Original Article

# Formulation And Evaluation Of Lansoprazole Oral Thin Films

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## Abstract

Lansoprazole is a proton-pump inhibitor and was used in the treatment of gastric acid disorders. Lansoprazole oral thin films are fast dissolving films and are a new, patient-friendly, and more convenient formulation of lansoprazole, which can be taken with or without water. It disintegrates rapidly in the mouth and is swallowed easily with the patient's saliva. This is an improved alternative formulation for all patients and offers the benefit of an alternative choice of administration of lansoprazole. This article deals with the formulation and evaluation of Lansoprazole oral thin films (OTFs). The main objective of this study was to study the effect of combination of synthetic polymers [Polyvinyl alcohol (PVA) and / or polyvinyl pyrrolidone (PVP)] and natural polymers (gelatin or maltodextrin) on the film forming properties and dissolution rate of the drug. The films were prepared by solvent casting method, using natural and synthetic film forming polymers in different concentrations, PEG 400 is used as plasticizer, aspartame and vanilla flavor as artificial sweetener and artificial flavor respectively. The prepared films were evaluated for weight uniformity, film thickness, folding endurance, dispersion test, drug content, and in vitro dissolution studies to ensure the physical stability of films. The formulation F11 with (PVP: PVA: Gelatin in the ratio of 2:1:1 respectively) has physicochemical, mechanical properties. F11 films exhibits lower values a $t_{50}$, $t_{90}$ of less than 2 min and 10 min respectively, and highest dissolution efficiency at 10 min ($DE_{10}$) of 66.40. It follows a first order drug release profile of with regression coefficient ($r^2$) of 0.995 and a first order rate constant ($K_1$) of 0.216 $min^{-1}$. F11 is considered as optimized formulation with desired properties. Hence the combination of synthetic polymers (PVA and PVP) and natural polymer (gelatin) in the ratio of (PVP: PVA: Gelatin: 2: 1: 1) had a significant effect on the film forming properties and dissolution rate of the drug. Fast dissolving lansoprazole oral thin films are suitable for effective and well-tolerated treatment option in the management of gastric acid-related disorders.

**KEYWORDS:** Lansoprazole, oral thin films, solvent casting method, polyvinyl alcohol polyvinyl pyrrolidone, gelatin, maltodextrin, folding endurance, dispersion test and in vitro dissolution studies

## INTRODUCTION:

Lansoprazole (LZ) is a proton-pump inhibitor (PPI) and was used in the treatment of gastric acid disorders (gastric ulcers, duodenal ulcers, gastro esophageal reflux (GER) and gastro duodenal lesions induced by over usage of NSAIDs.[1] It's mechanism of action is on in gastric parietal cells, by inactivating the final step of gastric acid secretion pathway in a dose-dependent manner.[2,3] LZ is also effective in eradication of H. pylori through different regimens and it is a first-line PPI used for this purpose.[4-7] Lansoprazole oral thin films (LZOTFs) are orally dissolving films and is a new, patient-friendly, and more convenient formulation of lansoprazole, which can be taken with or without water. It disintegrates rapidly in the mouth and is swallowed easily with the patient's saliva. This is an improved alternative formulation for all patients requiring LZ, offering the benefits of an alternative choice of administration. LZOTFs maintain the same pharmacological properties as LZ capsules and can be taken

by any patient who is currently prescribed LZ. The ability to take a tablet either with or without water will offer increased convenience and flexibility, particularly when patients are traveling, and may help to improve compliance in some patients. In addition, LZOTFs may be suitable for certain groups of patients, such as those with dysphasia associated with gastro esophageal reflux disease,[8]dynophagia or strictures, and the elderly o r long-term care patients.[9] This article summarizes the formulation and evaluation of LZOTFs. The main objective of this study was to select the best combination of polymer and excipients to formulate LZOTFs.

## MATERIALS

Lansoprazole was procured as gift sample from M/S Aurobindo Pharmaceuticals, Hyderabad. Polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), Polyethylene glycol (PEG 400), gelatin, maltodextrin were commercially procured from M/S Yarrow Chem Products, Mumbai. Aspartame was procured commercially from M/S Yarrow Chem Products, Chennai. All the materials used in the formulation were of analytical grade.

## METHODS:

**Pre-formulation studies:** Pre-formulation is the vital and initial process in any formulation studies. They are aimed to establish the compatibility of drug with common excipients. The ultimate objective of pre-formulation studies is to formulate robust formulation which will retain its stability until its shelf life.[10]

**Drug-polymer compatibility studies by FT-IR analysis:** FT-IR absorption spectra of pure LZ and the combination of LZ and polymers were taken to confirm the identity of the LZ and to detect the interaction of the drug with the polymers. FT-IR spectra of pure LZ and LZ: Polymer (in the ratio1:1 physical mixtures) were recorded, in the frequency range of 400-4000 $cm^{-1}$ with a resolution of 2 $cm^{-1}$, by the direct sampling method with isopropyl alcohol as solvent, using FT-IR Cary 630 spectrophotometer.

**Standard calibration curve of LZ in pH 6.8 Phosphate Buffer Solution (PBS):**

**Preparation of pH 6.8 PBS:** Transfer accurately 500 mL of 0.2 M dihydrogen phosphate and 112 mL of 0.2 M sodium hydroxide to a 1000 mL volumetric flask and makeup to 1000 mL with purified water.

**Preparation of stock Solution-I (1 mg/mL):** 50 mg of LZ was dissolved in 5 mL of methanol and the vol. was adjusted in a 50 mL vol. flask with pH 6.8 PBS which was placed in a sonicator for 5 min to obtain a clear solution.

**Preparation of stock solution-II (100 µg/mL):** 10 mL of stock Solution-I was transferred to a 100 mL volumetric flask and the volume was made up to the mark with pH 6.8 PBS [128].

**Preparation of working dilutions:** 0.4, 0.8, 1.2, 1.6, and 2 mL of stock solution-II was transferred to a series of 10 mL volumetric flasks and diluted with pH 6.8 PBS up to the mark to obtain the conc. of 4, 8, 12, 16, and 20 µg/mL LZ solutions respectively.

