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# Formulation and Evaluation of Letrozole Loaded Hydrogels for Targeted Drug Release

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**KEYWORDS**

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**ABSTRACT:**

Hydrogels are three-dimensional, hydrophilic polymeric networks capable of absorbing significant amounts of water or biological fluids. Their high-water content, porosity, and soft, tissue-like consistency make them particularly suitable for topical drug delivery, offering enhanced patient comfort, sustained release, and reduced systemic side effects. The present study focuses on the formulation and evaluation of Letrozole-loaded hydrogel systems designed for localized delivery in hormone-responsive breast cancer treatment. Letrozole, a non-steroidal aromatase inhibitor, is typically administered orally, where it can lead to GIT discomfort and systemic toxicity. To address these limitations, a topical hydrogel formulation was developed using biocompatible gelling agents such as Carbopol 940 and PVA. FTIR analysis confirmed drug-excipient compatibility, preserving Letrozole's structural integrity within the hydrogel matrix. Five hydrogel batches were prepared and assessed for physical characteristics, pH, viscosity, spreadability, drug content, and skin compatibility. Among the formulations, F2 demonstrated optimal properties with a skin-friendly pH, good spreadability, and no signs of irritation, indicating its suitability for topical administration. The study highlights the potential of hydrogel-based Letrozole delivery as an effective, patient-friendly alternative to oral administration, supporting targeted drug release with minimal systemic exposure.

## INTRODUCTON

Breast cancer is the most common cancer diagnosed in women which is the primary cause of mortality. It is the third fastest-growing cancer diagnosed globally. Breast cancer is a complex illness in terms of histopathology, genetics, and treatment. Treatment of breast cancer is a major therapeutic challenge because of its complexity, aggressiveness, and heterogeneity [1].

The WHO Global Breast Cancer Initiative (GBCI) aims to prevent 2.5 million breast cancer deaths between 2020 and 2040 by lowering the worldwide breast cancer mortality rate by 2.5% annually. Breast cancer incidence has been rising globally, with 2021 estimates showing it accounted for about 30% of all new cancer diagnoses in women in the US, with 15% leading to death. A new case is diagnosed every 18 seconds. Despite little change in mortality rates, survival rates have been improved due to awareness campaigns, early detection, and ongoing research into new treatments [2].

Breast cancer is classified into three main subcategories based on biomarkers: hormone receptor+/HER2-, HER2+, and triple-negative [3].

Breast cancer is a hormone-dependent, with estrogen playing a key role in its progression. For postmenopausal women, the concentration of 17β-estradiol (E2) in breast tumors can be significantly higher than in plasma, due to increased uptake or local conversion of androgens to estrogens [4].

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Traditional chemotherapy for breast cancer can cause several side effects, such as vomiting, nausea, fatigue, and organ damage, due to poor drug efficiency from systemic administration. Therefore, developing a new drug delivery system is crucial for more effective tumor cell eradication and reducing side effects [3].

Letrozole is a non-steroidal, third-generation triazole aromatase inhibitor that reduces estrogen levels in postmenopausal women by binding to the heme ion of cytochrome P-450, which converts testosterone into small amounts of estrogen [5]. It is used as the very first phase of breast cancer treatment [6][7]. It improves survival rates, reduces metastasis risk, and prevents recurrence [8].

Food and Drug Administration (FDA) has approved the letrozole for the treatment of postmenopausal women with advanced stage breast cancer [9]. Letrozole tablets at a dose of 2.5 mg/day have been approved by the US Food and Drug Administration for the treatment of postmenopausal women with locally progressed or metastatic breast cancer that is hormone receptor-positive or hormone receptor-unknown [10].

Letrozole is more effective than other aromatase inhibitors (AIs), including exemestane, anastrozole, aminoglutethimide, and formestane. Letrozole has demonstrated potent anticancer effects in a variety of animal models. Aromatase activity in breast cancer and mammary adipose tissue was effectively decreased by low nanomolar concentrations of letrozole [11]. Letrozole, a potent drug, inhibits aromatase from producing estrogens by binding to its cytochrome P450 unit's heme by >99% [4].

