Formulation and evaluation of fast-dissolving films of lisinopril

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Objective
The aim of this study was to formulate and evaluate the oral fast-dissolving film of lisinopril for the effective management of hypertension and cardiac diseases.

Materials and methods
Fast-dissolving films were prepared by the solvent-casting method using a combination of different polymers, HPMC E5 LV, HPMC E 3 and HPMC 4KM, along with PEG as a plasticizer. The Fourier-transform infrared study for the drug-polymer interaction was carried out. Evaluation of physical parameters such as physical appearance, surface texture, uniformity of weight, uniformity of strip thickness, surface pH, folding endurance, uniformity of drug content and percentage of moisture absorption were performed. Kinetic data analysis for the release study and the stability study were also performed.

Result and conclusion
Results of uniformity of weight, thickness, folding endurance, surface pH, tensile strength, percentage drug content, swelling index, tensile strength and percentage elongation of all the films were found to be satisfactory with respect to variation of these parameters between films of same formulation. The Fourier-transform infrared study indicated that there was no interaction between the drug and the polymers. The *in-vitro* drug release study showed that a better rate of drug release was achieved by formulations FA3, FB1, FB4 FC8 and FD10 compared with other formulations. The stability study did not show any significant difference in the external appearance, the drug content and the *in-vitro* drug release. The *ex-vivo* study indicated that the drug has a better ability to cross the sublingual barrier at a faster rate, and hence the delivery system was found to be promising as it has the potential of overcoming the drawbacks associated with tablet formulations available in the market presently.

Keywords:
fast-dissolving film, HPMC 4KM, HPMC E3, HPMC E5 LV, lisinopril, polymeric effect, solvent casting

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Introduction

Fast-dissolving drug-delivery systems (FDDS) were developed first as tablets, capsules and syrups for pediatric and geriatric patients, who experience difficulty in swallowing traditional oral solid dosage forms. Generally, the design pill is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. Many pediatric and geriatric patients are unwilling to take solid preparations due to the fear of choking. Such problems can be resolved by means of FDDS [1].

The FDDS was an advancement that came into existence in the early 1970s and combats the use of the tablets, syrups and capsules, which are the other oral drug-delivery systems. These delivery systems serve a major benefit over the conventional dosage forms because the drug gets disintegrated rapidly and dissolves in the saliva without the use of water. Inspite of the downside, that is, a lack of immediate onset of action, these oral dosage forms have beneficial purposes such as self-medication, increased compliance, ease of manufacturing and lack of pain [2].

Lisinopril is the lysine analog of enalapril. Lisinopril is a potent, competitive inhibitor of angiotensin-converting enzyme, the enzyme responsible for the conversion of angiotensin I to angiotensin II. Angiotensin II regulates blood pressure and is a key component of the reninangiotensin-aldosterone system. Lisinopril may be used to treat hypertension and symptomatic congestive heart failure, to improve survival in certain individuals after myocardial infarction and to prevent the progression of renal disease in hypertensive patients with diabetes mellitus and microalbuminuria or overt nephropathy.

The onset of action is 1–2 h and the duration of action is found to be 24 h (once daily dosing). The drug is found to be absorbed slowly and incompletely from the gastrointestinal tract (oral), and the peak plasma concentration is achieved after 7 h. The drug distribution is up to 25%, that is the protein is not significantly bound. The excretion of the drug is through urine in the unchanged form of the drug, and

the elimination half-life of the drug is found to be 12 h. The drug is given orally in case of hypertension. The adult dose is initially 5–10 mg daily given at bedtime to avoid a precipitous decrease in blood pressure. In patients with renovascular hypertension, volume depletion and severe hypertension 2.5–5 mg is administered once daily initially. Diuretic patients are given 5 mg once daily. For maintenance of the dose, 20 mg once daily up to 80 mg daily may be used if required. In case of children of at least 6 years, initially up to 0.07 mg/kg (up to 5 mg once daily) can be given, and the dose adjusted until the desired blood pressure is achieved. Bioavailability of the drug is ~25%, but a wide range of 6–60% is also reported [3].

Hence, an attempt was made to develop fast-dissolving films of lisinopril using suitable polymers such as hydroxypropyl methyl cellulose (HPMC K4M), HPMC E-3 and HPMC E-5 in different ratios and in combination with a sweetener such as aspartame along with a plasticizer such as propylene glycol.

Materials and methods

Materials

Lisinopril was obtained from Mylan laboratories Pharma (Hyderabad, India). HPMC K4M, E3, E5 were purchased from HiMedia Ltd (Mumbai, India). Aspartane was purchased from Jai Radhe sales (Ahmedabad, India). PEG 400 was purchased from Loba Chemie Pvt Ltd (Mumbai, India). All the reagents and chemicals used were of analytical grade.

