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Orodispersible Film of Letrozole for Enhancing Compliance in Breast Cancer Treatment

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ABSTRACT

***Background**: Breast cancer is a leading cause of morbidity and mortality in women worldwide, with adherence to long-term endocrine therapy proving to be a major clinical challenge. Letrozole (LTZ), a third-generation aromatase inhibitor, is widely used in hormone receptor-sensitive breast cancer; however, its conventional oral tablet form often leads to poor compliance, especially in elderly and dysphagic patients. Objective: The current study aimed to develop and evaluate a patient friendly orodispersible film (ODF) of LTZ to enhance convenience, acceptability, and therapeutic adherence. Methods: LTZ-ODFs were formulated by solvent casting method using hydroxypropyl methylcellulose (HPMC E5) as a film-forming polymer and sodium starch glycolate (SSG) as superdisintegrant and the impact of varying amount of these excipients was evaluated on physicochemical properties and dissolution rate of LTZ. Various formulations (F1-F10) were prepared, the optimized formulation (F3) presented uniform thickness of 0.087 ± 0.013 mm, neutral surface pH (6.9 ± 0.4), excellent folding endurance, and rapid disintegration (14 ± 2 s). Results: In vitro dissolution studies demonstrated more than 95% drug release within 5 min, indicating rapid onset and effective drug dispersion. FTIR spectra confirmed drug excipient compatibility, and stability testing exhibited no significant changes under the accelerated conditions. Conclusion: The developed LTZ-ODF thus may represent a promising alternative delivery system offering improved compliance and enhanced therapeutic efficacy for breast cancer management.*

Keywords
Letrozole, Orodispersible film, Polymers, Breast cancer, Patient compliance

INTRODUCTION

Breast cancer is the leading cause of cancer-related deaths among women and remains the most frequently diagnosed malignancy among this population. The World Health Organization (WHO) reported that 2.3 million women were diagnosed with breast cancer, and approximately, 670,000 deaths were reported. Among Asia, Pakistan bears the greatest burden of the cancer, where 90,000 new cases are reported yearly (1). Chemotherapy, surgery, and radiotherapy, being the traditional cancer therapy methods, are associated with severe side effects, such as high recurrence rates, complications, and low patient satisfaction (2). Furthermore, these therapies often do not precisely target cancer cells, thus lead to dose escalation and non-adherence by the patients. The lingual route of drug administration offers many advantages. It allows patients to take their medication easily, without needing help or water, which makes it especially convenient and safe. Solid dosage forms designed for this route can precisely deliver the required dose while staying stable under standard conditions (3). Nevertheless, swallowing traditional tablets or capsules can be difficult for some patients particularly children, older adults, and those with throat problems or dysphagia who often worry about choking or discomfort during ingestion (4). To address these challenges, scientists and pharmaceutical companies have developed rapidly dispersible drug delivery systems. These innovative formulations use techniques like wet granulation, direct compression, or lyophilization to produce drugs that dissolve quickly in the mouth. By using special ingredients that promote fast disintegration, these systems permit the drug to disperse immediately without the need for water. Thanks to their ease of use and better patient acceptance, such formulations are becoming increasingly popular in modern drug delivery (5).

Oral drug delivery via thin films is considered a superior alternative to conventional dosage forms, as it eliminates common issues such as choking and swallowing difficulties. Additionally, these films disintegrate rapidly within seconds, ensuring quick and convenient drug administration. Moreover, the challenges related to enzyme activity and variations in stomach pH, which can interfere with drug absorption and metabolism, can be overcome by formulating rapidly dispersible films that allow for pre-gastric absorption (6). In recent decades, such challenges have often been addressed by administering medications through parenteral routes. However, this approach is associated with poor patient compliance. Consequently, pharmaceutical scientists have increasingly focused on developing novel, innovative, and patient-friendly dosage forms to improve acceptability and therapeutic outcomes (7, 8). The per-oral rapid dissolving composite is placed onto the surface of the tongue, where it stays for

a while before dissolving or dispersing to release the active pharmaceutical ingredients. This innovative approach offers several advantages that align with modern pharmaceutical industry requirements, including enhanced stability, improved bioavailability and solubility profiles, and an extended biological half-life of the active drug.

Hydroxypropyl methylcellulose (HPMC) is a highly versatile, viscoelastic polymer widely utilized in contemporary pharmaceutical formulation and drug delivery systems. Its multifunctional properties make it an indispensable excipient in dosage form design. HPMC servers as a film-forming, thickening, emulsifying, dispersing, and adhesive agent, while also acting as a prospective colloid that enhances the stability and performance of various formulations (9). In oral dosage forms, HPMC is commonly employed as a coating agent, binder, and matrix-forming polymer for sustained or controlled drug release. During granulation processes, both wet and dry, it is typically used at concentration of 2-5% w/w as a binder to ensure uniformity and mechanical integrity. For controlled release tablets and capsules, higher viscosity grades of HPMC are incorporated at levels ranging from 10-80% w/w to modulate drug release kinetics. In film-coated tablets, concentration of 2-20% w/w is applied to achieve smooth and protective coatings. Beyond its role in solid dosage form, HPMC also functions as a thickening and suspending agent in liquid and semisolid dosage formulations. At concentrations of 0.45–1.0% w/w, it is added to provide viscosity and acts as a vehicle in artificial tear solutions and eye drops. Furthermore, it is valuable in emulsifying, stabilizing, and suspending topical ointments and gels (10).

