

**DESIGN, FORMULATION, AND EVALUATION OF
DEXLANSOPRAZOLE ORAL THIN FILMS**

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ABSTRACT

Dexlansoprazole is a proton-pump inhibitor and was used in the treatment of gastric acid disorders. Dexlansoprazole oral thin films are fast dissolving films and are a new, patient-friendly, and more convenient formulation of dexlansoprazole, 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 dexlansoprazole. This article deals with the formulation and evaluation of dexlansoprazole oral thin films (OTFs). The main objective of this study was to study the effect of combination of synthetic polymer [Hydroxypropyl methyl cellulose (HPMC15CPS)] and natural polymers (carrageenan / pectin / 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 F12 with (HPMC15CPS: carrageenan: pectin in the ratio of 2:1:1 respectively) has physicochemical, mechanical properties. F12 films exhibits lower values a t50, t90 of less than 2 min and 10 min respectively, and highest dissolution efficiency at 10 min (DE10) of 66.76%. It follows a first order drug release profile of with regression coefficient (r^2) of 0.996 and a first order rate constant (K_1) of 0.249 min^{-1} . F12 is considered as optimized formulation with desired properties. Hence the combination of synthetic polymer (HPMC15CPS) and natural polymers (carrageenan and pectin) in the ratio of (HPMC15CPS: carrageenan: pectin: 2: 1: 1) had a significant effect on the film forming properties and dissolution rate of the drug. The optimized formulation (F12) passes the accelerated stability studies as per ICH guidelines. Fast dissolving dexlansoprazole oral thin films are suitable for effective and well-tolerated treatment option in the management of gastric acid-related disorders.

KEYWORDS: Dexlansoprazole, oral thin films, solvent casting method, HPMC15CPS, carrageenan, pectin, Maltodextrin, folding endurance, dispersion test and in vitro dissolution studies.

INTRODUCTION

Dexlansoprazole (DZ), the new S-isomer of omeprazole, is introduced to reduce gastric acid secretion more efficiently compared to omeprazole.^[1-3] In addition, a recent crossover study demonstrated that DZ at a standard dose of 40 mg once daily provides more effective control of gastric acid at steady state than standard doses of pantoprazole, lansoprazole, and rabeprazole in patients with symptomatic gastroesophageal reflux disease (GERD).^[4] DZ is combined with the antibiotics clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the 7-14 days eradication triple therapy for *Helicobacter pylori*, which is the causative factor in the majority of peptic and duodenal ulcers.^[5] In addition, DZ treatment yields higher erosive esophagitis healing rates and provides sustained resolution of heartburn in more patients than any other.^[5-7] Esmoeprazole oral thin films (DZOTFs) are orally dissolving films and is a new, patient-friendly, and more convenient formulation of DZ, 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 DZ, offering the benefits of an alternative choice of administration. DZOTFs maintain the same pharmacological properties as DZ capsules and can be taken by

any patient who is currently prescribed DZ. 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, DZOTFs may be suitable for certain groups of patients, such as those with dysphasia associated with gastro esophageal reflux disease,^[8]odynophagia or strictures, and the elderly or long-term care patients.^[9] This article summarizes the formulation and evaluation of DZOTFs with the main objective to select the best combination of polymers to formulate the robust DZOTFs.

MATERIALS

Esmoeprazole was procured as gift sample from M/S Aurobindo Pharmaceuticals, Hyderabad. Hydroxypropyl methyl cellulose (HPMC15CPS), polyethylene glycol (PEG 400), carrageenan, pectin, Maltodextrin, aspartame and powder vanilla flavour were commercially procured from M/S Yarrow Chem Products, Mumbai. 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 DZ and the combination of DZ and polymers were taken to confirm the identity of the DZ and to detect the interaction of the drug with the polymers. FT-IR spectra of pure DZ and DZ: Polymer (in the ratio 1:1 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 (Bruker Alpha II, Germany) spectrophotometer.

Standard calibration curve of DZ 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 DZ 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 PBS¹²⁸.

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 DZ solutions respectively.

The median working dilution 12 µg/mL DZ 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 (λ_{max}). The working dilutions were analysed at determined λ_{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 \pm SD).

Formulation studies

Preparation of Dexlansoprazole oral thin films: Oral thin films of DZ were prepared by solvent casting method.^[11] **Solution A:** Aqueous solutions of film forming agents (HPMC15CPS, carrageenan, Maltodextrin and pectin) were made individually in 100 mL beakers to attain clear solutions. Then, the aqueous solutions were mixed as per the combinations mentioned in the (table1) 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 dexlansoprazole oral thin films was given in (Table 1) and the formulated films were shown in (Fig.1).

