ORIGINAL ARTICLE

# Simultaneous Determination of Gimeracil, Oteracil, and Tegafur in Pure Blend and their Combined Capsules by Stability-indicating RP-UPLC Method

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## Abstract

**Aim:** A trouble-free, simple, specific, and highly sensitive stability indicating phase UPLC method was developed for concurrent assessment of Gimeracil, Oteracil and Tegafur in pure and in their combined tablet formulation. **Method:** A separation was accomplished by using X-bridge BEH C18 (100 x 2.1 mm, 2.5 µm) column, mobile phase composition of ACN: Buffer (0.5M ammonium formate) (20:80 v/v) and isocratic elution at a flow rate of 0.2 mL/min and detection wavelength of 220nm. The extreme stress conditions like hydrolysis with acid and base, peroxide oxidation, thermal decomposition was used as per ICH specifications to assess the stability of the analytes in bulk and dosage forms. **Results and Discussion:** The retention times of Gimeracil, Oteracil and Tegafur were found at 1.610, 3.502 and 2.985 min. respectively. The proposed method has linear response in the concentration ranges from 14.5 to 87 µg/mL, 39.5 to 237 µg/mL and 50 to 300 µg/mL of Gimeracil, Oteracil and Tegafur respectively. The LOD and LOQ values were determined as 0.009 µg/mL and 0.026 µg/mL for Gimeracil, 0.23 µg/mL and 0.69 µg/mL for Oteracil and 0.93 µg/mL and 2.81 µg/mL for Tegafur respectively. The acceptance limits of Q2 of the ICH procedures were met by all method validation parameters. The stability of the approach may be seen in the fact that the degradation products from forced degradation tests were well-resolved from Gimeracil, Oteracil and Tegafur. **Conclusion:** The suggested RP-UPLC method was very sensitive, exact, stable indicator, and cost-effective. Because of this, the method has the potential for use in regular analysis in the quality control department as well as pharmaceutical manufacture of Gimeracil, Oteracil and Tegafur.

**Key words:** Gimeracil, Oteracil, Tegafur, Stability indicating, Isocratic elution

## INTRODUCTION

The second main cause of cancer-related death is gastric cancer. The global annual prevalence rate of gastric cancer is approximated to be 934,000 cases, with 700,000–800,000 lives lost.[1] An oral fixed-dose combination of tegafur (TGF) (20 mg) + gimeracil (GMR) (5.8 mg) + oteracil (OTR) (15.8 mg) used to treat advanced gastric and colon cancers in conjunction with cisplatin.[1,2] The combo is also used in head and neck cancer, colorectal cancer, non-small-cell lung cancer, breast cancer, and pancreatic cancer in several Asian countries.[2] TGF, a chemotherapeutic agent, is a precursor to the active ingredient 5-fluorouracil. GMR inhibits fluorouracil degradation by inhibiting the dehydrogenase enzyme dihydropyrimidine dehydrogenase in a reversible manner.[3-5] As a result, 5-FU levels rise, and the half-life of the substance is extended. OTR primarily remains in the gut due to its low permeability, where it inhibits the production of 5-FU by inhibiting the enzyme orotate phosphoribosyltransferase.[5-7] Reduced 5-FU levels in the gut result in less gastrointestinal toxicity.[5] The chemical structures of GMR, TGF, and OTR are depicted in Figure 1.

A proficient analytical method is required to estimate a drug substance alone or in combination with other drugs

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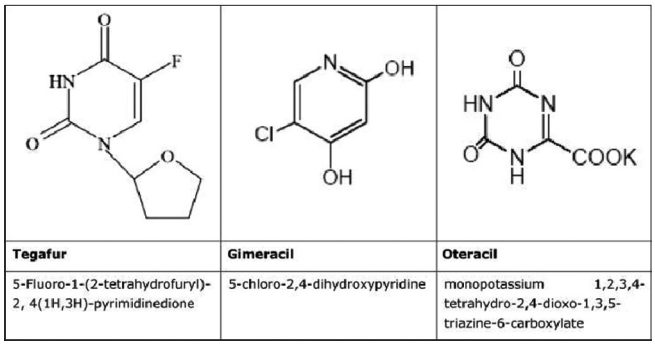


| Tegafur | Gimeracil | Oteracil |
|---|---|---|
| 5-Fluoro-1-(2-tetrahydrofuryl)-2, 4(1H,3H)-pyrimidinedione | 5-chloro-2,4-dihydroxypyridine | monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate |

