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Research

Formulation and Evaluation of Fast Dissolving Oral Film of Lisinopril

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Abstract:
The present study focuses on the formulation and evaluation of fast-dissolving oral films of Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor used for the management of hypertension. Fast-dissolving films offer several advantages over conventional oral dosage forms, such as ease of administration, enhanced patient compliance, and rapid drug release. Various formulation strategies were employed, including the use of different polymers and excipients to optimize the film's mechanical properties, disintegration time, drug release profile, and stability. The films were prepared using a solvent-casting method and evaluated for appearance, thickness, weight, folding endurance, tensile strength, disintegration time, moisture content, and assay. Formulation F7 showed the best performance, with a rapid disintegration time of 32 seconds, excellent mechanical properties, and a high cumulative drug release (98.89%) at 10 minutes. The in-vitro drug release profile of F7 followed the Peppas model with a non-Fickian diffusion mechanism. Stability studies indicated minimal changes in drug content over a 3-month period, confirming the stability of the optimized formulation. These findings suggest that F7 could serve as a promising fast-dissolving oral film for the delivery of lisinopril, offering a patient-friendly and efficient alternative to conventional tablets.

Keywords: Lisinopril, Fast-dissolving oral films, Drug delivery, Disintegration time, Tensile strength, In-vitro drug release, Stability study, Polymers, Solvent-casting method, Antihypertensive drug

Introduction

Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, is widely utilized in the treatment of hypertension, heart failure, chronic kidney disease, and diabetic nephropathy. Its mechanism of action involves the inhibition of the enzyme that converts angiotensin I to angiotensin II, thus leading to vasodilation and a reduction in blood pressure. Lisinopril is typically administered orally in tablet or capsule form; however, these conventional solid dosage forms present certain challenges, especially in terms of patient compliance and drug efficacy. For patients, particularly the pediatric, geriatric, and those with swallowing difficulties, taking solid dosage forms can be a cumbersome process. Moreover, oral tablets require water for administration and often exhibit slower onset times due to the need for gastrointestinal absorption (Patel & Patel, 2012).

In response to these challenges, the pharmaceutical industry has turned to alternative dosage forms,

particularly fast-dissolving or rapidly disintegrating films, as an innovative approach to improve patient convenience, compliance, and therapeutic outcomes (Gupta & Kaur, 2015). Fast-dissolving oral films are thin, flexible sheets that disintegrate quickly when placed on the tongue, bypassing the need for water, and offering a convenient method of drug delivery. They provide a rapid onset of action as the drug is absorbed directly through the mucous membranes of the oral cavity, avoiding the first-pass metabolism in the liver (Thakur & Thakur, 2013). This route of administration enhances bioavailability, allowing for faster therapeutic effects, which is particularly beneficial for conditions requiring immediate relief, such as hypertension (Arora & Jain, 2014).

The use of fast-dissolving oral films presents several significant advantages over conventional oral dosage forms. These include ease of administration without the need for water, rapid disintegration in the oral cavity, and a potential for improved bioavailability. Furthermore, fast-dissolving films are discreet and portable, making them ideal for individuals on the go, as well as for patients who may have difficulty swallowing tablets (Aulton & Taylor, 2013). These characteristics not only improve patient adherence to prescribed therapy but also provide a novel, effective method of drug delivery. Fast-dissolving films can be an especially useful alternative for drugs like lisinopril, which requires a rapid onset of action to manage blood pressure effectively (Bhise & Sharma, 2016).

However, the formulation of fast-dissolving films comes with its own set of challenges. One of the most pressing concerns is the need to mask the bitter taste of the drug, which could affect patient compliance. The bitter taste of lisinopril, like many other drugs, must be effectively masked using excipients such as cyclodextrins or sweeteners (Gupta & Kaur, 2015). In addition to taste masking, ensuring that the films maintain adequate strength and flexibility while dissolving rapidly is crucial for both patient experience and drug release (Sugimoto & Tanaka, 2016). Stability is also a major consideration, as the films must remain intact and effective throughout their shelf life, without degrading or losing their mechanical properties (Hegde & Bhat, 2015).

Materials used in the formulation of fast-dissolving films include various polymers, plasticizers, and excipients. Commonly used polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and pullulan help form the base structure of the film and contribute to its rapid dissolution (Ghosh & Kumari, 2014). Plasticizers like glycerin are incorporated to enhance the film's flexibility, preventing it from becoming brittle. Additionally, taste-masking agents such as sweeteners or flavoring agents are added to make the formulation more palatable (Bhowmik & Chiranjib, 2013). The proper selection of these excipients plays a pivotal role in ensuring that the film dissolves rapidly, delivers the drug effectively, and maintains a desirable taste (Arora & Jain, 2014).

