Original Article
DOI: https://doi.org/10.70749/ijbr.v3i8.2062

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://ijbr.com.pk
ISSN: 2960-2793/ 2960-2807

A Novel Combination of Esomeprazole and Domperidone in a Unit-dose for Potential Application in Gastroesophageal Reflux Disease

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ARTICLE INFO

Keywords: Solvent casting method, Fast dissolving film, Polysaccharide, Polymer, Mouth dissolving film, Immediate release.

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Declaration
Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 05-06-2025 Revised: 18-07-2025
Accepted: 29-07-2025 Published: 10-08-2025

ABSTRACT

The current study is designed to develop an orodispersible film (ODF) incorporating esomeprazole (EOZ) and domperidone (DPD) using synthetic (polyvinyl alcohol), semisynthetic (hydroxypropylmethyl cellulose, HPMC; hydroxylethyl cellulose, HEC), and natural (xanthan gum) polymers. The solvent casting method was employed to formulate the ODF, which resulted in a homogenous, transparent, and smooth surface film. The prepared formulations were evaluated through Fourier Transform Infrared (FTIR) spectroscopy, mechanical strength, physico-chemical properties, and an *in vitro* drug release study. The disintegration time, surface pH, tensile strength, percentage elongation, moisture uptake, moisture loss, and loss on drying were observed in the range between 29-53 sec., 5.89-6.63, 13-22 N, 5.3-7.3%, 2.1-3.9%, 0.9-2.2%, 0.04-0.07%, respectively. Maximum concentration of both drugs was released from all the ODF formulations within 5 min during the *in vitro* drug release study performed in simulated saliva of pH 6.8. During the accelerated stability study, the values of all essential parameters were observed within the standard range. Hence, the combination of EOZ and DPD in an ODF could be a novel approach for the potential treatment of gastroesophageal reflux disease (GERD).

INTRODUCTION

Oral route is still considered a preferred and the safest route for the administration of many drug delivery systems due to patient compliance, acceptability, non-invasiveness, adaptability, and simplicity (Homayun et al., 2019). Although the oral route shows some issues for the nauseous, noncompliant, pediatric, and geriatric populations. Many substitutes to oral routes have been established for this specific group of population group. Among these alternatives, orally disintegrating delivery systems, i.e., oral disintegrating tablets (ODTs) and orodispersible films (ODFs), are the most favored routes to administer the drugs (Liang et al., 2001). However, ODFs have given preference due to the choking hazard. The important features of ODFs are convenient and accurate dosing, rapid onset of action, convenient in swallowing for pediatric, geriatric, and dysphasic patients, better bioavailability, and stability (Irfan et al., 2016).

Preparation of ODFs by using the hydrophilic polymers not only increased the mechanical strength of the film but also ensured the fast release of the drug due to increased disintegration. Incorporation of a large range of active ingredients, ODFs exhibit different pharmacological actions, e.g., anti-hypertensive, gastroesophageal reflux disease (GERD), anti-epileptic, anti-asthmatic, anti-diarrheal, expectorant, vasodilators, muscle relaxant, pain relief, anti-depressants, and anti-tussives.

Natural, synthetic, and semisynthetic polymers are being used for developing different drug delivery systeems (Feroze et al., 2025; Hussain et al., 2024; Englert et al., 2018). ODFs are also prepared by using natural, semisynthetic, and synthetic polymers depending on the nature of drugs and other physical and chemical parameters (Pacheco et al., 2021). HPMC and HEC are excellent film-forming polymers that are used in ODF and available in different grades. Besides these polymers, natural polymers are also used in developing ODF due to their biocompatibility.

ODFs are prepared through the solvent casting method, hot melt extrusion method, spray method, electrospinning, etc. (Irfan et al., 2016; He et al., 2021). Among these methods, the solvent casting technique is usually

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employed in which the drug, polymer, and other ingredients are mixed in water and then poured on a petri dish to make a thin film.