**Figure 1:** Chemical structures of TGF, GMR, and OTR

at the same time.[8] A review of the literature revealed that only just few analytical methods such as RP-HPLC and LC-MS methods were reported to estimate TGF and GMR in combined dosage forms.[9-11] In addition to RP-HPLC methods, bioanalytical liquid chromatographic methods and LC-MS methods for estimating TGF with other chemotherapeutic agents were described in the literature.[12,13] Along with the aforementioned method, only one method for OTR with impurities was reported.[13] A single RP-UPLC method for the simultaneous estimation of GMR, OTR, and TGF in blended powder and combined capsule form was not available until now. In this reference, efforts have been made to establish a proficient, highly sensitive, and cost-effective RP-UPLC method for determining the assay of GMR, OTR, and TGF, as well as assessing the stability of GMR, OTR, and TGF under forced degradation (FD) conditions in premixed powder and combined capsules at the same time. Following method development, validation was carried out in accordance with ICH Q2 guidelines.[14-16]

## MATERIALS AND METHODS

APIs of GMR, OTR, and TGF were obtained from Shree Icon Labs, Vijayawada. All analytical grade solvents were purchased from Finar Chemicals Limited. The method was completed by using WATERS ACQUITY UPLC with PDA detector. In addition, balance (1 mg) (SCALETEC-SAB224CL), a digital pH meter (SMIS-PH-7000), and water (Milli-Q) were used.

### Chromatographic method conditions

A sample and successful separation of GMR, OTR, and TGF were done with Xbridge BEH C18 (50 × 2.1 mm, 1.7 µm) column, using a mobile system consisting of ACN: buffer (0.5M ammonium formate) (20:80 v/v) at a flow rate of 0.2 mL/min and a wavelength of 220 nm. The same composition of mobile system is used as diluent.

### Preparation of standard solution

58 mg of GMR, 158 mg of OTR, and 200 mg of TGF API powders were accurately weighed and dissolved to 100 mL with diluent in suitable volumetric flask. 1 mL of the prepared solution was diluted 10 mL to ascertain concentration of 58 µg/mL, 158 µg/mL, and 200 µg/mL for GMR, OTR, and TGF correspondingly represented as standard or 100% level concentrations.

### Preparation of sample solution

The capsule powder equivalent to 58 mg of GMR, 158 mg of OTR, and 200 mg of TGF was weighed and dissolved 100 mL of diluent. 1 mL of the prepared solution was diluted 10 mL to ascertain concentration of 58 µg/mL, 158 µg/mL, and 200 µg/mL for GMR, OTR, and TGF correspondingly. 0.4 µm Nylon filters were used to filter the sample solution before injection.

### Method validation

Validation is written documentation that offers a high level of assurance about a procedure or method. According to the ICH guidelines' Q2 specification, analytical methods are validated.

### System suitability test

The method's system suitability was tested by injecting standard solution in 6 successive injections and evaluating parameters such as theoretical plates (N), %RSD, and tailing factors.

### Linearity

The linearity of method represents the proportional relation between the experiential results and the mentioned concentrations. It was performed for the concentrations ranging from 14.5 to 87 µg/mL, 39.5 to 237 µg/mL, and 50 to 300 µg/mL of GMR, OTR, and TGF, respectively. A liner plot was drawn between concentration and peak area to calculate the regression coefficient ($R^2$).