Letrozole (LTZ) is a highly potent third-generation aromatase inhibitor that can suppress peripheral aromatase activity by more than 98%, thereby substantially lowering circulating estrogen levels in postmenopausal women (11). It acts by blocking the electron transferring chain plus active portion of CYP19A1. This competitive inhibition prevents the conversion of androgens into estrogens, resulting in a reduction in uterine weight and an increase in luteinizing hormone levels. In postmenopausal women, aromatase activity leads to elevated estrogen production, making its inhibition a key therapeutic strategy.

Aromatase, a key enzyme in the biosynthesis of estrogens, catalyses the conversion of androgens to estrogens and remain active even after menopause. Unfortunately, this peripheral aromatization becomes the primary source of systemic estrogens in postmenopausal women, thus causing proliferation of estrogen-dependent tumor. Thus, effective inhibition of aromatase activity mitigates estrogen production, thereby tempting regression of such hormone-dependent malignancies. In this regard, aromatase inhibitors of third generation possess no prominent action on levels of thyroxin, cortisol and aldosterone. As dosage form, it is commercially available as a 2.5 mg oral tablet under the brand Femara®. Nevertheless, many patients, especially the elderly or those with limited mobility, may struggle to swallow traditional solid dosage forms, which can adversely affect adherence to long-term endocrine therapy (12). In addition, patients frequently experience adverse effects such as constipation, diarrhea, fever, and fatigue, which can significantly compromise adherence to therapy. To address this limitation, an oro-dispersible thin film formulation of LTZ can be a more patient-friendly alternative. This dosage form aims to improve compliance and ease of administration in individuals undergoing extended therapy for hormone receptor-positive postmenopausal breast cancer. Another advantage of the oro-dispersible thin film is its rapidly dissolving ability in saliva which allows the drug to reach systemic circulation faster through pre-gastric absorption in the oral mucosa (13). Moreover, the administration of multiple films can be combined to provide flexible and individualized dosing when required. To accomplish this objective, HPMC was selected as the film-forming polymer, while sodium starch glycolate (SSG) was incorporated as a superdisintegrant. The influence of polymer concentration, drug loading, and superdisintegrant level on the performance of the developed orodispersible films (ODF) was systematically evaluated.

MATERIALS AND METHODS

LTZ was gifted by Lianyungang Guike Pharmaceutical Co. Ltd, China. 99% Methanol was acquired from Daejung chemicals (Daejung chemicals, Korea). Citric acid (analytical grade) was sourced from Merck (Darmstadt, Germany). Sodium starch glycolate was purchased from Sigma-Aldrich (USA). HPMC E5 grade was obtained from Dow Chemical Co. (Midland, MI, USA). Aspartame (analytical grade) was procured from Sigma-Aldrich (St. Louis, MO, USA). Deionied/distilled water of laboratory grade was used for all formulation and analyses.

Optimizing film preparation

Ten formulations of LTZ oral films (F1-F10) were prepared by the solvent casting technique, employing varying concentrations of HPMC E5 as the film-forming polymer, LTZ, and sodium starch glycolate (SSG), as detailed in Table 1. All components were accurately weighed under controlled laboratory conditions to prevent contamination. The polymer was initially dissolved in distilled water with the aid of sonication, followed by the incorporation of a plasticizer. The resulting dispersion was subjected to magnetic stirring at 700 rpm for 45 minutes to ensure homogeneity. Subsequently, the remaining excipients, including the flavoring agent and citric acid, were incorporated and stirred under identical conditions for an additional 30 minutes. The prepared mixture was then allowed to stand for 90 minutes to facilitate the removal of entrapped air bubbles. In parallel, the drug solution was prepared by dissolving LTZ in methanol within a covered beaker, followed by sonication using an ultrasonic bath (E-30H Elma, Elmasonic, Germany) for 1 minute at 50% amplitude. The drug solution was kept undisturbed for 30 minutes to ensure complete dissolution. Thereafter, the organic phase was slowly added to the aqueous phase under continuous stirring for 40 minutes to obtain a uniform mixture. The resulting solution was again kept aside for 1 hour to eliminate residual air bubbles. The degassed solution was cast either directly onto clean Petri dishes or onto plastic film-lined Petri dishes to facilitate film removal. The molds were placed in a hot-air oven (Memmert, Germany) and dried at 28 °C for 24 hours. The dried films were conditioned in a desiccator for 4 hours, carefully peeled off, and examined for surface uniformity and physical integrity. Uniform films were cut into pieces of 4 cm^2 and stored in labeled, airtight zipper pouches at room temperature until further analysis. The prepared LTZ films were subsequently evaluated for their physicochemical characteristics, in vitro drug release behavior, and stability.

Characterization of ODFs of LTZ

The LTZ-loaded thin films were visually examined for their exterior, including their color, surface texture, size, uniformity, transparency and overall homogeneity. Each strip was carefully examined for deficiencies such as air bubbles, surface irregularities, or gritty appearance. Films showing any visible defects or inconsistencies were excluded from subsequent evaluations.

Thickness

For determination of the thickness of formulated strips, a Vernier-calliper was used. For this purpose, the thickness was determined at different sites of the strips to estimate conformity and reproducibility, considering that mean variation in thickness remain below 5% in accordance with established guidelines.

Folding endurance

Folding endurance imitates the capability of a film to withstand repeated folding at the same location without breaking. To determine folding endurance, each strip was repeatedly folded at the same point until rupture occurred. The total number of folds required to break the film was recorded as the folding endurance value.

