Formulation And Evaluation Of Mouth Dissolving Film Of An Antihypertensive Drug

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Abstract

Objective: The present research work is focused to formulate and evaluate mouth dissolving film of an antihypertensive drug to enhance the convenience and compliance by the Geriatric patients.

Methods: The formulation was prepared using Lisinopril drug, and excipients such as HPMC E5, glycerine, aspartame, citric acid, etc. by solvent casting method. The formulations were subjected to evaluation characteristics such as appearance, weight variation, thickness, folding endurance, surface pH, tensile strength, disintegration time, drug content, and in-vitro drug release studies.

Results: All the prepared A1 to A9 batches shown pH was found in the range of 6.5 to 6.7, disintegration time was found in range of 19.49 to 24.38 seconds, drug content was found in range of 88 to 95%, and % drug release was found in range of 82.02 to 95.20%. As compared to other formulation batches, A6 batch selected as an optimized formulation because it gave the highest drug content that is 95%, and highest drug release of 95.20% after 70 seconds.

Conclusion: It concluded that the mouth fast dissolving films of Lisinopril for control of Hypertension could be successfully formulated using HPMC E5 polymer by solvent casting method.

Keywords: mouth dissolving film, Lisinopril.

INTRODUCTION

The oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. The most popular dosage forms are tablets and capsules. In last two decades, due to enhanced demand of patient compliance vast research took place in this area. There are around 350 drug delivery systems developed in accordance with patient compliance. Geriatric patients may have difficulty in swallowing and chewing the tablets resulting in patient noncompliance and ineffective therapy. To overcome these problems mouth dissolving tablets are a very good option. They disintegrate and get dissolved faster in saliva without the usage of water. As a result, it explains good patient compliance. The demand for this fast and mouth dissolving technology was approximately 16.50 billion US dollars in the year 1996 but now it is expected to grow about 80 billion US dollars every year. To overcome such problems in geriatric patients a newer dosage form has been introduced which is regarded as mouth dissolving tablets or films. It is one of the novel approaches which involves rapid disintegration or dissolution of dosage form inside the mouth without the need for water [1].

Mouth dissolving film is the one of the most advanced oral solid dosage forms because of its flexibility and comfort in use. Mouth dissolving films are oral solid dosage form that disintegrate and dissolve within a minute when placed in mouth without taking water or chewing. This dosage form allows the medication to bypass the first pass metabolism so bioavailability of medication may be improved [2].

Mouth dissolving film has potential to improve onset of action lower the dosing and eliminate the fear of chocking. Formulation of mouth dissolving films involves both the visual and performance characteristics as plasticized hydrocolloids; API taste masking agents are being laminated by solvent casting and semisolid casting method. Solvent casting method being the most preferred method over other methods because it offers great uniformity of thickness and films prepared having fine glossy look and better physical properties. Mouth dissolving films are evaluated for its various parameters like thickness, physical property like folding endurance, disintegration and dissolution time [3].

MATERIALS AND METHODS Materials

Lisinopril was procured as a gift sample from Manish pharmaceutical pvt. limited, Mumbai. Hydroxypropyl methylcellulose E5, glycerine, aspartame, citric acid was purchased from Loba chemie, Mumbai, India.

Methodology Preformulation evaluation

Preformulation study is the first step in the preparation of any formulation. The preformulation study confirms the formulation under consideration.

Description

The sample of Lisinopril was observed for its colour and nature.

Melting point

The melting point of drug Lisinopril was determined with the help of melting point apparatus. In this method drugwas poured in capillary tube with one end closed. Insert the capillary tube in melting apparatus. Start the apparatus andwait till the drug melts. Record the temperature at which drug melt [4].

Solubility

Solubility of Lisinopril was determined in different solvents like water, methanol, ethanol, and Phosphate buffer Solution pH 6.8 [5].

Determination of λ_{max} of Lisinopril

Accurately weighed 100mg of Lisinopril was transferred to the 100ml volumetric flask and volume was made with phosphate buffer (pH 6.8). From this solution 10ml was withdrawn and added to the 100ml volumetric flask and make up volume with phosphate buffer (pH 6.8) Finally, the standard solution (100µgm/ml) of Lisinopril in phosphate buffer pH 6.8 was scanned between 200-400 nm on UV-visible spectrophotometer to record the wavelength of maximum absorption (λ_{max}) [6].

Calibration curve of Lisinopril in PBS pH 6.8 Procedure

for Preparation of PBS pH 6.8

28.8 g of sodium dihydrogen phosphate, 11.45 g of potassium dihydrogen phosphate was dissolved in 1000 ml of distilled water.