### Precision

Precision is defined as the close proximity of the experimental values of a homogeneous sample on multiple consecutive samplings. It must be done as system precision and method precision in common. Six times during the day, the system precision standard solution was analyzed. Method precision was also applied to the sample solution. The % RSD values of peak areas and assays in system and method precision were calculated.

### Accuracy

The % recovery method can be used to determine the analytical methods' correctness to a significant extent, in

which a pre-determined amount of sample solution is added to the standard solution at concentrations of 50%, 100%, and 150%. At each % level, the mean recovery added amount was calculated.

### Specificity

It is the ability of an analytical approach to identify the desired drug substance in the vicinity of some of the other compounds without interference. Approximately 5 µL of blank solution, standard solution, sample solution, and degradation solution were each separately injected into the UPLC. In-depth examination was performed to ensure that no other peaks interfered with the intended analyte peak.

### Sensitivity

The LOD and LOQ were determined using standard deviation method.

$$LOD=3\sigma/S \quad LOQ = 10\ \sigma/S$$

Where, σ is the standard deviation of the intercept
*S* is the slope of the linear curve

### Robustness

Robustness of the method was evaluated by intentionally altering the optimized method conditions vaguely. The parameters such as flow rate (±0.1 mL/min) and mobile phase were altered vaguely and intentionally.

### FD studies

In the FD studies, the drug product or substance was deliberately subjected to more stress than in the accelerated stability conditions. The FD studies provide information about the drug's chemical stability and how to create a stable formulation with appropriate storage conditions. A few degradation requirements are mentioned specifically in the ICH federal regulations, such as acid and base hydrolysis, oxidative degradation, photo, and thermal degradation. To perform acid, base hydrolysis, and oxidative degradation, separate 2 mL portions of standard stock solution were mixed with 2 mL of 1N HCl, 2mL of 1N NaOH, and 2 mL of 3% H2O2 in individual flasks, refluxed at 600 C for 30 minutes, and cooled. All of the solutions were further diluted to achieve concentrations of about 58 g/mL, 158 g/mL, and 200 g/mL of GMR, OTR, and TGF, respectively. The standard stock solution was thermally and photolytically degraded for 24 h in a hot air oven at 80°C/75% RH and a UV chamber (254 nm). 1 mL of the above-mentioned exposed solution was further diluted to obtain concentrations of GMR, OTR, and TGF of 58 g/mL, 158 g/mL, and 200 g/mL, respectively. The degradation solutions were introduced into the UPLC system, and the percentage degradation of GMR, OTR, and TGF was calculated. According to regulatory guidelines, up to 20% degradation of the drug substance is the most effective and appropriate for the validation of the stability-indicating UPLC method.

### Assay

By injecting consecutive injections of standard and sample solution, the % purities of GMR, OTR, and TGF in commercially available tablet were estimated.

## RESULTS AND DISCUSSION

The method development was started with solubility studies of the GMR, OTR, and TGF. Based on the solubility of GMR, OTR, and TGF, water and ACN in 50:50 ratios were selected as diluent.

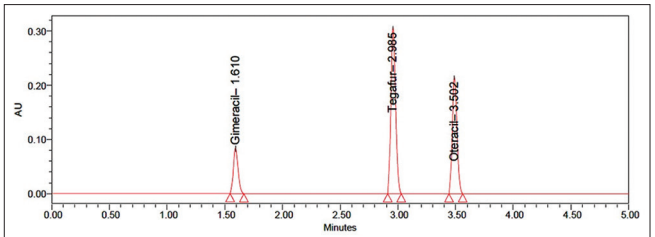
### Method optimization

Method optimization was done with trial and error method. After numerous trials, a method Xbridge BEH C18 (100 × 2.1 mm, 2.5 µ) column, using a mobile system, consists of ACN: buffer (0.5M ammonium formate) (20:80 v/v) at a flow rate of 0.2 mL/min and a wavelength of 220 nm. The experimental results obtained in trial and error method have been mentioned in Table 1, trial 6 chosen as optimized conditions, and the chromatogram of optimized method is shown in Figure 2. The retention times of TGF, GMR, and OTR were found at 2.9, 1.6, and 3.5 min, respectively.