The median working dilution 12 µg/mL LZ solution was scanned by using a double beam UV-Vis spectrophotometer with a limit of 1nm in the spectral range of 200 to 400 nm, for to determine maximum absorbance ($\lambda_{max}$). The working dilutions were analysed at determined $\lambda_{max}$. The standard curve was constructed by taking absorbance on Y-axis and conc. on X-axis. All the estimations were done in triplicate and represented as (mean ± SD).

**Formulation studies:**

**Preparation of lansoprazole oral thin films:** Oral thin films of lansoprazole were prepared by solvent casting method.[11]

**Solution A:** Aqueous solutions of film forming agents such as PVA and PVP were made individually in 100 mL beakers to attain clear solutions. Then, the aqueous solution of PVP was added to PVA solution and stirred well to get a homogenous solution

**Solution B:** Weighed amounts of drug, aspartame and powder vanilla flavor were dissolved in suitable quantities of PEG 400 and ethanol to get a drug and plasticizer solution.

The solution B was added to solution A with constant stirring. The obtained solution was drawn on the Petri dish and dried under infrared (IR) lamp for 24 h. After drying, the films were cut into required size. The composition of various lansoprazole oral thin films was given in (Table 1) and the formulated films were shown in (Fig.1).

**Table1. Composition of Lansoprazole oral thin films**

| Ingredients | PVP | PVA | G | M | PVP+PVA (1:1) | PVP+PVA (1.25:1) | PVP+PVA (1.67:1) | PVP+PVA (2.5:1) | PVP+G (1:1) | PVP+M (1:1) | PVP+PVA+G (2:1:1) | PVP+PVA+M (2:1:1) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
| Lansoprazole | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| PVP | 500 | -- | -- | -- | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| PVA | -- | 500 | -- | -- | 250 | 200 | 150 | 100 | -- | -- | 125 | 125 |
| Gelatin | -- | -- | 500 | -- | -- | -- | -- | -- | 250 | -- | 125 | -- |
| Maltodextrin | -- | -- | -- | 500 | -- | -- | -- | -- | -- | 250 | -- | 125 |
| PEG 400 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| Aspartame | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Vanilla flavor | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Ethanol | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

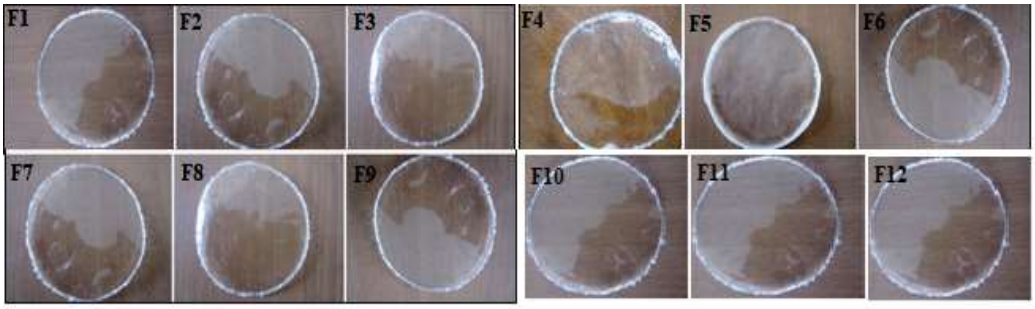


**Fig.1. Lansoprazole oral thin films (F1 to F12)**

**Evaluation of oral thin films:**

**Physicochemical properties:**

**Morphological studies:** Properties such as homogeneity, colour, transparency, and surface of OTFs were tested visually. All the films were packed in aluminium foil pouches and stored at room temperature (25 ± 3 °C) and 65 ± 5% relative humidity until the other evaluation tests are carried out.[12]

**Weight variation:** Mass of 1 $cm^2$ film from different batches of the formulations was noted on electronic balance (Shimadzu Electronic Balance, Japan). Uniformity in weight denotes the uniform distribution of drug in the films. The estimations were carried out in triplicate. [11]

**Film thickness:** The film thickness was measured using screw gauge (Baker Precision Measuring Instruments, China) with a range of 0-10 mm, and a least count of 0.01 mm, at different locations on the film. The estimations were carried out in triplicate. [13]

**In vitro disintegration time:** It gives an indication about the disintegration and dissolution characteristics of the film. In case of OTFs the disintegration and dissolution procedures are hardly distinguishable. If the OTF disintegrates it concurrently dissolves in a small amount of saliva which makes it difficult to mimic these natural conditions and measures with an adequate method. However, in the present investigation two methods of disintegration were adopted. [14]

**a. Drop method:** One drop of distilled water was dropped by a pipette onto the OTFs. The films were placed on a glass slide and then the glass slide was placed planar on a Petri dish. The time until the film dissolved and caused a hole within the film was measured. The estimations were carried out in triplicate.

**b. Petri dish Method:** 2 mL of distilled water was placed in a Petri dish and one film was added on the surface of the water and the time required until the oral film dissolved completely was measured. The estimations were carried out in triplicate.

