MOUTH DISSOLVING FILM: A NOVEL APPROACH TO DELIVERY OF LISINOPRIL

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Abstract

Purpose: Orodispersible dosage forms are promising new approaches for drug delivery for patients. They are easy for application, no need to drink high amounts of water or swallow large solid dosage forms. The aim of this study is to formulate and evaluate the mouth dissolving film of Lisinopril as an ACE inhibitor used to treat high blood pressure (hypertension), congestive heart failure and improved bioavailability of drugs as compared to conventional solid oral dosage forms. **Method:** The films were prepared using combination of Hydroxy propylmethyl cellulose E15 and PVA (polyvinylalcohol) polymers by solvent casting method. Glycerine as plasticizer, aspartame as sweetener. **Result:** The IR spectral studies showed no interaction between drug and the polymers. Satisfactory results obtained when subjected to physico-chemical tests such as weight uniformity, thickness, folding endurance, drug content and disintegration time. Films in vitro drug release studies also done by using USP dissolution apparatus. In case of F4 and F5 formulations about 99.529% and 95.29% of drug was released at 2min. **Conclusion:** The Lisinopril mouth dissolving film was formulated. The given film disintegrates within eleven second which release drug rapidly and gives action.

Keywords: Mouth dissolving film, HPMC, PVA, Lisinopril, Solvent casting method.

Introduction

Oral route is commonly used route for the delivery of the drugs till date as it bears various advantages over the other route of drug delivery, but oral drug delivery systems still a date need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms . Many pediatric and geriatric patients who having difficulty in swallowing are unwilling to take solid preparations as a result of concern of choking. So, fast-dissolving drug-delivery systems came into existence in the late 1970's as another to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. It was developed on the basis of technology of the transdermal patch. The fast dissolving drug delivery system consists of a very thin strip that is just placed on the patient's tongue or any oral mucosal tissue, instantly wet by secretion the film rapidly hydrates and adheres onto the location. It then quickly disintegrates and dissolves to release the drug for oromucosal and intragastric absorption.

The development of mouth dissolving films containing Lisinopril offers an alternative to conventional tablets, syrups and suppositories for the treatment of hypertension.

Lisinopril is angiotensin converting enzyme inhibitor that category is employed to treat high blood pressure, congestive heart failure(CHF) and to improve survival after a heart attack. Drug belongs to the BCS class III & shows water solubility. The drug has low dose i.e. 10 mg. Duration of action is found to be 24 hours (once daily dosing). The drug absorption is found to be absorbed slowly and incompletely from GI tract (oral) and peak plasma concentration is achieved after 7 hours .The drug distribution i.e; protein binding is not significantly bound i.e., is up to 25%.Thus aim of study is to develop and characterise mouth dissolving film which disintegrate in oral cavity without need of water. This helps in easy swallowing, increases bioavailability of drug and quick onset of action can takes place.

In the view of above fact, in the present investigation an attempt was made to develop mouth dissolving film of Lisinopril using suitable polymer like hydroxypropyl methyl cellulose (HPMC E15) and Polyvinyl alcohol (PVA) in different ratios and in combination with Aspartame as sweetener ,citric acid as saliva stimulating agent, glycerine as plasticizer.

Material and Methods

Lisinopril was obtained as gift sample from Lupin Ltd, Aurangabad, and Maharashtra. HPMC E15, PVA polymers, aspartame, citric acid and glycerine used were of analytical grade.

Compatibility studies

IR (Infrared Spectroscopy) spectroscopy study was carried out for the following drug and polymers: (a) pure drug Lisinopril (b) HPMC E15 (c) PVA (d) Lisinopril with HPMC E15 and PVA.

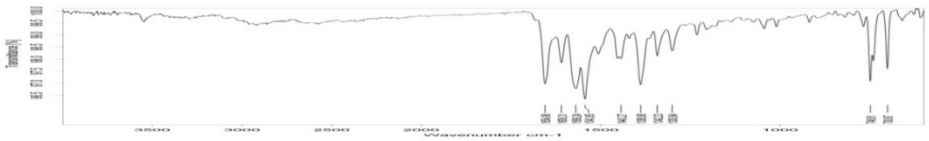

Figure 1 Infra red spectra of Lisinopril

Spectra shows peaks

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
C=O	1654	1600-1900
N-H	1609	1500-1700
O-H	1388	1200-1500