Table1. Composition of DZOTFs.

Ingredients	HP MC	CG	M	P	HPMC +CG (1:1)	HPMC +CG (1.25:1)	HPMC +CG (1.67:1)	HPMC +CG (2.5:1)	HPM C+M (1:1)	HPM C +P (1:1)	HPMC+C G +M (2:1:1)	HPMC+ CG +P (2:1:1)
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	150	150	150	150	150	150	150	150	150	150	150	150
HPMC15 CPS	500	--	--	--	250	250	250	250	250	250	250	250
Carragenan	--	500	--	--	250	200	150	100	--	--	125	125
Maltodextrin	--	--	500	--	--	--	--	--	250	--	125	--

Pectin	--	--	--	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

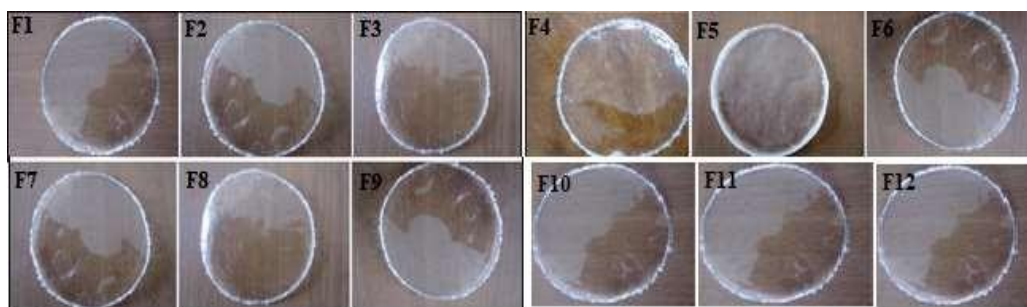


Fig. 1: DZOTFs (F1 to F12).

Evaluation of oral thin films

Physicochemical properties

Morphological studies: Properties such as homogeneity, color, transparency, and surface of OTFs were tested visually. All the films were packed in aluminium foil pouches and stored at room temperature ($25 \pm 3^\circ\text{C}$) and 65

$\pm 5\%$ 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 cm² 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.

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

It was measured using (Shimadzu AG-100 kNG, Winsoft tensile and compression testing). The film of size $3 \times 2 \text{ cm}^2$ 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

$$\text{Percentage elongation} = \frac{[L - L_0] \times 100}{L_0} \quad \text{Eq. No. (2)}$$

Where, L = final length and L_0 = 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

$$\text{Young's modulus} = \text{slope} \times 100$$

$$\text{Film thickness} \times \text{cross head speed} \quad \text{Eq. No. (3)}$$

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]

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

Initial wt

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]

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

Initial wt

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 DZ 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 296 nm. The estimations were carried out in triplicate.^[19]

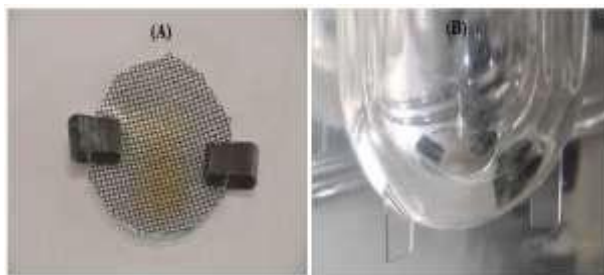


Fig. 2A: Watch glass covered with nylon wire mesh and B) Modified type 5 dissolution apparatus.

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 (DE10) were calculated from dissolution profiles. DE10 was

determined by trapDZoid rule from the below equations.^[21]

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

$$\text{DE}_{10} = \frac{[\text{AUC}] \frac{t_2}{t_1}}{\text{Total area under 10 min}} \times 100 \quad \text{Eq. No. (9)}$$

Where:

$[\text{AUC}] \frac{t_2}{t_1}$ = Area under curve between time points t_1 to t_2

Total area under 10 min = $10 \times 100 = 1000 \text{ cm}^2$

Accelerated stability studies on optimized DZOTFs as per ICH guidelines

Was carried, by placing 20 films each of the optimized formulation of DZOTFs (F12), into a labelled and carefully sealed aluminium foils. Which are loaded into stability chamber and maintained up to 6 months at accelerated conditions ($45 \text{ }^\circ\text{C} \pm 2 \text{ }^\circ\text{C} / 75 \% \pm 5 \% \text{ RH}$). 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 $400\text{-}4000 \text{ cm}^{-1}$ 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 $20^\circ\text{C}/\text{min}$ at a temperature range of $25\text{-}250 \text{ }^\circ\text{C}$. 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 $0.1^\circ/\text{s}$ over a range of two values from 3° to 45° .^[22]

RESULTS AND DISCUSSION

Pre-formulation studies

Drug-polymers compatibility studies of DZOTFs by FT-IR analysis

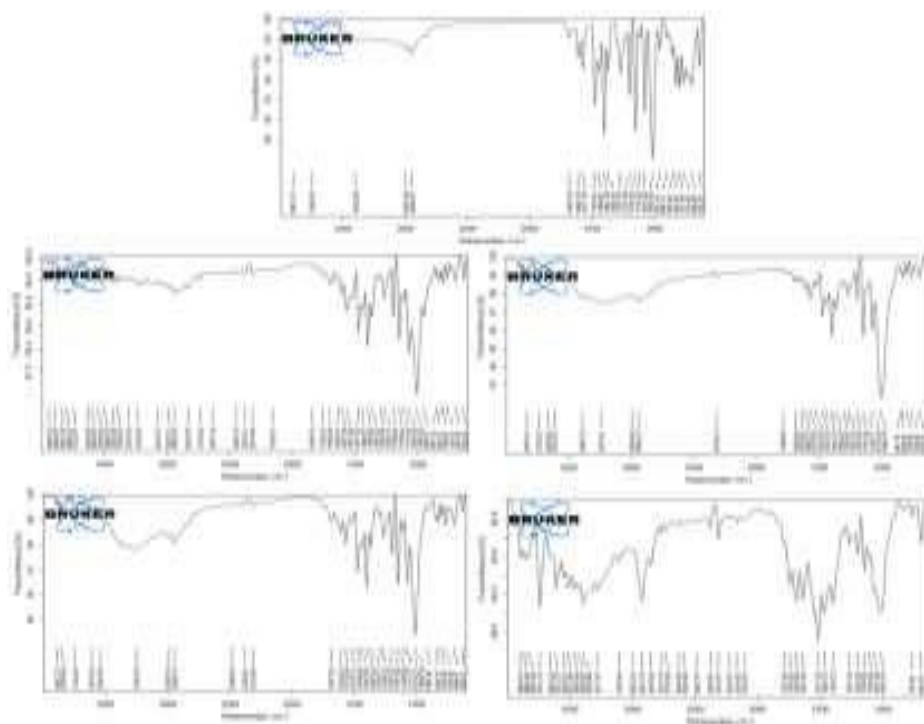
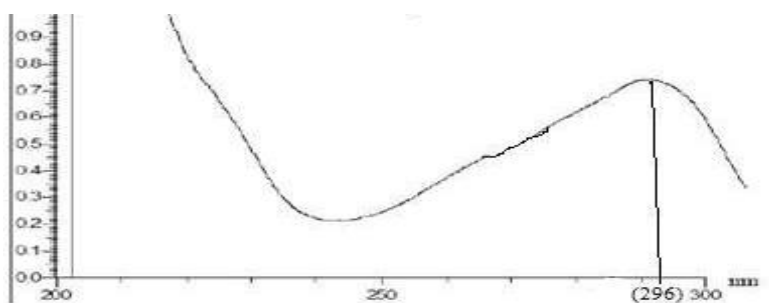
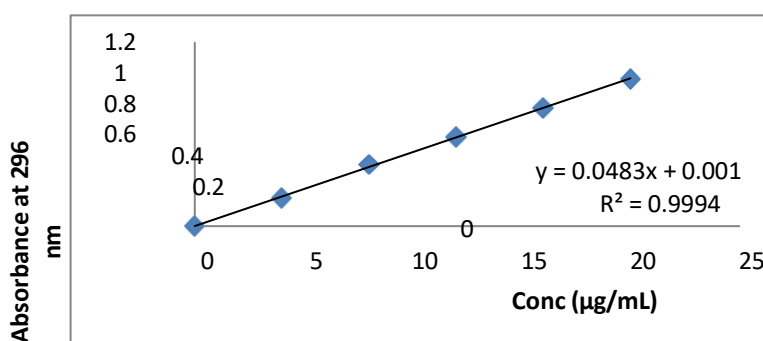


Fig. 3: FTIR spectrum of A) DZ, B) DZ + HPMC15CPS, C) DZ + Carragenan, D) DZ + Maltodextrin and E) DZ + Pectin

Table 2: Interpretation of FT-IR spectrum of DZ.