**Dispersion test:** A film equivalent to 5 mg of lansoprazole was placed in 200 mL of pH 6.8 phosphate buffer and was stirred for 3 min. Then, the resulting solution was passed through sieve number 22. The film passed the dispersion test only when no residue is left on the screen.[12]

**Surface pH:** Was determined to investigate the possibility of any side effects in in vivo studies. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was ensured to keep the surface pH as close to pH 6.8 (oral cavity pH). The pH of an oral film was usually determined by putting the film in Petri dish and film was made wet with distilled water and noting pH by touching the film surface with a pH paper.[13]

**Drug content:** 1 $cm^2$ film was taken in a 10 mL volumetric flask and dissolved in 5 mL of methanol and then final volume was made up with pH 6.8 PBS. Samples were suitably diluted with pH 6.8 PBS (artificial saliva) and the absorbance was measured spectrophotometrically at 284 nm. The estimations were carried out in triplicate.[10]

## Mechanical properties:

**Tensile strength:** Is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the load at rupture divided by the cross-sectional area of the film as given below:

$$\textbf{Tensile strength} = \frac{\textbf{Load at failure X 100}}{\textbf{Film thickness X Film width}} \qquad \textbf{Eq. No. (1)}$$

It was measured using (Shimadzu AG-100 kNG, Winsoft tensile and compression testing). The film of size 3 × 2 $cm^2$ and free of physical imperfections was placed between two clamps held 10 mm apart. The film was pulled by a clamp at a rate of 5 mm/min. The estimations were carried out in triplicate.[14]

**Percent Elongation (% E):** When stress is applied the film sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally elongation of the film increases as the plasticizer concentration increases. Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula:

$$\textbf{Percentage elongation} = \frac{[L - L0] \times 100}{L0} \qquad \textbf{Eq. No. (2)}$$

Where, $L$ = final length and $L0$ = initial length.

The estimations were carried out in triplicate.[15]

**Young's or elastic modulus:** Is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\textbf{Young's modulus} = \frac{\textbf{slope} \times 100}{\textbf{Film thickness} \times \textbf{cross head speed}} \qquad \textbf{Eq. No. (3)}$$

Hard and brittle film demonstrates a high tensile strength and Young's modulus with small elongation. The estimations were carried out in triplicate.

**Folding endurance:** Was determined by repeated folding of the film at the same place till the film breaks. This gives an indication of the brittleness of the film. The number of times the film was folded without breaking was noted as the folding endurance value. The estimations were carried out in triplicate. [16]

**Moisture loss:** Moisture loss was determined by weight variation. Initial weight of the film was determined and afterward film was kept in a desiccator containing calcium carbonate for about 72 h. Films were then taken out and weighed. Percentage moisture loss is calculated by using the following formula as below.[17]

$$\textbf{\% Moisture loss} = \frac{\textbf{Initial wt} - \textbf{Final wt}}{\textbf{Initial wt}} \times 100 \qquad \textbf{Eq. No. (4)}$$

Moisture uptake: Was determined by expose to the environment with a relative humidity 75% at room temperature for 72 h. Percentage moisture uptake is calculated as % weight gain of the films as per below formula.[18]

$$\textbf{\% Moisture uptake} = \frac{\textbf{Final wt} - \textbf{Initial wt}}{\textbf{Initial wt}} \times 100 \qquad \textbf{Eq. No. (5)}$$

**In vitro dissolution studies:** Were conducted using 500 mL of pH 6.8 PBS (artificial saliva) as dissolution medium with modified type 5 dissolution apparatus. A temperature of 37 °C and 50 rpm was used. Each film with

a dimension of appropriate size equivalent to 15 mg of LZ was placed on a watch glass covered with nylon wire mesh as shown in (Fig.2). The watch glass was then dropped into a dissolution flask. 5 mL samples were withdrawn at 2, 5, 10, and 15 min time intervals and every time replaced with 5 mL of fresh dissolution medium. The samples were suitably diluted with the dissolution medium if necessary and analyzed at 284 nm. The estimations were carried out in triplicate.[19]


**Fig.2. A) Watch glass covered with nylon wire mesh and B) Modified type 5 dissolution apparatus**

**In vitro dissolution parameters:** The in vitro dissolution data was fitted into zero-order plots/ dissolution profiles; % cumulative drug dissolved (%CDD) on y-axis Vs time on x-axis and first order plots, Log % cumulative drug un-dissolved on y-axis (Log % CDUD) Vs time on x-axis as per the following equations.[20]

**Zero order equation: $Q_t = Q_0 + K_0t$** **Eq. No. (6)**

**First order equation: $\text{Log } Q_t = \text{Log } Q_0 - K_1t/2.303.$** **Eq. No. (7)**

Where; $Q_t$ is the amount of the drug dissolved in time t, $Q_0$ is the initial amount of drug in the solution; $K_0$ & $K_1$ refers to the rate constants of zero & first order respectively.

Parameters like time for 50 % drug release ($t_{50}$), time for 90 % drug release ($t_{90}$) and dissolution efficiency at 10 min ($DE_{10}$) were calculated from dissolution profiles. $DE_{10}$ was determined by trapezoid rule from the below equations. [21]

$$[AUC]_{t1}^{t2} = \Sigma \left[\frac{1}{2}(c_1+c_2)\,(t_2-t_1)\right] \quad \text{Eq. No (8)}$$

$$DE_{10} = \frac{[AUC]_{t1}^{t2}}{\text{Total area under 10 min}} \times 100 \quad \text{Eq. No. (9)}$$

Where:

$[AUC]_{t1}^{t2}$ = Area under curve between time points $t_1$ to $t_2$

Total area under 10 min = 10 x 100 = 1000 $cm^2$

**Accelerated stability studies on optimized LZOTFs as per ICH guidelines:** Was carried, by placing 20 films each of the optimized formulation of LZOTFs (F11), into a labelled and carefully sealed aluminium foils. Which are loaded into stability chamber and maintained up to 6 months at accelerated conditions (45 °C ± 2 °C / 75 % ± 5 % RH). Evaluation studies were performed on the samples withdrawn at the end of every month up to 6 months. The results were statistically analysed (one-way ANOVA-Dunnett's test) and the differences were significant if $p < 0.05$. The FT-IR, DSC & XRD studies performed on the 6M- accelerated stability sample, and were compared with that of pure drug. FT-IR spectra were recorded, in the frequency range of 400-4000 $cm^{-1}$ with a resolution of 2 $cm^{-1}$, by the direct sampling method with isopropyl alcohol as solvent, using FT-IR Cary 630 spectrophotometer. DSC thermograms were obtained using differential scanning calorimeter (SHIMZDO and DSC-60), by placing the samples in a sealed aluminium crucible and evaluated with a heating rate of 20°C/min at a temperature range of 25-250 °C. XRD diffractograms were obtained using X-ray powder diffractometer (SHIMADZO XRD-7000) with copper target instrument by maintaining the conditions at 40 Kv voltages, with 40 MA at room temperature. The scanning rate employed was 0.1°/s over a range of two values from 3° to 45°. [22]