Methods

Drug excipient compatibility studies

The Fourier-transform infrared (FTIR) spectral method was used for the detection of any possible chemical interaction between the drug and the polymers. The individual sample of drug and polymer/s powder and the three different drugs: polymer combination films were prepared and mixed with a suitable quantity of potassium bromide. About 50 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 15 tons' pressure. The pellets were scanned over a wave number range of 4000–600 cm^{-1} using an FTIR JASCO instrument (Jasco corporation, Tokyo, Japan).

Formulation of the fast-dissolving film of lisinopril

Fast-dissolving films of lisinopril were prepared by the solvent-casting technique. A petriplate having a surface area of ~70 cm^2 was used for casting the films [4].

Preparation of casting solutions

Casting solutions were prepared with the following different combination of polymers: HPMC K4M and HPMC E3 (FA1, FA2, FA3); HPMC K4M and HPMC E5 (FB4, FB5, FB6); and HPMC E3 and HPMC E5 (FB7, FB8, FB9). The weighed quantity of drug and polymers were dissolved in 5 ml of water. Aspartame was dissolved in 3 ml of ethanol in a beaker, and both the solutions were mixed together and stirred until dissolved. Propylene glycol was added as a plasticizer. The beaker was covered with an aluminium foil, and the solution was allowed to stand overnight to remove air bubbles [4,5] (Tables 1–3).

Preparation of fast-dissolving films

The casting solution (8 ml) was poured into a petriplate (70 cm^2) and kept aside to allow for controlled evaporation of the solvent. The films were removed by peeling and cut into squares with a dimension of 2 × 2 cm (4 cm^2) so that each film contained about 2.8 mg of drug. These films were kept in a desiccator for 2 days for further drying and wrapped in an aluminium foil [5].

Evaluation of fast-dissolving films

Physicochemical parameters [6–9]

Physical appearance: All films were inspected visually for colour, flexibility, homogenecity and smoothness, uniformity of weight and film thickness. The individual weight of films was determined and the average weight was calculated. The thickness was determined using digital Vernier calipers (Mitutoyo Absolute Digimatic Caliper, Aurora, Illinois, USA).

Surface pH: The surface pH of the film was determined to investigate the possibility of any irritation to the sublingual region during administration due to change in the pH *in vivo*, because an acidic or alkaline pH may cause irritation to the buccal mucosa. The films were placed in a petri dish, moistened with 10 ml of distilled water and kept for 30 s. The pH was recorded after bringing the electrode of the pH meter in contact with the surface of the formulation and allowed for equilibrium for 1 min. The average of three determinations for each formulation was taken.

Folding endurance: The folding endurance was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times the film could be folded at the same place without breaking yields the value of the folding endurance.

Table 1 Formulation of HPMC K4M and HPMC E3

Formulation code	Polymer ratio	HPMC K4M (mg)	HPMC E3 (mg)	Drug (mg)	Propylene glycol (ml)	Aspartane (mg)
FA1	1: 2	50	100	50	0.25	25
FA2	1: 4	50	200	50	0.25	25
FA3	1: 6	50	300	50	0.25	25

HPMC, hydroxypropyl methyl cellulose.

Table 2 Formulation of HPMC K4M and HPMC E5

Formulation code	Polymer ratio	HPMC K4M (mg)	HPMC E3 (mg)	Drug (mg)	Propylene glycol (ml)	Aspartane (mg)
FB1	1: 2	50	100	50	0.12	25
FB2	1: 4	50	200	50	0.12	25
FB3	1: 6	50	300	50	0.12	25

HPMC, hydroxypropyl methyl cellulose.

Table 3 Formulation of HPMC E3 and HPMC E5

Formulation code	Polymer ratio	HPMC E3 (mg)	HPMC E5 (mg)	Drug (mg)	Propylene glycol (ml)	Aspartane (mg)
FC1	1: 1	100	100	50	0.12	25
FC2	1: 2	100	200	50	0.12	25
FC3	1: 3	100	300	50	0.12	25

HPMC, hydroxypropyl methyl cellulose.

In-vitro disintegration studies: The disintegration time is the time when a film breaks or disintegrates. The test was performed using the same method as mentioned by Setouhy *et al.*[10] with partial modification. A film size of 2 × 2 cm (4 cm^2) was placed on a glass petri dish containing 10 ml of pH 6.8 phosphate buffer. The time required for breaking the film was noted as the *in-vitro* disintegration time.

Measurement of the swelling index: The swelling index (SI) of the films was determined in simulated salivary fluid of pH 6.8. The film sample (surface area 4 cm^2) was weighed and placed in a preweighed stainless steel wire sieve of ~800 μm mesh. The mesh containing the film sample was submerged into 15 ml of simulated salivary medium contained in a porcelain dish. At definite time intervals, the stainless steel mesh was removed and excess moisture was removed by carefully wiping with absorbent tissue and reweighed. Increase in the weight of the film was determined at each time interval until a constant weight was observed.

The degree of swelling was calculated using the formula:

$$\text{SI} = \frac{W_t - W_o}{W_o}$$

where W_0 is the weight of film at time $t = 0$, W_t weight of film at time 't' and SI is the swelling index.

