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Formulation and evaluation of oral dissolving films of lisinopril

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Abstract
Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and leads to better patient compliance. These delivery systems either dissolves or disintegrate in mouth rapidly, without requiring any water to aid in swallowing. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial product. These novel drug delivery systems can also be beneficial for meeting the current needs of the industry as improved solubility, stability and bioavailability of drugs. Although oral disintegrating tablets have an advantage of administration without chocking and fast disintegration; the disintegrated materials contained in them are insoluble and remain until swallowing. In such case formulation of fast dissolving films will be advantageous. In the present work, an attempt was made to prepare and evaluate oral fast dissolving films of lisinopril for effective management of hypertension and cardiac disease. Lisinopril fast dissolving films were formulated by using natural and synthetic polymers by solvent casting method. Drug- excipient interactions were studied by FTIR. Oral films were evaluated for surface pH, mechanical strength, thickness, folding endurance, tensile strength and *in- vitro* release profile.

Keywords: Lisinopril, Oral dissolving films, FTIR

1. Introduction
Oral dissolving films (ODF) are a novel dosage form that disintegrate or dissolves in the oral cavity. These are ultra-thin postage stamp size with an active agent or pharmaceutical excipients. These dosage forms are placed on the tongue or any mucosal tissue. When wet with saliva, the films rapidly hydrates and adheres on to the site of application [1, 2]. It rapidly dissolves or disintegrates to release the medicine for mucosal absorption or with modification, allows for oral GIT absorption with quick dissolving properties [3]. An important benefit of these dosage forms is accurate dosing as compared to liquid dosage form, no water is needed and there is no fear of choking as compared to tablets and capsules. Fast dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within one minute when placed in the mouth without drinking of water or chewing. After disintegrating in the mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [4, 5 and 6].
Formulation of fast dissolving buccal film involves the application of both aesthetic and performance characteristics such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents [7, 8]. From the regulatory perspectives, all excipients used in the formulation of oral drug strips should be approved for use in oral pharmaceutical dosage forms.

Material and Methods
Formulation of fast dissolving films of lisinopril
Placebo film trials
In the initial phase of development ten number of placebo trials were taken to explore various polymers for their film forming capacity. Composition of placebo trials is given in Table 1.

Optimization of Placebo film trials
All the trials for the development of Placebo film were done. On the basis of that a concentration of film forming material was selected and different steps were taken for the formulation of Lisinopril as oral dissolving film. Based on trials, HPMC E5 was selected as one of the best film forming agent. Composition for optimization of placebo HPMC film is given in Table 2

Table 1: Composition of various placebo trials

Ingredients	Trial 1	Trial2	Trial3	Trial 4	Trial 5	Trial6	Trial 7	Trial8	Trial 9	Trial 10
HPMC E5		✓		✓		✓		✓		✓
HPMC K15			✓ -							
HPMC K100	✓						✓		✓	
Cross povidone									✓	
Maltodextrin						✓		✓		✓
Polyvinyl Alcohol					✓					
Glycerol	✓	✓	✓		✓	✓				
Propylene Glycol				✓			✓	✓	✓	✓

Table 2: Optimization of placebo HPMC film

Ingredients	Concentration (mg)				
	F1	F2	F3	F4	F5
HPMC E5	460	480	500	520	54O
Glycerol	80	90	100	110	120
Water	14ml	14ml	14ml	14ml	14ml

F3 was observed as best where the polymer and plasticizer are used in the ratio of 5:1.