## RESULTS AND DISCUSSION:

**Pre-formulation studies:**

**Drug-polymers compatibility studies of LZOTFs by FT-IR analysis:**

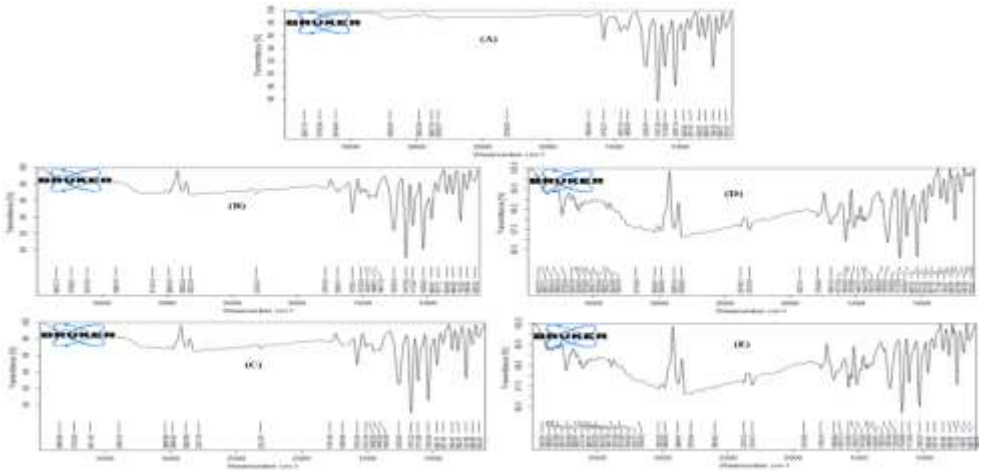

**Fig.3. FTIR spectrum of A) LZ, B) LZ + Maltodextrin, C) LZ + PVP, D) LZ + PVA and E) LZ + Gelatin**

**Table2. Interpretation of FT-IR spectrum of LZ**

| **Frequency ($cm^{-1}$)** | **Functional Group** |
|---|---|
| 3231 | NH- stretching vibration |
| 2984 | NH- stretching vibration |
| 2930 | - $CH_2$ stretching vibration |
| 1580 | aromatic ring stretching vibration |
| 1282 | C-O stretching vibration |
| 1118 | Ether bond stretching vibration |

The characteristic absorption peaks of Lansoprazole appeared at 3231, 2984 & 2930, 1580, 1282, 1118 denoting stretching vibration of NH-, - $CH_2$, aromatic ring, C-O and ether bond, respectively (Fig.3 and Table 3). These characteristic bands were observed in all of the recorded IR spectra of LZ: Polymers (1:1 ratio physical mixtures) shows no significant shifts or reduction in intensity of the bands (Fig.3), hence they are compatible.

**Standard calibration curve for the estimation LZ in pH 6.8 PBS:**

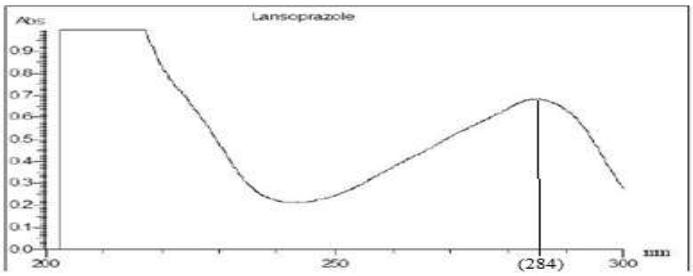


**Fig.4. Determination of $\lambda_{max}$ for LZ in pH 6.8 PBS**

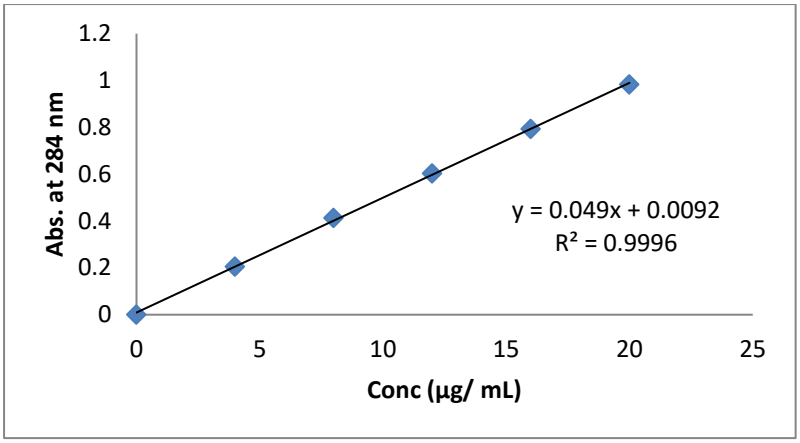


**Fig.5. Standard calibration curve for the estimation of LZ in pH 6.8 PBS**

It has max absorbance ($\lambda_{max}$) at 284 nm (Fig.4). This analytical method obeys Beer's law in the conc. range 0-20 µg/mL defined by a straight line, y = 0.049x + 0.009, with a regression ($r^2$) of 0.999 (Fig.5).

**Formulation studies:** LZOTFs were prepared by solvent casting method using PVP and PVA which were used at different concentrations as film forming polymers. PEG 400 was used as plasticizer. Aspartame and vanilla flavor were used as artificial sweetener and flavor respectively in the formulation. The films were prepared under identical conditions to minimize processing variables. Composition of Lansoprazole oral thin films is given in (Table1) and the formulated films were shown in (Fig.1).

**Evaluation studies:**

**Physicochemical properties:** Results of physicochemical properties (Morphological properties, weight variation, thickness, disintegration time, dispersion test, surface pH and drug content) of LZOTFs are tabulated in (Table 2).