Tensile strength: Tensile strength (TS) is the maximum stress (applied at one point) required to break the film. A film size of 2 × 2 cm (4 cm^2) that was free of any physical imperfection was placed between two clamps held 10 mm apart. The film was pulled by clamps at a rate of 5 mm/min: the force and elongation were measured when the film broke. Results from film samples that broke at and not between the clamps were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties, namely the TS and the percentage elongation, were computed for the evaluation of the film. TS is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture (as a mean of three measurements) divided by the cross-sectional area of the strip of fractured film as given in the equation below:

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross-sectional area of the sample } (mm^2)}$$

Percentage elongation: When stress is applied, a film sample stretches, and this is referred to as strain. Strain is basically the deformation of the film divided by the original dimensions of the sample. The percentage elongation can be obtained by the following equation:

$$\%\ \text{Elongation at break} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

Percentage drug content: This parameter was determined by dissolving one film of dimension 2×2 cm (4 cm^2) containing 2.8 mg of lisinopril by homogenization in 20–30 ml of simulated salivary fluid of pH 6.8 for 30 s with continuous shaking. The solution was filtered, and after suitable dilution with the simulated salivary fluid, the absorbance was measured at 217 nm using a Shimazdu double-beam ultraviolet-visible spectrophotometer (UV-1700; Shimadzu Corporation,

Tokyo, Japan). The experiments were carried out in triplicate for all the formulations.

In-vitro dissolution studies

A film size of 2 × 2 cm (4 cm^2) was placed in a beaker containing 20 ml of simulated salivary fluid (pH 6.8) as the dissolution medium maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of samples were taken at 5-s time intervals, and the same volume of fresh phosphate buffer was replaced. Samples were filtered, diluted suitably and analyzed at 217 nm using a Shimazdu double-beam ultraviolet-visible spectrophotometer (UV-1700; Shimadzu Corporation). Three trials were carried out for all the samples, and the average value was taken. The percentage of drug dissolved at various time intervals was calculated and plotted against time [11].

The *in-vitro* diffusion study

In-vitro diffusion study through a cellophane membrane was carried out using a modified Franz diffusion cell of internal diameter 2.5 cm. The cellophane membrane was mounted between the donor and the receptor compartments. The donor compartment was filled with the drug dissolved (2.8 mg equivalent to 4 cm^2) in 15 ml of simulated salivary fluid of pH 6.8, which was maintained at 37 ± 0.2°C, and hydrodynamics were maintained using a magnetic stirrer. Samples (5 ml) were withdrawn from the receptor compartment (phosphate buffer pH 7.4) at suitable time intervals of 10 s and replaced with an equal amount in the receptor compartment with phosphate buffer. The percentage amount of drug presence (diffused from the donor to the receptor compartment) in the receptor compartment was determined by measuring the absorbance in UV spectrophotometer at λ_{max} of 217 nm [11,12].

The *ex-vivo* permeation study

The *ex-vivo* permeation study through porcine oral mucosa (ventral surface of the tongue) was carried out using the modified Franz diffusion cell of internal diameter 2.5 cm. The sublingual mucosa was excised and trimmed evenly from the sides, washed in isotonic phosphate buffer of pH 6.8 and used immediately. The membrane was stabilized before mounting to remove soluble components. The mucosa was mounted between the donor and the receptor compartments. The receptor compartment was filled with 15 ml of isotonic phosphate buffer of pH 7.4, which was maintained at 37 ± 0.2°C, and hydrodynamics were maintained using a magnetic stirrer. One film of dimension 2 × 2 cm (4 cm^2 equivalent to 2.8 mg of drug) was moistened previously with a few drops of pH 6.8 phosphate buffer and placed in the donor compartment. The donor compartment was filled with 1 ml of pH 6.8 phosphate buffer. Samples (1 ml) from the receptor compartment were withdrawn at suitable time intervals, which were then replaced with 1 ml of pH 7.4 phosphate buffer. The percentage of drug that permeated was determined by measuring the absorbance in UV visible spectrophotometer at λ_{max} of 217 nm [13,14].

Kinetic analysis of *in-vitro* release data

To analyze the *in-vitro* release data, various kinetic models, the zero-order, the first-order, the Higuchi and the Korsmeyer-Peppas models, were used to describe the release kinetics.

Stability studies

Stability studies of the formulated fast-dissolving films were carried out at different temperatures. The film was packed in aluminium foil and stored in a stability chamber for stability studies at 2–8°C (45% relative humidity (RH) and 25–30°C (60% RH) for a period of 45 days. The films were characterized for drug content and other parameters at the end of 45 days [15].