Preparation of standard stock solution

100 mg of Lisinoprilwas accurately weighed with the help of weighing balance and poured in to 100 ml volumetric flask. Drug was dissolved in 100 ml phosphate buffer pH 6.8 and volume was made up to 100 ml in volumetric flask. From the resulting solution 10 ml was pipetted out and diluted to 100 ml with PBS pH 6.8 giving the stock solution of 100 µg/ml.

Preparation of working solutions:

From the above stock solution, aliquots of 0.5ml, 1.0ml, 1.5ml, 2.0ml, to 4.5ml and 5.0 ml were withdrawn and transferred to the 10 ml volumetric flask containing PBS pH 6.8 to get concentrations of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, to 45µg/ml and 50µg/ml respectively. Finally the absorbances of prepared solutions were measured against blank (PBS pH 6.8) at 207 nm by using UV visible spectrophotometer and standard calibration graph was plotted for absorbance vs. concentration [6].

Drug excipient interaction study by FT-IR

Interaction of Lisinopril with all the polymers like HPMC E5 was observed with the help of FTIR technique. The spectrum of drug is taken with the help of KBr pellet technique. Pellets of drug and KBr were prepared using hydraulic press and analysed in FT-IR spectrophotometer [7].

Differential scanning calorimetry (DSC)

DSC technique helps to detect crystallization, degradation, phase transformation, glass transition temperatures in solid sample. DSC was performed in order to assess the thermotropic properties and thermal behaviour of the drug. Differential scanning calorimetry thermogram of the pure drug, was recorded on a thermal analyser. Sample was placed in aluminium pans and constant heating range of 30°c to145°c at a heating rate of 15°C/min in an inert nitrogen atmosphere. Nitrogen was used as purge gas through DSC cell [8].

Formulation of drug loaded mouth dissolving film

The solvent-casting method was used for the preparation of mouth dissolving film formulation. Lisinopril films were prepared by solvent casting technique using film forming polymer (Table 1.) Required amount of HPMC E5 was weighed accurately and soaked aside for 1hour in 5ml of water for swelling of polymer. Simultaneously Lisinopril was weighed

accurately and dissolved in 5ml of distilled water in another beaker. Then drug solution was added to the polymer solution, Glycerine was added as plasticizer, Aspartame as sweetener, and citric acid as saliva stimulating agent was mixed thoroughly with the help of magnetic stirrer [9].

Entrapped air bubbles were removed by applying vacuum. The resulting 10 ml solution with the help of measuring cylinder was transferred into moulds slowly drop by drop and was spread uniformly. Funnel was inverted and placed over the moulds to have uniform evaporation. The mould containing polymeric solution of drug was kept for 24 hours at room temperature for drying. After drying the films were removed by peeling from the moulds then cut into a square dimension of 2.5× 2.5 cm. Films were packed in aluminium foil and stored in air tight container to maintain their integrity and elasticity [10].

Table 1: Formulation of Mouth dissolving films of Lisinopril

Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9
Lisinopril	40	40	40	40	40	40	40	40	40
HPMC E-5	150	150	150	200	200	200	250	250	250
Glycerine	0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
Aspartame	25	25	25	25	25	25	25	25	25
Citric acid	15	15	15	15	15	15	15	15	15
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

All ingredients are measured in milligram. Dose of drug per film is 40mg. area of film is 2.5×2.5 cm

Evaluation of mouth dissolving film

The mouth dissolving films of Lisinopril were evaluated with the help of different parameters.

Appearance

The physical appearance of mouth dissolving film of Lisinopril was observed by visual inspection.

Weight Variation

The films of different formulation were weighed individually using digital balance and average weight was calculated [11].

Thickness

The thickness of each film was measured using digital vernier calliper at different positions of the film and the average thickness was calculated. This is essential to ascertaining uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip [12].

Folding endurance test

Folding endurance of film was determined by repeatedly folding a small strip of film (2.5×2.5cm) at the same place till it breaks is noted as the folding endurance value [13].

Surface pH of film

It was determined by allowing contact of surface of film with 1 ml of distilled water. After sometime, surface pH of film was obtained by dipping pH paper in the solution for around 1 minute [14].

Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied force at rupture as a mean of three measurements and the cross-sectional area of the fractured film as described in the equation. In this test the film was tied between two clamps and the one end of clamp was directly attached to pan through pulley. The stress was applied to the film by putting load in the pan and finally the reading of load at failure was noted. All determinations were performed in triplicate with standard deviation. It was calculated by the following formula [14]:

Tensile strength = Load at failure ×100/ Film width × film thickness

In vitro disintegration time

In this method take a piece of film (2x2 cm). place it on a glass petri dish containing 10 ml of distilled water. The time required for film to break the first particle of film was noted down which is considered as In vitro disintegration time [15].