**Table3. Physicochemical properties of LZOTFs**

| F. Code | Appearance | Texture | Weight variation (mg) | Film thickness (mm) | Disintegration time (sec) | | Dispersion test | Surface pH | Drug content (mg/cm$^2$) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Drop method | Petri dish Method | | | |
| F1 | Transparent | Smooth | 95±0.03 | 0.032±0.03 | 62.67 ± 0.31 | 66.67 ± 0.07 | + | 6-7 | 13.25±0.12 |
| F2 | Transparent | Smooth | 98±0.02 | 0.033±0.02 | 74.63 ± 0.39 | 83.33 ± 0.76 | + | 6-7 | 14.22±0.21 |
| F3 | Transparent | Smooth | 96±0.05 | 0.032±0.01 | 55.00 ± 0.73 | 58.33 ± 0.89 | + | 6-7 | 13.88±0.14 |
| F4 | Transparent | Smooth | 95±0.12 | 0.031±0.04 | 26.33 ± 0.58 | 55.33 ± 0.58 | + | 6-7 | 11.55±0.09 |
| F5 | Transparent | Smooth | 97±0.03 | 0.032±0.02 | 21.33 ± 0.58 | 36.67 ± 0.53 | + | 6-7 | 11.75±0.13 |
| F6 | Transparent | Smooth | 98±0.05 | 0.031±0.03 | 19.67 ± 0.53 | 36.33 ± 0.15 | + | 6-7 | 12.88±0.12 |
| F7 | Transparent | Smooth | 99±0.04 | 0.032±0.01 | 17.67 ± 0.51 | 30.67 ± 0.08 | + | 6-7 | 14.99±0.14 |
| F8 | Transparent | Smooth | 97±0.02 | 0.032±0.01 | 14.67 ± 0.48 | 31.33 ± 0.53 | + | 6-7 | 13.88±0.11 |
| F9 | Transparent | Smooth | 95±0.01 | 0.031±0.02 | 21.67 ± 0.81 | 49.33 ± 0.58 | + | 6-7 | 11.33±0.13 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| F10 | Transparent | Smooth | 95±0.12 | 0.031±0.04 | 23.67 ± 0.34 | 45.33 ± 0.52 | + | 6-7 | 11.55±0.09 |
| F11 | Transparent | Smooth | 97±0.01 | 0.031±0.02 | 10.33 ± 0.21 | 20.67 ± 0.51 | + | 6-7 | 14.25±0.14 |
| F12 | Transparent | Smooth | 98±0.03 | 0.032±0.01 | 12.33 ± 0.15 | 23.33 ± 0.58 | + | 6-7 | 13.35±0.21 |

**Morphological studies:** All the formulations showed no change in their morphological properties, all the films are transparent and have smooth texture. Especially no crystallization of the LZ was observed.

**Weight Variation:** The weight uniformity of the films is in the range of 95±0.03 to 99±0.04. No significant weight variation of films was obtained with all the batches indicating reproducibility by method employed for the preparation of OTFs. This in turn reflected in the uniformity in the drug content of OTFs.

**Thickness:** The thickness of all the films was found to be in the range of 0.031 ± 0.03 to 0.034 ± 0.01 mm. A good uniformity of thickness was observed in OTFs, which in turn reflected the uniformity in the drug content of OTFs.

**Disintegration time:** The results revealed that the films with the combination of two synthetic polymers (PVP and PVA) and natural polymer (gelatin or maltodextrin) had faster disintegration time values by both the methods. The films with the combination of two synthetic polymers (PVP and PVA) and PVP and natural polymer (gelatin or maltodextrin) had moderate disintegration time values by both the methods. The films with the single synthetic (PVP or PVA) and natural polymers (gelatin or maltodextrin) had slower disintegration time values by both the methods.

**Dispersion test:** All the films passed the test for dispersion, indicating no coarser particles were remained after disintegration and hence the films will not cause grittiness after placing in the mouth.

**Surface pH:** The surface pH of the film should be similar to that of saliva i.e. 6.8 as it is being kept in the oral cavity for dissolution for avoiding the irritation. The pH of LZ OTFs of all the batches found in the range from 6.0 - 7.0, which indicates that pH range was well within the targeted pH of oral cavity.

**Drug Content:** The drug content of all the films was found in the range of 11.33±0.13 to 14.99±0.14 mg. These results indicated a good uniformity and solubilization of LZ in the formulated OTFs.

**Mechanical properties:** Results of mechanical properties (Tensile Strength, % Elongation, Young's / Elastic Modulus, Folding Endurance % Moisture loss and % Moisture uptake) of LZOTFs are tabulated in (Table 3).

**Table4. Mechanical properties of LZOTFs**

| F. Code | Tensile strength ($N/cm^2$) | % Elongation ( %) | Young's modulus ($N/cm^2$) | Folding endurance | % Moisture loss (%) | % Moisture uptake (%) |
|---|---|---|---|---|---|---|
| F1 | 6.80 ± 0.45 | 72.06 ± 0.73 | 3.38 ± 0.24 | 79± 0.96 | 2.35 ± 0.15 | 3.81± 0.23 |
| F2 | 7.23 ± 0.65 | 71.43 ± 0.40 | 7.87 ± 0.23 | 75± 0.17 | 2.26± 0.11 | 3.78± 0.16 |
| F3 | 1.90 ± 0.17 | 69.16 ± 0.18 | 8.09 ± 0.43 | 71± 0.45 | 2.59± 0.51 | 4.01± 0.32 |
| F4 | 1.84 ± 0.31 | 58.96 ± 0.47 | 9.81 ± 0.35 | 70±0.13 | 2.52± 0.13 | 3.95± 0.25 |
| F5 | 4.53 ± 0.40 | 77.26 ± 0.75 | 3.32 ± 0.24 | 83± 0.15 | 2.23 ± 0.21 | 3.75± 0.30 |
| F6 | 3.40 ± 0.28 | 79.90 ± 0.35 | 2.76 ± 0.21 | 89± 0.13 | 2.13 ± 0.41 | 3.70± 0.15 |
| F7 | 3.26 ± 0.19 | 80.83 ± 0.22 | 2.68 ± 0.16 | 93± 0.21 | 2.10± 0.18 | 3.63± 0.36 |
| F8 | 2.90 ± 0.22 | 82.63 ± 0.95 | 2.36 ± 0.07 | 96± 0.16 | 1.81 ± 0.26 | 3.51± 0.20 |