Results and discussion

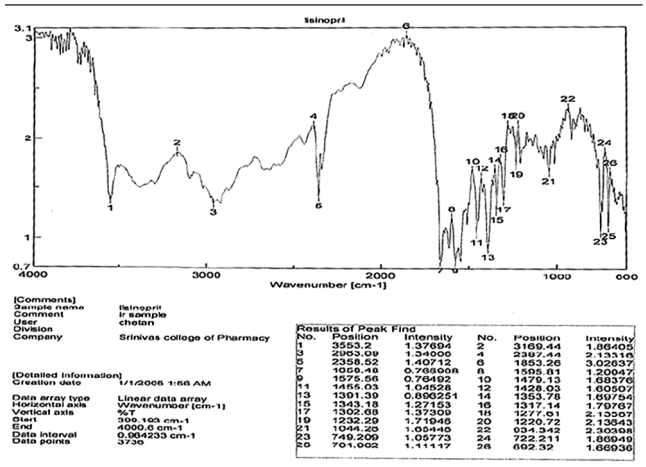
Compatibility study

FTIR studies of the pure drug, HPMC K4M, HPMC E3, HPMC E5 and the formulated films indicated that there was no interaction between the drug and the polymers. Lisinopril displayed the principal peaks at 3553.2 cm^{-1} due to N–H stretching around 3557.85 cm^{-1}, O–H stretching around 3300 cm^{-1}, aromatic C–H stretching around 3200 cm^{-1}, sp3 C–H stretching at 2957 cm^{-1}, C = O stretching around 1700 cm^{-1} and C–O stretching around 1045 cm^{-1}. The spectra of drug with polymers showed all the characteristic peaks of the drug, and thus indicated the compatibility of the drug with the polymers (Figs 1–3).

Physicochemical properties

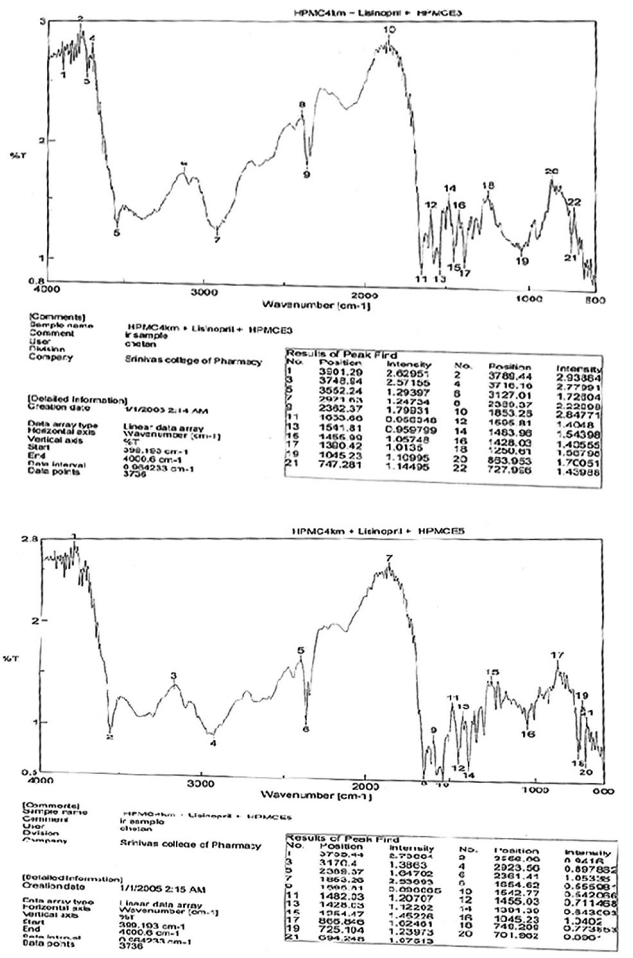
All the films prepared with different polymer concentrations were found to be flexible, smooth, transparent, nonsticky and homogeneous, indicating that the polymers used in the study had good film-forming properties. The individual weight of 10 samples of each type of formulation was determined, and the average weight was calculated. It was observed that the weight of the films in each batch of formulation was uniform (Fig. 4). Among the HPMC K4M and HPMC E5 formulations, the weight increased with increasing content of the polymer used due to the viscosity (higher concentration of polymer produces higher viscosity)