Tensile Strength

The strip should exhibit adequate tensile strength, high drug release, and good elongation capacity. The mechanical strength of the formulated strips was evaluated using a Chatillon Force Tensile Strength Tester (Ametek, Inc., USA). For this analysis, each film was clamped at both ends and stretched at a constant speed until it broke, and the maximum force required to cause breakage was recorded to determine the tensile strength. The value was estimated by using following formula:

$$Tensile\ Strength = \frac{Load\ at\ failure\ \times 100}{Chip\ thickness\ \times chip\ width}$$

Weight variation

Film samples of 4 cm² from different batches were precisely cut, and their individual weights were determined using an electronic balance (IKA Works, Inc., USA). The variation in film weights was evaluated to assess the uniformity of the formulations and the reproducibility of the preparation method.

Surface pH

The surface pH of the medicated films was determined using a 4 cm² sample placed in a Petri dish. Each film was moistened with 0.5 mL of distilled water and allowed to equilibrate for 30 seconds. The surface pH was then measured by gently placing the electrode of a calibrated pH meter (Mettler Toledo, USA) in contact with the film surface and maintaining contact for 1 minute to ensure stabilization of the reading. The mean value of three independent measurements was recorded as the surface pH of the film.

Fourier Transform Infrared (FTIR) Spectroscopic Analysis

To evaluate potential drug–excipient interactions, Fourier Transform Infrared (FTIR) spectra of the pure drug, individual excipients, their physical mixture, and the formulated films were recorded using an FTIR spectrophotometer (Nicolet 380, Thermo Electron Corporation, USA). The characteristic peaks of the pure drug were compared with those of the excipients and formulations to identify any possible chemical interactions or shifts in functional groups.

Disintegration time

Disintegration time refers to the duration required for a film to break down into smaller fragments upon contact with water. According to the Center for Drug Evaluation and Research (CDER) guidelines, the acceptable disintegration time for orally fast-dissolving dosage forms is 30 seconds or less, a criterion that also applies to rapidly dissolving oral films. Therefore, the disintegration time of the prepared strips was expected to be within 30 seconds to meet the standard requirements for fast-dissolving formulations. The disintegration time of the films was evaluated using two methods as described below:

Beaker Method: Three milliliters of distilled water were placed in a 50 mL beaker maintained at room temperature. A 4 cm² film sample containing 2.5 mg of LTZ was carefully placed in a beaker and stirred using a magnetic stirrer at 100 rpm. The time required for the complete disintegration of the film was recorded visually and noted as the disintegration time.

Swirl Method: In this method, 3 mL of distilled water were added to a Petri dish of 6.5 cm diameter. A 4 cm² film sample was placed in the dish, which was gently swirled at room temperature. The time taken for the film to completely disintegrate in water was measured and recorded as the disintegration time.

Dissolution studies

The in vitro drug release profile of the LTZ films was evaluated using a USP type II (paddle) dissolution apparatus (Pharmatest, Germany). Although dissolution testing is generally performed under sink conditions as recommended in USP <711>, maintaining true sink conditions for highly hydrophobic drugs such as LTZ is difficult because of their extremely low aqueous solubility. For this reason, a reduced dissolution volume of 400 mL phosphate buffer (pH 6.8) was intentionally used. This setup was chosen to better reflect physiologically relevant conditions for orodispersible films. Similar non-sink or reduced-volume approaches have been widely reported in the literature as biorelevant and appropriate for evaluating poorly soluble drugs, even though they do not strictly meet sink condition requirements (14). The paddle rotation speed was set at 75 rpm, and the film samples were securely positioned in the basket to prevent floating. In details, a 4 cm² film strip was placed in the dissolution vessel using a customized stainless-steel mesh holder to prevent floating and ensure uniform exposure of the film surface to the dissolution medium. The use of a film holder ensured reproducible hydrodynamic conditions without restricting film swelling or disintegration. Aliquots of 5 mL were

withdrawn at predetermined time intervals (0, 10, 20, and 45 seconds; and 1, 2, 5, 10, and 30 minutes), followed by the immediate replacement of an equal volume of fresh dissolution medium to maintain sink conditions. The concentration of LTZ in the collected samples was determined spectrophotometrically at the appropriate wavelength using a UV–visible spectrophotometer (UV-1601PC, Shimadzu, Japan). Each dissolution study was conducted in triplicate (n = 3), and results were expressed as mean ± SD.

Stability study

A stability study was conducted to assess the impact of stress conditions on the prepared formulations. Strips (4 cm^2) were stored for three months under various environments: room temperature, 40°C, and 40°C with 75% relative humidity. To evaluate any changes in performance, the drug release rate and disintegration time of the formulations were determined at intervals up to the three-month mark.

Statistical analysis

All studies were executed in triplicate and data was expressed as mean + SD using Graphpad Prism software.

RESULTS

The oral dissolvable LTZ-loaded thin strips were prepared using the solvent casting method, which were optimized through preliminary blank trials. HPMC was selected as the film-forming polymer, and SSG was chosen as the superdisintegrant after evaluating various excipients. Distilled water and methanol were employed as solvents: distilled water was used to dissolve the water-soluble polymer and excipients, while methanol was used to solubilize LTZ. The two solutions were then combined, and the resulting mixture was cast into strips, dried, and carefully removed. A major challenge during development was selecting a suitable casting surface. Strips cast in conventional glass petri dishes adhered strongly to the surface, leading to breakage and poor texture upon peeling. To overcome this, hard plastic sheet pouches were designed and used as the casting mold. This modification enabled easy removal of intact strips, preserving their smooth surface and mechanical integrity. Overall, this approach provided a reliable method for producing oral dissolvable strips with desirable physical and mechanical characteristics.