GERD is a common disease normally observed in young individuals and both genders, which is being treated with different sets of drugs. Among such drugs, domperidone (DPD) and esomeprazole (EOZ) are extensively used to treat this disease. The DPD is a peripheral dopamine 2-receptor antagonist used to regulate the GI motility and exhibit some regulatory effects on the motor action of the esophagus. Due to the blockage of dopamine receptors, the antiemetic activity of DPD can be observed. DPD also gives short-term relief from symptoms of dyspepsia or the gastroesophageal reflux, vomiting, and nausea related to chemotherapy and GI and emetic side effects for drugs of parkinson's disease. The EOZ belongs to an important class, i.e., proton pump inhibitors, and is used to treat gastric ulcer, Zollinger-Ellison syndrome, and GERD.

This study aims to use both EOZ and DPD in ODF using synthetic, semisynthetic, and natural polymers. Such combinations have not yet been explored and are being reported first time in ODFs. Moreover, the use of different polymers for the administration of this combination of drugs broadens the horizon and applications of both the drugs and different types of polymers. The prepared ODFs will be characterized through different physico-chemical parameters, mechanical properties, *in vitro* drug release studies, and accelerated stability studies.

MATERIALS AND METHODS

Material

Hydroxypropyl methyl cellulose (HPMC) E5 and E50, polyvinyl alcohol (PVA), and hydroxyethyl cellulose (HEC) were obtained from Sigma-Aldrich, Germany. Xanthan gum, croscarmellose sodium, aspartame, and polyethylene glycol (PEG) 400 were provided by Riedel-de Haen, Germany. Esomeprazole (EOZ) and domperidone (DPD) were gifted by Trison Research Laboratories Pvt. Ltd., Sargodha, Pakistan. The whole study was carried out using distilled water (DW).

Preparation of ODF

Five different formulations of the ODF were prepared using synthetic, semisynthetic, and natural polymers. A combination of two drugs, i.e., EOZ and DPD, was used in each of the five formulations. The composition of each formulation is depicted in Table 1. In a typical formulation, the polymer was dissolved in a sufficient amount of DW and stirred continuously for 30 min. at 50 °C. After 30 min., the polymer solution was allowed to cool at room temperature, followed by the addition of EOZ, DPD, and PEG 400 and mixed for 30 min. at room temperature. Other excipients like croscarmellose sodium and aspartame were added to the above mixture and stirred continuously for 2 h at 50 °C. Air bubbles present in the mixture were removed through sonication for 10 min. The bubble-free mixture was poured into a specially designed plastic mold having dimensions of 2 × 2 cm. After drying, the film was detached from the mold and kept in a closed container until further use.

Table 1

Composition (mg) of Different ODF Formulations

Ingredients	F1	F2	F3	F4	F5
Esomeprazole	40	40	40	40	40
Domperidone	10	10	10	10	10
HPMC E5	60	-	-	-	-
HPMC E50	-	35	-	-	-
HEC	-	-	40	-	-
PVA	-	-		50	-
Xanthan gum	-	-	-	-	25
Croscarmellose sodium	20	25	25	30	25
Aspartame	40	40	40	40	40
PEG 400	20	20	20	20	35
Total	190	170	175	190	175

Drug-Excipient Interaction Study

FTIR Study

FTIR spectroscopy was carried out to examine any possible drug-excipient interaction. It was performed by using the KBr pellet technique (Khatoon et al., 2025). In this analysis, drugs, different excipients, and all five formulations were co-ground separately with KBr. FTIR spectra were recorded from 4000-400 cm^{-1} using an FTIR spectrophotometer (IR Prestige-21, Shimadzu, Japan).

Characterization of ODF

Film Thickness and Weight Variation

The thickness of all films was measured at three different points by using the micrometer screw gauge, and the average of the values was reported. Five samples from each formulation were accurately weighed, and the average was calculated. The weight variation was determined from the difference between the average values and the individual weight of each film. Weight variation and film thickness were performed in triplicate, and then the average values of these parameters were reported along with the standard deviation (SD).

Disintegration Time of ODF

Disintegration time of the ODF was determined through two different methods as reported in the literature (Irfan et al., 2016; Sheikh et al., 2021). Each method was performed thrice, and the average values of the disintegration time were reported with SD.