Lisinopril is an ideal candidate for a fast-dissolving oral film formulation due to its high solubility and ability to provide immediate therapeutic effects. The quick dissolution and absorption of lisinopril in the oral cavity could enhance the drug's bioavailability and onset of action, both of which are critical for managing hypertension and other cardiovascular conditions (Al-Ghananeem & Desu, 2013). By bypassing the gastrointestinal tract and the first-pass effect, a fast-dissolving oral film of lisinopril could potentially offer superior bioavailability compared to conventional tablet formulations (Hegde & Bhat, 2015).

In light of these factors, this study aims to develop and evaluate a fast-dissolving oral film formulation of lisinopril that ensures efficient drug release and enhanced patient compliance. The formulation will be designed to provide rapid dissolution, taste masking, and adequate stability while delivering a pharmacologically effective dose of lisinopril. It is anticipated that this novel dosage form will not only address the shortcomings of traditional tablet formulations but also offer an improved therapeutic approach for patients suffering from hypertension and related conditions.

Material and Methods

Material

The materials used in the formulation of fast-dissolving oral films of lisinopril include the active ingredient lisinopril (gift sample from Bioplus Life Science, Bangalore) and several excipients to ensure

proper film formation and drug release. Carbopol acts as a gelling agent, Sodium starch glycolate and Croscarmellose sodium serve as disintegrants for rapid dissolution. Hydroxypropyl methylcellulose (HPMC) is used as a film-forming agent. Citric acid adjusts pH, while solvents like Methanol, Ethanol, and Chloroform aid in the formulation process. Polyethylene glycol 400 (PEG 400) acts as a plasticizer to provide flexibility. Aspartame is used to mask the bitter taste, and Potassium phosphate monobasic and Sodium hydroxide help maintain pH stability. All materials are sourced from reliable suppliers such as Loba Chemie Pvt. Ltd., Qualigens Fine Chemicals, and others.

Methods

Formulation development of oral film of Lisinopril

Lisinopril containing fast dissolving films were fabricated by the solvent casting method[62]. 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, SSG, CP and CCS 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 7.2. 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
SSG	20	30	40	-	-	-	-	-	-
CP	-	-		20	30	40	-	-	-
CCS	-	-	-	-	-	-	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 50 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 600mg.

Evaluation of prepared Film

Thickness

The thickness of patches was measured at three different places using a vernier caliper[63].

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[64].

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[65].

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[66].

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[67].

Disintegrating time

The most important criteria of present work is 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 agent (Sodium starch Glycolate, Crospovidone and Croscarmellose Sodium) were selected for this work.

***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, 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[68].

Stability studies

Stability studies were carried out with optimized formulation F8 which was stored for a period of one, two and three months at 40±2°C 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. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

Solvent casting technique

Lisinopril containing fast dissolving films were fabricated by the solvent casting method[62]. 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, SSG, CP and CCS 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 7.2. 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.

Results and Discussion

The results obtained from the formulation and evaluation of fast-dissolving oral films of lisinopril provide valuable insights into the quality, performance, and stability of the prepared films. Various parameters were evaluated to ensure the optimal characteristics of the films, including general appearance, thickness, weight, folding endurance, disintegration time, tensile strength, moisture content, assay, and in-vitro drug release.

As seen in Table 2**,** all formulations (F1-F9) exhibited a transparent appearance, which is a desirable characteristic for oral films as it ensures acceptability for patients. The film thickness ranged from 55 µm (F1) to 68 µm (F6), with F5 showing the highest average thickness of 68 µm. The variation in thickness is expected due to the different concentrations of excipients used in each formulation. Weight values also varied slightly across the formulations, ranging from 85 mg (F1) to 106 mg (F9). The slight variations in thickness and weight are

likely due to differences in the formulation composition, which could influence the final weight and thickness of the films.

The folding endurance of the films, an important parameter to evaluate the film's ability to withstand mechanical stress without breaking, showed excellent results. Formulation F7 exhibited the highest folding endurance (220±2), indicating that it can withstand a large number of folds without losing its integrity, which is crucial for patient compliance and ease of handling. On the other hand, F1 had a lower folding endurance (147±5), suggesting that modifications in the composition and excipients can improve the mechanical properties.

