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RESEARCH ARTICLE

Formulation and Evaluation of Oral Disintegrating Film Containing Lisinopril for the Effective Management of Hypertension and Cardiac Diseases

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Abstract

This study was aimed to develop oral disintegrating film (ODF) containing an anti-hypertensive drug Lisinopril. Five trial formulations (F1-F5) of Lisinopril ODF were prepared using Hydroxypropyl methylcellulose E15 (HPMCE15), polyvinyl pyrrolidone (PVPK30), Polyethyleneglyco l400, Polyplasdonexl, Mannitol, Peppermint oil, Propylparaben, Citric acid, and Allura red. The prepared formulations were evaluated for their Physico-chemical characters like weight, thickness, surface pH, folding endurance, and disintegration time. They were also evaluated for the content of Lisinopril. The above studies revealed that formulations trial F4 was better than other Formulations. Because it has exhibited a faster disintegration time (21.32 sec) when compared to the other formulation. So, F4 was selected for stability study (40°C, 75% RH) for six months and Scanning Electron Microscopy (SEM). The results of the above studies have shown that F4 was stable and has a uniform distribution of Lisinopril.

Keywords: *Cardiac diseases, Oral disintegrating films, Lisinopril, Solvent casting.*

Introduction

Oral disintegrating dosage forms have become a significant new drug delivery system; these dosage forms disintegrate in the oral cavity within a fraction of a second and can be taken without water or by chewing; these dosage forms help in improving the patient compliance and hence, it can be useful for pediatric, geriatric and also dysphagia patients.

They are also suitable for the mentally ill, bedridden, and for the patients who do not have easy access to water [1, 2]. The basic approach in the development of ODF is the use of super disintegrants like Polyplasdone XL, which provide instantaneous disintegration of films after putting on the tongue, thereby releasing the drug in saliva.

The bioavailability of some drugs may be increased due to their absorption in the oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach [3, 4, 5, 6]. The research and development in the oral drug delivery segment have led to the transition of dosage forms from straightforward conventional tablets/capsules to the oral disintegrating tablet (ODT) to wafer to the recent development of oral films (ODF). The disadvantage of most ODT is that they are fragile and brittle which warrants special packages for protection during storage, transportation, and consumer handling [7].

The Oral disintegrating film or strip can be defined as a dosage form that employs water dissolving polymer which allows the dosage form to hydrate by saliva quickly, adhere to mucosa and disintegrate within few seconds, dissolves and releases medication for oral mucosal absorption when placed on the tongue or oral cavity.

The sublingual mucosa is relatively permeable due to thin membrane and large veins; it gives rapid absorption and instant bioavailability of drugs due to high blood flow [8]. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats [1]. The objectives of this study were to prepare Lisinopril oral disintegrating films by solvent casting

method, to achieve the rapid disintegration time, to evaluate this Lisinopril formulation by *in vitro* methods, and to select the best formulation among them.