Drug content
A film of 2.5 × 2.5 cm diameter was cut and placed in 100 ml of phosphate buffer solution (PH 6.8). The contents were stirred by using magnetic stirrer to dissolve the film. The contents were transferred to a volumetric flask (100 ml). To this solution 1ml is withdrawn and diluted to 10ml the absorbance of the solution was measured against the corresponding blank solution at 207 nm. As the absorbance noted above 1ml of the stock was further diluted to 10 ml of phosphate buffer solution (pH 6.8) and absorbance was measured at 207 nm [16].

In vitro drug release studies
In this method take a piece of film (2.5 x 2.5 cm). It was placed in a stainless- steel wire mesh with sieve opening of 700 µm. The mesh is placed in dissolution media (PBS pH 6.8) around 300 ml. The dissolution process is carried out by 6 stage paddle apparatus at 37 ℃ at 50rpm. 5ml of sample is withdrawn at time intervals 0,1,2,3,4,5,10,15 and 30 minutes. After withdrawing sample, a fresh 5ml blank is added to the apparatus to maintain the sink condition. The cumulative percentage of drug released was determined using UV visible spectrophotometer at 207 nm [17].

FTIR spectroscopy of optimized formulation A6
Infrared spectrum of optimized formulation that is A6 was recorded on a FTIR spectroscopy.

Differential scanning calorimetry of optimized formulation A6
Differential scanning calorimetry thermogram of optimized formulation that is A6 was recorded on a thermal analyser [18].

Results Description
The sample of Lisinopril was found to be white to off white crystalline powder with bitter taste.

Melting Point
Melting point of Lisinopril was observed between 158-160ºC, hence the drug sample passed the identification test. Standard melting point of Lisinopril, according to literature is 160ºC.

Solubility
Lisinopril was found to be freely soluble in water and slightly soluble in methanol and practically insoluble in ethanol.

Determination of λ_{max} of Lisinopril:
For characterization of drug by UV spectroscopy, it is important to know the wavelength of maximum absorption (λ_{max}). The spectrum of Lisinopril phosphate buffer 6.8 was taken. The λ_{max} of Lisinopril in phosphate buffer was found out to be 207 nm it was found that it exhibited maximum absorbance at 207.0 nm. So, absorbance at 207.0 nm was considered as λ_{max} for Lisinopril.

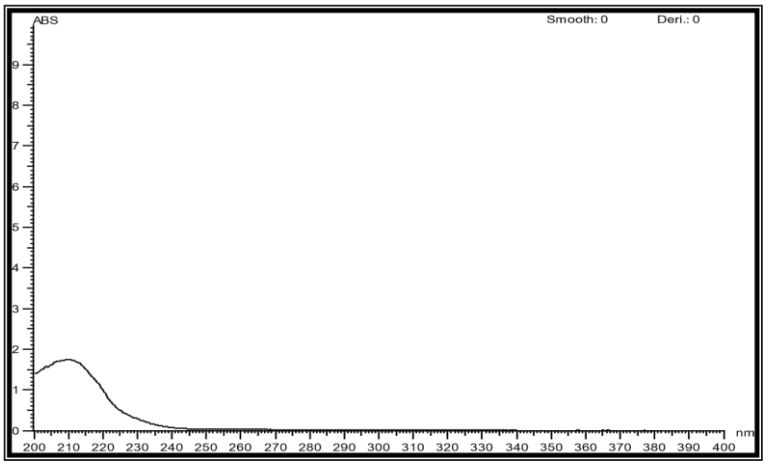

Fig. 1: UV Spectra of lisinopril in phosphate buffer pH 6.8

Calibration curve of lisinopril in phosphate buffer pH 6.8
The calibration curve for Lisinopril in pH 6.8 buffer is shown in figure. The graph of absorbance vs. concentration for Lisinopril was found to be linear in the concentration range of 5-50 µg/ml and Coefficient of correlation was found to be 0.9942, Slope 0.0248, Intercept: 0.00685.