Preparation of Drug (Lisinopril) containing film

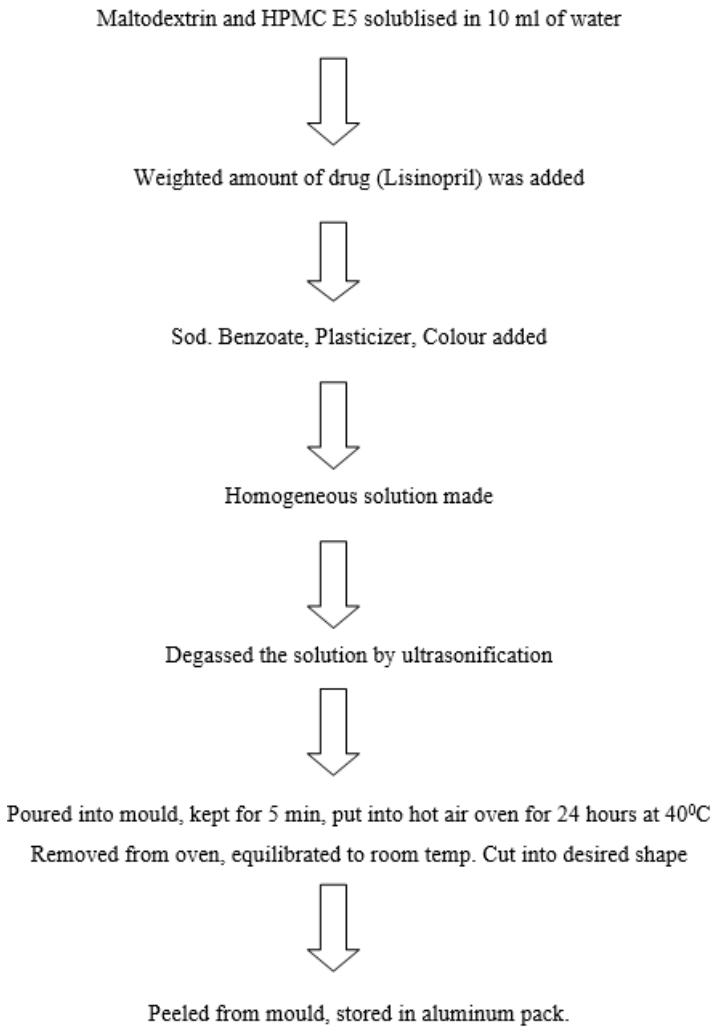
Different trials were taken along with drug on the basis of optimized placebo formulations. All the formulations were made using solvent casting method. Films were made by six different formulations whereby using different excipients in different concentrations. On the basis of their parameters of evaluation final conclusion for optimized film were made. Formulation K5 was considered as the best formulation amongst above mentioned six formulations.

The above mentioned formulations results in preparation of eight films from each batch with dose of 20 mg in each film. i.e. total no. of films produced from all batches were 48. Composition of trials of drug loaded films is given in Table 3.

Table 3: Trials of drug loaded films

Ingredients	Concentration (mg)					
	K1	K2	K3	K4	K5	K6
Lisinopril	80	80	80	80	80	80
HPMC E5	400	400	400	400	400	400
Maltodextrin	320	340	360	380	400	420
Glycerol	80	80	80	80	80	80
Sodium Benzoate	10	10	10	10	10	10
Tween 80	50	50	50	50	50	50
Menthol	20	20	20	20	20	20
Citric Acid	20	20	20	20	20	20
Water	Qs 14ml	Qs 14ml	Qs 14ml	Qs 14ml	Qs 14ml	Qs 14ml

Method of preparation for oral dissolving film (Solvent Casting Method)



Results and Discussion

Various tests were performed to evaluate the formulation. Details of the results observed from the experimental part is as below:

1) Drug Characterization

a) Determination of λ max of Lisinopril

λ max of Lisinopril was determined in distilled water, using acidic and basic medium.

It was observed that absorption of Lisinopril takes place at 212nm and hence the drug used during project work was found to comply as per IP 2010.

b) Melting Point

Limit of Melting point as per IP, 2010 is 146 to 148 ^{0}C.

Melting point of Lisinopril was determined by using digital veego meter and it was observed at148 ^{0}c.

c) FTIR characterization

FTIR spectrum of pure drug Lisinopril

FTIR Spectra shows the specific peak of functional groups at specific IR range. Here the Lisinopril IR spectra was compared with the standard IR spectra of Lisinopril and no variation in the absorption peak for the functional groups was found. Hence the drug used was found to be pure (Figure-1).

FTIR spectrum of Lisinopril film

FTIR specrum of Lisinopril film was mixture of Lisinopril, Maltodextrin and HPMC E5. There isno specific interaction was found in between drug and excipients as there was no shift in peaks of FTIR spectrum of Lisinopril. (Figure-2).

FTIR spectra of the drug shows bands at 1472 cm^{-1},1748 cm^{-1} 1596 cm^{-1} which correspond to phenyl, carboxylic acid and primary amine ofthe pure drug (Lisionpril) respectively.

As the same bands appears in the spectra of Lisinopril film at 1470 cm^{-1}, 1730 cm^{-1} and 1633 cm^{-1} respectively which clearly indicates that phenyl group, carboxylic acid and primary amine group of the drug are free and they do not react with the excipients. Hence, there was no chemical interaction between drug and polymer.