### Method validation system

#### *Suitability*

The experimental data was attained by injecting standard solution in six consecutive injections satisfying the acceptance limits of parameters such as % RSD (≤2), tailing factor (≤2), and number of plate (>2000). The results are illustrated in Table 2.




| | Name | Area | USP Tailing | USP Plate Count | USP Resolution |
|---|---|---|---|---|---|
| 1 | Gimeracil | 815354 | 1.01 | 4874 | |
| 2 | Tegafur | 2794621 | 1.15 | 8532 | 7.28 |
| 3 | Oteracil | 2275038 | 1.04 | 6556 | 3.55 |

**Figure 2:** Chromatogram of the optimized method (58 µg/mL GMR, 158 µg/mL OTR, and 200 µg/mL TGF)

### Linearity

The method has appropriate linearity GMR, OTR, and TGF which were in the range of 14.5–87 µg/mL, 39.5–237 µg/mL, and 50–300 µg/mL determined by linearity curve plotted between concentration and peak area [Table 3 and Figure 3]. The statistically obtained regression coefficient value for the drugs was 0.999, which satisfied the acceptance limit.

### Accuracy

The mean percentage recovery of the GMR, OTR, and TGF at three different levels of the spiked solutions was found to be 99.45–100.57%, which represents that the method has considerable accuracy as per Q2 provision of ICH guidelines. The experimental results are revealed in Table 4.

### Precision

The %RSD values of the peak responses thus attained by injecting standard solution in 6 successive replicates were ≤2 [Table 5] which describes that the method precision was accomplished.

### Sensitivity

The LOD and LOQ values were determined as 0.009 µg/mL and 0.026 µg/mL for GMR, 0.23 µg/mL and 0.69 µg/mL for OTR, and 0.93 µg/mL and 2.81 µg/mL for TGF, respectively.

### Robustness

Deliberate alterations to the optimized method's mobile phase ratio, flow rate, and absorption wavelength could only slightly affect the findings for the system suitability

**Table 1:** Different trials

| Trial | Column | Buffer | Mobile Phase | Flow rate mL/min | Observation |
|---|---|---|---|---|---|
| 1 | Inertsil C18 (100×2.1 mm, 1.7 µm) | 0.5M ammonium formate | Buffer: ACN (30:70) | 0.2 | Longer RT for OTR |
| 2 | Inertsil C18 (100×2.1 mm, 1.7 µm) | | Buffer: ACN (40:60) | 0.2 | Longer RT for OTR and GMR peak not eluted |
| 3 | Inertsil C18 (100×2.1 mm, 1.7 µm) | | Buffer: ACN (50:50) | 0.2 | Peak tailing in GMR peak |
| 4 | X-bridge BEH C18, (100×2.1 mm, 2.5 µm) | | Buffer: ACN (60:40) | 0.2 | Peak tailing in GMR peak |
| 5 | X-bridge BEH C18, (100×2.1 mm, 2.5 µm) | | Buffer: ACN (70:30) | 0.2 | Peak response of TGF was not good |
| 6 | X-bridge BEH C18, (100×2.1 mm, 2.5 µm) | | Buffer: ACN (80:20) | 0.2 | Good resolution and peak shape of TGF, OTR and GMR were good |

XBD: Extra dense bonding, ACNL: Acetonitrile

**Table 2:** Results of system suitability parameters of standard solution

| Parameter | Sample name | GMR | OTR | TGF |
|---|---|---|---|---|
| Peak area | Mean±SD | 814140±1615.7 | 2259316±19603.94 | 2766010±17980.82 |
| | %RSD | 0.198 | 0.868 | 0.65 |
| Plate count | Mean±SD | 4873±175.1 | 8497±203.7 | 6471±128.6 |
| Tailing | Mean±SD | 1.08±0.6 | 1.12±0.3 | 1.04±0.7 |
| Resolution | Mean | - | 7.19 | 3.37 |