Hydrogels have emerged as a promising vehicle for the localized delivery of anticancer drugs such as Letrozole. Hydrogels are three-dimensional (3D) cross-linked polymer networks formed by the crosslinking of hydrophilic monomers or polymer chains in water, capable of absorbing and retaining large amounts of water and biological fluids-sometimes up to 99%. The presence of hydrophilic functional groups in their structure permits rapid water uptake. Hydrogels are extremely adjustable and can be made to fit particular biomedical needs in terms of porosity, size, surface morphology, and shape. They are frequently used in drug administration, diagnostic agents, tissue engineering, agent transport, and most notably, localised and controlled therapeutic release.

Hydrogels are perfect for long-term, site-specific immunotherapy for malignancies like breast cancer because they can encapsulate immunomodulatory substances, including antibodies, cytokines, and immune checkpoint inhibitors [12].

Chemotherapeutic chemicals, proteins, nucleic acids, or nanoparticles can be encapsulated in hydrogels and released in response to tumor-specific stimuli. This targeted delivery method not only improves drug bioavailability but it also helps to fight against multidrug resistance by maintaining therapeutic concentrations within the tumor environment. Letrozole-loaded hydrogel formulation, due to its optimized physicochemical characteristics and favorable topical properties, offers a significant advantage in the treatment of breast cancer. Its ability to remain on the skin surface, release the drug in a sustained manner, and avoid systemic circulation contributes to enhanced therapeutic outcomes with minimized adverse effects. This makes it a patient-friendly, non-invasive option for long-term hormone-based therapy, especially for patients seeking localized treatment alternatives.

Hydrogels are revolutionizing breast cancer research by replicating the extracellular matrix, enhancing drug delivery, and modulating the tumor microenvironment. Their adaptive properties-biocompatibility, monitored release, and responsiveness to physiological signals-make them excellent for targeted therapy. Cutting-edge advances in hydrogel-based drug delivery, immunotherapy, and tissue engineering are enabling more effective, personalized treatments with fewer adverse effects. This article examines the transformative role of hydrogels in advancing precision medicine for breast cancer.

## MATERIALS AND METHODS

### Materials

Letrozole was obtained from Natco Pharma Ltd, Selakui, Uttarakhand. Carbopol 940 was purchased from Sisco Chem Ltd, Maharashtra. Poly Vinyl Alcohol (PVA) was purchased from Paskem Finechemical Industries from New Arya Nagar, Ghaziabad, Uttar Pradesh. Ployethylene Glycol (PEG) was purchased from Nice Chemicals Ltd, Manimala Road, Edappally, Kerala.

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Tween 80 was purchased from Central Dug House Ltd, Daryaganj, New Delhi. Triethanolamine (TEA) was purchased from Avarice Industries, Ghaziabad, Uttar Pradesh. Dimethyl Sulphoxide (DMSO) was purchased from Central Dug House Ltd, Daryaganj, New Delhi.

**PREFORMULATION STUDY**

Preformulation studies involve the assessment of the physicochemical properties of a drug substance, both in its pure form and when mixed with various excipients. These investigations aim to identify key attributes that can impact the formulation strategy, preparation technique, and the eventual pharmacokinetic behavior of the final product. Such studies typically examine parameters like organoleptic characteristics, melting point, solubility profile, moisture content, flow properties, and drug-excipient compatibility.