| | | | | | | |
|---|---|---|---|---|---|---|
| F9 | 2.23 ± 0.15 | 88.26 ± 0.96 | 2.16 ± 0.19 | 107± 0.40 | 2.43± 0.21 | 3.87± 0.12 |
| F10 | 2.46 ± 0.21 | 85.53 ± 0.60 | 2.26 ± 0.15 | 99± 0.22 | 2.48± 0.21 | 3.92± 0.16 |
| F11 | 2.13 ± 0.25 | 94.43 ± 0.66 | 1.28 ± 0.10 | 121±0.14 | 2.41± 0.78 | 3.85± 0.29 |
| F12 | 2.20 ± 0.36 | 88.96 ± 0.12 | 1.61 ± 0.28 | 119± 0.25 | 2.37± 0.13 | 3.83± 0.11 |

**Tensile strength, % Elongation, and Young's / Elastic modulus:** OTFs should possess moderate tensile strength, high % elongation and low Young's / Elastic modulus. The results revealed that the films with the combination of synthetic and natural polymers (F11 and F12) moderate tensile strength values 2.13 ± 0.25 and 2.20 ± 0.36 respectively, contrary to the films with single polymers or combination of synthetic polymers alone which have highest tensile strength values. The films with the combination of synthetic and natural polymers (F11 and F12) have highest % elongation values of 94.43 ± 3.66 and 88.96 ± 3.12 respectively. The films with the combination of synthetic and natural polymers (F11 and F12) have lowest Young's / Elastic modulus values of 1.28 ± 0.10 and 1.61 ± 0.28.

**Folding Endurance:** The folding endurance values of the films ranged from 70±0.13 to 121±0.14. All the prepared OTFs have an acceptable folding endurance. Films of F11, which are formed with the combination of synthetic polymers (PVP and PVA) and natural polymers (gelatin) has highest folding endurance of 121±0.14.

**% Moisture loss:** A reduced % moisture loss was observed with increase in polymer concentration. Films formed with natural polymers (gelatin and maltodextrin) alone have experienced higher % moisture loss when compared to the films formed by the combination of synthetic polymers alone or synthetic and natural polymers, owing to the hygroscopicity of the natural polymers.

**% Moisture uptake:** The moisture uptake studies indicated an increase in uptake of moisture with increase in concentration of polymer. Films formed with natural polymers (gelatin and maltodextrin) alone have experienced higher % moisture loss when compared to the films formed by the combination of synthetic polymers alone or synthetic and natural polymers. This may be due to increased hygroscopicity of the natural polymers.

**In vitro dissolution studies:** All the formulations were found to release more than 90% of the drug within 15 min. The formulation F11 was found to exhibit rapid dissolution readily in the pH 6.8 phosphate buffer which indicated fast dissolving characteristics of the film as its releases 90% of the drug within 10 min when compared to others. The In vitro dissolution profiles of the prepared LZOTFs are shown in (Fig.6)

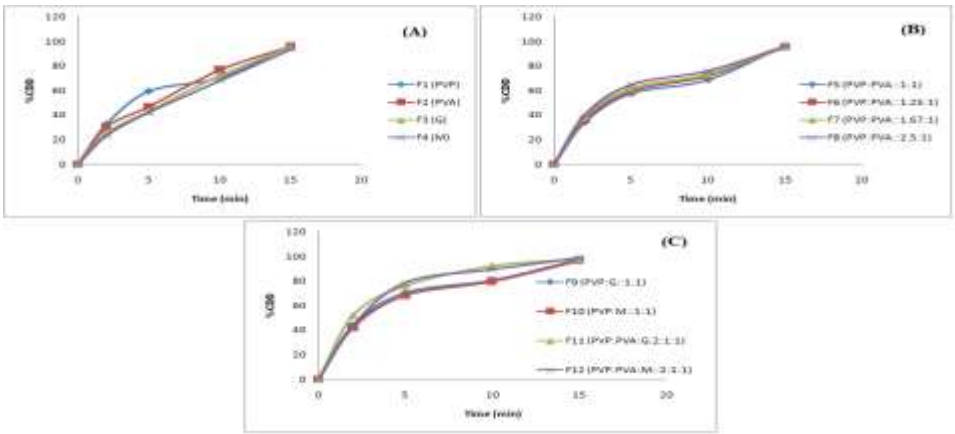


**Fig.6. In vitro dissolution profiles of ZOTFs; A) F1 to F4, B) F5 to F8 and C) F9 to F12**

**In vitro dissolution kinetics:** From the in vitro dissolution profiles, various parameters such as $t_{50}$, $t_{90}$, $DE_{10}$ were calculated. From the first-order plots, first order rate constant ($K_1$) and first order regression coefficient ($r^2$) were calculated. The formulations F11 and F12 **(**with PVA, PVP and gelatin or maltodextrin) show the highest DE10 values of 66.40 % and 64.73% respectively. The formulation F12 **(**with PVA, PVP and gelatin) show the $t_{90}$ value at less than 10min when compared to all. The first-order plots for various fast dissolving LZOTFs were found to

be linear with correlation coefficient ($r^2$) values in the range of 0.886-0.995, indicates that the drug release from the films was found to be concentration dependent. Among all the formulations, F11 with first order rate constant ($K_1$) of 0.216 $min^{-1}$ and first order correlation coefficient ($r^2$) of 0.995 is showing the faster dissolution profile with perfect first order kinetics. The in vitro dissolution plots are shown in (Fig.6) and the in vitro dissolution parameters are given in (Table 5).