Table 2: Spectrophotometric data for the calibration curve of Lisinopril in phosphate buffer pH 6.8

Sr.no.	Concentration µg/ml	Absorbance
1	5	0.1678
2	10	0.2011
3	15	0.3266
4	20	0.4183
5	25	0.5096
6	30	0.6073
7	35	0.6113
8	40	0.8077
9	45	0.8211
10	50	1.1331

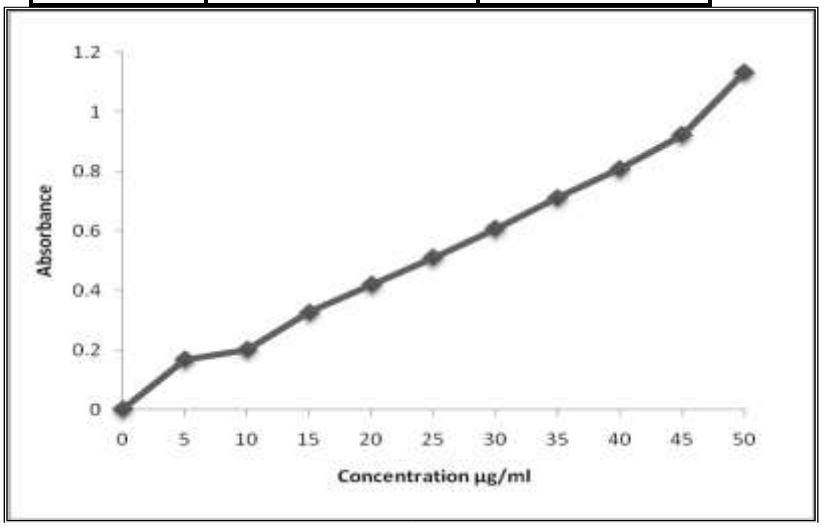

Fig. 2: Calibration curve of Lisinopril in PBS pH 6.8

Drug Excipient compatibility Studies by IR Spectroscopy

The proper design and formulation of a dosage form require consideration of physical, chemical and biological characteristics of all the drug substances and excipients to be used in fabricating the product. The drug and excipients polymers must be compatible with one another to produce a product that is stable, effective, attractive, easy to administer and safe.

IR Spectroscopy of Pure Lisinopril

All the peaks of drug were found in the provided gift sample of drug were mentioned in following Table 3. Which confirm the drug sample as authentic It was compared with standard functional group frequencies of lisinopril. Principle peaks were found in the range corresponding to functional group. Appearance of the peak in spectrum confirms that the sample of lisinopril. IR spectra of lisinopril was shown in figure 3.

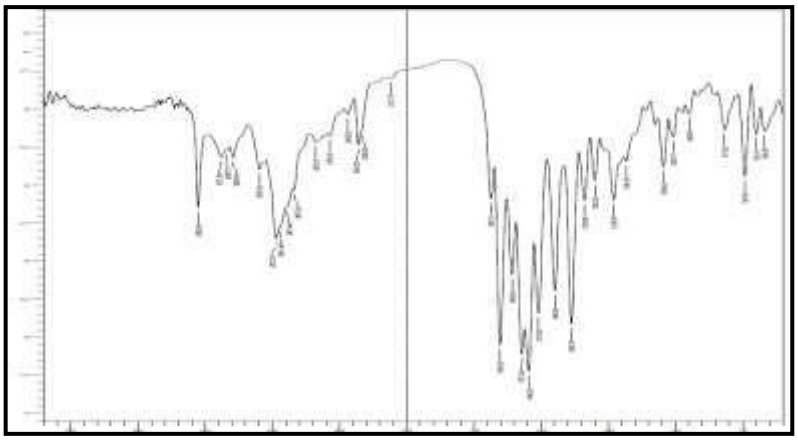

Fig. 3: IR spectrum of lisinopril

Table 3: Interpretation of IR spectrum of lisinopril

Functional group	Observed Wavenumber (cm^{-1}) in mixture IR	Theoretical Wavenumber range (cm^{-1})
Amide N-H Streching	3550cm^{-1}	3300-3500cm^{-1}
O – H stretching	3290cm^{-1}	2800-3200cm^{-1}
Aromatic C-H stretching	2972cm^{-1}	2900-3000cm^{-1}
Ketones C=O Streching	1653cm^{-1}	1650-1700cm^{-1}
C-O Streching	1045cm-1	1050-1000cm-1

IR Spectroscopy of physical mixture of Lisinopril and HPMC E5

The IR spectrum of physical mixture of Lisinopril and hydroxy propyl methyl cellulose E5 was determined as shown in figure 4. All peaks of functional groups of Lisinopril were found to be present in the IR spectrum of mixture. The result indicated that there was no interaction between lisinopril and HPMC E-5 since there was no any extensive change in the absorption peaks of Lisinopril in the mixture. Interpretation of physical mixture of Lisinopril and HPMC E5 shown in table 4.