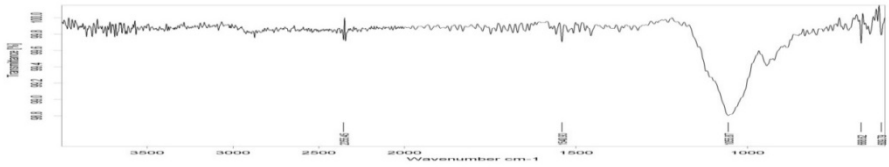

Figure 2 Infra red Spectra of HPMC E15

Spectra shows peaks

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
C-O	1055	900-1300
C-H	1540	1300-1500

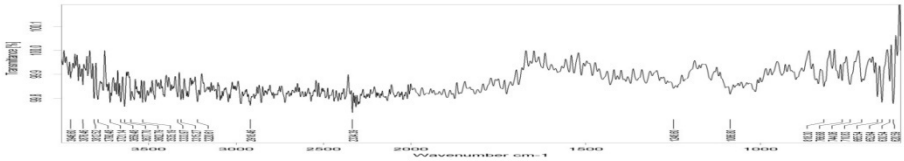

Figure 3 Infra red Spectra of PVA

Spectra shows peaks

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
C=O	3333	3300-3600
C-H	818	800-830
O-H	1248	1200-1500
C-C	1086	800-1200

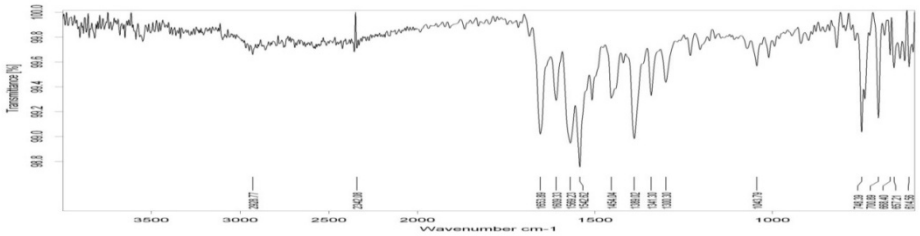

Figure 4 Infra red spectra of Lisinopril +HPMC E15+ PVA

Spectra shows peaks

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
C=O	1654	1600-1900
N-H	1609	1500-1700
C-O	1043	900-1300
C-H	1542	1300-1500

Figure shows no incompatibility in physical mixture of drug, polymer and plasticizer.

Full factorial design

A 3^2 randomized full factorial design was utilized in the present work. In this full factorial design two factors were evaluated, every at three levels, and experimental work were distributed at all nine possible combinations. The amount of polymer HPMC E15and PVA (X1) and amount of plasticizer, Glycerin (X2) were selected as independent variables and each factor being studied at -1, 0, +1 level. Percent drug release was selected as dependent variable .The table 1 lists the design variables with its coded values and actual values, and table 2 provides the factorial design layout i.e. all possible 9 combinations respectively.

Table1 Design variables

Coded values	Actual values (mg)	
	X1	X2
-1	300+75	50
0	300+100	60
+1	300+125	70

Table 2 Full Factorial Designs Layout

Formulation code	Variable level	
	X1	X2
F1	**-1**	**-1**
F2	**0**	**-1**
F3	**+1**	**-1**
F4	**-1**	**0**
F5	**0**	**0**
F6	**+1**	**0**
F7	**-1**	**+1**
F8	**0**	**+1**
F9	**+1**	**+1**

Table 3 Factorial Batches Composition

Formulation	Drug	HPMC E15+PVA (mg)	Glycerin (mg)	Aspartame (mg)	Citric Acid (mg)	Water (ml)
F1	200	300+75	50	50	18	10
F2	200	300+100	50	50	18	10
F3	200	300+125	50	50	18	10
F4	200	300+75	60	50	18	10
F5	200	300+100	60	50	18	10
F6	200	300+125	60	50	18	10
F7	200	300+75	70	50	18	10
F8	200	300+100	70	50	18	10
F9	200	300+125	70	50	18	10

Preparation of mouth dissolving film

Solvent casting method was selected to prepare Mouth dissolving film of Lisinopril. HPMC E15 and PVA used as polymer. Add PVA in 10 ml distill water was mixed using magnetic stirrer then HPMC E15 was added slowly. Subsequent to that Lisinopril was added to the aqueous solution of the polymers then after citric acid is added to the above solution followed by addition of the sweetener and plasticizer. The solution was casted on the casting surface (Teflon mold) and dried at room temperature for 10 hours. Then film was removed from the surface and cut into the desired size of equivalent dose of Lisinopril. The same method was used to cast all batches as shown in figure

The figure shows teflon mold was prepared with help of local carpenter and used for casting films.