Figure 1



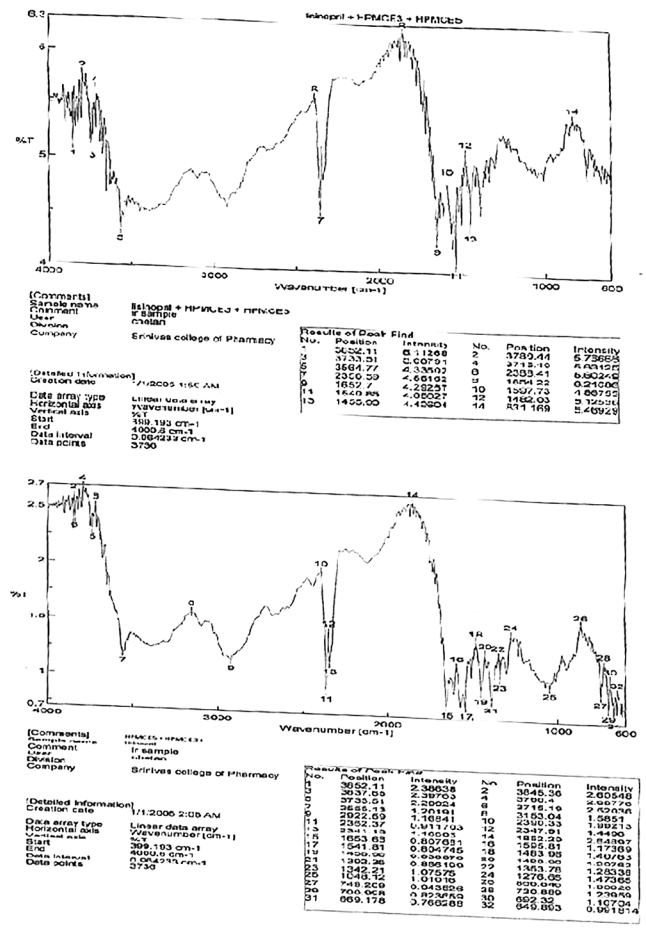
The FTIR spectrum of lisinopril.

Figure 2



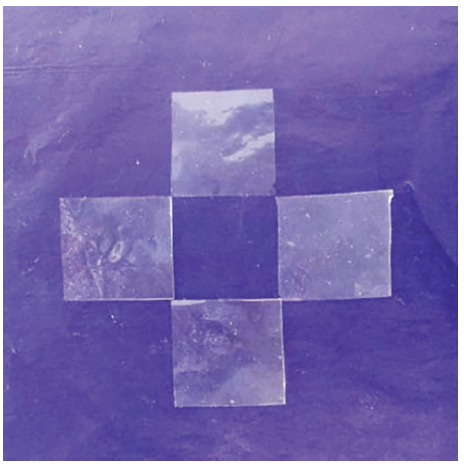
The FTIR spectrum of formulation of FA and FB.

Figure 3



The FTIR spectrum of FC and FD.

Figure 4



The sublingual film of lisinopril.

and the thickness of the films. The thickness of 12 films of each formulation was determined using a micrometer screw gauge, and the average thickness was determined. The values were found to be in the range of 100–200 μm, which is said to be acceptable for fast-dissolving films. It was also observed that the thickness of films having a combination of polymers (HPMC K4M and HPMC E3 and HPMC E3 and HPMC E5) were uniform in each formulation. The films with increased polymer content showed a moderate increase in thickness. The surface pH

of three films in each formulation was determined, and values were found to be in the range of 6.2–7.6, which is close to the neutral pH, and is less irritant to the sublingual mucosa. All the formulations showed a good folding endurance value of greater than 300. The *in-vitro* disintegration time was found to be in the range of 12.5–28.1 s (Table 4). The hydration and swelling behavior of the polymer is crucial for its bioadhesive nature because it is necessary to initiate the intimate contact of the film with the mucosal surface. The adhesion increases with the degree of hydration until a point where overhydration leads to an abrupt decrease in the adhesive strength due to disentanglement at the polymer tissue interface. The rate and the extent of film hydration and swelling also affect the film adhesion and consequently the drug release from the film. Studies have shown that excessive hydration can lead to weakening of the adhesive bond due to dilution of functional groups responsible for the adhesive interaction between the bioadhesive film and the mucosa (Table 5).

The TS gives an indication of the strength and the elasticity of the film reflected by the parameters TS and elongation at break (E/B). A weak and soft polymer is characterized by low TS and E/B, a hard and brittle polymer shows a moderate TS and low E/B and a soft and tough polymer shows a high TS and E/B. The percentage elongation increased with the increase in the percentage of polymer. The percentage drug content of all formulations was found to be in the range of 89–97% (Table 6).

In-vitro drug release studies

In-vitro dissolution testing in phosphate buffer pH 6.8 with formulations containing a combination of polymers showed that as the concentration of the polymer increased, drug release decreased due to an increase in the time required for wetting and movement of drug molecules present in the polymer matrices through the highly viscous fluid. Among the HPMC K4M–HPMC E3 films (FA1, FA2 and FA3), the extent of drug release was greater in FA3 films. It was observed that with the increased content of HPMC E3, the rate of drug release was faster because of the highly water-soluble polymer HPMC E3, which results in increased wetability and penetration of water into the film matrices, and hence increased diffusion of the drug. Among the HPMC E5–HPMC E3 films (FD10, FD11 and FD12), the extent of drug release was greater in FD10 films. It was observed that with the increased content of HPMC E3, the rate of drug release was found to be faster because of the water-soluble polymer HPMC E3, which results in increased wetability and penetration of water into the film matrices and hence increased diffusion of the drug.