1. **Organoleptic Properties of a Drug:** A small amount of the drug powder was placed on butter paper and examined under proper lighting conditions.

| S. No. | Drug | Observation | | |
|---|---|---|---|---|
| 1. | Letrozole | **Color** | **Odor** | **Taste** |
| | | White | Odorless | Bitter |

**Table 1. Organoleptic Properties of a Drug**

2. **Melting Point:** The melting point of the drug was determined using the open capillary method. The powdered drug was packed into a capillary tube, which was then sealed and inserted into the melting point apparatus. The temperature range from the onset of melting to complete liquefaction of the drug was recorded.

| S. No. | Drug | Observation |
|---|---|---|
| 1. | Letrozole | 184-185ºC |

**Table 2. Melting Point**

3. **Solubility:** To estimate the solubility quantitatively, a fixed amount of solute was placed in a test tube, and the solvent are added gradually in small increments, after each addition, the mixture was thoroughly shaken and visually examined for any signs of dissolution.

| S. No. | Solvents | Letrozole Solubility |
|---|---|---|
| 1. | Distilled Water | Practically Insoluble |
| 2. | Ethanol | Slightly Soluble |
| 3. | Methanol | Sparingly Soluble |
| 4. | Dimethyl Sulfoxide (DMSO) | Freely Soluble |

**Table 3. Solubility Profile of Letrozole**

4. **FTIR analysis:** FTIR studies are performed to determine the drug excipient compatibility. It helps to identify functional groups and possible chemical interactions. In this study, FTIR analysis was conducted on pure Letrozole and its physical mixtures with Carbopol 940 and PVA to assess any potential interactions between the drug and the polymers. Letrozole contains functional groups such as nitrile (C≡N), triazole (C=N), and fluoro-substituted aromatic rings, all of which produce characteristic peaks in the IR spectrum. The sample was analysed in the range of 4000-400cm$^{-1}$.

**Method**

**1. Hydration of Polymers**

Disperse Carbopol 940 in purified water and allow it to swell for 30-60 minutes. Dissolve PVA separately in hot water (80 °C) to ensure proper solubilization. Mix PEG into the PVA solution to enhance flexibility and moisture retention.

**2. Incorporation of API**

Dissolve the letrozole in DMSO (1-2 ml), then mix it in the polymer mixture, ensuring uniform dispersion.

**3. pH Adjustment and Gel Formation**

Slowly add TEA while stirring to neutralize Carbopol 940 and induce gel formation. Adjust the pH to the desired range (5.5-6.5 for topical applications).

**4. Final Mixing and Homogenization**

Blend all the components thoroughly. Add tween 80 to improve emulsification and stability. Stir for 5-10

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min. to ensure uniformity. Remove air bubbles (sonicate or let it sit for a few hours). Store the gel in a clean, airtight container at room temperature or in the fridge.

| Formulation Batches | Letrozole (gm) | Carbopol 940 (gm) | Polyethylene Glycol (ml) | Polyvinyl Alcohol(gm) | Tween 80 (ml) | Distilled Water (ml) |
|---|---|---|---|---|---|---|
| F1 | 0.1 | 1 | 4 | 0.4 | 1 | Q.S. |
| F2 | 0.1 | 0.5 | 7 | 2 | 2 | Q.S. |
| F3 | 0.1 | 0.5 | 10 | 1 | 4 | Q.S. |
| F4 | 0.1 | 1 | 10 | 0.5 | 5 | Q.S. |
| F5 | 0.1 | 1 | 5 | 0.5 | 5 | Q.S. |

**Table 4. Formulation table**

## EVALUATION PARAMETER

### 1. Physical Characteristics.

The pH, colour, homogeneity, consistency, grittiness, texture, and phase separation of the produced hydrogel formulation were all visually examined.

### 2. pH Determination

To determine the pH, one gram of the gel was mixed with 25 ml of distilled water. A digital pH meter was used, with the electrode immersed in the mixture for 30 minutes until a stable reading was obtained. This procedure was repeated three times for each formulation, and the average pH values were recorded.

### 3. Washability Test

Each hydrogel formulation was applied to the skin, and its ease of removal using water was evaluated manually.