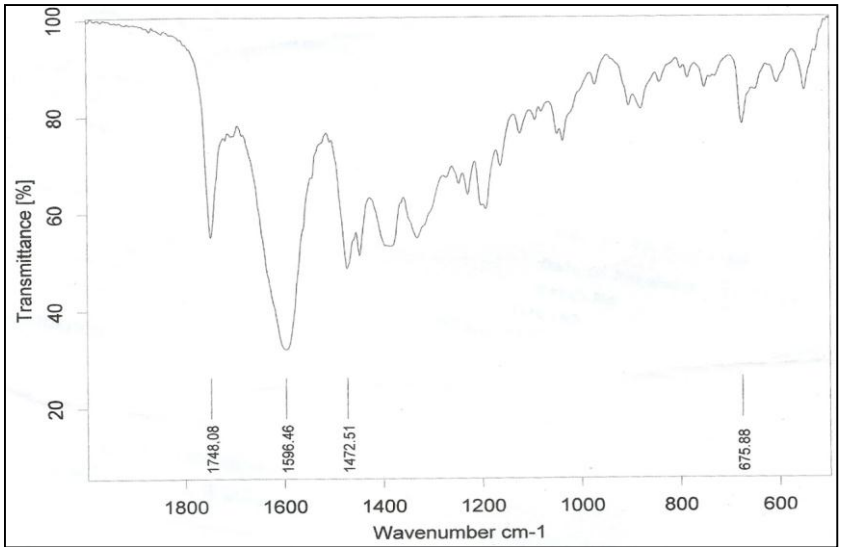


Fig 1: FTIR Spectra of Lisinopril drug

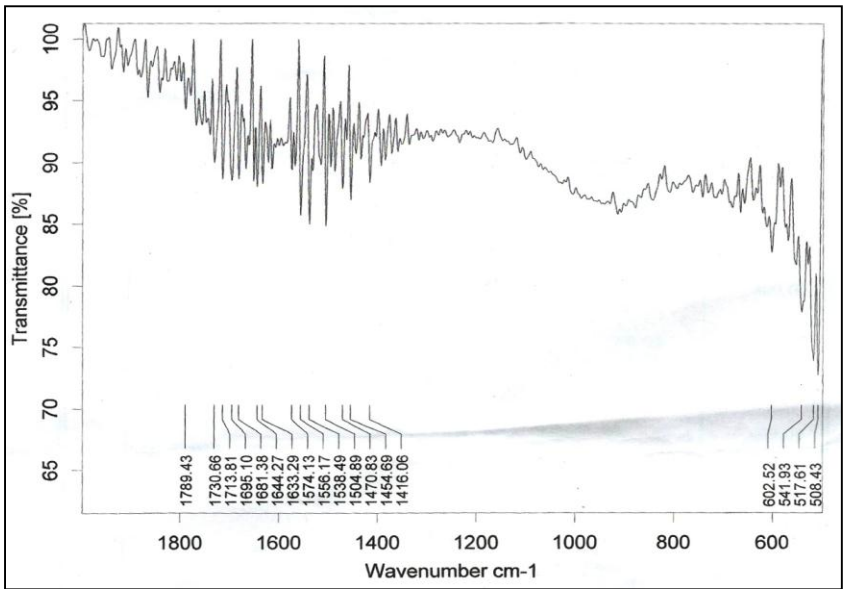


Fig 2: FTIR Spectra of Lisinopril Film

Table 4: Comparison study of FTIR Spectra of Lisinopril pure drug and Lisinopril film

S. No.	Functional Group	Wave Number (cm^{-1})	Observed Wave Number (cm^{-1})	
			Drug	Film
1	Phenyl	1450-1500	1472	1470
2	Carboxylic acid	1725-1700	1748	1730
3	Amine (i)	1650-1580	1596	1633

d) Particle size determination

Slurry of the Lisinopril was made and characteristics shape of particles of Lisinopril and their sizes were observed by light microscope. Sizes of the particles of Lisinopril were found to be in the range of 5-7micron meter.

2) Evaluation of oral dissolving film

Table 5: Results obtained from evaluation of oral dissolving film

Batch	Thickness (mm)	Drug content(mg)	Disintegration time(sec)	Folding endurance	Tensile strength(gms)	Moisture permeation
K1	0.364±0.05	19.23± 0.03	22±2	295±2	121.32±7	NIL
K2	0.378± 0.03	18.53± 0.01	24± 1	306±4	118.35±3	NIL
K3	0.383± 0.02	16.51± 0.06	25± 1	302±6	113.19±2	NIL
K4	0.38 ± 0.05	18.54± 0.08	21± 1	291±1	109.3±5	NIL
K5	0.390± 0.04	19.53± 0.03	15± 2	295±8	106.2±1	NIL
K6	0.398± 0.04	18.51± 0.02	17± 4	298±5	102.8±4	NIL

3) Dissolution Data

From the above dissolution data as given in Table-6, the percentage drug release of different formulations were observed at the different time intervals such as 1 min, 3 min and 5 min. Therefore, from the above different formulations, K5 shows the maximum percentage drug release after 5 min.