Table 4 Physicochemical properties

Formulation code	Weight (mg)	Thickness (mg)	Surface pH	Folding endurance	Disintegration (s)
FA1	35.5 ± 0.507	0.14 ± 0.02	6.34 ± 0.007	>300	27.6 ± 1.07
FA2	52.5 ± 0.802	0.16 ± 0.02	6.54 ± 0.021	>300	26.8 ± 2.03
FA3	72.5 ± 0.667	0.18 ± 0.02	6.58 ± 0.007	>300	27.9 ± 2.03
FB4	38.5 ± 0.791	0.172 ± 0.01	6.44 ± 0.028	>300	27.02 ± 1.02
FB5	73.5 ± 0.850	0.184 ± 0.01	6.76 ± 0.021	>300	27.30 ± 2.01
FB6	84.52 ± 0.913	0.191 ± 0.08	6.68 ± 0.014	>300	28.01 ± 1.30
FC7	32.5 ± 0.580	0.10 ± 0.075	6.83 ± 0.021	>300	12.05 ± 1.21
FC8	49.40 ± 0.897	0.11 ± 0.076	7.04 ± 0.001	>300	15.80 ± 2.14
FC9	70.12 ± 0.315	0.13 ± 0.092	6.34 ± 0.014	>300	20.20 ± 2.58
FD10	60.55 ± 0.025	0.14 ± 0.055	6.71 ± 0.012	>300	16.65 ± 1.11
FD11	70.44 ± 0.29	0.17 ± 0.032	6.55 ± 0.014	>300	21.03 ± 1.23
FD12	68.98 ± 0.202	0.18 ± 0.025	6.95 ± 0.002	>300	24.30 ± 1.05

Data are represented as mean ± SD ($n = 3$).

Table 5 The swelling index

Time (s)	Swelling index[a]											
	FA1	FA2	FA3	FB4	FB5	FB6	FC7	FC8	FC9	FD10	FD11	FD12
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	0.273	0.89	0.94	0.63	0.91	1.04	1.11	0.82	0.72	1.01	0.93	0.80
10	0.362	1.38	1.42	1.23	1.40	1.54	1.26	1.01	0.90	1.28	1.18	0.96
15	0.83	1.84	1.32	1.70	1.86	2.01	1.53	1.23	1.12	1.47	1.27	1.90
20	1.18	1.31	1.84	1.63	1.81	1.85	1.66	1.37	1.26	1.31	1.56	0.90
25	1.09	1.47	1.86	1.80	0.91	0.89	0.58	0.32	0.23	–	–	–
30	–	0.99	0.40	–	–	–	–	–	–	–	–	–

[a]Average of three determinations.

Among the HPMC 4KM–HPMC E5 (FB4, FB5 and FB6), FB6 showed a slower release, and this may be due to the extensive swelling of HPMC E5, which created a high-viscosity gel barrier for drug diffusion. It was also observed that in the combination of HPMC E3–HPMC E5 formulation (FC7, FC8 and FC9), FC7 shows a slower release due to the moderate solubility of HPMC E5, so that if there is an increase in the HPMC E5 content, it leads to a decrease in the drug release. The K series of HPMC contains a greater number of long fibrous particles relative to the E series, which leads greater diffusional resistance to water; this directly reduces the diffusion of the drug out of the matrix and indirectly affects the state of hydration within the film, thus affecting the drug release due to erosion. Among the formulations, FA3, FB4, FC9 and FD10 were found to be better formulations in terms of drug release (Figs 5 and 6).

Table 6 Results of tensile strength, percentage elongation and percentage drug content

Formulation code	Tensile strength[a] (kg/cm^2)	Percentage elongation[a]	Percentage drug content in 2 cm^2
FA1	1.143 ± 0.030	32.86 ± 0.472	90.18
FA2	1.326 ± 0.020	32.23 ± 0.351	91.07
FA3	1.476 ± 0.025	42.13 ± 0.404	94.97
FB4	0.356 ± 0.015	21.73 ± 0.585	88.48
FB5	0.500 ± 0.025	26.73 ± 0.416	85.46
FB6	0.613 ± 0.020	29.93 ± 0.405	84.21
FC7	1.055 ± 0.025	53.83 ± 0.450	89.63
FC8	1.133 ± 0.026	58.76 ± 0.351	89.63
FC9	1.233 ± 0.015	66.16 ± 0.602	90.53
FD10	1.492 ± 0.023	46.05 ± 0.368	96.44
FD11	1.341 ± 0.030	35.42 ± 0.40	94.54
FD12	1.112 ± 0.021	31.52 ± 0.42	93.85

[a]Data are represented as mean ± SD (n = 1).