Figure 5 Film of HPMC E15+PVA

The figure shows films of plasticizer and polymer-plasticizer blend were casted using petri plate

Figure 6 Film of polymer HPMC E15

The figure shows film of polymer HPMC E 15 was casted using Teflon mold.

Figure 7 Film of polymer PVA

The figure shows film of polymer PVA was casted using petri plate.

Figure 8 Lisinopril mouth dissolving film casting using Teflon mold.

The figure shows final batch film casting of Lisinopril

Evaluation of mouth dissolving film

Weight Variation

The weight variation test is determined by measuring the weight of the individual film of 2cm x2 cm area. For the measurement of the weight digital analytical balance was used. The weight of three films was measure and min is taken.

Thickness

The thickness of film was measured by digital vernier caliper at different locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. How many times the film is folded without breaking is computed as the folding endurance value.

Disintegration time

The disintegration time deadline of 30 s or less for orally disintegrating tablets described in CDERGuidance can be applied to fast dissolving oral strips. There is no official guidance is available for oral fast disintegrating films/strips, this strip may be used as a guideline for quality control test or at development stage. Typical disintegration time for strips is 5–30 s. For the present work disintegration was measured by taking the 25 ml water in50 ml beaker and individual film is dipped into that solution and disintegration time was recorded.

In Vitro dissolution study

The in vitro release of drug from all formulations was determined using USP apparatus type II (Paddle method). The following conditions were followed to study the in-vitro dissolution study of Lisinopril mouth dissolving film

1. USP dissolution apparatus: Type II (Paddle method)
2. Volume of dissolution medium: 900 ml
3. Speed: 50 rpm
4. Temperature: 37±0.50 C
5. Dissolution medium: simulated salivary fluid (pH6.75)

6. Sampling interval: 1 min
7. Quantity of sample withdrawn: 5ml

Aliquots of dissolution medium of 5 ml were withdrawn at 1min interval for 3min. The volume withdrawn was replaced by fresh volume of dissolution medium. The filtered samples were analyzed by UV at 206 nm and absorbance was noted. Cumulative percent drug release was calculated.

Drug content

For determination of the drug content Lisinopril moth dissolving film equivalent to dose of 10 mg was dissolved in 50 ml of Distill water .The solution was solution was sonicated for 10 minutes and then filtered through Whatmann filter paper no. 41, to separate out the insoluble excipient. 1ml of filtrate was diluted to 100ml with Distill water. The absorbance of resultant solution was measured using U. V. spectrophotometer at 206 nm and drug content was calculated.

Result and Discussion

Evaluation of mouth dissolving film

Weight Variation

The weight of all factorial batches observed between 29 to 33 mg with standard deviation less than 0.2% for all batches which indicates uniformity in the weight.

Thickness

The thickness of the film lies between 0.06 to 0.08 mm .With uniformity in the thickness. It was observed that increase in the polymer concentration the thickness of film increases with 0.01mm.

Folding Endurance

The folding endurance of all batches observed between209 to 280. For the batches F4, F7, F9 the folding endurance observed 247,280,300 respectively. Form the evaluation of folding endurance it was concluded that with increase in polymer concentration folding endurance decrease and with increase in plasticizer concentration folding endurance increases.

Disintegration Time

The in vitro disintegration time for all batches measured between 9.2 to 18.4 seconds which indicated faster disintegration time as compared to the mouth dissolving tablet which have normal disintegration time 30 seconds in many reported literature.

Surface PH

The Surface pH of all formulation observed between 6 to 6.8.It was observed that after addition of the plasticizer the pH moves slightly towards basic pH. The pH between 6 to 6.8 indicates the pH of formulation near to ph of saliva.

% Drug content

The percent drug content observed between 97.09 to 99.17 %.The values ensures good uniformity in the drug content in mouth dispersible film of Lisinopril. All the evaluation parameters are discussed of F1 to F9 formulation are discussed in following table no 4.