Physicochemical Parameters

The LTZ-loaded thin-film strips were visually examined to assess their physical characteristics, and the observations are summarized in Table 2. The thickness of each film was measured using a micrometer gauge at five distinct points, one at the center and four at the corners, to ensure uniformity. The results revealed a direct correlation between polymer concentration and film thickness, indicating that increasing the polymer content led to thicker films. The measured thickness values ranged from 0.065 ± 0.012 to 0.133 ± 0.017 mm. The surface pH of the films was found to be within the physiologically acceptable range for oral administration, varying between 6.89 ± 0.1 and 7.0 ± 0.1. These findings confirm that the developed films are unlikely to cause irritation to the oral mucosa. Weight variation analysis further demonstrated uniformity across all batches, reflecting the reproducibility and consistency of the solvent casting process. Mechanical characterization revealed that formulation F3 exhibited the highest folding endurance, signifying superior flexibility and enhanced mechanical strength, likely due to optimal polymer–plasticizer interactions.

In contrast, formulations F5 and F6 showed comparatively lower folding endurance, suggesting reduced mechanical integrity associated with lower polymer concentrations. Overall, all formulations displayed satisfactory mechanical strength and flexibility suitable for oral film applications. Notably, formulation F2 exhibited the highest tensile strength, whereas F5 showed the lowest, reinforcing the influence of polymer concentration on film robustness.

Table 1. Composition of LTZ orodispersible buccal films.

Ingredients (g)*	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
HPMC	0.3	0.5	0.3	0.5	0.15	0.22	0.3	0.3	0.3	0.3
Sodium starch glycolate	-	-	0.07	0.1	0.07	0.07	0.03	0.09	0.07	0.07
LTZ	0.025	0.025	0.025	0.025	0.025	0.025	0.025			

*all prepared solutions contain 0.06g and 0.04g of citric acid, aspartame respectively.

Table 2. Physicochemical attributes of LTZ-loaded Orodispersible film (F1-F10).

Formulation	Colour	Transparency	Thickness, (mm)	Average weight (mg)	Folding endurance	Tensile strength, (N/cm2)	pH
F1	Colourless, uniform	Transparent	0.088±0.013	64.2±0.6	77±0.8	3.21±0.15	7.0 ± 0.2
F2	Clear, uniform	Transparent	0.129±0.020	64.5±0.6	51±0.6	3.92±0.15	6.9 ± 0.3
F3	Whitish	Translucent	0.087±0.013	64.6±1.5	78±1.3	3.14±0.25	6.9 ± 0.4
F4	Whitish	Translucent	0.133±0.017	63.0±1.0	49±2.2	3.90±0.17	7.0 ± 0.1
F5	Whitish clear	Transparent	0.065±0.012	63.6±1.5	29±2.3	2.80±0.20	6.99 ± 0.2
F6	Whitish but fragile	Opaque	0.071±0.012	64.3±1.5	31±1.1	2.96±0.20	6.9 ± 0.2
F7	Clear but fragile	Opaque	0.083±0.015	64.3±0.6	70±2.8	3.27±0.15	7.0 ± 0.1
F8	Clear	air Entrapped, thin but hard, brittle	0.087±0.014	63.6±1.0	72±1.4	3.30±0.15	6.9 ± 0.3
F9	Whitish	Translucent	0.088±0.016	64.5±0.5	76±0.7	3.33±0.15	7.0 ± 0.3
F10	Whitish	Translucent	0.084±0.014	64.6±1.5	78±3.1	3.34±0.15	6.9 ± 0.2

Drug excipient interaction studies

FTIR spectra of the pure drug, polymer, superdisintegrant, their physical mixture, and the prepared formulations were analyzed to assess potential chemical interactions and to confirm the absence of any drug–excipient incompatibility. The spectra showed no evidence of interaction, as all characteristic peaks of the individual components were preserved in the physical mixture and formulations (Figure 1). Here, the pure LTZ drug served as the reference, displaying its characteristics functional group fingerprint. Whereas, the characteristics peaks of functional groups were identified at ~ 2245 cm-1, 1500-1600 cm-1, and 3100-3000 cm-1 corresponding to nitrile group (-C≡N), triazole ring, and aromatic C-H stretches, respectively. However, HPMC, SSG, and individual polymers, exhibited their own distinct profiles. HPMC is characterized by its broad, intense O-H stretching band around 3400 cm-1, C-H stretched just below 3000 cm-1. Whereas, a broad O-H stretch was also observed for SSG, a modified starch. The results of analysis from the physical mixture indicate a clear absence of interaction among the constituents.