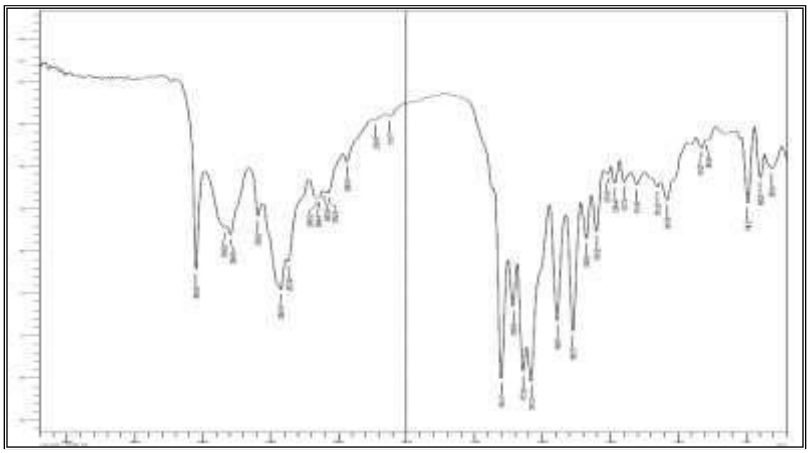

Fig. 4: IR spectrum of physical mixture of Lisinopril and HPMC E5

Table 4: Interpretation of physical mixture of Lisinopril and HPMC E5

Functional group	Observed Wavenumber (cm^{-1}) in mixture IR	Observed Wavenumber (cm^{-1}) in lisinopril IR	Theoretical Wavenumber range (cm^{-1})
Amide N-H Streching	3549cm^{-1}	3550cm^{-1}	3300-3500cm^{-1}
O – H stretching	3294cm^{-1}	3290cm^{-1}	2800-3200cm^{-1}
Aromatic C-H stretching	2970cm^{-1}	2900cm^{-1}	2900-3000cm^{-1}
Ketones C=O Streching	1651cm^{-1}	1653cm^{-1}	1650-1700cm^{-1}
C-O Streching	1043cm^{-1}	1045cm-1	1000-1050cm-1

Differential Scanning Calorimetry (DSC)

DSC technique helps to detect crystallization, degradation and phase transformation in solid samples. The thermogram of pure Lisinopril shows sharp exothermic peak starting at 170ºC with melting peak at 180ºC**.** DSC thermogram of Lisinopril shown in figure 5.

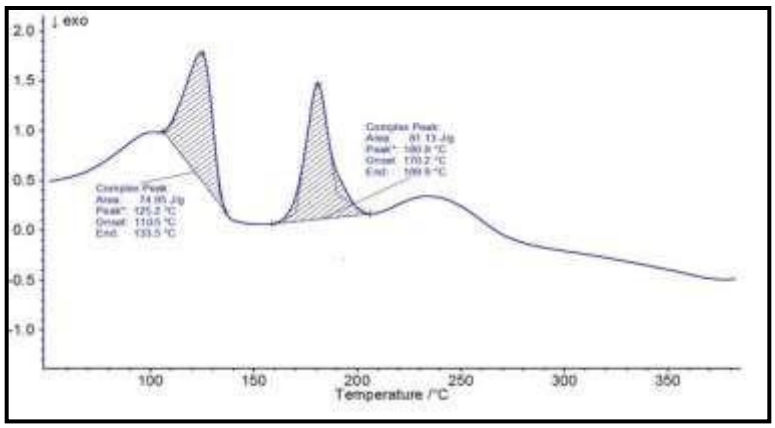

Fig. 5: DSC thermogram of pure Lisinopril

Evaluation of mouth dissolving film of Lisinopril Table 5: Evaluation of mouth dissolving films

Formulation	Appearance	Wt. of films (mg)	Thickness of film (µ)	Folding endurance
A1	Transparent	20.2 ± 0.20	0.07±0.01	100 ± 1.13
A2	Transparent	27.2 ± 0.40	0.08±0.06	110 ± 1.00
A3	Transparent	30.33±0.35	0.11±0.00	119 ± 1.40
A4	Transparent	32.17±0.15	0.07±0.00	101 ± 1.23
A5	Transparent	34.25±0.17	0.09±0.03	112 ± 1.00
A6	Transparent	38.20±0.10	0.11±0.04	123 ± 1.52
A7	Transparent	40.14±0.15	0.08±0.00	105 ± 1.52
A8	Transparent	44.26±0.30	0.09±0.01	118 ± 1.50
A9	Transparent	47.17±0.10	0.12±0.05	130 ± 1.00

Values are expressed as mean ± S.D (n=3)