SD: Standard deviation, %RSD: Relative standard deviation

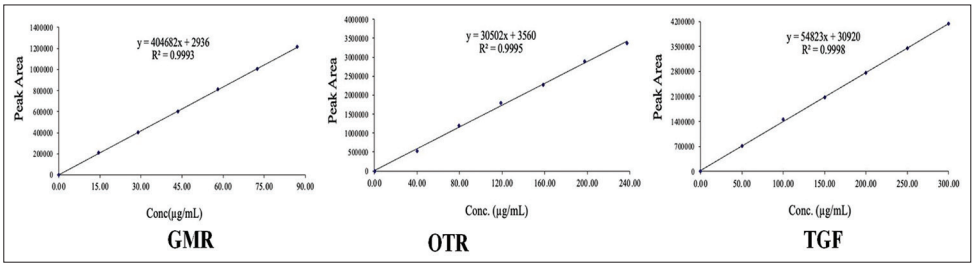



**Figure 3:** Linearity curve of GMR, OTR, and TGF

**Table 3:** Peak areas of linearity level solution GMR, OTR, and TGF

| % level | GMR | | OTR | | TGF | |
|---|---|---|---|---|---|---|
| | Concentration (µg/mL) | Peak area | Concentration (µg/mL) | Peak area | Concentration (µg/mL) | Peak area |
| 25 | 14.50 | 209337 | 39.50 | 524301 | 50.00 | 711715 |
| 50 | 29.00 | 402045 | 79.00 | 1189653 | 100.00 | 1463987 |
| 75 | 43.50 | 600437 | 118.50 | 1795299 | 150.00 | 2077973 |
| 100 | 58.00 | 812224 | 158.00 | 2278191 | 200.00 | 2764341 |
| 125 | 72.50 | 1005632 | 197.50 | 2888539 | 250.00 | 3457487 |
| 150 | 87.00 | 1215632 | 237.00 | 3370639 | 300.00 | 4132107 |
| Regression coefficient value ($R^2$) | | 0.999 | | 0.999 | | 0.999 |

**Table 4:** Results of % recovery of GMR, OTR, and TGF

| Drug name | % Level | Amount added (µg/mL) | Amount recovered (µg/mL) | *% Recovery (*n*=3) Mean±SD |
|---|---|---|---|---|
| GMR | 50 | 29 | 29.03 | 100.11±0.71 |
| | 100 | 58 | 58.3 | 100.57±0.94 |
| | 150 | 87 | 87.13 | 100.15±0.46 |
| OTR | 50 | 79 | 78.5 | 99.45±0.82 |
| | 100 | 158 | 158.6 | 100.35±0.42 |
| | 150 | 237 | 236.9 | 99.98±0.23 |
| TGF | 50 | 100 | 99.84 | 99.84±0.47 |
| | 100 | 200 | 200.17 | 100.08±0.02 |
| | 150 | 300 | 300.13 | 100.04±0.08 |

**Table 5:** Results of system and method precision GMR, OTR, and TGF

| Precision | Sample name | GMR | OTR | TGF |
|---|---|---|---|---|
| Intermediate Precision | Mean±SD | 100.1±0.187 | 99.8±0.937 | 99.7±1.152 |
| | %RSD | 0.19 | 0.94 | 1.16 |
| Method Precision | Mean±SD | 99.9±0.152 | 99.6±0.797 | 100.6±0.504 |
| | %RSD | 0.15 | 0.8 | 0.5 |