Table 3. Disintegration time of the prepared strip formulation.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DT (Swirl method)	21 ± 2	23 ± 2	17 ± 3	19 ± 2	13 ± 1	16 ± 2	22 ± 4	12 ± 2	16 ± 2	24 ± 1
DT (Beaker stirring)	18 ± 3	20 ± 1	14 ± 2	15 ±3	9 ± 2	13 ± 2	17 ± 3	8 ± 3	12 ±2	20 ± 3

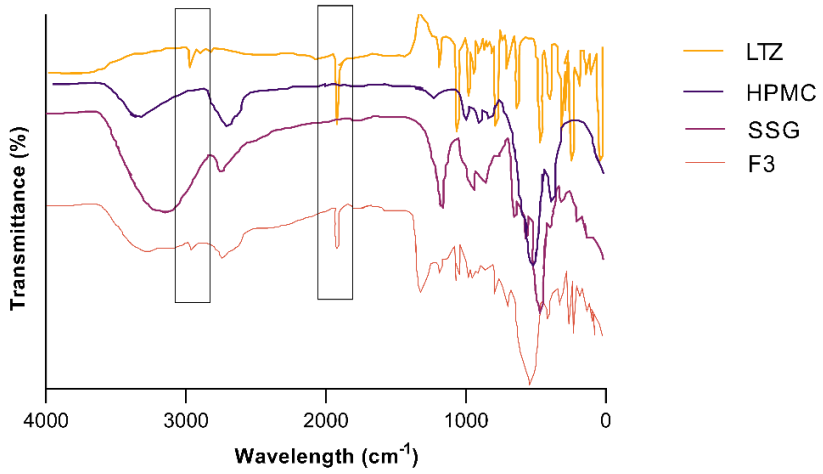

Figure 1. FTIR spectrum of pure LTZ, polymer (HPMC E5), sodium starch glycolate, and the optimized LTZ-ODF formulation showing no significant peak shifts, indicating good drug-excipient compatibility.

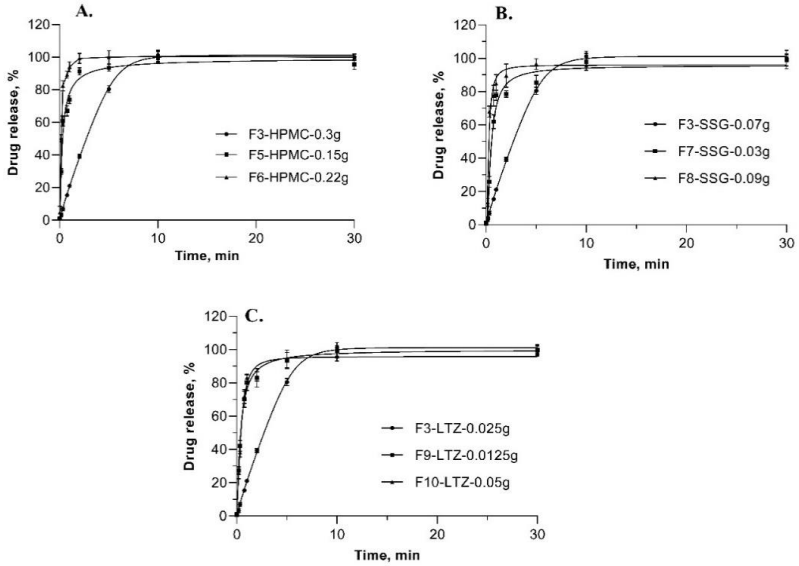

Figure 2. In-vitro release profiles of LTZ-loaded orodispersible film showing the effect of (A) HPMC concentration (F3, F5, F6), (B) sodium starch glycolate (SSG) concentration (F3, F7, F8), and (C) drug loading (F3, F9, F10). Drug release was evaluated in simulated salivary fluid (pH 6.8) at 37 °C using the USP basket apparatus at 75 rpm.

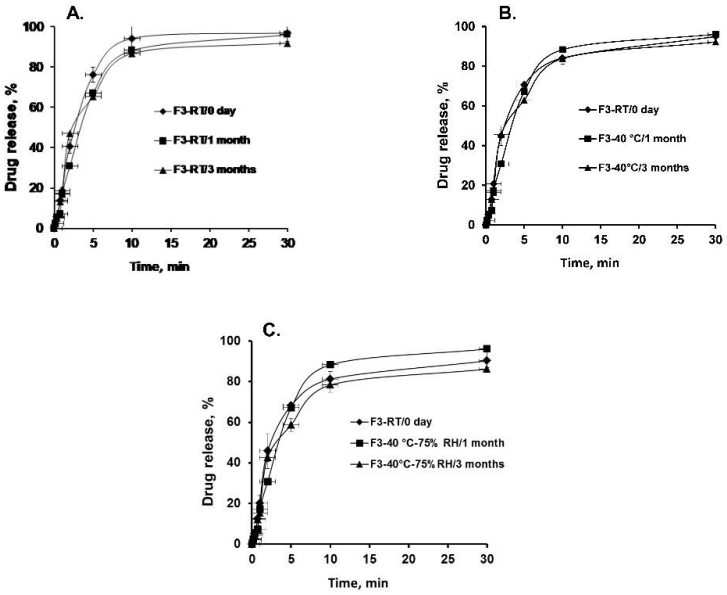

Figure 3. Stability study showing the in-vitro drug release profiles of optimized formulation F3 stored under different conditions: (A) room temperature (RT) for 0, 1, and 3 months, (B) 40 °C for 0, 1, and 3 months, and (C) 40 °C with 75% relative humidity (RH) for 0, 1, and 3 months.

