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Effect of Combination of Natural and Synthetic Film-Forming Polymers on The Dissolution Rate of Lansoprazole from Its Immediate Release Oral Thin Films

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

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 a 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 the 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 a natural and synthetic film-forming polymer in different concentrations, PEG 400 is used as a plasticizer, aspartame, and vanilla flavor as an 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 F11with (PVP: PVA: Gelatin in the ratio of 2:1:1 respectively) has physicochemical, mechanical properties. F11 films exhibit 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 with a regression coefficient (r^2) of 0.995 and a first-order rate constant (K_1) of 0.216 min^{-1}.F11 is considered as an 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 options in the management of gastric acid-related disorders.

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INTRODUCTION:

Lansoprazole (LZ) is a proton-pump inhibitor (PPI) and was used in the treatment of gastric acid disorders (gastric ulcers, duodenal ulcers, gastroesophageal reflux (GER) and gastroduodenal lesions induced by over usage of NSAIDs.[1]It'smechanism 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 the 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 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 requiring LZ, offering the benefits of a 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 gastroesophageal reflux disease,[8]dynophagia or strictures, and the elderly or 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 a 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:

Formulation studies:

Preparation of lansoprazole oral thin films: Oral thin films of lansoprazole were prepared by solvent casting method.[10]

solution: Aqueous solutions of film-forming agents were prepared individually in 100mLbeakerstoattainclearsolutions.Then, the aqueous solutions were mixed and stirred well to get a homogenous solution.

solutions: 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.

Solution B was added to solution A with constant stirring. The obtained solution was drawn on the Petri dish and dried under an infrared (IR) lamp for 24 h. After drying, the films were cut into the 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 (mg)	**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

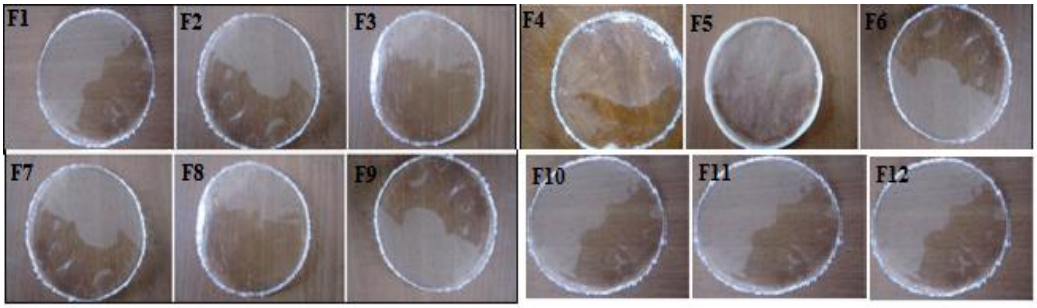

Fig.1. Photographs of Lansoprazole oral thin films (F1 to F12)

Evaluation of oral thin films:

Physicochemical properties:

Morphological studies: Properties such as homogeneity, color, transparency, and the surface of OTFs were tested visually. All the films were packed in aluminum foil pouches and stored at room temperature (25 ± 3°C) and65 ± 5% relative humidity until the other evaluation tests are carried out.[11]

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

Film thickness: The film thickness was measured using a 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. [11]

***In-vitro* disintegration time:** It indicates the disintegration and dissolution characteristics of the film. In the 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. [11]

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: 2mL 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 3min. 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 vivo* studies. As an acidic or alkaline pH may irritate 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 a Petri dish and the film was made wet with distilled water and noting pH by touching the film surface with a pH paper.[13]

Drug content: 1 cm^2film was taken in a 10 mL volumetric flask and dissolved in 5 mL of methanol and then the 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.[11]

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:

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

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 were placed between two clamps held 10mm 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 a strain. Strain is 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:

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

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 the stiffness of film. It is represented as the ratio of applied stress overstrain in the region of elastic deformation as follows:

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

The 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: This was determined by repeated folding of the film at the same place till the film breaks. This indicates 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. The initial weight of the film was determined and afterward, the 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]

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

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

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

***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 an 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 15min 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.[11]

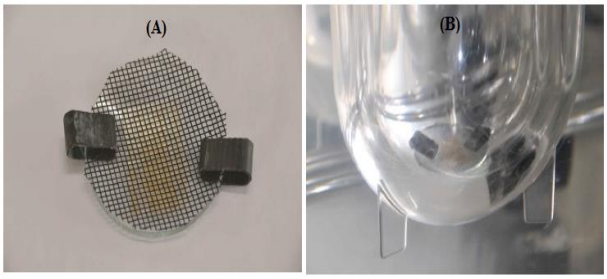

Fig.2. (A)Watch glass covered with nylon wire mesh and (B)Modified type 5 dissolution apparatus

***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 the x-axis and first-order plots, Log % cumulative drug un-dissolved on the y-axis (Log % CDUD) *Vs* time on the x-axis as per the following equations.[19]

$$\textit{Zero-order equation: } Q_t = Q_0 + K_0 t \quad \textit{Eq. No. (6)}$$

$$\textit{First-order equation: } \text{Log } Q_t = \text{Log } Q_0 - K_1 t/2.303. \quad \textit{Eq. No. (7)}$$

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_1refers 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 the trapezoid rule from the below equations. [20]

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

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

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

Characterization of optimized LZOTFs: Dissolution studies were performed on all the formulations; among these, the optimized formulation F7 was further evaluated by Fourier-transform Infra-Red (FTIR), Differential Scanning Calorimetry (DSC), X-ray powder diffraction (XRD), and Scanning electron microscopy (SEM).[21]

FTIR: FTIR spectra of lansoprazole, film-forming agents (PVP and PVA), and optimized LZOTFs (F7) were obtained using Brucker FTIR spectrophotometer to study the interaction between drug and carrier in films. The samples were prepared in KBr discs (2 mg sample in200 mg KBr), and the sampling range was 400-4000 $cm^{-1}$and the resolution was 4/cm.

DSC: DSC thermograms of lansoprazole, film-forming agents (PVP and PVA), and optimized LZOTFs (F7) were obtained using a differential scanning calorimeter (SHIMZDOandDSC-60). The samples were placed in a sealed aluminum crucible and evaluated withaheatingrateof20°C/min at a temperature range of 25-250 °C.

XRD: The diffractograms of lansoprazole and film-forming agents (PVP and PVA) and optimized LZOTFs (F7) were obtained using an X-ray powder diffractometer (SHIMADZU XRD-7000) with a copper target instrument. The conditions were maintained 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°.

SEM: SEM photographs of lansoprazole (pure drug) and optimized LZOTFs (F7) were taken with the Scanning Electron Microscope (Tescan, Vega 3 SBH, Czech Republic). The samples were mounted onto aluminum stubs using carbon double-sided tape, gold-coated with a sputter coater (Quorum sputter coater, SC7620, UK), and examined at an excitation voltage of 5 kV, to study their surface morphology.

RESULTS AND DISCUSSION:

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 the 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. The composition of Lansoprazole oral thin films is given in (Table1).

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).

