity, releasing the drug for absorption through the mucosal lining. This delivery method bypasses

hepatic first-pass metabolism, potentially leading to improved bioavailability and faster therapeutic effects compared to traditional oral dosage forms.

Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, is widely prescribed for managing hypertension and heart failure. Its incorporation into FDOFs aims to address challenges related to dosing adherence, particularly among elderly and pediatric patients. By offering a user-friendly alternative to conventional tablets and capsules, Lisinopril FDOFs have the potential to improve medication adherence and therapeutic outcomes [2].

The aim of this study is to develop and evaluate a fast-dissolving oral film of Lisinopril, an antihypertensive drug, utilizing natural disintegrants to enhance patient compliance and facilitate rapid drug delivery. Fast dissolving oral films represent an advancement in drug delivery systems, offering advantages over conventional dosage forms and orally disintegrating tablets due to their ease of administration and quick dissolution in the oral cavity.

The objectives of the study include selecting appropriate natural disintegrants to facilitate rapid disintegration of the oral film, optimizing the composition of the film with respect to film-forming polymers, plasticizers, and other excipients, and evaluating the physical characteristics such as appearance, thickness, and weight variation of the developed oral films. Furthermore, the study aims to assess the content uniformity of Lisinopril within the films, measure the disintegration time to confirm rapid disintegration properties, and conduct in vitro dissolution testing to analyze the release profile of Lisinopril and ensure it meets predetermined specifications.

By achieving these objectives, the study seeks to contribute to the development of a novel dosage form that enhances drug delivery efficiency and patient adherence, particularly beneficial for individuals with swallowing difficulties or those requiring immediate drug action.

Material and Discussion

Material

The materials used for developing fast dissolving oral films (FDOFs) include Lisinopril (from Bioplus Life Science, Bangalore) as the active ingredient, along with excipients such as Carbopol, Sodium starch glycolate, Croscarmellose sodium, and Hydroxypropyl methyl cellulose (HPMC) from Loba Chemie Pvt. Ltd., Mumbai. Solvents like Methanol, Ethanol, and Chloroform from Qualigens Fine Chemicals, Mumbai, are utilized, along with additives such as Hydrochloride, Polyethylene glycol 400, Aspartame, Potassium phosphate monobasic (from Parth Chemical and Herbals, Indore), and Sodium hydroxide (from Shri Mahalaxmi Chemical Works, Indore). These

materials are chosen for their roles in enhancing drug stability, solubility, and taste masking in the formulation of FDOFs.

Methods

Formulation development of oral film of Lisinopril

Lisinopril containing fast dissolving films were fabricated by the solvent casting method [3]. HPMC is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely HPMC K4, and HPMC K15 were evaluated as film formers. For the fabrication of films, glycerin was used as a humectant. PEG 400 is also reported as lubricant and solubilizer. Therefore PEG 400 along with glycerol was also used for fabrication of films. Apart from these film formers, Guar gum, Xanthan gum and Sodium Alginates along with other excipients were tried. Citric acid for saliva stimulating agent and mannitol as sweeteners used to fabricate the films. The composition of various formulations is given in Table 1. The polymer was soaked in water for 30 min or heated in water bath to 80° to get a clear solution. Then a plasticizer was added to it and mixed so as to get homogeneous solution. This solution was then casted onto glass moulds (15*5cm) and was dried in hot air oven at 45° for 24 h.

Table 1: Selection and optimization of film forming agents

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril	120	120	120	120	120	120	120	120	120
HPMC K4	25	50	100	-	-	-	12.5	25	50
HPMC K15	-	-	-	25	50	100	12.5	25	50
PEG-400	50	50	50	50	50	50	50	50	50
Guar gum	20	30	40	-	-	-	-	-	-
Xanthan gum	-	-		20	30	40	-	-	-
Sodium Alginates	-	-	-	-	-	-	20	30	40
Mannitol	20	20	20	20	20	20	20	20	20
Citric acid	20	20	20	20	20	20	20	20	20
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

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 10 mg of drug.
- 12 no. of films contains mg of drug = 10×12 = 120mg
- The amount of Lisinopril added in each plate was approximately equal to 120mg.

Evaluation of prepared Film

Thickness

The thickness of patches was measured at three different places using a vernier caliper[4].

Weight uniformity

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 [5].

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 [6].

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 [7].

Drug content analysis

The film 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 reacted by UV spectrophotometer at 210nm[8].