### 4. Extrudability Assessment

The formulations were packed into collapsible metal or aluminium tubes. Pressure was applied to the tubes to dispense the gel, and the ease with which the product was extruded was used to evaluate its extrudability.

### 5. Skin Irritation

The evaluation of formulation was performed on healthy human volunteers. About 0.5 g of hydrogel was applied to an area of $6cm^2$ of skin. At the end of the exposure period of 1 hour, the skin was checked for any irritation or redness.

### 6. Viscosity

The Brookfield Digital Viscometer was used to measure the viscosity of the hydrogel formulation.

### 7. Spreadability

To assess spreadability, two glass slides measuring 6×2 cm were used. A measured amount of the hydrogel formulation was placed on one slide,and the second slide was placed on the top. A specific weight (20 gm) was attached to the upper slide to facilitate spreading. The spreadability was calculated using the formula:

Spreadability (S) = (m×l)/t

Where, S = Spreadability (g.cm/sec), m = Mass applied to the upper slide (20 gm), l = Length of the slide (6 cm), t = Time in seconds taken for the upper slide to move a certain distance.

### 8. Drug Content

A 1 g sample of the hydrogel was accurately weighed and dissolved in 100 mL of phosphate buffer with pH 7.4. The resulting solution was placed in a volumetric flask and shaken for 2 hours to ensure complete dispersion. After shaking, the solution was filtered, and the drug content was analysed using a UV-Visible spectrophotometer at wavelengths of 240nm.

## RESULT AND DISCUSSION

### Result

### 1. Physical Characteristics

| Formulation | Colour | Homogeneity | Consistency | Phase Separation |
|---|---|---|---|---|
| F1 | White | Excellent | Excellent | None |
| F2 | White | Good | Good | None |
| F3 | White | Average | Average | None |
| F4 | White | Average | Average | None |
| F5 | White | Good | Good | None |

**Table 5. Physical Characteristics of Formulation**

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**2. pH Determination**

| S. No. | Formulations | pH |
|---|---|---|
| 1. | F1 | 6.15±0.02 |
| 2. | F2 | 6.00±0.05 |
| 3. | F3 | 5.55±0.06 |
| 4. | F4 | 6.23±0.03 |
| 5. | F5 | 5.26±0.01 |

**Table 6. pH determination of different formulations**

**3. Washability Test**

**4. Extrudability Assessment**

| S. No. | Formations | Washability | Extrudability |
|---|---|---|---|
| 1. | F1 | Excellent | Good |
| 2. | F2 | Excellent | Excellent |
| 3. | F3 | Excellent | Excellent |
| 4. | F4 | Excellent | Excellent |
| 5. | F5 | Excellent | Good |

**Table 7 shows the result of washability and extrudability**

**5. Skin Irritation**

All five formulations were subjected to a skin irritation study on voluntary individuals. No formulation showed any sign of skin irritation and redness. This implies that the formulations are not allergic to the skin.

**6. Viscosity**

| S. No. | Formulation | Viscosity (cp) |
|---|---|---|
| 1. | F1 | 8500 ± 2 |
| 2. | F2 | 9586 ± 5 |
| 3. | F3 | 8893 ± 2.5 |
| 4. | F4 | 9400 ± 3 |
| 5. | F5 | 9590 ± 5 |

**Table 8. Viscosity of different formulations**

**7. Spreadability**

| S. No. | Formulation | Spreadability (gcm/sec) |
|---|---|---|
| 1. | F1 | 12.12±0.02 |
| 2. | F2 | 14.23±0.01 |
| 3. | F3 | 13.56±0.01 |
| 4. | F4 | 12.36±0.03 |
| 5. | F5 | 13.15±0.05 |

**Table 9. Spreadability Result**

**8. Drug Content**

For all the hydrogel formulation, drug content analysis was done using the PBS (pH7.4) as the medium.