Table 6: Percentage drug release from the formulations

S. No	Formulation code	1 min	3 min	5 min
1	K1	72.82%	90.17%	95.18%
2	K2	79.31%	89.45%	95.23%
3	K3	84.28%	91.68%	97.27%
4	K4	91.41%	96.35%	98.28%
5	K5	93.96%	97.34%	99.91%
6	K6	89.22%	92.56%	96.03%

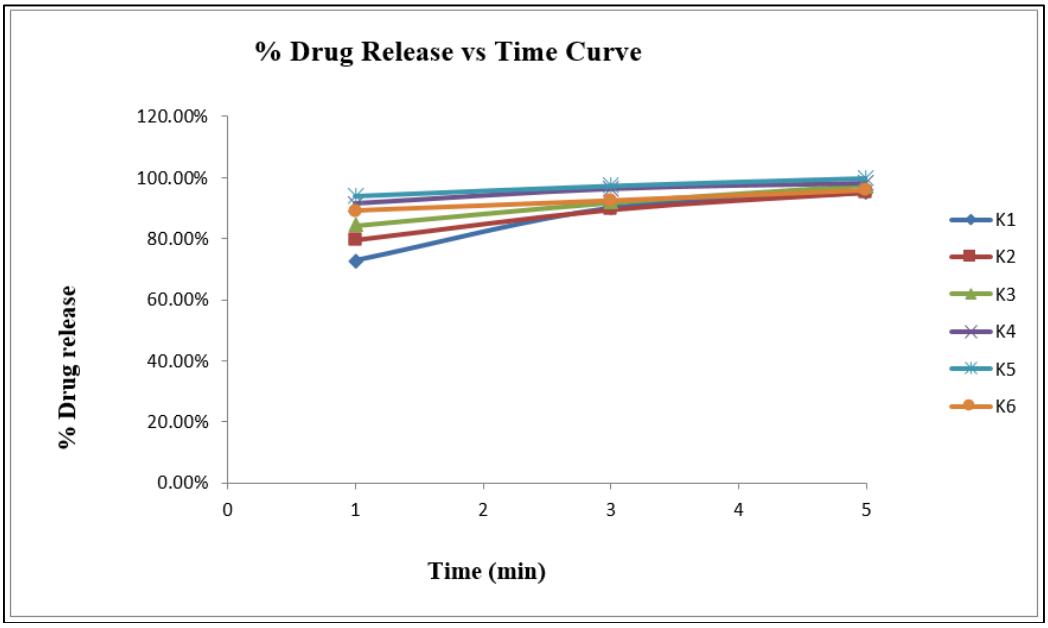


Fig 6: Percentage drug release from the formulations

4) Stability Data

Table 7: Stability Profile of Formulation K5 at Different Temperatures

Time in days	Real Time (30°C/65%RH)		Accelerated (40°C/75%RH)	
	% Drug release	Drug content (mg)	% Drug Release	Drug content (mg)
0	99.43%	19.53	99.46%	19.53
7	99.29%	19.37	99.17%	19.39
14	99.06%	19.21	98.83%	19.29
28	98.81%	19.16	98.54%	19.21
42	98.63%	19.09	98.37%	19.08
60	98.31%	18.97	98.07%	18.25

Conclusion

It can be concluded that fast dissolving Lisinopril film can be prepared by solvent casting method. HPMC E5 and Maltodextrin can be used as film forming agent for formulation of oral dissolving film of Lisinopril. HPMC E5 and Maltodextrin film shows dissolution in 300 seconds, films prepared by the above said polymer are superior in terms of flexibility, tensile strength and appearance etc. HPMC E5 and glycerol in a film gave optimum tensile strength, disintegration time, folding endurance and *in-vitro* dissolution profile.

Final formulation K5 show complete dissolution in all buffers, but as the pH of buffer decreased from 7.4 to 7.0 and 6.8 rate of dissolution also decreased. From, the present study it can be concluded that fast dissolving film can be potential novel drug dosage form for geriatric and pediatric population.

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