Drop method: ODF was placed in a beaker, followed by the addition of one drop (0.2 mL) of DW on the ODF. The time required for the disintegration of the film was noted.

Petri dish method: A Clean glass petri dish was used to place the film, and then DW (2 mL) was added. The petri dish was allowed to shake gently until the film disintegrated.

Surface pH of the Film

The pH of the surface of the ODF was examined by adding DW (5 µL) on its surface. Then touched the electrode to the surface of the film and noted the pH value. Surface pH of all the film formulations was measured thrice, and their means were reported with SD.

Content Uniformity

The content uniformity was examined by using the assay method as described in the United States Pharmacopeia.

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Standard analytical techniques were used to determine the content uniformity of twenty films from each sample. Films from each formulation were mixed in methanol (50 mL) for 1 h to extract the drug, followed by filtration. The filtrate was suitably diluted and scanned through a UV-Vis spectrophotometer at 299 nm and 287 nm for EOZ and DPD, respectively. The drug content in each formulation was calculated using the calibration curve method. According to USP 27, content uniformity must lie between 85-115% with SD ≤ 6%.

Moisture Uptake

Moisture uptake was determined by placing the films in a region of high relative humidity (RH), i.e., 75% for seven days at 25 °C (Sheikh et al., 2021). Increase in the weight of ODF indicated the moisture uptake and was calculated using Eq. (1).

$$M_u = \frac{W_f - W_i}{W_i} \times 100 \quad (1)$$

Where, M_u indicates the moisture uptake in percentage, W_i and W_f are the initial and final weight of the film before placing the film in a closed chamber, and after removal from the chamber after seven days.

Moisture Loss

Moisture loss shows the extent of the hygroscopic behavior of the film. This property is measured by placing the weighed film in the desiccator. The film was removed from the desiccator after three days, and moisture loss was estimated by the following Eq. (2).

$$M_l = \frac{W_i - W_f}{W_i} \times 100 \quad (2)$$

Where, M_l shows percentage moisture loss, W_f indicates final weight, while W_i is the initial weight of film.

Loss on Drying

Loss on drying (LOD) was measured by recording the weight of the film and then placing the film in a hot air oven for 1 h at 105 °C. After removal from the oven, the weight of the film was again noted, and LOD was calculated using Eq. (3).

$$LOD = \frac{W_f - W_i}{W_f} \times 100 \quad (3)$$

Where, W_i and W_f are the initial and final weights of the film, respectively.

Mechanical Properties of the Film

Tensile Strength

The maximum force applied to the film to break is the tensile strength of the film. Generally, this test is conducted to ensure mechanical strength for the film. Tensile strength was calculated from Eq. (4).

$$TS = \frac{L}{T \times W_d} \quad (4)$$

Where, TS shows tensile strength, L indicates load in Newton, T is film thickness, and W_d is the width of the film.

Percent Elongation

The strain is the stretching ability of the film on subjected the stress. It is the ratio of the change in length of the film to the initial length of the film. Percentage elongation is an estimation of the amount of added plasticizer in the film. Percent elongation is measured through Eq. (5).

$$E = \frac{L_f}{L_i} \times 100 \quad (5)$$

Where, E is the percentage elongation of the film, L_f depicts the change in the length of the strip, and L_i shows its initial length.

Folding Endurance

Folding endurance is another parameter to evaluate the mechanical property, i.e., the fragility of the film, and is observed by folding the film repeatedly at the same point until the film breaks. The folding endurance is dependent on the concentration of the plasticizer. Therefore, to reduce the brittleness and fragility, the concentration of the plasticizer can be adjusted. Hence, increased the value of folding endurance.

Visual Inspection

Visual inspection of the film was carried out to check the transparency, color, and homogeneity.

In Vitro Drug Release Study

In vitro drug release was performed through the USP dissolution apparatus II by using simulated saliva of pH 6.8 as a dissolution medium kept at 37 °C and adjusting the paddle speed at 100 rpm (Sheikh et al., 2021). Simulated saliva with pH 6.8 was formulated by using NaCl (40 mM), KH_2PO_4 (12 mM), $CaCl_2$ (1.5 mM), and then pH was adjusted to 6.8 using NaOH solution.