The disintegration time**,** as shown in Table 3**,** varied across the formulations, with F7 showing the fastest disintegration time (32±4 seconds). Faster disintegration times are ideal for fast-dissolving films as they allow for quick onset of action. F1 showed a disintegration time of 63±2 seconds, indicating that formulations with higher levels of disintegrants and other excipients contributed to faster disintegration. Faster disintegration is also essential for enhancing drug bioavailability.

The tensile strength values (ranging from 0.68 to 0.82 kg/cm²) suggest that the films are strong enough to withstand handling without breaking. F7**,** in particular, exhibited the highest tensile strength (0.82±0.06), indicating a robust film that can retain its structural integrity during storage and use. The tensile strength of the films is influenced by the film-forming agents, such as Hydroxypropyl Methylcellulose (HPMC) and Carbopol, which contribute to the film's mechanical strength.

The percentage moisture content of the films ranged from 3.65±0.74 (F7) to 7.65±0.60 (F4). Low moisture content is important for ensuring the stability of the films, preventing microbial growth, and reducing the likelihood of film degradation. F7, with the lowest moisture content, suggests better stability compared to other formulations.

The assay results (shown in Table 3) indicate that all formulations retained their active drug content well, with F7 showing the highest drug content (99.12±0.85%). This is an important consideration, as a higher drug content means better therapeutic efficacy.

The in-vitro drug release study (Table 4) demonstrated that the drug release profile from the films was time-dependent. All formulations, except F7, exhibited gradual increases in drug release, with F7 showing the highest release (98.89%) at 10 minutes. This formulation achieved a rapid drug release profile, which is ideal for fast-dissolving films designed for quick onset of action. In comparison, the marketed tablet formulation showed a slower drug release, with only 99.45% release at 10 minutes. The faster drug release from the films, especially F7, is indicative of the enhanced bioavailability that fast-dissolving oral films can offer compared to conventional tablets.

The release kinetics of F7 were analyzed using different models (zero order, first order, Higuchi, and Peppas models) and Table 6 presents the regression coefficients (r^2) for each model. The Peppas model exhibited the highest regression coefficient (0.984), suggesting that the drug release from the optimized formulation follows a non-Fickian diffusion mechanism. This indicates that both drug dissolution and diffusion contribute to the release process, a desirable characteristic for fast-dissolving films that aim for rapid absorption and quick therapeutic action.

The stability study of the optimized formulation (F7) over a 3-month period revealed minimal changes in the **assay** values, with the percentage assay remaining high (98.74% at 1 month, 98.05% at 2 months, and 97.88% at 3 months) (Table 7**).** This suggests that the formulation is stable under the storage conditions tested and retains its drug content over time, which is essential for maintaining the efficacy of the product throughout its shelf life.

Table 2: Evaluation of prepared film for general appearance, thickness and weight

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	55±6	85±7
F2	Transparent	59±8	88±6
F3	Transparent	58±4	92±5

F4	Transparent	62±3	96±3
F5	Transparent	68±5	92±2
F6	Transparent	68±8	98±4
F7	Transparent	63±6	102±6
F8	Transparent	62±4	105±2
F9	Transparent	67±6	106±3

Table 3: 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

Table 4: *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 5: Results of *In-vitro* release kinetics of optimized formulation F7

Time (min.)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0	39.98	1.602	60.02	1.778
2	1.414	0.30103	56.65	1.753	43.35	1.637
4	2.000	0.60206	69.98	1.845	30.02	1.477
6	2.449	0.77815	76.58	1.884	23.42	1.370
8	2.828	0.90309	86.65	1.938	13.35	1.125

10	3.162	1	98.89	1.995	1.11	0.045

Table 6: Comparative study of regression coefficient for selection of optimized batch

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

Table 7: Characterization of stability study of Optimized formulation

Parameter	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay	99.58	98.74	98.05	97.88

Conclusion

The results of the formulation and evaluation of fast-dissolving oral films of lisinopril indicate that formulation F7 is the most promising candidate among the nine tested formulations. It demonstrated the best combination of mechanical properties (folding endurance, tensile strength), rapid disintegration time, high drug release (98.89% in 10 minutes), and stability over time. Therefore, F7 could be considered as the optimal formulation for further development into a fast-dissolving oral film for the delivery of lisinopril. The study underscores the potential of fast-dissolving films as an effective and patient-friendly dosage form for delivering antihypertensive drugs like lisinopril.

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