Table 6: Evaluation of mouth dissolving films

Formulation	P^H	Tensile strength (kg/cm)	Disintegration Time (sec)	Drug content (%)
A1	6.7 ± 0.01	165±2.00	19.49 ± 0.18	88
A2	6.6 ± 0.05	159±2.50	22.42 ± 0.10	86
A3	6.5 ± 0.00	152±2.30	24.25 ± 0.00	89
A4	6.7 ± 0.00	180±2.22	20.31 ± 0.15	93
A5	6.8 ± 0.07	175±2.00	22.3 ± 0.00	90
A6	6.8 ± 0.04	160±2.23	23.45 ± 0.15	95
A7	6.7 ± 0.03	195±2.00	22.4 ± 0.20	92
A8	6.6 ± 0.06	180±2.51	23.47 ± 0.14	85
A9	6.5 ± 0.01	177±2.00	24.38 ± 0.11	87

Values are expressed as mean ± S.D (n=3)

In vitro Drug Release

All the nine formulations were subjected to in-vitro dissolution studies using a USP type -II Dissolution Test Apparatus. The dissolution medium 6.8 pH buffer was used to study the drug release. The samples were withdrawn at different

intervals of time and analyzed at 207.5 nm using UV spectrophotometer. Cumulative percentage drug release was calculated. The data obtained from in vitro release for formulations prepared by solvent casting technique are tabulated in the table 7.

Table 7: Cumulative % drug release profile of formulation A1 to A5

Time (sec)	A_1	A_2	A_3	A_4	A_5
0	0.00	0.00	0.00	0.00	0.00
10	15.25	13.4	19	18.5	21.25
20	28.59	25.1	34.86	21.5	38.45
30	36.23	35	46.79	39.75	45
40	54.47	46.16	58.90	53.12	51.37
50	68	54.45	68.1	69.75	64.75
60	70.68	71.16	83.07	87.4	76.37
70	82.02	83.85	92.29	90.35	88.5

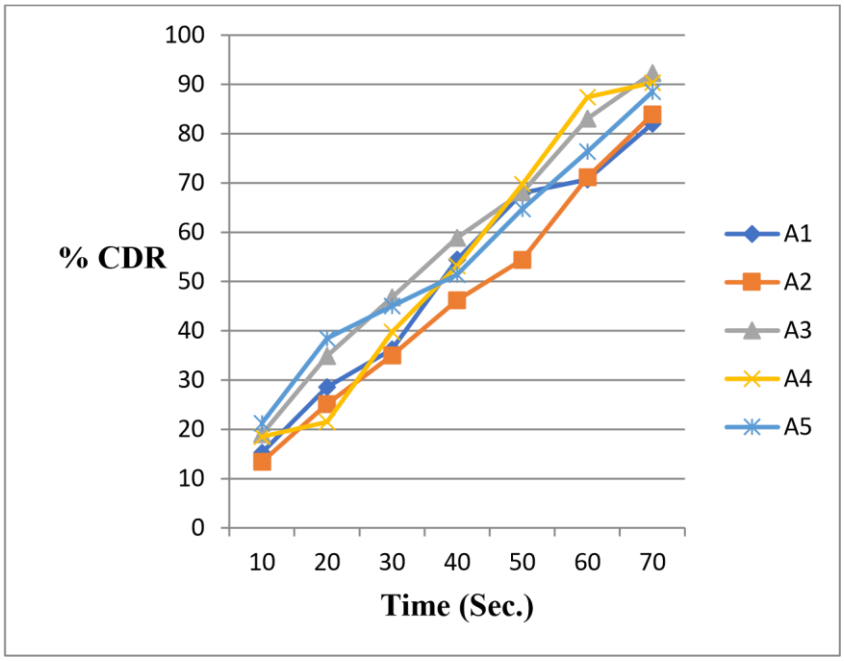

Fig. 6: Cumulative % drug release profile of formulation A1 to A5

Table 8: cumulative % drug release profile of formulation A6 to A9

Time (min)	A_6	A_7	A_8	A_9
0	0.00	0.00	0.00	0.00
10	23	16.57	14	20.9
20	39.42	27.25	33.02	31.45
30	53.2	38.7	45.5	44.20
40	60.10	57.52	55.10	59.25
50	77.94	64.9	65.87	71.22
60	84.5	77.95	80	81.25
70	95.20	89.75	86.10	93.75