Disintegration time

Because the buccal cavity contains only about 6 mL of saliva, using the standard 900 mL dissolution volume in a conventional disintegration apparatus does not accurately reflect physiological conditions. To better mimic the in vivo environment, disintegration testing was therefore performed using 3 mL of medium in a glass Petri dish with a diameter of approximately 3-4 cm, similar to that of the buccal region. All film formulations showed disintegration times within the acceptable range, between 9 and 20 seconds. Films prepared without a superdisintegrant took longer to disintegrate, whereas those containing different concentrations of superdisintegrant broke down much faster. This faster disintegration can be attributed to the ability of the superdisintegrant to rapidly absorb water and swell upon contact with the medium, generating enough pressure to quickly rupture and disperse the film. As expected, higher concentrations of superdisintegrant led to even faster disintegration. In contrast, films with lower levels of HPMC disintegrated more quickly than those with higher polymer content. This can be explained by the fact that increasing the amount of HPMC enhances the film's mechanical strength and cohesiveness, making it more resistant to disintegration.

Assessment of LTZ release profile

Among all the formulations, F3 was identified as the optimized formulation based on its mechanical strength, disintegration time, and drug release characteristics. Figure 2A illustrates the drug release profiles of strips containing varying concentrations of HPMC while maintain the other excipient and drug's amount constant in batch of F3, F5 and F6 where HPMC amount was 0.3, 0.25, and 0.22 g respectively. All formulations exhibited a reasonably rapid drug release; however, strips with lower HPMC concentrations (F5 and F6) demonstrated faster drug release rates compared to the formulation with a higher HPMC content (F3). Similarly, F7 and F8 were developed by altering the super-disintegrant amount to 0.03 and 0.09 g, respectively, while maintaining the proportions of all other ingredients identical to F3, which contained 0.07g SSG. The release profiles of F7 and F8 were compared with F3 to assess the impact of SSG concentration (2B). Both formulations displayed high overall drug release, with F8 exhibiting a faster rate due to higher superdisintegrant content, while F7 released more gradually because of its lower amount. Whereas, Figure 2C illustrates the impact of LTZ initial amount on the release profile of the drug over time. Although all formulations achieved 100% drug release, both higher F10 and lower F9 drug loading showed slightly faster release rates compared to the intermediate loading in F3.

Stability Studies

Stability studies were conducted to evaluate the ability of the formulations to maintain their chemical and physical integrity over a defined storage period. For this purpose, F3 formulation were stored at room temperature and under accelerated conditions of 40°C and 40°C with 75% relative humidity. Evaluations were performed at predetermined intervals, day 0, 1 month, and 3 months, to assess indirectly by applying in-vitro drug release. The in-vitro drug release profiles of formulation F3 remained essentially unchanged after storage under all tested conditions, indicating that the drug was stable within the dosage form. Minor variations in release were observed over 3 months at room temperature, 40 °C, and 40 °C/75% RH; however, these differences were negligible and did not alter the overall release pattern. These findings confirm that the formulation maintains good stability during storage.

DISCUSSION

Breast cancer remains a leading cause of cancer-related mortality among women worldwide, presenting a significant global health burden. Conventional therapies, including chemotherapy and radiotherapy, are often hampered by severe side effects, poor patient compliance, and a lack of precise targeting. Furthermore, the predominant use of solid oral dosage forms poses a major challenge for specific patient populations, such as the elderly and those with dysphagia, due to swallowing difficulties. To address these limitations, this study focuses on the development of a patient-centric ODF of LTZ, a potent aromatase inhibitor, using HPMC as a film-forming polymer. This innovative dosage form is designed to

disintegrate rapidly in the oral cavity, thereby enhancing ease of administration, potentially improving adherence to long-term endocrine therapy, and facilitating pre-gastric absorption for a more favourable pharmacokinetic profile.

Notwithstanding, it is technically challenging to ensure homogenous dispersion of a drug throughout the film matrix, espacially for poorly soluble drugs like LTZ (15). Non-uninform distribution may lead to content variation, dose inaccuracies and inconsistent drug release. Alternately, a significant in dissolution and disintegration may happened, when using an increasing polymer concentration which impacts tensile strength and flexibility of the film. Besides, excessive amounts of polymer may lead to brittle films that crack during handling (16). In this regard, the influence of polymer concentration, drug loading, and super-disintegrant level on the performance of the prepared strips was systematically investigated. The concentrations of all other excipients were kept constant during these evaluations to ensure reliable comparison. The successful synthesis of the ODF hinges not only on the choice of suitable excipients but also on the refinement of a synthesis process that ensures optimal films with suitable performance and mechanical properties. HPMC was a strategic choice as the film-forming polymer possesses excellent biocompatibility, non-toxic, and ability to form robust but reliable film (17). Super-disintegration is pre-requisite of a ODF film where SSG serves as an ideal super-disintegrant for enhancing oral drug delivery (18).

A binary solvent system served as a key aspect of the formulation approach, where distilled water successfully dissolves HPMC and SSG, while methanol was necessary to solubilize the poorly water soluble LTZ. This strategy ensured a homogenous distribution of LTZ within HPMC matrix, a pre-requisite of an ODF. Henceforth, all films exhibited homogeneous content, thickness and acceptable pH for buccal mucosa (Table 2). Another challenge was tenacious adhesion of the cast film to the substrate, a common hurdle in solvent casting. Initially, casting into conventional glass petri dishes resulted in strong adhesion, leading to irreversible cracking and tearing of the films upon removal. The strong adhesion forces observed at the film–substrate interface may be attributed to the high surface energy of the substrate and the specific composition of the polymer solution as evidenced previously (19). To address this issue, the use of hard plastic sheet pouches as casting mold demonstrated to be a pivotal modification, as the surface properties of the plastic likely to provide lower energy interface compared to glass (20).