Aliquot (5 mL) was withdrawn at the predetermined time intervals (0.5, 1, 2, 3, 4, 5, 10, and 15 min) and replenished with fresh simulated saliva. The sample was filtered, diluted (if needed), and evaluated through the UV-Visible spectrophotometer at 299 nm and 287 nm for EOZ and DPD, respectively.

Drug Release Kinetics and Mechanism

Drug release data were used to evaluate the drug release kinetics models. Zero order, first order, Higuchi, and Hixson-Crowell models were applied to EOZ and DPD release data using Eqs. (6), (7), (8), and (9), respectively (Gibaldi et al., 1967; Wagner et al., 1969; Higuchi et al., 1961; Hixson et al., 1931; Korsmeyer et al., 1983; Ritger et al., 1987). The coefficient of determination (R^2) was calculated, and the kinetics model having the highest value (~1) was considered the most appropriate and best fitted model.

$$Q_t = K_0 t \quad (6)$$

In Eq. (6), K_0 and Q_t are the zero-order rate constant and the amount of drug released, respectively, at time t.

$$\log Q = \log Q_0 - \left(\frac{K_1 t}{2.303}\right) \quad (7)$$

In the above Eq. (7), Q is the remaining drug in the formulation after time t, Q_0 is the concentration of drug at time t = 0, and K_1 is the first-order rate constant.

$$Q_t = K_H\left(t^{1/2}\right) \quad (8)$$

In the Higuchi model (Eq. (8)), K_H is the Higuchi rate constant, and Q_t is the amount of drug released at time t.

$$Q_0^{1/3} - Q_t^{1/3} = -K_{HC} \quad (9)$$

In Eq. (9), K_{HC} is the Hixson-Crowell rate constant, Q_0 and Q_t are the amount of drug present in the formulation at t = 0 and the amount of drug released at time t, respectively.

For the determination of drug release mechanism, the Korsmeyer-Peppas model was used as mentioned in Eq. (10).

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$$\frac{M_t}{M_\infty} = k_p t^n \quad (10)$$

where, M_t/M_∞ indicates the fraction of drug released in time t, k_p is the Korsmeyer-Peppas model constant, and n is the diffusion coefficient. The value of n indicates the drug release mechanism. Drug release is considered Fickian diffusion, non-Fickian, and supercase-II transport mechanism when the value of n is < 0.45, between 0.45 and 0.89, and greater than 0.89, respectively.

Stability Study

A stability study was conducted following the guidelines of the International Council for Harmonization (ICH) as mentioned in their protocol CPMP/ICH/2736/99. An accelerated stability study was performed to analyze the quality of the films over a long duration. All formulations of these ODFs were examined for the accelerated stability study at 40 ± 2 °C and 75 ± 5% RH for six months (Sheikh et al., 2022). For the same period and comparison purposes, ODFs were also placed at ambient temperature for the same period as of accelerated stability study. After predetermined time intervals (1, 2, 3, and 6 months), films were analyzed for mechanical and physico-chemical properties, disintegration time, pH, loss on drying, etc.

RESULTS

Preparation of ODF

The ODF was formulated with the help of aqueous solution/dispersion of natural, synthetic, and semisynthetic polymers incorporated with the solubilized form of the drugs.