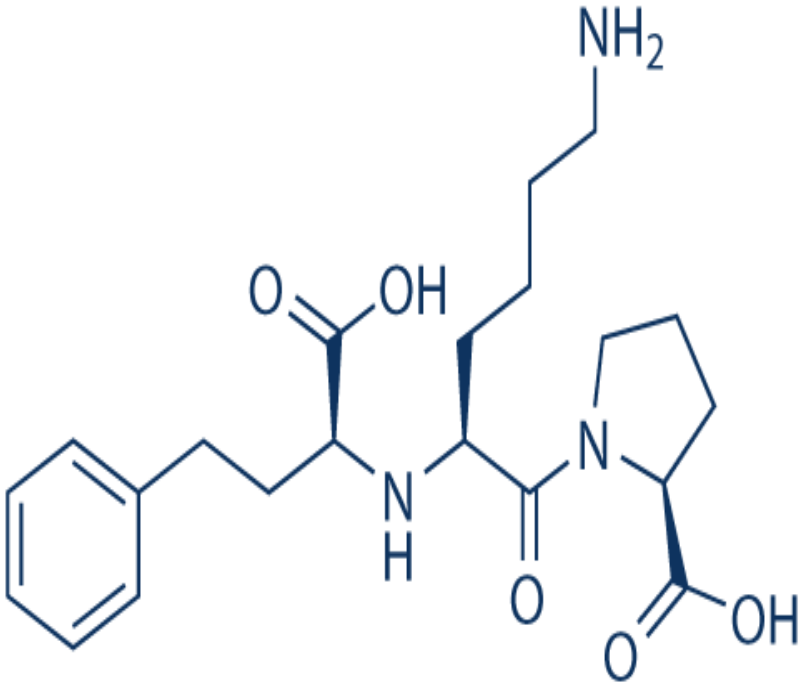

Fig: 1: Chemical structure of Lisinopril

Lisinopril is a potent competitive inhibitor of the Angiotensin-converting enzyme (ACE). The enzyme is responsible for the conversion of Angiotensin I to Angiotensin II. Angiotensin II regulates blood pressure and it is a vital component of the resin Angiotensin-Aldosterone system. Lisinopril may be used to treat hypertension and symptomatic congestive heart failure to improve survival in specific individuals after Myocardial infarction and prevent the progression of renal disease in hypertensive patients.

Many Pediatric and Geriatric patients are unwilling to take solid preparation due to fear of choking. Such a problem can be resolved by the fast-dissolving drug-delivery system (FDDS) [9]. Orally disintegrating drug delivery systems were first developed in the late 1970s as an alternative to tablets and capsules for Pediatric and Geriatric patients who had difficulties in swallowing conventional solid dosage forms.

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 to maintain the dose, 20 mg once up to 80 mg daily may be used if required [10].

Materials and Methods

Lisinopril, Polyvinyl pyrrolidone (PVPK30), Hydroxypropyl Methylcellulose (HPMCE 15) Polyplasdone xl, Polyethylene Glycol 400, Peppermint oil, Mannitol, Propylparaben, Indacol Allurared were procured from PAR formulations, Chennai. All other chemicals and reagents used were of analytical grade.

Formulation of the Oral Disintegrating Film of Lisinopril Calculation of dose for Lisinopril

The dose of Lisinopril is 2.5mg. Therefore, the amount of Lisinopril required in 4 cm films (2 cm× 2 cm) is 2.5 mg.

- Area of film of 2×2sq.cm is 4 sq.cm.
- The area of the Petri dish of 9cm diameter is 63.58 sq.cm.
- The amount of drug to be present in 4 sq.cm of the film is 2.5mg.
- The amount of drug to be present in 63.58 sq.cm of the Petri dish is 39-74 mg and rounded off to 40mg.
- Therefore, 4sq.cm of the film should contain 2.5mg of a drug. It is fixed for all formulations.

Table 1: Composition of Lisinopril oral disintegrating films

Formulation Code	F1	F2	F3	F4	F5
Lisinopril (mg)	40	40	40	40	40
HPMC E15 (mg)	240	160	120	80	-
PVPK30 (mg)	-	80	120	160	240
PEG400 (ml)	0.2	0.2	0.2	0.2	0.2
Polyplasdone xl (mg)	5	5	5	5	5
Mannitol (mg)	5	5	5	5	5
Propylparaben (mg)	5	5	5	5	5
Citric acid (mg)	10	10	10	10	10
Peppermint oil (ml)	0.1	0.1	0.1	0.1	0.1
Allura red	q.s	q.s	q.s	q.s	q.s
Distilled water (ml)	15	15	15	15	15

Note:

F1=Formula 1 uses a polymer combination (HPMCE15: PVPK30=3:0)
F2=Formula 2 uses a polymer combination (HPMCE15:PVPK30=2:1)
F3=Formula 3 uses a polymer combination (HPMCE15:PVPK30=1:1)
F4=Formula 4 uses a polymer combination (HPMCE15:PVPK30=1:2)
F5=Formula 5 uses a polymer combination (HPMCE15: PVPK30=0:3)
q.s = 2 drops

Preparation of Oral disintegrating film

The Oral disintegrating film was prepared by the solvent casting method. Film-forming polymers were dissolved in distilled water and were allowed to stand for swelling. Plasticizer Polyethylene Glycol 400 was added dropwise and stirred to obtain a homogeneous solution. The solution was kept to remove bubbles and then cast into the lubricated Petri dishes with a 9cm diameter.

Petri dishes were maintained at 38°C for 48hrs and an inverted funnel was placed over the Petri dishes to avoid fast evaporation of the solvent or in a hot air oven for 24 hrs at 40^0 for drying. After drying, films were removed and cut into the desired size ($2\times2cm^2$). The samples were stored in a glass container maintained at a temperature 30^0 and relative humidity 60% ± 5 %-for further analysis [11, 12].

This formulation development method is simple, easy to prepare, and economical. The ingredients are widely used in the pharmaceutical industry. HPMC film was too brittle.