**Table 10. Percent drug content of Hydrogel formulation.**

| Formulation | Percent of drug content (%) |
|---|---|
| F1 | 90.1 |
| F2 | 91.5 |
| F3 | 88.2 |
| F4 | 90.5 |
| F5 | 89.5 |

**9.FTIR analysis**

**9.1. FTIR for Letrozole:**

Letrozole's infrared spectrum reveals distinct absorption bands that align with its chemical structure. A broad signal near 3300 $cm^{-1}$ hints at hydrogen bonding, possibly from –OH or –NH groups. A sharp dip at around 2200 $cm^{-1}$ confirms the nitrile group's presence through C≡N stretching. The aromatic framework is evident from strong vibrations near 1600 $cm^{-1}$, corresponding to C=C bonds. Between 1400–1250 $cm^{-1}$, the spectrum shows bending and stretching associated with $CH_2$ groups and C–N/C–O linkages. Finally, sharp signals near 750–700 $cm^{-1}$ point to substituted aromatic rings, highlighting Letrozole's structural specificity.

| Wavenumber ($cm^{-1}$) | Functional Group | Molecular Vibration | Class | Associated Structure |
|---|---|---|---|---|
| ~3300 | –OH / –NH | Stretching (hydrogen-bonded or free) | Alcohol / Amine | Possibly from residual solvents or excipients |
| ~2200 | C≡N | Triple bond stretching | Nitrile | Aromatic nitrile group (Letroz |

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| | | | | |
|---|---|---|---|---|
| | | | | ole feature) |
| ~1600 | C=C | Aromatic ring stretching | Aromatic Hydrocarbon | Benzene ring in Letrozole |
| ~1450 | $CH_2$ / C–C | Bending / Scissoring | Alkane / Aromatic | Alkyl or aromatic side chains |
| ~1250–1050 | C–N / C–O | Stretching | Amine / Ether | Ether linkage or secondary amine |
| ~750–700 | C–H (aromatic) | Out-of-plane bending | Aromatic Hydrocarbon | Substituted aromatic ring |

**Table 11. FTIR Table for Letrozole**

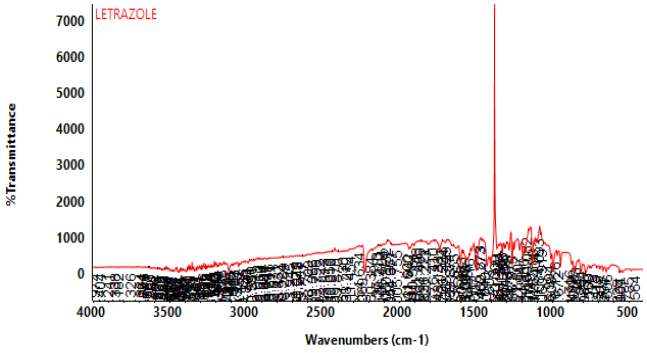


**Fig 1. Shows FTIR Spectrum of Letrozole**

### 9.2. FTIR for Letrozole + PVA

This IR graph illustrates the chemical composition of a Letrozole–Polyvinyl Alcohol (PVA) blend. The spectrum displays key absorption bands linked to functional groups such as hydroxyls (–OH), nitriles (C≡N), and aromatics (C=C, C–H), alongside typical polymeric features like C–H stretching and ring deformations. Broad peaks in the higher wavenumber range suggest hydrogen bonding from PVA, while sharp signals in the fingerprint region highlight Letrozole's aromatic and triazole structures. This spectrum showcases both Letrozole's pharmacophore signals and PVA's polymeric fingerprints, revealing potential intermolecular interactions and matrix compatibility.