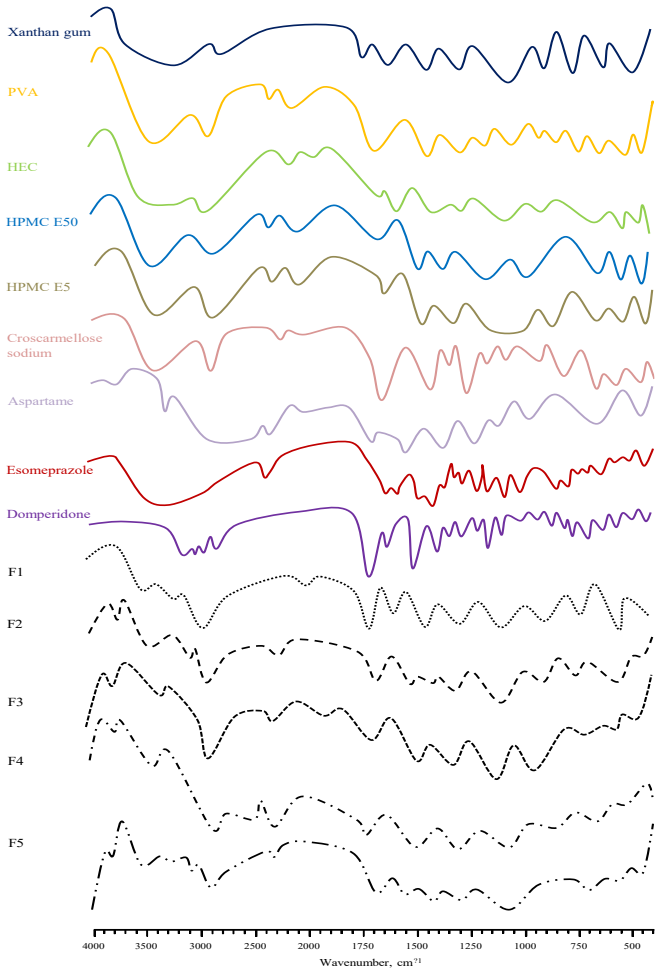
Drug Excipient Compatibility Study

FTIR Study

FTIR spectra of drugs, polymers, excipients, and different formulations are shown in Figure 1. In the FTIR spectrum of EOZ, some specific absorption bands appeared around 3200 cm^{-1} and 1530 cm^{-1} for C=N stretching, and 1080 cm^{-1} for S=O functional group(Jain et al., 2013). FTIR spectrum of DPD exhibited the characteristic bands at 1730, 1495, 1398, and 1163 cm^{-1} due to stretching vibration bands of some important functional groups, i.e., C=O, N-H, C-N, and C-O, respectively (Nagpal et al., 2016). The FTIR spectrum of the xanthan gum is shown in Figure 1, which reveals the presence of absorption bands around 3310 cm^{-1} for -OH, 1622 cm^{-1} for -C-O, 1739 cm^{-1} for -COOH, and 2930 cm^{-1} for -C-H. The FTIR spectra of both HPMC E5 and E50 are shown in Figure 1 and represent the characteristic bands of -OH between 3500 to 3400 cm^{-1}, $-CH_2$ between 2850 to 2950 cm^{-1}, -CO between 1670 to 1620 cm^{-1}, methoxy group between 1510-1440 cm^{-1}, and -C-O-C between 1320 to 1260 cm^{-1}. The specific and characteristic bands of HEC also appeared as described for HPMC. Absorption bands in FTIR of PVA are observed between 3550-3350 cm^{-1} for -OH stretching, at 2920 cm^{-1} for alkyl stretching, 1430 cm^{-1} for -CH bending, 1095 cm^{-1} for -CO deformation, and 920 cm^{-1} for out-of-plane hydrogen bonding. FTIR spectra of aspartame and croscarmellose sodium are similar to those already reported literature. The characteristic bands of each ingredient can be seen in the FTIR spectrum of their respective formulations, i.e., F1, F2, F3, F4, and F5.

Figure 1

FTIR Spectra of Drugs (esomeprazole and domperidone), Excipients (different polymers, croscarmellose sodium, and aspartame), and Orodispersible Film Formulations (F1, F2, F3, F4, and F5).



Characterization of ODF

Results of different parameters of all ODFs are shown in Table 2 and Table 3. The weight and thickness of all ODFs are in the range from 170-194 mg and 166-198 µm, respectively. Disintegration times of all formulations are < 1 min. The pH of the surface of film formulation ranges from 5.89 to 6.63. The values for percent elongation, tensile strength, moisture uptake, folding endurance, loss on drying, moisture loss, and content uniformity of all the formulations are given in Table 3.