The detailed evaluation of physicochemical attributes is critical to assure the patient acceptability, quality, and structural integrity of the synthesized ODF. The information in Table 2 endorse that the method was successful in producing uniform and pharmaceutical elegant ODFs. A positive relation between film thickness and HPMC concentration is observed and it is a well-established phenomenon in film technology (21). As the HPMC amount was raised, the solid content of the casting solution escalates, leading to a denser polymeric matrix upon solvent evaporation. Also, the thickness range (0.065 ± 0.012 to 0.133 ± 0.017) falls within the acceptable range, thus ensuring patient comfort. The pH of all formulations was found to be within the range of 6.89 ± 0.1 to 7.0 ± 0.1 close to pH of saliva, this further certifies patient compliance. Also, an acceptable weight variation across the different batches indicates reproducibility and robustness of the preparation method. The high folding endurance of F3 suggests an optimal balance of HPMC and SSG, creating a flexible and cohesive film that can withstand mechanical stress during handling and packaging of the films. Conversely, the lower folding endurance of F5 and F6 can be attributed to their reduced concentration of HPMC, which resulted in a weaker polymeric network, making film more brittle and fragile. The results of tensile strength further validate this trend, where the superior tensile strength of F2 indicates a strong cohesive film structure this withholding appropriate external stress.

The FTIR spectroscopy was conducted to probe potential physicochemical interaction between LTZ and selected excipients (22). The analysis confirmed the absence of any significant incompatibility, as the characteristic principal absorbance peaks of LTZ, HPMC, and SSG remained unaltered in both, the physical mixture and the final formulated films. This confirms the stability of LTZ within the polymeric matrix and establishes the compatibility of the selected excipients (23).

The buccal cavity possesses around 6 ml of saliva, henceforth conventional method of using 900ml medium is not representative of in-mouth condition. For that, 3ml of disintegrating medium in a glass petri dish is a more physiological relevant method, which mimics the buccal environment (24). The results showed that all formulation exhibited the disintegration time within the acceptable range of 9 to 20 seconds, and the films without superdisintegrants needed a longer time to disintegrate. The mechanism could be rapid swelling of the superdisintegrant particles upon contact with the medium, which produces strong swelling force that disorder the film matrix (25). Also, film containing lower HPMC amount disintegrated more quickly, likely due to weaker mechanical strength of the matrix.

The in-vitro dissolution testing showed that the formulations (F3, F5, and F6) made of different HPMC amount, demonstrated that polymer concentration plays a critical role in controlling the drug release rate. The strips owning lower amount of HPMC exhibited faster dissolution perhaps because of renowned ability of HPMC to form a viscous gel layer upon hydration (26), which can hinder the penetration of dissolution medium and thus retard drug diffusion. Whereas, increasing the SSG amount caused accelerated drug release, perhaps due to enhanced water uptake and faster matrix disintegration. Also, the effect if drug loading onto LTZ release showed that higher and lower drug loading resulted in slightly faster dissolution compared to formulation with intermediate LTZ loading (F3). This difference may be attributed to difference in drug-to-polymer ratio, which affects the film's porosity and diffusional pathways the drug (27).

Stability is a critical aspect of pharmaceutical development, as even minor changes in humidity of temperature may alter the physicochemical and other attributes of polymer based system. For this purpose, the optimized formulation (F3) was selected for the stability studies. The results declared that F3 preserved its physical appearance, flexibility, and texture under both the room temperature and accelerated conditions for up to three months. This consistency in in vitro drug release confirms that neither the polymeric network nor the drug-polymer interactions were adversely affected by storage conditions.

CONCLUSION

The LTZ-loaded oral thin films developed in this study showed favorable physicochemical and mechanical properties, featuring smooth surfaces, uniform thickness, and good flexibility. All formulations exhibited rapid disintegration, with times ranging from 9 to 20 seconds, and achieved complete drug release. The polymer and superdisintegrant concentrations were found to play a key role in the performance of the films, higher levels of superdisintegrant and lower amounts of polymer resulted in faster disintegration and drug release. FTIR analysis confirmed that no chemical incompatibilities occurred among the components, while stability testing under accelerated conditions (40 °C and 40 °C/75% RH for 3 months) demonstrated that the films remained stable throughout the study period. Overall, the optimized formulation offers a convenient and patient-friendly strategy for buccal delivery of LTZ. Its rapid onset of action, ease of administration, and potential to enhance patient compliance

make it a promising alternative to conventional oral dosage forms. These results highlight the potential of LTZ-loaded oral thin films as a viable and scalable platform for anticancer therapy.

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SUPPLEMENTARY DATA

Supplementary materials are provided by the authors to enhance transparency and reproducibility. These data support the findings reported in the main article.