Disintegrating time

The most important criteria of present work that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent was done to minimize the disintegrating

time. Three super disintegrating agents (Sodium starch Glycolate, Crospovidone and Croscarmellose Sodium) were selected for this work [9].

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 cm2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 4, 6, 8, and 10 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 drug was determined using UV-Visible spectrophotometer at 210nm. The results were presented as an average of three such concentrations[10].

RESULTS AND DISCUSSION

Table 1 provides an evaluation of the prepared films (F1 to F9) based on general appearance, thickness, and weight. The films exhibit uniform transparency with thickness ranging from 52 to 59 µm and weights varying between 95 to 99 mg.

Table 2 further assesses the films for folding endurance, disintegrating time, tensile strength, percentage moisture content, and assay percentages. Folding endurance ranges from 147 to 220 times, indicative of good mechanical durability. Disintegration times vary from 32 to 64 seconds, showing rapid dissolution properties. Tensile strength values range between 0.68 to 0.82 kg/cm2, demonstrating adequate film strength. Moisture content ranges from 3.65% to 7.65%, and assay percentages are consistently high, indicating uniform drug content.

Table 3 presents the in-vitro drug release profiles of formulations F1 to F9 over various time points. The cumulative drug release increases over time, with significant variations observed among formulations, reflecting different release rates and efficiencies.

Table 4 compares the regression coefficients (r2 values) for different kinetic models applied to formulation F7. The Higuchi and Peppas models demonstrate high coefficients (0.982 and 0.984, respectively), suggesting that these models fit well with the drug release data, indicating a diffusion-controlled release mechanism.

These tables provide comprehensive insights into the formulation characteristics, performance attributes, and drug release kinetics of the fast dissolving oral films, supporting their potential as effective drug delivery systems.

Table 1: Evaluation of prepared film for general appearance, thickness and weight

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	52±3	95±3
F2	Transparent	58±5	98±4
F3	Transparent	56±4	99±5
F4	Transparent	57±3	95±8
F5	Transparent	59±5	97±6
F6	Transparent	54±6	98±7
F7	Transparent	57±3	96±8
F8	Transparent	59±5	98±9
F9	Transparent	58±3	97±5

*Average of three determination (n=3±SD)

Table 2: Result of Folding Endurance, Disintegrating time, Tensile strength, Percentage Moisture Content and % Assay

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	147±5	63±2	0.68±0.08	5.95±0.85	97.85±0.32
F2	155±4	55±3	0.72±0.05	6.32±0.95	98.65±0.25
F3	165±6	52±5	0.69±0.06	4.85±0.74	97.74±0.22
F4	155±3	64±6	0.75±0.04	7.65±0.60	96.68±0.36
F5	169±4	53±5	0.79±0.03	6.85±0.32	96.65±0.74
F6	175±3	48±2	0.82±0.07	7.32±0.85	95.85±0.65
F7	220±2	32±4	0.71±0.05	3.65±0.74	99.12±0.85
F8	158±4	49±5	0.82±0.06	4.85±0.63	98.23±0.74
F9	163±5	59±3	0.78±0.07	6.95±0.75	98.74±0.32

*Average of three determination (n=3±SD)

Table 3: *In-vitro* drug release study of Formulation F1-F9

Time (Min.)	Cumulative % Drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed Tablets Formulation
1	20.23	23.65	26.65	21.25	24.56	26.65	39.98	32.25	30.78	36.65
2	43.32	55.56	58.89	46.65	55.65	55.56	56.65	45.65	49.98	69.98
4	54.45	63.32	67.78	63.32	69.98	71.23	69.98	56.87	63.36	88.95
6	69.98	75.65	85.65	75.56	78.89	86.65	76.58	69.98	74.45	99.45
8	75.56	83.32	90.23	83.32	91.32	92.23	86.65	75.56	89.98	-
10	85.65	92.23	94.58	89.98	94.56	96.65	98.89	82.23	93.32	-

Table 4: Comparative study of regression coefficient for selection of optimized batch F7

	Zero order	First order	Higuchi	Peppas model
r^2	0.957	0.799	0.982	0.984

CONCLUSION

The formulated fast dissolving oral films of Lisinopril, incorporating natural disintegrants and suitable excipients, exhibit potential as effective drug delivery systems. Their robust performance in terms of dissolution kinetics and mechanical properties underscores their suitability for enhancing patient compliance and facilitating rapid drug absorption. Further studies and optimization efforts can refine these formulations for practical pharmaceutical applications.

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