Simultaneous MEKC-DAD and smart spectrophotometric assays of thiocolchicoside and etoricoxib in challenging concentration ratio mixtures

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Abstract: Potent muscle relaxant (thiocolchicoside, TCC) and nonsteroidal anti-inflammatory drug (etoricoxib, ETXB) fixed-dose combination is formulated at relatively high 1:15 and 1:7.5 ratios for TCC and ETXB, respectively. Since the minor component (TCC) has lower absorptivity, assay of TCC/ETXB tablets presents an analytical challenge. The current study presents two novel methods: first is a micellar electrokinetic capillary chromatography (MEKC). Background electrolyte is borate buffer (40 mM, pH 9.2) containing 30 mM sodium dodecyl sulfate and methanol (ratio 80:20%; v/v), measured at 210 nm. Second is a direct double \( \lambda_{\text{max}} \) spectrophotometric method; minor component, TCC, is measured directly at its distant \( \lambda_{\text{max}} \) (373 nm), at zero absorption of ETXB. Then, a ten-fold dilution step is carried out to eliminate TCC spectral interference and ETXB is determined at its \( \lambda_{\text{max}} \) (282 nm). Both drugs' concentrations disclose obedient linearity at 2–100 \( \mu \text{g} \cdot \text{mL}^{-1} \) in MEKC, versus 3–25 and 40–350 \( \mu \text{g} \cdot \text{mL}^{-1} \) for TCC and ETXB, respectively, in spectrophotometry. All ICH validation elements have been fulfilled for the developed methods. MEKC and spectrophotometric assays achieve accuracy, precision, selectivity, and robustness to be recommended for industrial quality control routine analysis of TCC/ETXB pills formulated at cited ratios or even higher.

Keywords: electrochromatography, muscle relaxant, NSAID, direct spectrophotometry, formulation ratio

1 Introduction

One of the major obstacles for analytical method applicability is the high drug concentration ratio in pharmaceutical mixtures. Accurate estimation of the minor component in the presence of the major one(s) counts the analyst’s first target. Then, followed by the simultaneous determination of both or multi-components, minor and major, in the cited drug combination. Specific tailored assays have been efficiently developed to determine pharmaceutical drug mixtures in their challenging ratios [1–5].

Thiocolchicoside (TCC) is a thiocolchicine 2-glucoside analogue (Figure 1). It was the first to be officially listed in British Pharmacopoeia BP 2019 [6]. It is a semi-synthetic sulfur derivative of the well-known anti-gout natural alkaloid, colchicine. TCC is a potent skeletal muscle relaxant. In addition, it has anti-inflammatory and analgesic potentials. TCC is commonly indicated for acute and chronic orthotic or rheumatoid manifestations for patients above 16 years old. It selectively binds to g-aminobutyric acid A (GABA-A) receptors. As GABA is the main inhibitory neurotransmitter in the human cortex [7], TCC promotes GABA inhibitory pathways for muscular contractures.

Etoricoxib or etoricoxibum (ETXB) has not appeared yet in any pharmacopeial edition. It is a synthetic bipyruridine derivative (Figure 1). ETXB is classified as a selective cyclooxygenase-2 enzyme (COX-2) inhibitor. Its mechanism of action is the same as others in anti-COX-2 family through preventing prostaglandin production from arachidonic acid [8]. ETXB is a potent anti-inflammatory...
antipyretic drug with potential antineoplastic properties. It has been approved for medical use in 2002 as a strong nonsteroidal anti-inflammatory drug (NSAID). ETXB is indicated in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and gout.

Synergistic coadministration of NSAIDs and centrally acting muscle relaxants step forward in updated clinical trends. Moreover, fixed-dose combinations achieve better compliance, adherence, and therapeutic response than their corresponding free-equivalent combination therapies (fixed-dose poly pills). Thus, TCC is co-formulated with ETXB in pharmaceutical tablets and mainly indicated for painful muscle spasms such as torticollis, lumbago, backache, and neuralgias. TCC and ETXB are combined at two concentration ratios (1:15 and 1:7.5, respectively). Such ratios are high enough to be challengeable, considering that the minor component (TCC) owns lower absorptivity.

Updated quest of the literature disclosed few analytical methods that simultaneously estimate TCC and ETXB in their binary mixtures, either using RP-HPLC [9–11], HPTLC [12], or spectrophotometry [13]. However, the higher concentration ratio (1 TCC:15 ETXB) was only considered by Kumar et al. in simultaneous estimation of TCC and ETXB mixture by RP-HPLC [9]. Till date, no single literature statement reports a micellar electrokinetic capillary chromatographic (MEKC) method for the assay of TCC/ETXB binary mixture. In addition, none of the reported spectrophotometric methods afford direct simultaneous determination of the cited drugs.

The present work introduces two novel simple green and eco-friendly analytical techniques. The first approach is MEKC coupled to diode-array detection, while the second one is a UV-spectrophotometric one. Both techniques have been developed and specifically tailored for the simultaneous determination of TCC and ETXB in synthetic binary mixtures and pharmaceutical dosage forms at their challenging concentration ratios. For MEKC, the cited analytes are enveloped in sodium dodecyl sulfate (SDS) at its critical micelle concentration (CMC). The second method is an instant spectrophotometric double \( A_{\text{max}} \)-method. It relies on subsequent direct measurement of the minor component (TCC) followed by the major one (ETXB), after adequate dilution, both at their maximum wavelengths. Both the proposed techniques have been specifically developed, carefully optimized for one and each parameter, and then fully validated according to International Council for Harmonization (ICH) [14] guidelines.