PEG was then incorporated as a plasticizer to enhance the flexibility of the film Polyplasdone XL was incorporated as a super disintegrant for oral disintegration film when placed in the buccal cavity [13].

Evaluation of Orally Disintegrating Films Physicochemical Parameters

Physical Appearance

Films were inspected visually for color, flexibility, homogeneity, smoothness, uniformity of weight, and film thickness. The individual weight of films was determined and the average weight was calculated. Surface morphology of the film was studied using Scanning Electron Microscopy (SEM).

Uniformity of Thickness

The thickness was determined using a micrometer screw gauge [14, 15]. The thickness of each formulation (2×2cm) was measured using a micrometer screw gauge. At the four corners and center, five samples of each ODF formulation were measured. Uniformity of Weight

The individual weight of selected films was determined by the variation in weight was determined.

Surface pH:

The surface pH of the film was determined to investigate the possibility of any *in-vivo* side effect as an acidic or alkaline pH may irritate the oral mucosa. Therefore, the film was dissolved in 10 ml of distilled water and measured the pH by pH meter. The procedure was performed in triplicate and the standard deviation (SD) was reported.

Film Flexibility:

The ODF (2×2cm) was repeatedly folded at the same place. The total number of folding made before the film cracked was denoted as film flexibility value. The ODF was examined for cracks over the area of the bend under an intense light for each formulation; five samples were examined.

Uniformity of Drug Content:

The drug content was quantified using a validated High-Performance Liquid Chromatographic (HPLC) method [16, 17]. The system consisted of a Shimadzu model LC-10 ATVP pump Rheodyne manual injector fitted with a 20µl loop, a Shimadzu model & PD-20 AV variable wavelength UV-visible detector (Shimadzu corporation Kyoto, Japan) chromatographic system was integrated via Shimadzu model CBM-102 communication Bus module Analysis was performed on a Purospher star RP-18 end-capped (25cm×4.6 mmid) analyzed reversed-phase column Glass GC-10 software was used for data acquisition [18-20].

The mobile phase consisted of methanol-water 50:50 (v/v), pH was adjusted to 3.2 with phosphoric acid (85%) and 60:40(v/v) methanol-water as diluent before delivery into the system, it was filtered through 0.45µm filter and degassed using an ultrasonic bath. The analysis was carried out under isocratic conditions using a flow rate of 1.0 ml min^{-1} at room temperature. Chromatograms were recorded at 218 nm isosbestic point was considered satisfactory permitting the detection of all drugs with adequate sensitivity.

A piece of ODF film (2 × 2 cm) was dissolved in mobile phase by sonication after appropriate dilution, 20µl of the sample was injected into the HPLC, and the amount of drug was determined five ODF (2 × 2 cm) of each formulation were examined, and the acceptance value (AV) was calculated.

***In-Vitro* Disintegration Time**

The disintegration time is the time when a film breaks or disintegrates [11]. A film size of 2×2 cm ($4cm^2$) was placed on a glass Petri a dish containing 10ml of pH 6.8 phosphate buffer. The time required for breaking the film was noted as *in-vitro* disintegration time. Based on the results of the above studies best Formulations were selected for the following studies.

Stability Study:

The ODF formulation (2 × 2 cm) was stored at 40^0 and (75% RH) for six months. The films were checked for changes in their Appearance, Folding endurance, disintegration time, weight, and content at 0, 2, 4 & 6 months [16].

Scanning Electron Microscopy:

Scanning electron microscope (SEM) images of the ODF surface were obtained using the scanning electron microscope (JSM-IT200) The film was cut into smaller pieces and was mounted and scanned using SEM.