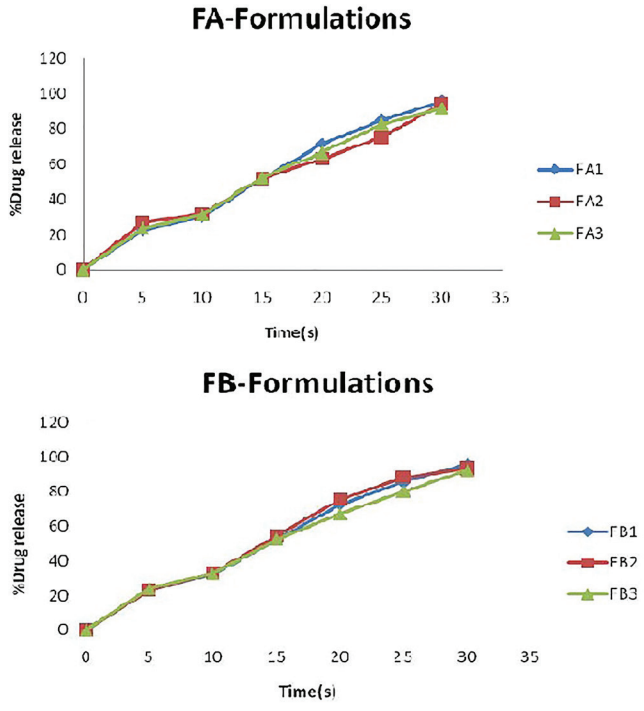
In-vitro diffusion studies

The percentage amount of drug diffusion is plotted against time to obtain the diffusion profile. It was found that in ~60 s, the entire quantity of the released drug from the formulation diffused completely and hence indicated a good diffusion coefficient, which is essential for faster onset of action. The *in-vitro* diffusion study using a cellophane membrane was used as a yardstick for the *ex-vivo* permeation study for comparison, and the results were found to be comparable (Figs 7 and 8).

Ex-vivo permeation studies

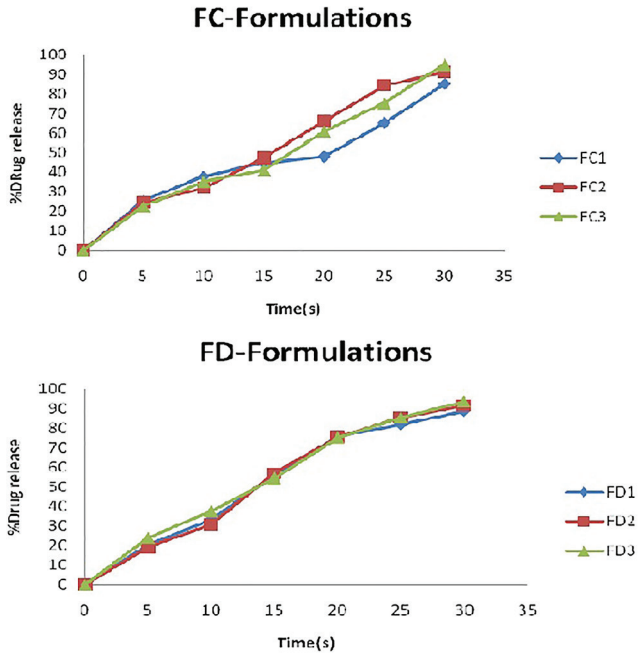
The *ex-vivo* permeation study of all formulation have been carried out and the formulation containing polymer HPMC 4KM, HPMC E3(FA1) showed better drug permeation, because HPMC E3 is a hydrophilic polymer and it gets disintegrated faster. The formulation containing polymer HPMC E5 and HPMC E3 (FD10) showed better drug permeation. The results obtained in the *ex-vivo* study indicated that the drug has a better ability to cross the sublingual barrier at a faster rate, and hence the delivery system has the potential of overcoming the drawbacks associated with tablet formulations available in the market presently (Table 7).

Figure 5



The dissolution profile of formulation FA and FB.

Figure 6



The dissolution profile of formulation FC and FD.

Kinetic data analysis

The mechanism and kinetics of drug release of lisinopril were determined by the application of the zero-order, the first-order, the Higuchi and the Korsmeyer-Peppas models. The kinetics of drug release for all the formulations was found to be first order. Using the Korsmeyer and Peppas model, n = 0.45 indicates case I or Fickian diffusion, 0.45 <n> 0.89 indicates anomalous behavior or non-Fickian transport, n = 0.89 indicates case II transport and n greater than 0.89 indicates super case II transport. Fickian release usually occurs by molecular diffusion of the drug due to a chemical potent gradient. Case II relaxation release is the drug transport mechanism associated with stresses and state transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. In the present investigation, release from the hydrophilic polymers followed the combination of diffusion and erosion as the 'n' values ranged from 0.56 to 0.77 as per the Korsmeyer and Peppas model, which in turn justified the suitability of polymers for the preparation of fast-dissolving films (Table 8).