| **Wavenumber ($cm^{-1}$)** | **Group** | **Molecular Vibration** | **Class** | **Associated Structure** |
|---|---|---|---|---|
| 3869–3626 | –OH (from PVA) | O–H stretching (broad) | Alcohol | Hydrogen bonding in Polyvinyl Alcohol |
| 3455–3363 | –NH or residual –OH | N–H or O–H stretching | Amine / Alcohol | Moisture or secondary amines |
| 2926–2854 | $–CH_3$ / $–CH_2$ | C–H symmetric/asymmetric stretch | Alkane | Methylene and methyl groups in PVA or drug |
| 1787 | C=O (trace) | Carbonyl stretching | Ester / Ketone | Possible excipient or degradation product |
| 1645 | C=C (aromatic) | Ring stretching vibration | Aromatic Hydrocarbon | Benzene rings in |

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| | | | | |
|---|---|---|---|---|
| | | | | Letrozole |
| 1455–1338 | –$CH_2$ bending | Scissoring / deformation | Alkane / Aromatic | Backbone vibrations in PVA / aromatic groups |
| 1245–1090 | C–N / C–O | Stretching vibrations | Amine / Ether | Triazole ring or ether groups in structure |
| 945–762 | C–H (aromatic) | Out-of-plane bending | Aromatic Hydrocarbon | Substituted phenyl rings |
| 687–445 | Ring modes / skeletal | In-plane ring deformation | Aromatic | Phenyl or triazole skeletal vibrations |
| 362–109 | Lattice vibrations | Low-frequency skeletal motions | Polymer / Drug Matrix | Interaction between Letrozole and PVA network |

**Table 12. FTIR Table for Letrozole + PVA**

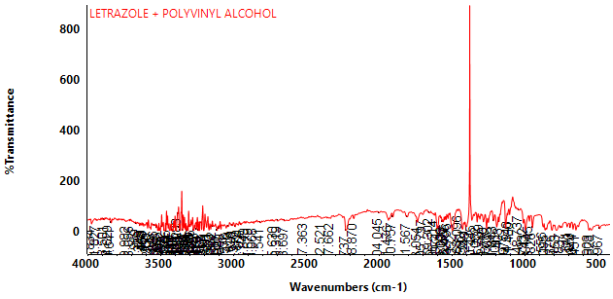


**Fig. 2 shows the FTIR Spectrum for Letrozole + PVA**

### 9.3. FTIR for Letrozole + Carbopol 940

The IR spectrum of the Letrozole-Carbopol 940 blend highlights key interactions between the drug and polymer matrix. Broad absorption near 3400 $cm^{-1}$ indicates hydroxyl groups from Carbopol, suggesting hydrogen bonding potential. A sharp peak close to 2200 $cm^{-1}$ confirms Letrozole's nitrile (C≡N) group, while signals around 1600 $cm^{-1}$ reflect aromatic C=C stretching. Mid-range vibrations reveal polymeric CH bending and stretching, and lower wavenumber features point to ring deformations and skeletal motions. Together, these peaks confirm structural integrity and possible intermolecular interactions in the formulation.

| **Wavenumber ($cm^{-1}$)** | **Group** | **Molecular Vibration** | **Class** | **Associated Structure** |
|---|---|---|---|---|
| 3400–3200 | –OH | O–H stretching (broad, H-bonded) | Alcohol / Polymer | Hydroxyl groups in Carbopol |
| ~2200 | C≡N | Nitrile stretching | Nitrile | Letrozole's triazole-linked nitrile |
| ~1600 | C=C | Aromatic ring | Aromatic | Benzene rings |

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| | | | | |
|---|---|---|---|---|
| | | stretching | Hydrocarbon | in Letrozole |
| ~1450 | $CH_2$ / $CH_3$ | Bending / deformation | Alkane / Polymer | Carbopol backbone and side chains |
| 1300–1100 | C–O / C–N | Stretching vibrations | Ether / Amine | Letrozole's ring system, Carbopol linkage |
| 900–700 | C–H (aromatic) | Out-of-plane bending | Aromatic Hydrocarbon | Substituted phenyl rings |
| 600–400 | Skeletal / Ring modes | Ring deformation | Aromatic / Polymer | Structural features from both components |