**Table5. In vitro dissolution parameters of LZOTFs**

| F. Code | Dissolution plots | | | First order plots | |
|---|---|---|---|---|---|
| | $t_{50}$ (min) | $t_{90}$ (min) | $DE_{10}$ (%) | $K_1$ ($min^{-1}$) | $r^2$ |
| F1 | > 5 | < 15 | 46.90 | 0.205 | 0.936 |
| F2 | > 5 | < 15 | 45.42 | 0.198 | 0.947 |
| F3 | > 5 | < 15 | 66.00 | 0.191 | 0.929 |
| F4 | > 5 | < 15 | 39.59 | 0.168 | 0.931 |
| F5 | < 5 | < 15 | 48.75 | 0.200 | 0.886 |
| F6 | < 5 | < 15 | 50.74 | 0.182 | 0.926 |
| F7 | < 5 | < 15 | 52.60 | 0.191 | 0.924 |
| F8 | < 5 | < 15 | 54.73 | 0.187 | 0.941 |
| F9 | < 5 | < 15 | 59.16 | 0.219 | 0.938 |
| F10 | < 5 | < 15 | 57.77 | 0.198 | 0.913 |
| F11 | < 2 | < 10 | 66.40 | 0.216 | 0.995 |
| F12 | < 5 | < 15 | 64.73 | 0.267 | 0.972 |

**Selection of optimized formulation:** The formulation F11 with (PVP: PVA: Gelatin in the ratio of 2:1:1 respectively) was found to exhibit the best physicochemical properties of transparency, smooth texture, weight variation 97±0.01 mg, thickness of 0.031±0.02 mm, disintegration time of 10.33 ± 0.58 and 20.67 ± 0.58 by drop and Petri dish methods respectively, passed the test for dispersion, surface pH of 6-7 and drug content of 14.25±0.14 mg/$cm^2$. It exhibits the mechanical properties with a moderate tensile strength, value of 2.13 ± 0.25 N/$cm^2$, highest % elongation value of 94.43 ± 3.66 %, lowest Young's / Elastic modulus value of 1.28 ± 0.10 N/$cm^2$ and highest folding endurance value of 121±0.14. It also exhibits the lower $t_{50}$ and $t_{90}$ values of less 2 min and 10 min when compared to all others and it has a first order $K_1$ of 0.216 $min^{-1}$ and the highest first order $r^2$ of 0.99, in vitro dissolution studies. Hence it is considered as an optimized formulation.

**Accelerated stability studies of optimized LZOTFs (F11):**

**Table6. Results of physicochemical properties of accelerated stability studies of optimized LZOTFs (F11)**

| Sample | Appearance | Texture | Weight variation (mg) | Film thickness (mm) | Disintegration time (sec) | | Dispersion test | Surface pH | Drug content (mg/$cm^2$) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Drop method | Petri dish Method | | | |
| Initial | Transparent | Smooth | 97±0.01 | 0.031±0.02 | 10.33 ± 0.21 | 20.67 ± 0.51 | + | 6-7 | 14.25±0.14 |
| 1st month | Transparent | Smooth | 98±0.02 | 0.033±0.01 | 10.35 ± 0.41 | 20.52 ± 0.25 | + | 6-7 | 14.21±0.12 |
| 2nd month | Transparent | Smooth | 98±0.11 | 0.034±0.11 | 10.42 ± 0.32 | 20.43 ± 0.32 | + | 6-7 | 14.21±0.11 |
| 3rd month | Transparent | Smooth | 99±0.12 | 0.035±0.12 | 10.43 ± 0.24 | 20.46 ± 0.21 | + | 6-7 | 14.20±0.08 |
| 6th month | Transparent | Smooth | 99±0.11 | 0.035±0.11 | 10.51 ± 0.33 | 20.44 ± 0.32 | + | 6-7 | 14.19±0.13 |

**Table7. Results of mechanical properties of accelerated stability studies of optimized LZOTFs (F11)**

| Sample | Tensile strength ($N/cm^2$) | % Elongation ( %) | Young's modulus ($N/cm^2$) | Folding endurance | % Moisture loss (%) | % Moisture uptake (%) |
|---|---|---|---|---|---|---|
| Initial | 2.13 ± 0.25 | 94.43 ± 0.66 | 1.28 ± 0.10 | 121±0.14 | 2.41± 0.78 | 3.85± 0.29 |
| 1st month | 2.11 ± 0.13 | 94.44 ± 0.12 | 1.28 ± 0.11 | 120±0.11 | 2.39± 0.32 | 3.87± 0.11 |
| 2nd month | 2.10 ± 0.18 | 94.46 ± 0.34 | 1.29 ± 0.23 | 118±0.09 | 2.37± 0.51 | 3.89± 0.23 |
| 3rd month | 2.09 ± 0.25 | 94.48 ± 0.23 | 1.29 ± 0.15 | 118±0.07 | 2.35± 0.11 | 3.91± 0.09 |
| 6th month | 2.07 ± 0.25 | 94.50 ± 0.15 | 1.30 ± 0.12 | 117±0.12 | 2.34± 0.21 | 3.93± 0.15 |