Table 2. Physicochemical properties of Lansoprazole oral thin films*

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 ± 1.31	66.67 ± 1.07	+	6-7	13.25±0.12
F2	Transparent	Smooth	98±0.02	0.033±0.02	74.63 ± 1.39	83.33 ± 0.76	+	6-7	14.22±0.21
F3	Transparent	Smooth	96±0.05	0.032±0.01	55.00 ± 1.73	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 ± 1.53	+	6-7	11.75±0.13
F6	Transparent	Smooth	98±0.05	0.031±0.03	19.67 ± 1.53	36.33 ± 1.15	+	6-7	12.88±0.12
F7	Transparent	Smooth	99±0.04	0.032±0.01	17.67 ± 0.58	30.67 ± 1.08	+	6-7	14.99±0.14
F8	Transparent	Smooth	97±0.02	0.032±0.01	14.67 ± 0.58	31.33 ± 1.53	+	6-7	13.88±0.11
F9	Transparent	Smooth	95±0.01	0.031±0.02	21.67 ± 0.58	49.33 ± 0.58	+	6-7	11.33±0.13
F10	Transparent	Smooth	95±0.12	0.031±0.04	23.67 ± 0.58	45.33 ± 1.52	+	6-7	11.55±0.09
F11	Transparent	Smooth	97±0.01	0.031±0.02	10.33 ± 0.58	20.67 ± 0.58	+	6-7	14.25±0.14
F12	Transparent	Smooth	98±0.03	0.032±0.01	12.33 ± 1.15	23.33 ± 0.58	+	6-7	13.35±0.21

*Except for the test for appearance, texture, dispersion test, and Surface pH; all other tests were carried out thrice (n = 3) and the values are expressed as mean ± SD.

Morphological studies: All the formulations showed no change in their morphological properties, all the films are transparent and have a 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 the 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. 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 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 methods. The films with the single synthetic (PVP or PVA) and natural polymers (gelatin or maltodextrin) had slower disintegration time values by both methods.

Dispersion test: All the films passed the dispersion test, indicating no coarser particles 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 irritation. The pH of LZ OTFs of all the matches found in the range from 6.0-7.0, which indicates that the pH range was well within the targeted pH of the 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).

Table 3: Mechanical properties of Lansoprazole oral thin films*

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 ± 2.73	3.38 ± 0.24	79± 0.96	2.35 ± 0.15	3.81± 0.23
F2	7.23 ± 0.65	71.43 ± 3.40	7.87 ± 0.23	75± 0.17	2.26± 0.11	3.78± 0.16
F3	1.90 ± 0.17	69.16 ± 3.18	8.09 ± 0.43	71± 0.45	2.59± 0.51	4.01± 0.32
F4	1.84 ± 0.31	58.96 ± 2.47	9.81 ± 1.35	70±0.13	2.52± 0.13	3.95± 0.25
F5	4.53 ± 0.40	77.26 ± 2.75	3.32 ± 0.24	83± 0.15	2.23 ± 0.21	3.75± 0.30
F6	3.40 ± 0.28	79.90 ± 1.35	2.76 ± 0.21	89± 0.13	2.13 ± 0.41	3.70± 0.15
F7	3.26 ± 0.19	80.83 ± 3.22	2.68 ± 0.16	93± 0.21	2.10± 0.18	3.63± 0.36
F8	2.90 ± 0.22	82.63 ± 1.95	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 ± 3.60	2.26 ± 0.15	99± 0.22	2.48± 0.21	3.92± 0.16
F11	2.13 ± 0.25	94.43 ± 3.66	1.28 ± 0.10	121±0.14	2.41± 0.78	3.85± 0.29
F12	2.20 ± 0.36	88.96 ± 3.12	1.61 ± 0.28	119± 0.25	2.37± 0.13	3.83± 0.11

*All the tests were carried out thrice (n = 3) and the values are expressed as mean ± SD.

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 the highest tensile strength values. The films with the combination of synthetic and natural polymers (F11 and F12) have the 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 the 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±0.13to121±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) have the highest folding endurance of 121±0.14.

% Moisture loss: A reduced % moisture loss was observed with an 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 an increase in the 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 the 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.3).