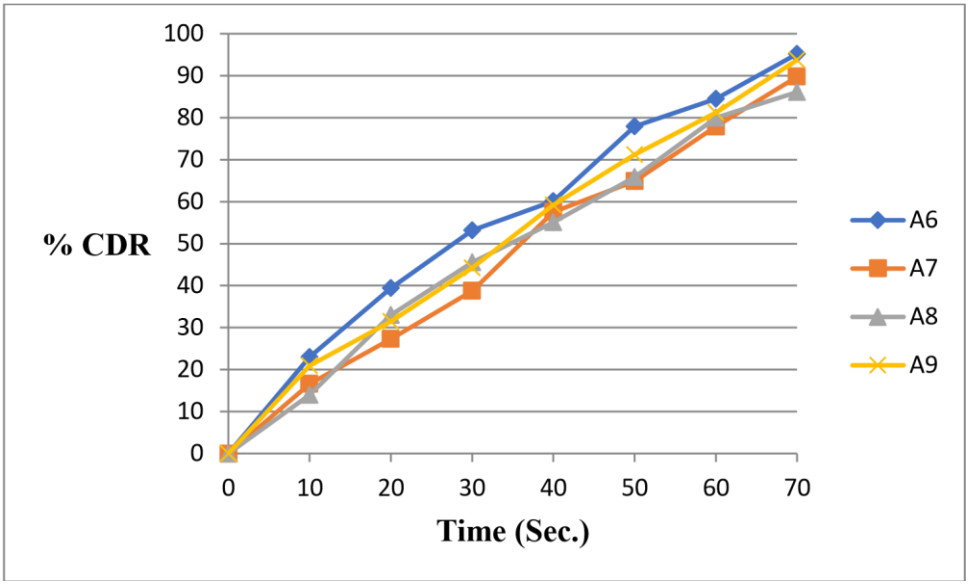

Fig. 7: Cumulative % drug release profile of formulation A6 to A9

FTIR spectroscopy of optimised formulation A6

Infrared absorption of A6 optimised formulation was investigated. The functional group peak of Lisinopril was found in the Spectrum.

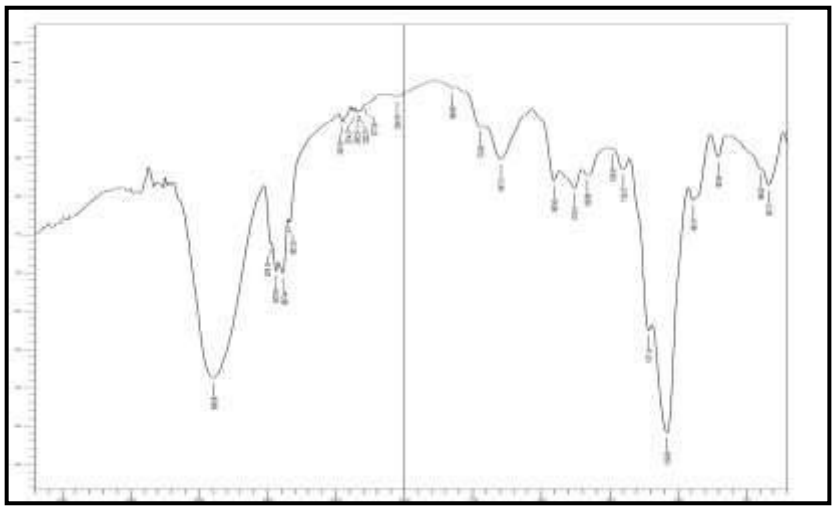

Fig. 8: IR spectrum of optimised formulation (A6)

Table 9: Values of peaks observed in IR spectrum of optimised formulation A6

Functional group	Observed Wavenumber (cm^{-1}) in optimised formulation (A6) of IR	Observed Wavenumber (cm^{-1}) in Lisinopril IR	Theoretical Wavenumber range (cm^{-1})
Amide N-H Streching	3390cm^{-1}	3550cm^{-1}	3300-3500cm^{-1}
O – H stretching	2887cm^{-1}	3290cm^{-1}	2800-3200cm^{-1}
Aromatic C-H stretching	2976cm^{-1}	2900cm^{-1}	2900-3000cm^{-1}
Ketones C=O Streching	1647cm^{-1}	1653cm^{-1}	1650-1700cm^{-1}
C-O Streching	1039cm^{-1}	1045cm-1	1000-1050cm-1

FTIR Spectrums of pure drug (Lisinopril), physical mixture, and optimized batch A6 were shown in Spectra 5. FTIR studies revealed that the fundamental peaks of the lisinopril are retained in the optimized film formulation. Results showed that there exists no chemical interaction between Lisinopril and excipients used in the formulation hence; these can be used in the formulation of mouth dissolving film of Lisinopril.