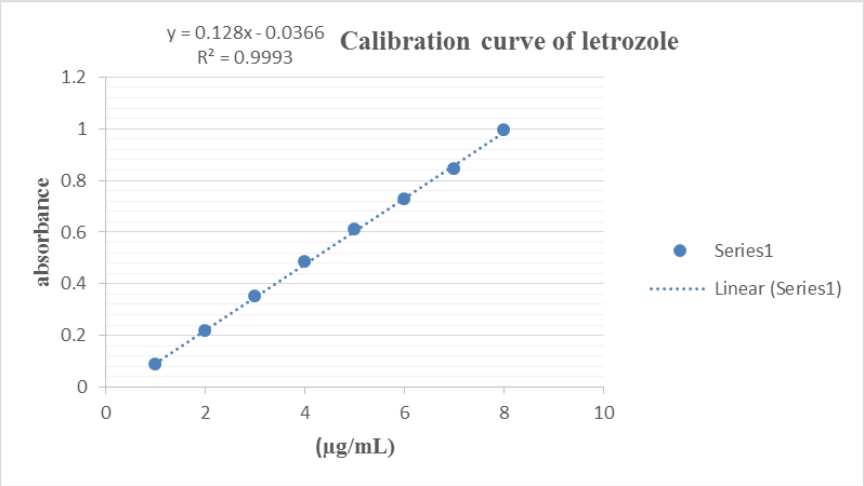

Figure 1s. Calibration curve of LTZ in mixture of water of methanol.

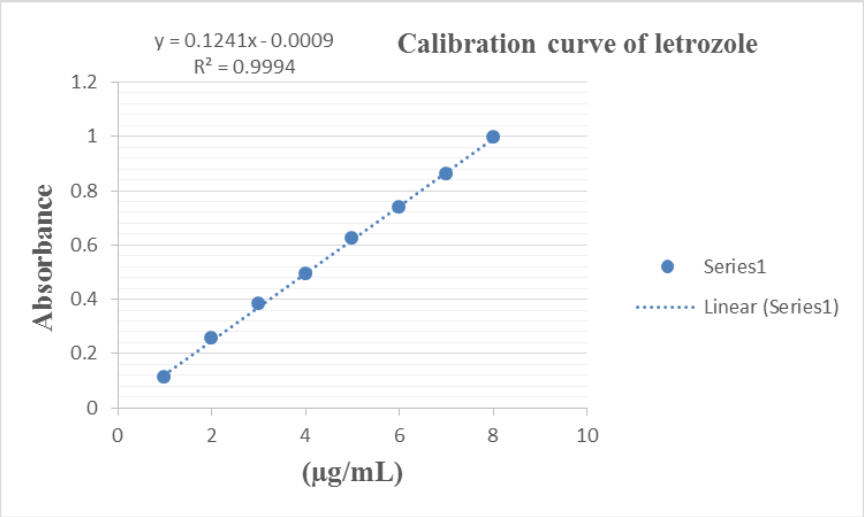

Figure 2s. Calibration curve of LTZ in buffer solution (pH 1.2).

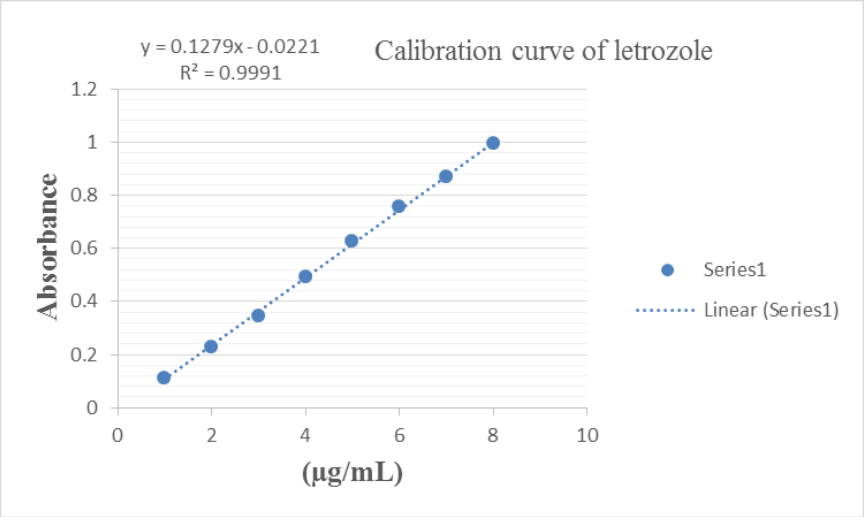

Figure 3s. Calibration curve of LTZ in buffer solution (pH 6.8).

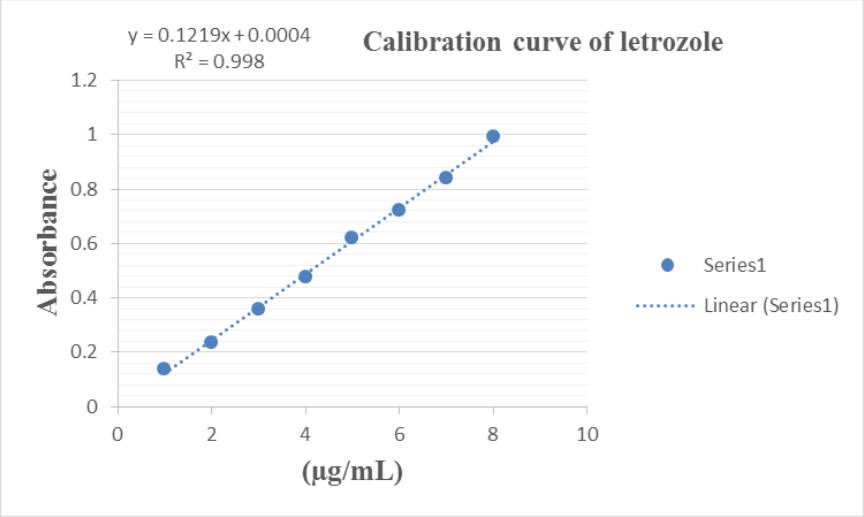

Figure 4s. Calibration curve of LTZ in buffer solution (pH 7.4).