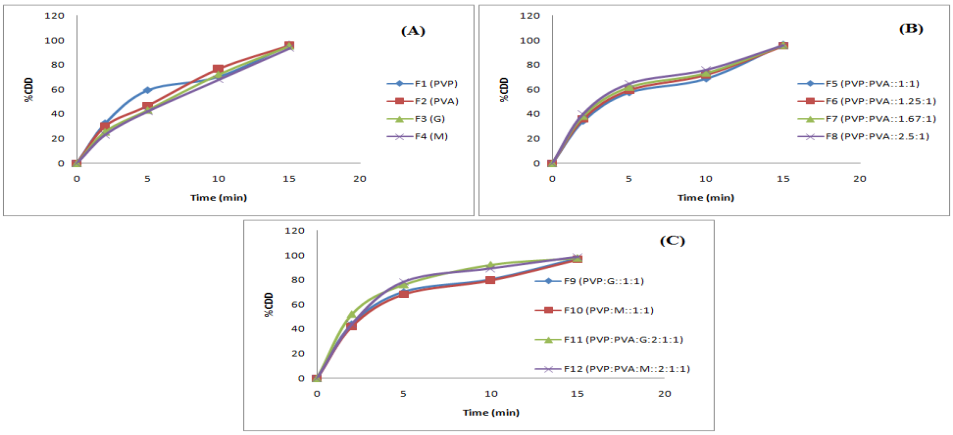

Fig.3. *In vitro* dissolution profiles of Lansoprazole oral thin films; (A) F1 to F4, (B) F5 to F8 and (C) F9 to F12

***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) shows 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, indicating that the drug release from the films was found to be concentration-dependent. Among all the formulations, F11 with a 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.2) and the *in vitro* dissolution parameters are given in (Table 4).

Table 4: *In Vitro* dissolution parameters of lansoprazole oral thin films*

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

*The*in vitro* dissolution profiles, which were carried out thrice (n = 3) per batch, and the values are expressed as mean ± SD. All the *in vitro* dissolution parameters values are calculated from the mean values.

Selection of optimized LZOTFs: 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, the thickness of 0.031±0.02 mm, disintegration time of 10.33 ± 0.58 and 20.67 ± 0.58 by dropping 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 moderate tensile strength, the 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 than 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 an optimized formulation.

Characterization of optimized LZOTFs: The optimized formulation (F11) was further subjected to characterization studies by FTIR, DSC, XRD, and SEM.

FTIR: The pure drug of lansoprazole displayed bands at 3236 cm^{-1} due to N-H Stretch and 2983 cm^{-1} due to C=C Stretching. The comparative FTIR spectra of lansoprazole (pure drug),

and optimized formulation (F11) shown in (Fig.4) indicates that there are no interactions between drug and excipients used in the study.

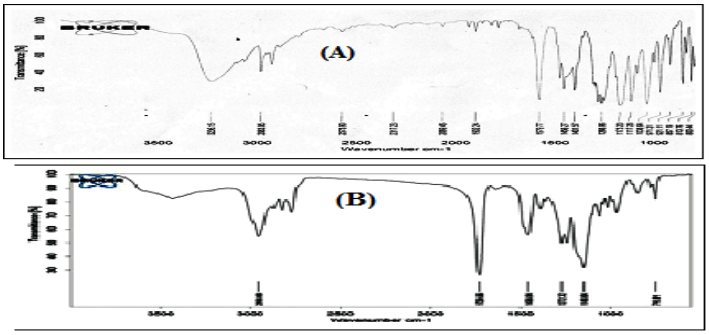

Fig.4. FTIR spectra of A) Lansoprazole (Pure drug) and B) Optimized Formulation (F11)

DSC: The exothermic peak for lansoprazole (pure drug) was obtained at 189.41°C. The short broad exothermic peak for PVP, PVA, and for the drug in optimized formulation (F11) were obtained at 227.07 °C, 161.41 °C, and 177.1°C respectively. Hence, no interaction between drug and excipients was observed in DSC studies. The comparative DSC thermograms of lansoprazole (pure drug) and optimized formulation (F11) are shown in (Fig.5).