Frequency (cm ⁻¹)	Functional Group
2966.624	O-H stretching Carboxylic acid
1509.500	-C=C- stretching aromatic
1474.239	C-C stretch in ring aromatics
1215.631	C-N stretch amines
781.495	N-H 1°, 2° amines
839.158	C-H out of plane bend aromatics

The characteristic absorption peaks of dexlansoprazole appeared at 2966.624, 1509.5, 1474.239, 1215.631, 781.495 and 839.158 denoting, O-H stretching Carboxylic acid, -C=C- stretching aromatic, C-C stretch in ring aromatics, C-N stretch amines, N-H 1°, 2° amines and C-H out-of plane bend in aromatics respectively (Fig.3 and Table2). These characteristic bands were observed in all of the recorded IR spectra of DZ: 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 DZ in pH 6.8 PBS**Fig. 4: Determination of λ_{\max} for DZ in pH 6.8 PBS.****Fig. 5: Standard calibration curve for the estimation of DZ in pH 6.8 PBS.**

It has max absorbance (λ_{\max}) at 296 nm (Fig.4). This analytical method obeys Beer's law in the conc. range 0-20 $\mu\text{g/mL}$ defined by a straight line, $y = 0.048x + 0.001$, with a regression (r^2) of 0.999 (Fig.5).

Formulation studies: DZOTFs were prepared by solvent casting method using HPMC15CPS, carrageenan, Maltodextrin and pectin, 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 dexlansoprazole 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 DZOTFs are tabulated in (Table 3).

Table 3: Physicochemical properties of DZOTFs.

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	98±0.04	0.028±0.03	60.12 ± 0.25	65.27 ± 0.07	+	6-7	14.25±0.12
F2	Transparent	Smooth	98±0.02	0.029±0.02	72.25 ± 0.27	81.31 ± 0.37	+	6-7	14.22±0.21
F3	Transparent	Smooth	97±0.05	0.031±0.01	53.22 ± 0.43	56.23 ± 0.43	+	6-7	14.88±0.14
F4	Transparent	Smooth	98±0.12	0.029±0.04	24.31 ± 0.42	54.11 ± 0.35	+	6-7	14.55±0.09
F5	Transparent	Smooth	97±0.03	0.029±0.02	22.33 ± 0.47	37.25 ± 0.38	+	6-7	14.75±0.13
F6	Transparent	Smooth	99±0.05	0.030±0.03	20.45 ± 0.41	35.33 ± 0.15	+	6-7	14.88±0.12
F7	Transparent	Smooth	97±0.03	0.031±0.01	18.52 ± 0.34	29.27 ± 0.28	+	6-7	14.99±0.14
F8	Transparent	Smooth	98±0.02	0.029±0.01	16.34 ± 0.26	29.32 ± 0.43	+	6-7	14.88±0.11
F9	Transparent	Smooth	96±0.01	0.030±0.02	21.51 ± 0.41	46.42 ± 0.47	+	6-7	14.33±0.13
F10	Transparent	Smooth	97±0.12	0.029±0.04	23.37 ± 0.22	42.23 ± 0.32	+	6-7	14.55±0.09
F11	Transparent	Smooth	97±0.01	0.028±0.02	13.12 ± 0.15	23.13 ± 0.22	+	6-7	14.25±0.14
F12	Transparent	Smooth	98±0.03	0.030±0.01	11.42 ± 0.17	19.23 ± 0.41	+	6-7	14.75±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 DZ was observed.

Weight Variation: The weight uniformity of the films is in the range of 96±0.01 to 99±0.05. 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 0.028±0.02 to 0.031 ± 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 polymers (HPMC5CPS and carrageenan) and polymers (HPMC5CPS and Maltodextrin / pectin) had faster disintegration time values by both the methods. The films with the combination of three polymers (HPMC5CPS + carrageenan + Maltodextrin / pectin) had moderate disintegration time values by both the methods. The films with the single polymer (HPMC5CPS/ carrageenan / Maltodextrin / pectin) 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 DZOTFs 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 14.22 ± 0.21 to 14.99 ± 0.14 mg. These results indicated a good uniformity and solubilisation of DZ 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 DZOTFs are tabulated in (Table 4).