Table 4 Evaluation of Lisinopril Mouth Dissolvinge Films

Batches	Thickens (mm)	Weight (mg)	Folding Endurance	Surface pH	%Drug Content	In vitro disintegration time (s)
F1	0.06±0.00	29.13±008	230.22±2.08	6.45±0.3	98.10±006	12.3±1.23
F2	0.07±0.00	31.14±007	217.13±17.5	6.61±0.8	99.11±003	9.4±1.52
F3	0.08±0.00	33.15±012	209.24±9.24	6.65±0.12	99.17±004	9.2±1.34
F4	0.06±0.00	29.26±005	247.09±5.14	6.45±0.5	99.16±008	11.2±2.34
F5	0.07±0.00	33.47±008	232.33±11.25	6.48±0.24	99.12±003	13.8±1.28
F6	0.08±0.00	29.42±004	212.33±7.01	6.56±0.32	98.12±002	15.2±2.34
F7	0.06±0.00	31.53±014	280.26±13.12	6.74±0.12	99.11±001	18.2±1.42
F8	0.07±0.00	32.12±002	236.14±4.17	6.82±0.18	99.10±007	17.9±1.52
F9	0.08±0.00	33.4±004	300.35±10.42	6.76±0.14	97.09±007	17.6±1.42

In Vitro dissolution study

The *in-vitro* drug release from film of all formulation was performed in triplicate using USP apparatus II (paddle method). Dissolution study was performed in simulated salivary fluid and the obtained results are summarized below.

Table 5 % Drug release of formulation F1 to F9

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00	00.00
1	71.47	68.82	66.17	76.76	87.35	82.05	82.05	76.76	84.70
2	94.76	90	95.29	99.529	95.29	92.64	92.38	89.47	91.32

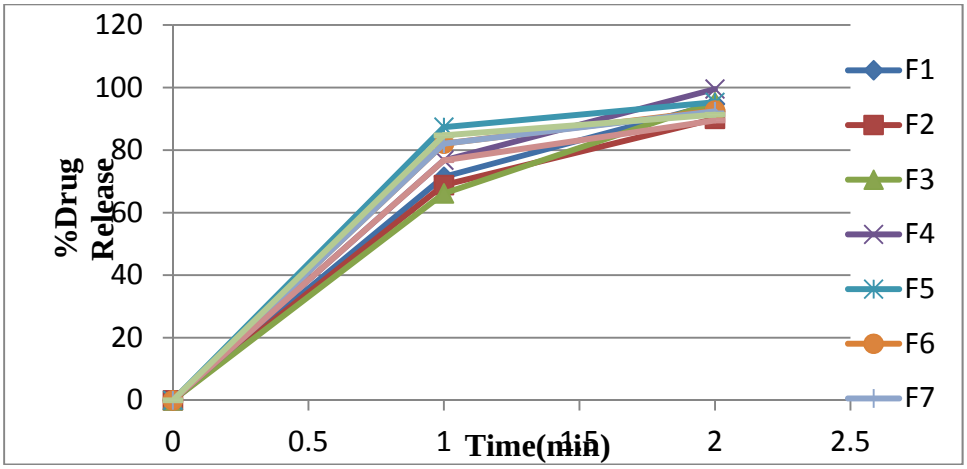

Figure 9 Dissolusion profile of batches F1 to F9

Stability studies

The stability study of the Lisinopril was done in stability chamber. Stability studies were carried out at 40 ^{0}C / 75 % RH for 2 months and following result were obtained. The optimized film did not show any significant change in appearance and weight loss on storage, disintegration time and % drug content. From these results it was concluded that, formulations containing Lisinopril is stable and retained their original properties. The results of disintegration time, drug content and transparency are shown in the Table, which indicates no alteration after storage.

Table 6 Stability study for optimized batch

Parameter	0 day	30 days	30 days	60 days	60 days
		A	B	C	D
Appearance	Transparent	Transparent	Transparent	Transparent	Transparent
Folding Endurance	247.09	247.06	247.06	246.05	246.05
Disintegration time(sec)	11±00	12±2	12±2	12±2	12±2
Weight (mg)	29.26	29.25	29.25	29.25	29.25
% Drug Content	99.16+00	99.14±00	99.14±00	99.12±00	99.12±00

Conclusion

This study shows that it is possible to formulate fast dissolving films of Lisinopril with the intention of obtaining better therapeutic efficiency with increasing bioavailability and improving patient compliance. Plasticizer used Glycerine resulted in better films in respect to physicochemical parameter like, tensile strength, % elongation, folding endurance and flexibility. Aspartame used as a sweetener will successfully mask the bitter taste of the drug Lisinopril. The given film disintegrates within eleven second which release drug rapidly and gives action. As compared to that of conventional dosage form mouth dispersible film has rapid onset of action. In case of F4 and F5 formulations about 99.529% and 95.29% of drug was released at 2min. In case of F2, F8 formulation about 90 % and 89.47 % of drug released at 2 min. This drug release pattern indicates was that the increased concentration of polymer decreases drug release and increased concentration of plasticizer increases drug release.

Figure 10 Lisinopril Mouth dissolving film

Acknowledgements

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