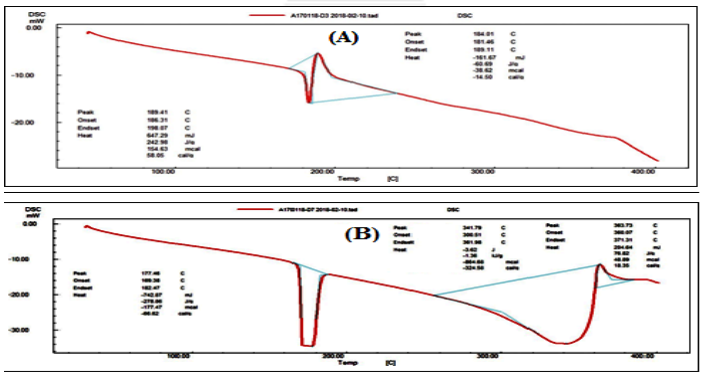

Fig.5. DSC thermograms of A) Lansoprazole (Pure drug) and B) Optimized Formulation (F11)

XRD: The diffraction patterns of lansoprazole (pure drug) showed characteristic high diffraction peaks, on the other hand, the diffraction patterns of optimized formulation (F11) showed a decrease in the peak intensity due to a change in the crystallinity of the drug, which may lead to enhanced dissolution rate of the drug from the prepared film.[22] The comparative XRD diffractograms of lansoprazole (pure drug)and optimized formulation (F11) is shown in (Fig.6).

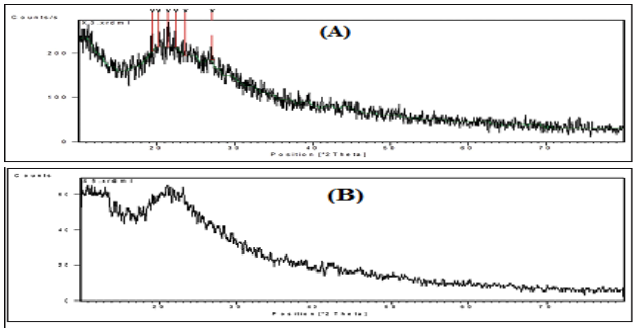

Fig.6. XRD diffractograms of A) Lansoprazole (Pure drug) and B) Optimized Formulation (F11)

SEM: SEM photograph of lansoprazole (pure drug) exposes discrete, elongated flake-like structures with rough edges covered on their surfaces by fine particles. Some structures are large with parallelogram shapes. It also reveals the hard and thick nature of the drug particles. In contrast, SEM of a photograph of optimized OTFs (F11) shows the rough and uneven surface with circular pits with the absence of particles suggesting the presence of the drug in dissolved state in the film-formed polymers. The comparative SEM photographs of lansoprazole (pure drug) and optimized formulation (F11) are shown in (Fig.7).

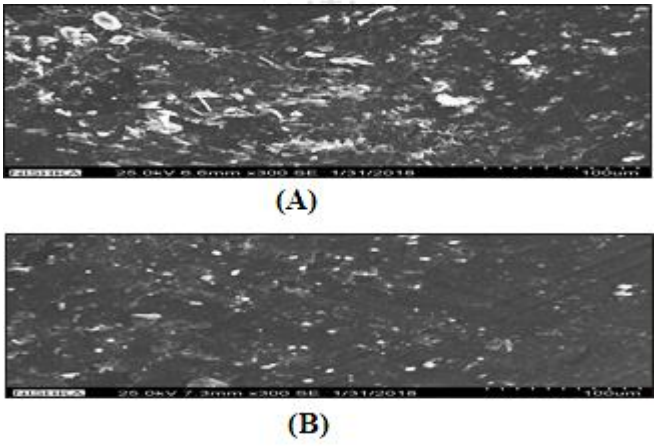

Fig.7. SEM photographs of A) Lansoprazole (Pure drug) and B) Optimized Formulation (F11)

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 filmF11 within 10 min which is advantageous for fast absorption of the

drug through the 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 enhanced the dissolution efficiency of the drugs meant for buccal absorption.[23, 24] 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 a found to be suitable for effective and well-tolerated treatment option in the management of acid-related disorders.

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