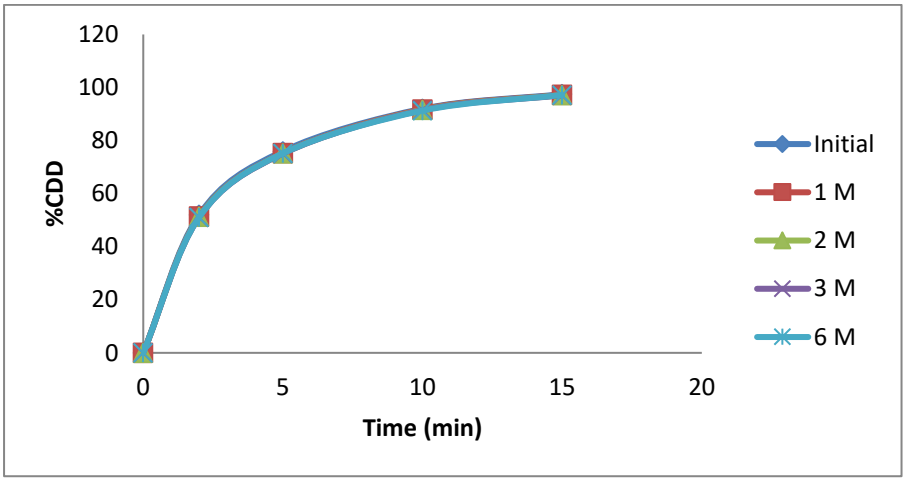


**Fig.7. In vitro dissolution plots of accelerated stability samples of optimized LZOTFs (F11)**

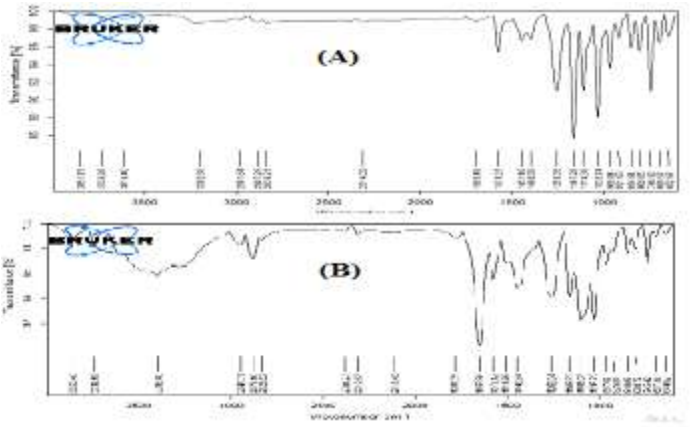


**Fig.8. Comparative FT-IR spectra of A. LZ (pure drug) and B. 6M-accelerated stability sample of optimized LZOTFs (F11)**

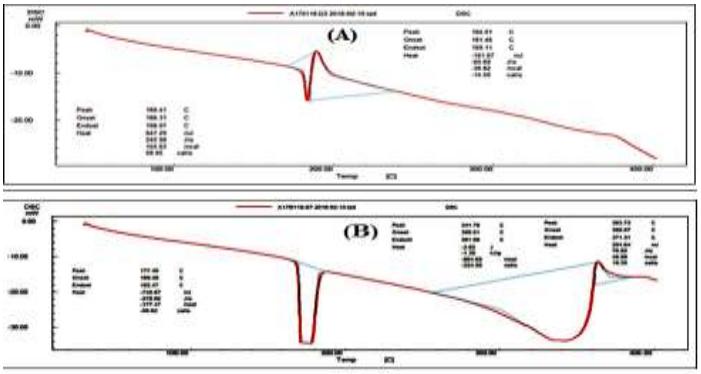


**Fig.9. Comparative DSC thermograms of A. LZ (pure drug) and B. 6M- accelerated stability sample of optimized LZOTFs (F11)**

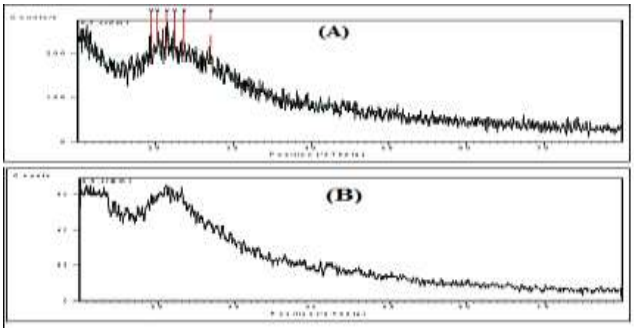


**Fig.10. Comparative XRD diffractograms of A. LZ (pure drug) and B. 6M- accelerated stability sample of optimized LZOTFs (F11)**

Statistically analysis by (one-way ANOVA - Dunnett's test) indicates the differences were not significant (as $p < 0.05$) of accelerated stability samples when compared with initial ones of optimized LZOTFs (F11). The Results of physicochemical properties of accelerated stability studies of optimized LZOTFs (F11) was tabulated in (Table6). The results of mechanical properties of accelerated stability studies of optimized LZOTFs (F11) were tabulated in (Table7). The in vitro dissolution plots of accelerated stability samples of optimized LZOTFs (F11) were shown in (Fig.7). Comparative FT-IR spectra of LZ and 6M-accelerated sample of optimized LZOTFs (F11) in (Fig.8), reveals the LZ and the polymers used in the study are compatible. Comparative DSC thermograms of LZ and 6M-accelerated sample of optimized LZOTFs (F11) (Fig.9), reveals that the exothermic peak for LZ and the sample obtained are 189.41°C and 177.1°C respectively, so the interaction between the drug and excipients was not observed. The comparative XRD diffractograms of LZ and 6M-accelerated sample of optimized LZOTFs (F11) (Fig.10) showed a decrease in the peak intensity due to change in the crystalinity of drug, which may lead to enhanced dissolution rate of drug from the prepared film.[23] Hence, the optimized formulation LZOTFs (F11) passes the test for stability as per ICH guidelines.

## CONCLUSION:

Fast dissolving lansoprazole oral thin films prepared in the present study should exhibit good film properties as indicated by the film thickness and folding endurance. All the films prepared were found to be stable, uniform, flexible, and pliable and 90% of drug was released from optimized oral thin film F11 within 10 min of time which is advantageous for fast absorption of the drug through buccal route. The combination of synthetic polymers (PVA and PVP) and natural polymers (gelatin and maltodextrin) had a significant effect on the film forming properties and enhancing the dissolution efficiency of the drugs meant for buccal absorption.[24, 25] In the present study the formulation F11, with (PVP: PVA: Gelatin in the ratio of 2:1:1 respectively) is selected as the optimized one, which was further characterized by (FTIR, DSC, XRD and SEM) studies. Hence, fast dissolving LZOTFs were found to be suitable for effective and well-tolerated treatment option in the management of acid-related disorders.

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