Table 2

Physicochemical Parameters of the Prepared ODF

Parameters	F1	F2	F3	F4	F5
Weight (mg)	193	174	176	194	170
Thickness (µm)	173	191	166	198	186
Disintegration time (Drop method) (s)	53±2.1	50±2.2	38±1.5	43±3.1	33±2.1
Disintegration time (Plate method) (s)	41±1.8	47±1.1	29±2.2	36±2.1	29±2.3
pH of film surface	6.51±0.13	5.94±0.16	5.89±0.19	6.63±0.15	6.24±0.18

All values are expressed as mean ± SD.

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Table 3

Different Mechanical Parameters of All Odf Formulations

Parameters		F1	F2	F3	F4	F5
Tensile strength (N)		13 ± 1	22 ± 2	19 ± 1	17 ± 3	16 ± 2
Percent elongation (%)		5.3 ± 0.8	6.2 ± 0.9	6.7 ± 1.1	7.3 ± 0.9	6.7 ± 0.6
Folding endurance		More than 150 times				
Content uniformity (%)	EOZ	98	97	99	98	97
	DPD	99	98	97	98	97
Moisture uptake (%)		2.1 ± 0.3	3.1 ± 0.6	2.1 ± 0.3	3.9 ± 0.5	3.2 ± 0.4
Moisture loss (%)		0.9 ± 0.1	1.1 ± 0.3	1.6 ± 0.9	1.5 ± 0.3	2.2 ± 0.4
Loss on drying (%)		0.07±0.01	0.06±0.02	0.08±0.02	0.05±0.03	0.04±0.02

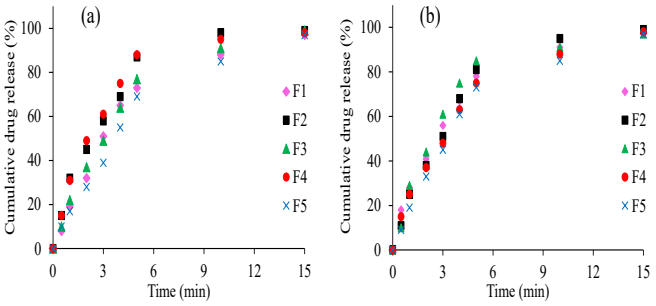
EOZ: Esomeprazole, DPD: Domperidone. All values are expressed as mean ± SD.

Drug Release Study

The drug release study for EOZ and DPD has been shown in Figures 2a and 2b, respectively. It can be observed that approximately 80% of the drug was released within 10 min. from all formulations.

Figure 2

Drug Release Study of EOZ (a) and DPD (b) from Different Formulations at Ph 6.8.



Drug Release Kinetics and Mechanism

The values of different drug release kinetic models for EOZ and DPD are expressed in Table 4. Based on the highest value of the regression coefficient (R^2), it was observed that both drugs followed the first-order release kinetics. Similarly, the value of diffusion coefficient (n) lies between 0.45-0.89, which indicates that both drugs followed the non-Fickian diffusion

Table 4

Esomeprazole and Domperidone Release Kinetics Models of all ODF Formulations.