Table 4: Mechanical properties of DZOTFs.

F. Code	Tensile strength (N/cm ²)	% Elongation (%)	Young's modulus (N/cm ²)	Folding endurance	% Moisture loss (%)	% Moisture uptake (%)
F1	5.72 ± 0.12	73.12 ± 0.43	3.42 ± 0.42	78 ± 0.45	2.31 ± 0.12	3.78 ± 0.14
F2	6.45 ± 0.13	71.52 ± 0.23	7.51 ± 0.31	76 ± 0.23	2.24 ± 0.23	3.65 ± 0.11
F3	1.53 ± 0.09	69.11 ± 0.11	7.65 ± 0.33	72 ± 0.52	2.56 ± 0.42	4.11 ± 0.27
F4	1.65 ± 0.11	57.92 ± 0.38	8.32 ± 0.52	69 ± 0.11	2.49 ± 0.21	3.83 ± 0.20
F5	4.21 ± 0.10	76.23 ± 0.42	3.45 ± 0.41	82 ± 0.23	2.20 ± 0.14	3.64 ± 0.23
F6	3.34 ± 0.18	78.47 ± 0.51	2.53 ± 0.11	87 ± 0.42	2.11 ± 0.36	3.72 ± 0.11
F7	3.11 ± 0.19	80.12 ± 0.37	2.62 ± 0.13	91 ± 0.31	2.09 ± 0.21	3.58 ± 0.34
F8	2.65 ± 0.20	82.51 ± 0.61	2.41 ± 0.52	94 ± 0.22	1.79 ± 0.23	3.42 ± 0.22
F9	2.53 ± 0.13	87.12 ± 0.52	2.23 ± 0.26	105 ± 0.23	2.41 ± 0.23	3.76 ± 0.14
F10	2.42 ± 0.11	84.33 ± 0.45	2.21 ± 0.23	98 ± 0.41	2.45 ± 0.19	3.84 ± 0.21

F11	2.18 ± 0.16	87.24 ± 0.11	1.82 ± 0.25	117 ± 0.52	2.34 ± 0.11	3.72 ± 0.23
F12	2.11 ± 0.12	93.15 ± 0.23	1.42 ± 0.21	123 ± 0.42	2.38 ± 0.31	3.74 ± 0.17

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 three polymers (F11 and F12) moderate tensile strength values 2.18 ± 0.16 and 2.11 ± 0.12 respectively, contrary to the films with single polymers or combination of two polymers; which have highest tensile strength values. The films with the combination of three polymers (F11 and F12) have highest % elongation values of 87.24 ± 0.11 and 93.15 ± 0.23 respectively. The films with the combination of three polymers (F11 and F12) have lowest Young's / Elastic modulus values of 1.82 ± 0.25 and 1.42 ± 0.21 .

Folding Endurance: The folding endurance values of the films ranged from 69 ± 0.11 to 123 ± 0.42 . All the prepared OTFs have an acceptable folding endurance. Films of F12, which are formed with the combination of three polymers [HPMC5CPS + carrageenan + pectin (2:1:1)] has highest folding endurance of 123 ± 0.42 .

% Moisture loss: A reduced % moisture loss was observed with increase in polymer concentration. Films formed with single natural polymers (carrageenan / pectin / maltodextrin) alone have experienced higher % moisture loss when compared to the films formed by the combination of two or three polymers, owing to the hygroscopic nature 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 (carrageenan / pectin / maltodextrin) alone have experienced higher % moisture uptake when compared to the films formed by the combination of polymers. This may be due to higher hygroscopic nature 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 F12 was found to exhibit rapid dissolution readily in the pH 6.8 phosphate buffer which indicated fast dissolving characteristics of the film as it releases 90% of the drug within 10 min when compared to others. The In vitro dissolution profiles of the prepared DZOTFs are shown in (Fig.6).