Results and Discussion

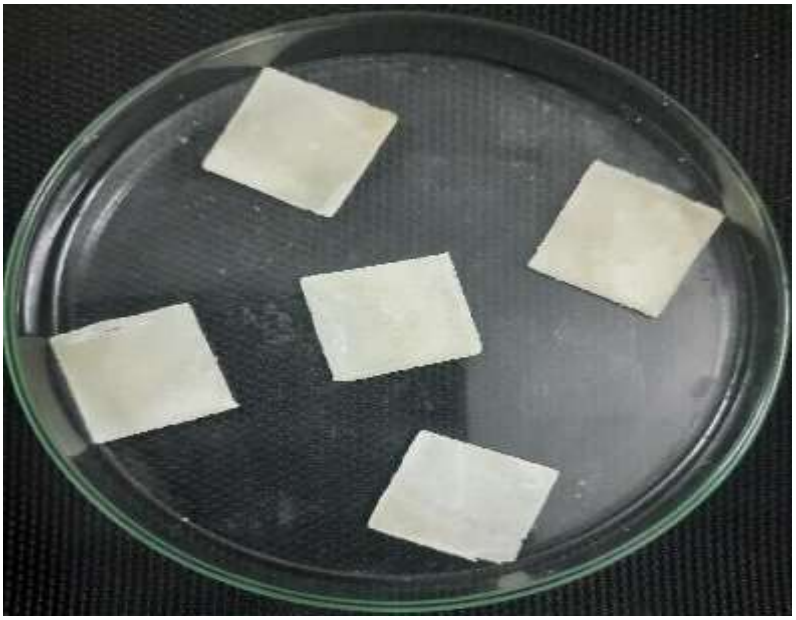

Fig. 2: Images of Lisinopril oral disintegrating films of F4 formulation

Table 2: Physicochemical properties

Formulation code	Weight (mg)	Thickness (mg)	Surface pH	Folding endurance	Disintegration time (Sec)
F1	37.2±0.82	0.32±0.03	6.5±0.3	40±1.5	24.1±1.7
F2	39.4±1.16	0.36±0.01	7.1±0.7	42±2.0	28.4±0.64
F3	40.7±1.01	0.38±0.02	6.9±0.1	38±3.1	26.1±0.6
F4	38.3±0.90	0.39±0.04	7.4±0.1	42±1.5	21.0±0.38
F5	41.3±0.43	0.38±0.02	7.3±0.1	40±1.5	27.9±0.6

Physicochemical Properties

The films were prepared with different polymer concentrations that were found to be flexible, smooth, transparent, non-stick, and homogeneous, indicating that the polymers used in the study had good film-forming properties. The individual weight of 5 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 the formulation was uniform. Among the HPMCE15 and PVPK30 Formulation, the weight increased with increasing content of the polymer used due to the viscosity (higher concentration of polymer produces higher viscosity) and the thickness of the films.

The thickness of 5 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 (0.32-0.39 mm), which is said to be acceptable for oral disintegrating films. It was also observed that the thickness of films having a combination of polymers (HPMCE15 and PVPK30) were uniform in each formulation.

The films with increased polymer content showed a moderate increase in thickness. The surface pH of five films in each formulation was determined, and the value was found to be in the range of 6.5-7.4, which is close to the neutral pH and is less irritant to the sublingual mucosa.

The film flexibility study showed that the film cracked after an average of approximately 40 times of folding. The ODF did not show any crack when folded 180 ° at the same place up to 40 times. Hence the ODF could be termed as flexible. The *in-vitro* disintegration time was found to be in the range of 21.3-28.4. There was no statically significant difference ($p>0.05$) in the *in vitro* disintegration time among the five formulations [21-23].

Table 3: The results of drug content

Formulation	Mean (%)	SD (%)	Acceptance value (%)
F1	97.14	1.10	5.28
F2	96.71	3.11	6.81
F3	98.10	4.89	12.42
F4	98.13	0.24	2.81
F5	98.28	1.85	3.44

The result of Drug content is presented in Table.3. The Lisinopril content in all the five formulations ranged from 96.71% to 98.28% of the theoretical concentration with relative Standard Deviations (SD) ranged from 0.24% to 4.89%. There was no statistically

significant difference ($p>0.05$) in the Lisinopril content among the formulations.

Thus, all the ODF met the criteria for the content uniformity test. Moreover, the acceptance value was found to be in the range of 2.81% to 12.42% which was also within the 15% limit of the uniformity of dosage units for Japanese pharmacopoeia15 [24]. In the above results, it was observed that Formulation F4 is found to be better than other Formulation with respectively. Physicochemical properties and drug content. So, F4 was selected for stability studies & Scanning Electron Microscopy.

Stability Studies of Orally Disintegrating Films as Per ICH Guidelines

For stability studies, Lisinopril ODF was stored at 40℃/75% RH. The samples were withdrawn at six months and subjected to tests for Appearance, Folding endurance, disintegration time, weight, and drug content. Less than 5% of the Lisinopril was lost for six months. From the above results, Lisinopril ODF appeared to be stable in the storage conditions.