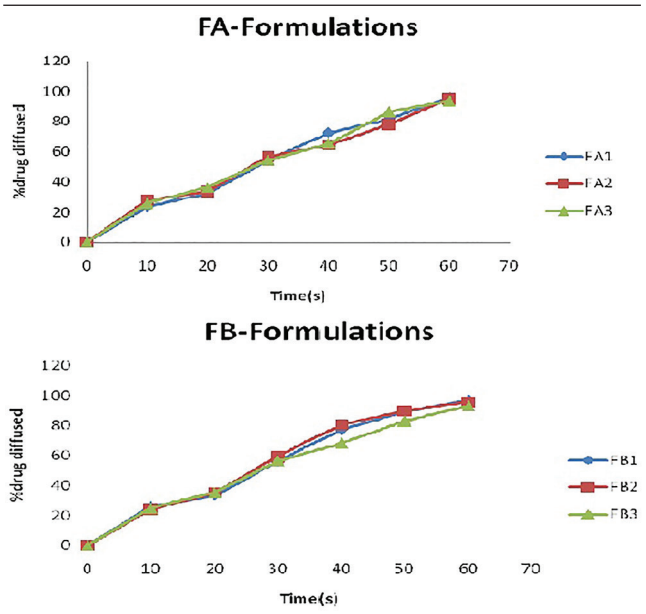
Stability studies

Stability studies were carried out for 45 days at 2–8°C (45% RH) and 25–30°C (60% RH). The films were observed for physical changes, the percentage drug content and the percentage drug release. Fast-dissolving films of lisinopril were found to be physically and chemically stable and showed no significant change in terms of physical characteristics, the percentage drug content and the percentage drug release.

Conclusion

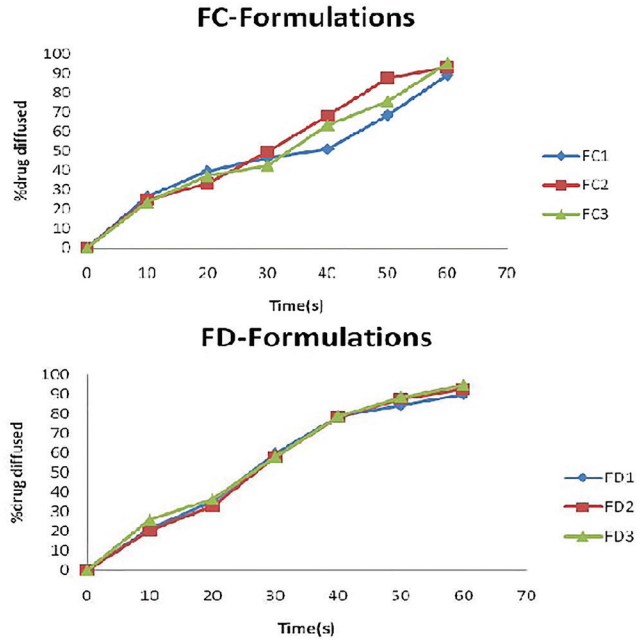
The objective of the present investigation has been achieved by preparing fast-dissolving films of lisinopril for the effective management of hypertension and cardiac diseases. The present study also investigated the feasibility of the drug for sublingual delivery by formulating into fast-dissolving films using polymers for the purpose of improving their bioavailability and quick onset of drug action. The drug has a metallic taste and hence an attempt was made to mask the taste by adding the artificial sweetener aspartame, which also acts as a saliva stimulant. On the basis of

Figure 7



Diffusion profile of formulation FA and FB.

Figure 8



The diffusion profile of FC and FD.

Table 7 *Ex-vivo* permeation study

Time (s)	Percentage drug diffused											
	FA1	FA2	FA3	FB4	FB5	FB6	FC7	FC8	FC9	FD10	FD11	FD12
00	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
10	25.16	24.68	24.20	22.05	21.33	20.85	30.68	29.72	28.76	32.87	37.15	36.67
20	53.82	53.07	52.08	43.32	42.08	41.57	62.56	63.22	61.96	92.97	90.53	89.78
30	81.54	80.02	78.98	77.58	75.79	74.77	79.29	77.12	76.26	–	–	–

Table 8 Kinetic analysis of *in-vitro* drug release data of all the formulations

Formulation code	Zero-order R^2	First-order R^2	Higuchi kinetics R^2	Korsmeyer-Peppas equation N
FA1	0.9118	0.9668	0.9929	0.72
FA2	0.9820	0.9923	0.9902	0.72
FA3	0.9251	0.9773	0.9710	0.73
FB4	0.9258	0.9919	0.9686	0.63
FB5	0.9619	0.9937	0.9897	0.69
FB6	0.9859	0.9896	0.9842	0.56
FC7	0.9209	0.9844	0.9882	0.68
FC8	0.9792	0.9853	0.9809	0.68
FC9	0.9887	0.9915	0.9875	0.67
FD10	0.9011	0.6427	0.8297	0.68
FD11	0.9212	0.6184	0.8057	0.77
FD12	0.9224	0.5648	0.7986	0.73

the encouraging results, lisinopril fast-dissolving films can be considered to be suitable for clinical use in the treatment of all myocardial infractions, angina and in case of hypertension, wherein quicker onset of action is desirable along with convenience of administration without using water. The method of preparation was found to be simple and required minimum excipients, thus making the product cost-effective. Finally, it can be concluded that this delivery system has the potential of overcoming the drawbacks associated with tablet formulations available in the market presently.

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Conflicts of interest

There are no conflicts of interest.

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