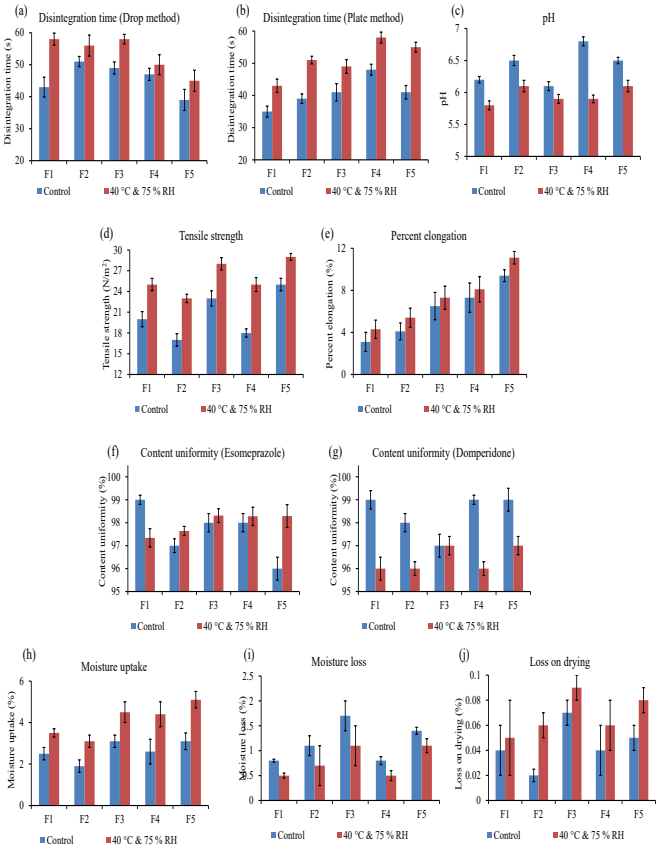
Models	Parameters	Esomeprazole	Domperidone
		F3	F3
Zero order	R^2	0.7532	0.5761
	K_0	11.588	12.496
First order	R^2	0.9924	0.9884
	K_1	0.250	0.322
Higuchi	R^2	0.9520	0.9274
	K_H	29.577	32.619
Hixson-Crowell	R^2	0.9907	0.9867
	K_{HC}	0.071	0.092
Korsmeyer-Peppas	R^2	0.9608	0.9679
	K_{KP}	26.273	43.220
	n	0.573	0.566

Stability study

Results of the accelerated stability study are depicted in Figure 3, showing the results of different physico-chemical parameters and mechanical properties after 6 months.

Figure 3

Results of the disintegration time, pH, tensile strength, percent elongation, content uniformity, moisture uptake, moisture loss, and loss on drying of formulations F1, F2, F3, F4, and F5 placed at ambient temperature (control) and accelerated temperature and relative humidity, i.e., 40 °C and 75% for six months.



DISCUSSION

FTIR spectroscopy was used to analyze the compatibility or the possible interaction among the drugs, polymers, and other excipients used for the formulation design of ODF. In the FTIR spectra of all five formulations, the characteristic bands of both EOZ and DPD appeared at their respective positions without any significant shifting of these bands. Therefore, it can be concluded that all ingredients of the formulations are compatible with each other and free from any significant physical or chemical interaction (Sheikh et al., 2020). The disintegration time was recorded through the plate and drop method. The values of disintegration time from both methods are less than 1 min. that are well below the upper limit, i.e., 3 min. Moreover, the values of disintegration time measured through the plate method were lower as compared to the drop method, which may be associated with the high surface/contact area of the film with the disintegration solvent (Irfan et al., 2016). The appearance of the film was smooth and flexible with homogeneous distribution of all the ingredients. The pH of the film is close to neutral, which is acceptable for ODFs as the acidic or basic pH irritates the mucous membrane of

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the buccal cavity. The tensile strength and percentage elongation of the ODFs indicated a stable and good mechanical strength that withstands the high shear force during transportation. A reasonable moisture is retained within the film as revealed through moisture uptake, moisture loss, and loss on drying study, which prevents the formulation from brittleness, crumbliness, and dryness. Maximum drugs were released within 5 min of the start of the dissolution study at the pH mimicking the saliva, i.e., 6.8. The fast release of the drugs in the buccal cavity is important for the absorption of the drug from the oral mucosa. Hence, the bioavailability of the drugs may be enhanced through the ODF formulations. The drug release kinetics models indicated that both drugs followed the first-order release kinetics and non-Fickian diffusion mechanism as the value of *n* is greater than 0.45. The result of accelerated stability studies indicated that the values of all essential parameters remained within the standard range (Swain et al., 2015).

CONCLUSION

The ODFs were successfully prepared through the solvent casting method. The effect of synthetic, semisynthetic, and natural polymers on the formation of ODF and the release of EOZ and DPD was evaluated. The ODF prepared with HEC exhibited better results than the formulations prepared with other polymers in terms of tensile strength, percentage elongation, and folding endurance. The HEC-based formulation has shown less disintegration time as compared to other formulations. Therefore, the formulation prepared with HEC is better than other formulations. However, the in vivo study is recommended to ascertain the efficiency of these ODF formulations, assess the enhanced bioavailability of EOZ and DPD, and effectiveness in diseases, especially GERD.

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