Table 4: The results of stability studies

Parameter	0 day	60 days	120 days	180 days
Appearance	Transparent	Transparent	Transparent	Transparent
Folding Endurance	42±1.5	42±1.4	42±1.4	42±1.3
Disintegration time (sec)	21.0±0.38	21±0.2	21±0.1	21±0.2
Weight(mg)	38.3±0.90	38±0.80	38±0.8	38±0.8
% Drug Content	98.13±0.1	98.12±0.1	98.11±0.1	98.11±0.1

Scanning Electron Microscopy

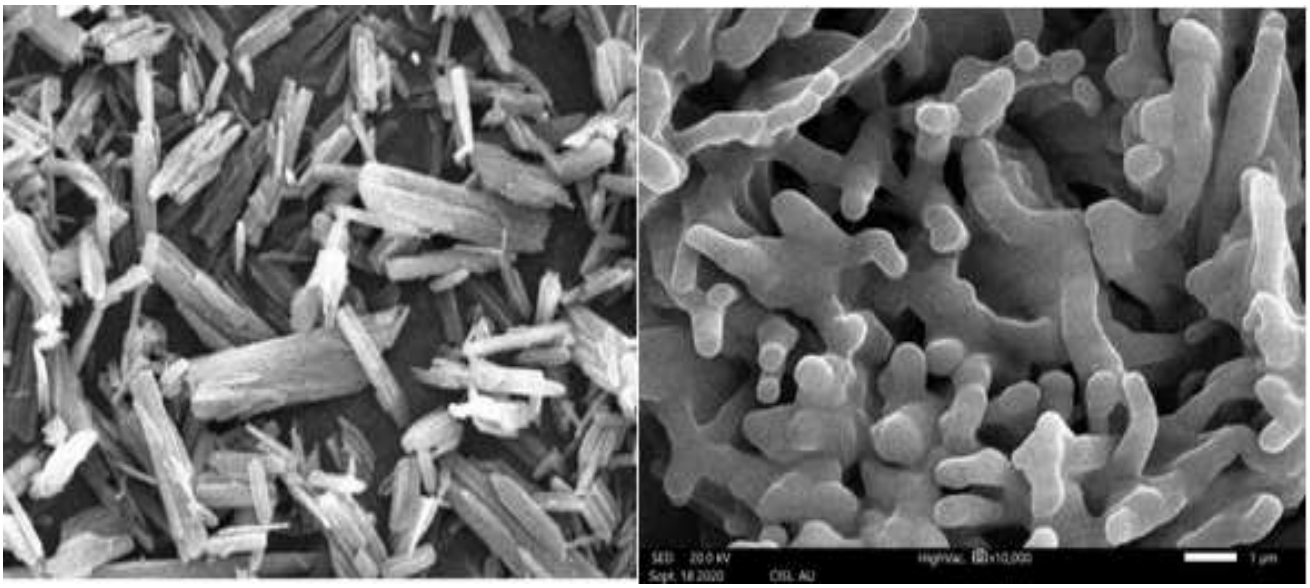

Fig. 3: (a) Scanning Electron Microscopy of Lisinopril pure drug and (b) Lisinopril film (2×2) (F4)

The SEM images of the pure Lisinopril drug shown in the Fig.3 (a) Lisinopril oral disintegrating film of F4 formulation made up of polymers like HPMC E15 and PVPK30 were shown in Fig. (b) Respectively from the above SEM images it is evident that the films made up of drug and HPMC E15, PVPK30 combination has a uniform distribution of the drug and film appears clear this is due to the less viscous nature HPMC E15 and PVPK30 its freely soluble nature made them the uniform distribution of the drug.

Conclusion

The objective of the present investigation has been achieved by preparing the oral disintegration film of Lisinopril for the effective management of hypertension and cardiac diseases. Lisinopril was successfully

formulated by using film-forming agents in combination with plasticizer by the solvent casting method. The films are smooth textured. From F1 to F5 the F4 formulation processing HPMC E15

and PVPK30 as film-forming agents and PEG as a plasticizer optimum formulation F4 has a clear surface morphology. The study is evidence that Lisinopril oral disintegrating films provide the fast onset of action.

The formulation F4 was found to be the best among all the five ODF formulation because; it has exhibited faster disintegration time (21.32 sec) when compared to the other formulation. So, ODF formulated with the composition of HPMC E15 and PVPK30 (F4) is the best formulation results showed all batches of ODF formulation release more than 90% of drug within 8 min. The method of preparation was found to be simple and required minimum excipients, Lisinopril oral disintegrating films can be considered to be suitable for clinical use in the treatment of hypertension wherein quicker onset of action is desirable along with the convenience of administration without using water.

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