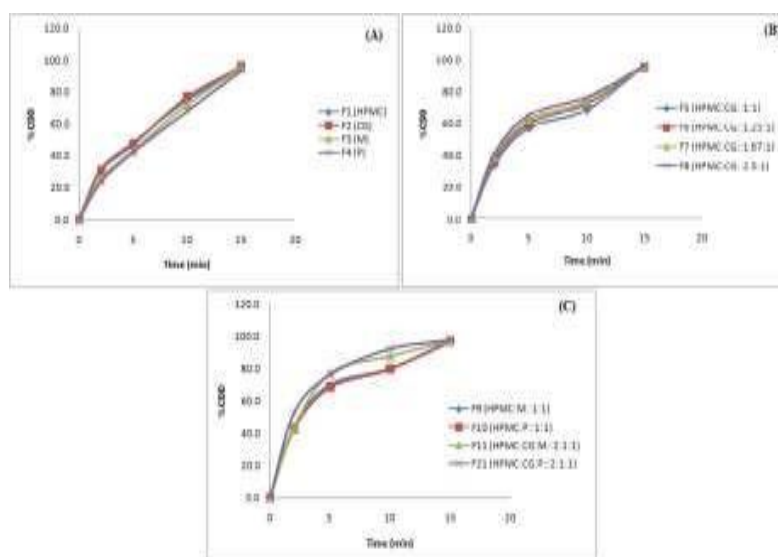


Fig. 6: In vitro dissolution profiles of DZOTFs; A) F1 to F4, B) F5 to F8 and C) F9 to F12.

In vitro dissolution kinetics: From the in vitro dissolution profiles, various parameters such as t_{50} , t_{90} , DE10 were calculated. From the first-order plots, first order rate constant (K_1) and first order regression coefficient (r^2) were calculated. The formulations with the combination of three polymers (HPMC+CG+P/M) F11 and F12 show the highest DE10 values of 63.74 % and 66.76% respectively. The formulation F12 (HPMC5CPS + carrageenan + pectin) show the t_{90} value at less than 10 min when compared to all. The first-order plots for various fast dissolving DZOTFs were found to be linear with correlation coefficient (r^2) values in the range of 0.890 to 0.996, indicates that the drug release from the films was found to be concentration dependent. Among all the formulations, F12 with first order rate constant (K_1) of 0.249 min^{-1} and first order correlation coefficient (r^2) of 0.996 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 kinetic parameters are given in (Table 5).

Table 5: In vitro dissolution parameters of DZOTFs

F. Code	Dissolution plots			First order plots	
	t_{50} (min)	t_{90} (min)	DE10 (%)	K_1 (min^{-1})	r^2
F1	> 5	< 15	45.73	0.189	0.949
F2	> 5	< 15	45.60	0.203	0.946
F3	> 5	< 15	41.62	0.189	0.930
F4	> 5	< 15	39.68	0.170	0.931
F5	< 5	< 15	48.39	0.193	0.890
F6	< 5	< 15	51.01	0.187	0.923

F7	< 5	< 15	52.96	0.196	0.919
F8	< 5	< 15	55.18	0.193	0.937
F9	< 5	< 15	58.98	0.214	0.941
F10	< 5	< 15	57.93	0.207	0.949
F11	< 5	< 15	63.74	0.233	0.981
F12	< 2	< 10	66.76	0.249	0.996

Selection of optimized formulation: The formulation F12 with (HPMC15CPS: carrageenan: Pectin in the ratio of 2:1:1 respectively) was found to exhibit the best physicochemical properties of transparency, smooth texture, weight variation 98 ± 0.03 mg, thickness of 0.030 ± 0.01 mm, disintegration time of 11.42 ± 0.17 and 19.23 ± 0.41 by drop and Petri dish methods respectively, passed the test for dispersion, surface pH of 6-7 and drug content of 14.75 ± 0.21 mg/cm². It exhibits the mechanical properties with a moderate tensile strength, value of 2.11 ± 0.12 N/cm², highest % elongation value of 93.15 ± 0.23 %, lowest Young's / Elastic modulus value of 1.42 ± 0.21 N/cm² and highest folding endurance value of 123 ± 0.42 . It also exhibits the lower t₅₀ and t₉₀ values of less 2 min and 10 min when compared to all others and it has a first order rate constant (K₁) of 0.249 min^{-1} and the highest first order r² of 0.996, in vitro dissolution studies. Hence it is considered as an optimized formulation.

Accelerated stability studies of optimized DZOTFs (F12)

Table 6: Results of physicochemical properties of accelerated stability studies of optimized DZOTFs (F12).