Differential scanning calorimetry of optimised formulation A6

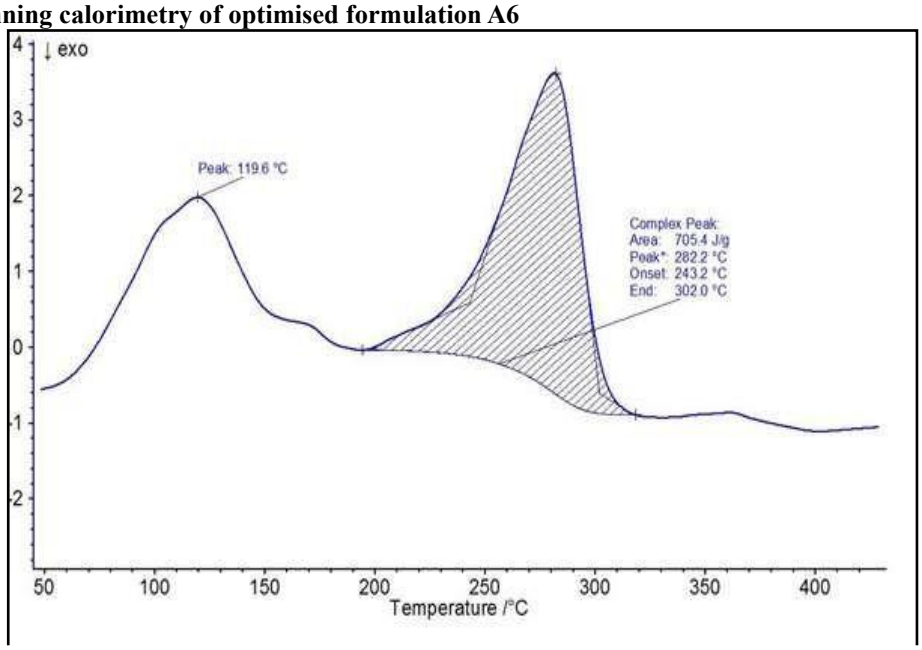

Fig. 9: DSC thermogram of A6 optimised formulation

The thermogram of optimised film formulation of Lisinopril shows exothermic peak starting at 243.2 ℃ with melting peak at 282.2 ℃. Slight shifting of exothermic peak with decrease in its intensity indicates crystalline form of the drug another peak observed in formulation at 119 ℃ may be due to excipients present in it.

DISCUSSION

Lisinopril is a hypertension drug. Hypertension is one of the primary risk factors for cardiovascular diseases, including cardiovascular stroke. The present work was formulation and evaluation of mouth dissolving film of an antihypertensive drug of Lisinopril. The oral fast dissolving films of lisinopril were prepared using different film forming materials with different concentration of polymer i.e. HPMC E 5 by solvent casting method.

FTIR spectroscopic studies were carried out in order to establish compatibility between drug and excipients. The results were concluded that there were no chemical interactions between drug and the excipients used, so they could be used for the formulation of Lisinopril fast dissolving films. The thermogram of optimised film formulation of Lisinopril shows exothermic peak observed at 243.2 ℃ with melting peak at 282.2 ℃ 127 °C, it corresponding to its melting point of the drug. From DSC and FTIR, the results were concluded that there were no chemical interactions between drug and the carriers used. So, the drug was found to be compatible with other excipients. Results of drug identification confirmed the purity of Lisinopril. All the films prepared were non sticky, soft and transparent surface of all the films were smooth. The results of folding endurance and tensile strength revealed that, as concentration of Glycerine was increased folding endurance was increased and tensile strength was decreased. When the concentration of film formers was increased, disintegration time, tensile strength of film was increased and folding endurance and in vitro drug release was decreased. The release of the drug from the films was increased as the concentration of plasticizer was increased. All the oral fast dissolving films formulated showed satisfactory in vitro dissolution and physicomechanical characteristics. The bitter taste of film could be successfully masked by using aspartame as a sweetening agent. The surface pH of all the formulation was found to be in the range of 6.6-6.8 and hence will not cause any irritation to oral mucosa. The formulation was optimized on the basis of disintegration time, folding endurance, in vitro drug release and physicomechanical properties. Thus, formulation A6 containing HPMC E5 was selected as an optimized formulation because it gave the high drug release in fast release manner that is 95.20%.

CONCLUSION

From FTIR and DSC study, it was concluded that there is no any significant change in nature of drug and no any interaction between drug and polymer. It could be concluded that the mouth fast dissolving films of Lisinopril for control of Hypertension could be successfully formulated using hydrophilic polymers by suitable method of solvent casting. Therefore, the present oral fast dissolving film containing Lisinopril is considered as a potentially useful dosage form for treatment of hypertension.

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AUTHORS CONTRIBUTIONS
All the authors have contributed equally.

CONFLICT OF INTERESTS
Declared none

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