**Table 6:** Results of robustness of standard solution of GMR, OTR, and TGF

| Drug name | Peak area | Flow rate (0.2±0.1 mL/min.) | | Mobile phase-Organic phase (20±5 mL) | |
|---|---|---|---|---|---|
| | | 0.1 | 0.3 | 85:15 | 75:25 |
| GMR | Mean (n=3) | 823117 | 796526 | 835500 | 787336 |
| | SD | 1922.37 | 2000.50 | 1780.74 | 971.37 |
| | % RSD | 0.23 | 0.25 | 0.21 | 0.12 |
| OTR | Mean (n=3) | 2442295 | 2144251 | 2534006 | 2346323 |
| | SD | 29725.56 | 20383.26 | 7697.11 | 21163.62 |
| | % RSD | 1.21 | 0.95 | 0.30 | 0.90 |
| TGF | Mean (n=3) | 2971727 | 2556051 | 3072226 | 2448892 |
| | SD | 22357.66 | 22941.18 | 19610.22 | 39086.70 |
| | % RSD | 0.75 | 0.89 | 0.64 | 1.59 |

parameters, which were only achieved inside the acceptable range [Table 6]. This illustrates the resilience of the method.

## FD

In majority of the stability-indicating analytical methods, up to 20% degradation in the drug substance is considered by scientists. The percentage degradation of drug substance was assessed at different time points 0, 6, 12, 18, and 24 h by comparing the peak areas produced by pure standard solution and stressed standard solution after 24 h. The peaks in degradation studies showed the purity angles below the set threshold indicating in high level of purity, i.e., 1.34 and 5.44 for GMR, 0.54 and 9.45 for OTR, and 2.15 and 8.34 for TGF. The attained results are shown in Table 7. The chromatograms of degradation studies are mentioned in Figure 4. The three analytes were highly stable at the mention thermal degradation conditions in comparison with acid, base, and oxidative degradations.

**Table 7:** Results of forced degradation studies

| Type of degradation | % Degradation | | |
|---|---|---|---|
| | GMR | OTR | TGF |
| Acid hydrolysis | 18.7 | 23.1 | 20.8 |
| Base hydrolysis | 20.4 | 26.6 | 24.3 |
| Oxidation | 21.8 | 19.5 | 17.2 |
| Photolytic | 18.8 | 18.6 | 18.7 |
| Thermal | 5.3 | 7.5 | 5.3 |
| Water | 3.4 | 4.8 | 10.1 |

## Assay

The % purity of the GMR, OTR, and TGF (tegonat with label claim: 5.8 mg/15.8 mg/20 mg) capsule form was in the limit of 100% ± 2 [Table 8].

A number of RP-HPLC, UPLC, and LC-MS techniques has been established in the past for GMR, OTR, and TGF either alone or in combination with other agents. However, there was no single RP-UPLC approach with a straightforward mobile phase and short elution periods. As a result, efforts have been undertaken to create a system with a straightforward mobile phase and minimal RT. The