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	98 ± 0.03	0.030 ± 0.01	11.42 ± 0.09	19.23 ± 0.41	+	6-7	14.75 ± 0.15
1 st month	Transparent	Smooth	98 ± 0.02	0.033 ± 0.01	11.35 ± 0.22	19.52 ± 0.32	+	6-7	14.43 ± 0.21
2 nd month	Transparent	Smooth	98 ± 0.11	0.034 ± 0.11	11.38 ± 0.14	19.43 ± 0.21	+	6-7	14.32 ± 0.07
3 rd month	Transparent	Smooth	99 ± 0.12	0.035 ± 0.12	11.43 ± 0.15	20.46 ± 0.14	+	6-7	14.20 ± 0.11
6 th month	Transparent	Smooth	99 ± 0.11	0.035 ± 0.11	11.51 ± 0.321	20.44 ± 0.09	+	6-7	14.17 ± 0.06

Table 7: Results of mechanical properties of accelerated stability studies of optimized DZOTFs (F12).

Sample	Tensile strength (N/cm ²)	% Elongation (%)	Young's modulus (N/cm ²)	Folding endurance	% Moisture loss (%)	% Moisture uptake (%)
Initial	2.11 ± 0.09	93.15 ± 0.23	1.42 ± 0.21	123 ± 0.42	2.38 ± 0.31	3.74 ± 0.17
1 st month	2.13 ± 0.11	94.43 ± 0.11	1.34 ± 0.11	122 ± 0.23	2.32 ± 0.21	3.85 ± 0.09
2 nd month	2.21 ± 0.12	94.43 ± 0.13	1.31 ± 0.21	122 ± 0.21	2.30 ± 0.11	3.92 ± 0.12
3 rd month	2.24 ± 0.08	94.43 ± 0.21	1.29 ± 0.07	121 ± 0.16	2.28 ± 0.09	3.95 ± 0.17
6 th month	2.26 ± 0.13	94.43 ± 0.07	1.28 ± 0.12	121 ± 0.11	2.25 ± 0.14	4.01 ± 0.12

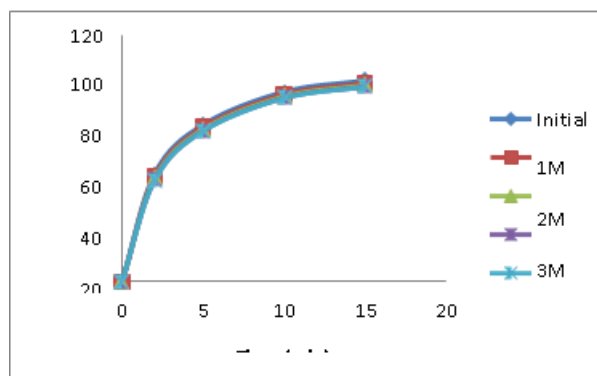


Fig. 7: In vitro dissolution plots of accelerated stability samples of optimized DZOTFs (F12).

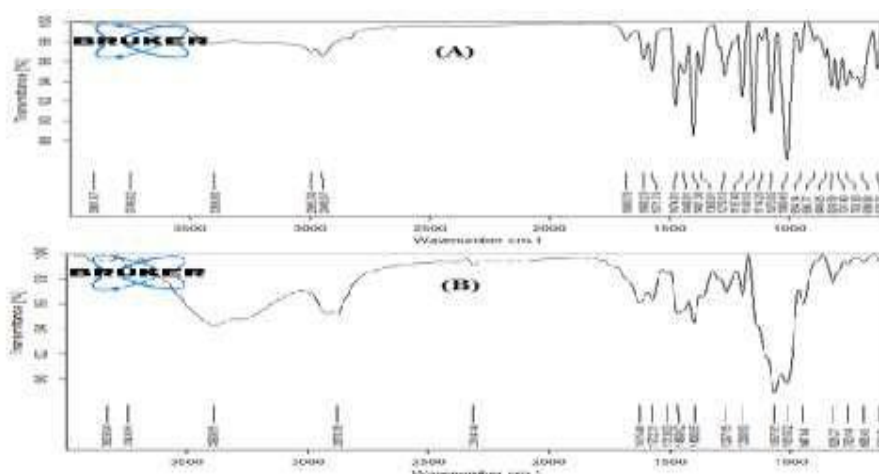


Fig. 8: Comparative FT-IR spectra of A. DZ (pure drug) and B. 6M-accelerated stability sample of optimized DZOTFs (F12).