**Table 13. FTIR Table for Letrozole + Carbopol 940**

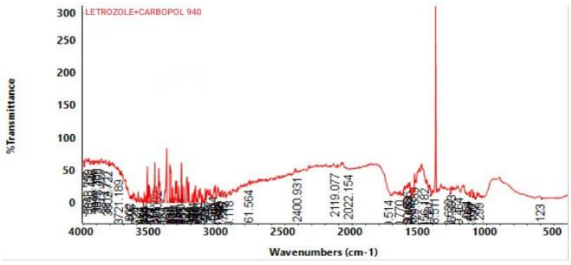


**Fig.3 shows the FTIR Spectrum for Letrozole + Carbopol 940**

**Discussion**

Conventional drug administration, such as the systemic drug delivery system, often requires repeated administration at a high dosage to provide a sufficient therapeutic effect; however, this may result in low efficiency, poor patient compliance, and serious side effects. The hydrogel system was found to be a good platform for the delivery of anticancer drugs to target sites for improved anticancer effects.

FTIR analysis confirmed that Letrozole remained chemically stable in the presence of both Carbopol and PVA, with no significant structural alterations. The presence of hydrogen bonding, as indicated by shifts in O–H and C≡N bands, suggests favourable polymer-drug interactions. Among the five hydrogel formulations (F1–F5) developed for the topical delivery of Letrozole, Formulation F2 was found to be the most suitable based on a series of evaluation parameters. It exhibited an ideal pH (6.00 ± 0.05), which falls within the skin-compatible range, ensuring minimal risk of irritation upon application. In terms of physical appearance, F2 showed good homogeneity, consistency, and no phase separation, indicating formulation stability. It also demonstrated excellent washability and extrudability, which are important for user convenience and application from containers. The viscosity (9586 ± 5 cps) of F2 was sufficiently high to provide good retention on the skin, while still maintaining a high spreadability (14.23 ± 0.01 g cm/sec), allowing for easy and uniform application. Importantly, no signs of skin irritation or redness were observed in volunteers, confirming its safety for topical use. . All formulations showed good drug content between 88% and 91%. F2 had the highest (91 ± 0.5%), while F3 showed the lowest (88 ± 0.2%). Overall, these characteristics make F2 the most effective and patient-friendly formulation for localized Letrozole delivery in breast cancer treatment. These findings suggest that Letrozole-loaded hydrogels can effectively deliver the drug through the skin with minimal irritation, enhancing patient compliance. This hydrogel-based approach not only improves drug bioavailability but also supports targeted therapy, potentially leading to better therapeutic outcomes and reduced adverse effects in the treatment of hormone receptor-positive breast cancer.

**CONCLUSION**

The present study successfully demonstrates the potential of hydrogel-based topical delivery of Letrozole, offering a promising alternative to conventional oral administration in hormone-dependent breast cancer therapy. Hydrogels, being three-dimensional, hydrophilic polymers, have several uses in conventional, current, and emerging pharmaceutical fields. Hydrogel

properties such as biocompatibility, porosity, resemblance to natural tissues, tunable viscoelasticity, high permeability for oxygen and nutrients, and high-water holding capacity bring about new transformations in the field of drug delivery.

By utilizing biocompatible polymers such as Carbopol 940 and PVA, a range of formulations were developed. The selected formulation exhibited desirable physicochemical properties, including physical characteristics, pH, and viscosity. Compatibility between Letrozole and the excipients was confirmed.

The findings support the feasibility of Letrozole-loaded hydrogels for topical application, with enhanced patient compliance, reduced systemic toxicity, and improved therapeutic outcomes. This approach holds significant promise for targeted, localized treatment strategies in oncology and could be extended to other poorly soluble or systemically toxic drugs.

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**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

**ABBREVIATIONS**

**PVA:** Polyvinyl alcohol; **PEG:** Polyethylene glycol; **FTIR:** Fourier Transform Infrared Spectroscopy.

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