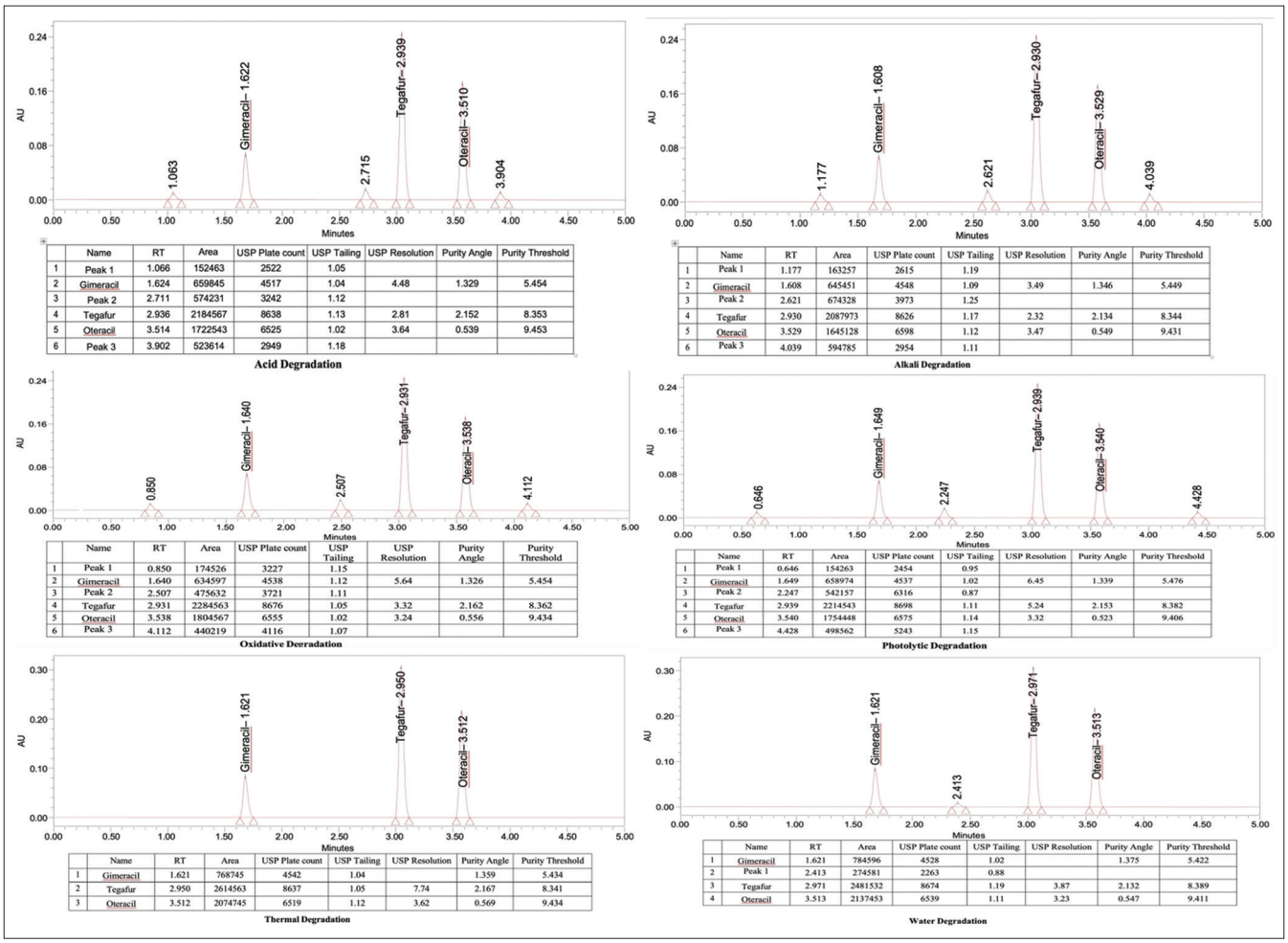



**Figure 4:** Chromatograms of forced degradation studies

**Table 8:** Assay of GMR, OTR, and TGF in the marketed tablet formulation

| Drug | Peak name | Peak Area | Label claim (mg) | Amount Found (mg) | Assay (% w/w) |
|---|---|---|---|---|---|
| GMR | Standard | 814364 | 5.8 | 5.78 | 99.65 |
| | Test | 812319 | | | |
| OTR | Standard | 2258309 | 15.8 | 15.69 | 99.30 |
| | Test | 2244786 | | | |
| TGF | Standard | 2765353 | 20 | 20.10 | 100.05 |
| | Test | 2769274 | | | |

RT described for GMR, OTR, and TGF was lower than the prior technique, which is suggested as being more affordable because it reduces the elution time and mobile phase use. As a result, the time required for sample analysis was reduced, enabling more samples to be evaluated within the allotted time.

## CONCLUSION

To simultaneously measure GMR, OTR, and TGF in bulk blended powder and their mixed capsules, a simple, sensitive, accurate, robust, specific, and isocratic RP-UPLC method was established. The stability of the approach is represented by the application of harsh and purposeful FD conditions to the analytes. The suggested approach successfully separated GMR, OTR, and TGF from their degradation products. The approach that is now developed has excellent stability-indicating capacity, specificity, and sensitivity which can be significantly implemented in the analytical research division in the pharmaceutical industry.

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## AUTHORS' CONTRIBUTIONS

All the authors contributed equally to design and frame of the work, acquisition, and interpretation of data and manuscript preparation, and all authors have read the prepared manuscript and approved for the publication.

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