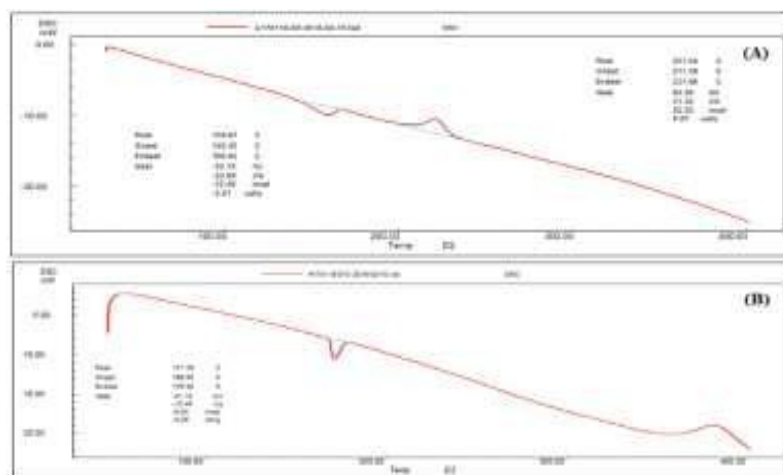


Fig. 9: Comparative DSC thermograms of A. DZ (pure drug) and B. 6M- accelerated stability sample of optimized DZOTFs (F12).

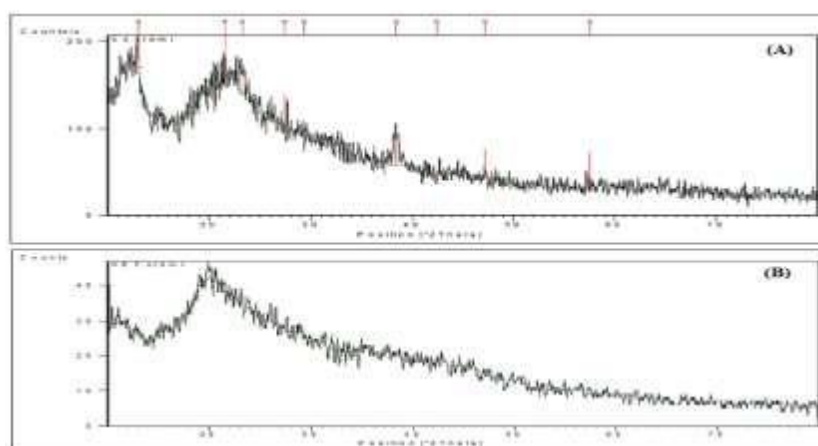


Fig.10: Comparative XRD diffractograms of A. DZ (pure drug) and B. 6M- accelerated stability sample of optimized DZOTFs (F12).

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 DZOTFs (F12). The Results of physicochemical properties of accelerated stability studies of optimized DZOTFs (F12) was tabulated in (Table6). The results of mechanical properties of accelerated stability studies of optimized DZOTFs (F12) were tabulated in (Table7). The in vitro dissolution plots of accelerated stability samples of optimized DZOTFs (F12) were shown in (Fig.7). Comparative FT-IR spectra of DZ and 6M-accelerated sample of optimized DZOTFs (F12) in (Fig.8), reveals the DZ and the polymers used in the study are compatible. Comparative DSC thermograms of DZ and 6M-accelerated sample of optimized DZOTFs (F12) (Fig.9), reveals that the exothermic peak for DZ and the sample obtained are 159.67°C and 171.59°C respectively, so the interaction between the drug and excipients was

not observed. The comparative XRD diffractograms of DZ and 6M-accelerated sample of optimized DZOTFs (F12) (Fig.10) showed a decrease in the peak intensity due to change in the crystallinity of drug, which may lead to enhanced dissolution rate of drug from the prepared film.^[23] Hence, the optimized formulation DZOTFs (F12) passes the test for stability as per ICH guidelines.

CONCLUSION

Fast dissolving DZ 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 F12 within 10 min of time which is advantageous for fast absorption of the drug through buccal route. The combination of synthetic polymer (HPMC15CPS) and natural polymers (carrageenan and pectin) had a significant effect on the film forming properties and enhancing the dissolution efficiency of the poorly soluble drug like dexlansoprazole meant for buccal absorption.^{24, 25} In the present study the formulation F12, with (HPMC15CPS: carrageenan: pectin in the ratio of 2:1:1 respectively) is selected as the optimized one. The optimized formulation DZOTFs (F12) passes the test for stability as per ICH guidelines. Hence, fast dissolving DZOTFs were formulated, evaluated and found to be suitable for effective and well-tolerated treatment option in the management of acid-related disorders.

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