For the first time, the current research presents simultaneous capillary electrophoretic separation and quantitation of TCC/ETXB binary mixture. Moreover, the suggested \( A_{\text{max}} \)-determination is the first direct spectrophotometric attempt to be applied for the assay of the cited drugs in their mixture, coming over the methods addressed in the literature [13]. Binary mixtures and combined tablets of TCC/ETXB (in two-level ratios: 1:15 and 1:7.5, respectively) have been accurately and precisely quantified in robust, affordable, simple, and green flowing manner. Reliable results of the proposed methods can recommend their application in routine quality control analysis of TCC/ETXB fixed-dose combinations.

2 Experimental

2.1 Instrumentation

Agilent CE instrument 7100 series, Agilent Technologies Deutschland GmbH, Waldbronn, Germany. It is equipped with Diode array detector, DAD, and data handling system comprising a computer loaded with Agilent Chemstation software. A pH-Meter, Model pH211 (Hanna Instruments, RI, USA), was employed to determine pH values. It was calibrated using standard buffers of pH 4 and 7 at room temperature.

Spectrophotometric measurements were accomplished using UV-1800 thermospectronic Helios Alpha (UK) UV-VIS spectrophotometer, Shimadzu Corporation, Japan, connected to Harvest computer system. Quartz cells of 1 cm were employed.
2.2 Reagents and materials

TCC and ETXB were gifted by Memphis Co. for Pharmaceutical & Chemical Industries and DBK Pharma, respectively. Fisher Scientific, UK, was the source of HPLC-grade acetonitrile, ACN, and methanol. Analytical-grade boric, acetic, and phosphoric acids, in addition to SDS, were purchased from Oxford Lab Chem, India. Sodium hydroxide (El-Nasr Chemical Co., Egypt) and highly pure distilled water were used.

The used tablets were laboratory-prepared as reported in the pharmaceutical market regarding commercial TCC/ETXB combined tablets. They incorporated both concentrations (4/60 and 8/60 mg TCC/ETXB/tablet). Microcrystalline cellulose, lactose monohydrate, povidone, and magnesium stearate were added as excipients.

2.3 Chromatographic conditions

2.3.1 Separation conditions

The method was performed in a deactivated fused silica capillary (Agilent Technologies, Waldbronn, Germany). Capillary dimensions were a total length of 33.5 cm, an effective length of 25 cm, and an internal diameter of 50 μm. Detection was performed at 210 nm for both TCC and ETXB.

2.3.2 Preparation of running buffer

Borate buffer (40 mM, pH 9.2) was prepared by weighing 0.248 g of boric acid and 0.02 g of sodium hydroxide in 100 mL of distilled water, and then pH was checked and adjusted. The buffer contains 30 mM SDS, 0.602 g of SDS was added to 100 mL of the previously prepared buffer, and then sonicated for 10 min till complete dissolution of SDS powder. The finally used background electrolyte (BGE) consists of 80 parts of 10 mM borate buffer (pH 9.2) containing 25 mM SDS and 20 parts of HPLC-grade methanol.

2.3.3 Capillary conditioning

Volume of 0.5 M NaOH was employed for 15 min capillary flushing, followed by 15 min flushing. Then, capillary was flushed with NaOH at lower concentration (0.1 M) for 5 min and left for 150 s to ensure complete activation of the capillary inner wall. At the end, it was exposed to washing with distilled water and equilibration with BGE for 5 min and 600 s, respectively.

Between successive runs, the capillary was rinsed with BGE for 60 s. Buffer vials were refilled after each five successive runs to ensure proper reproducibility of run-to-run injections. Injections were performed using hydrodynamic mode under voltage of 30 KV, pressure of 50 mbar, and for 16 s.

2.4 Preparation of standard solutions and construction of calibration curves

Separate stock standard solutions of TCC and ETXB were made in HPLC-grade methanol at a concentration level of 1,000 μg·mL⁻¹.

2.4.1 MEKC method

Corresponding to concentration range of 2–100 μg·mL⁻¹, proper aliquots of TCC and ETXB stock solutions were added into a set of 10 mL volumetric flasks. The volume was completed with distilled water. Triplicate injections were performed for each of these working solutions. Peak areas were plotted against the corresponding concentrations (Table 1).

2.4.2 Spectrophotometric method

Working solutions were prepared by transferring proper aliquots of TCC and ETXB stock solutions into a set of 10 mL volumetric flasks. They were completed to mark with distilled water to reach concentration ranges of 3–25 and 40–350 μg·mL⁻¹ for TCC and ETXB, respectively. Absorbance values of the prepared solutions were recorded at TCC λₘₐₓ (373 nm). Then, the same prepared solutions were 10-fold diluted with distilled water and absorbance values were measured at ETXB λₘₐₓ (282 nm). For both TCC and ETXB, the selected amplitudes were plotted versus the corresponding concentrations and regression equations were computed (Table 1).

2.5 Assay of pharmaceutical dosage forms

Ten tablets from each tablet ratio (4/60 and 8/60 mg TCC/ETXB) were separately weighed and ground well.
### Table 1: Validation and regression parameters of the proposed methods

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MEKC</th>
<th>Double $A_{max}$ spectrophotometry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TCC</td>
<td>ETXB</td>
</tr>
<tr>
<td>Selectivity$^a$</td>
<td>100.47 ± 1.30</td>
<td>100.33 ± 1.39</td>
</tr>
<tr>
<td>Accuracy$^b$</td>
<td>99.65</td>
<td>100.60</td>
</tr>
<tr>
<td>Precision$^c$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-day</td>
<td>1.44</td>
<td>1.63</td>
</tr>
<tr>
<td>Inter-day</td>
<td>1.38</td>
<td>1.56</td>
</tr>
<tr>
<td>LOD ($\mu$g·mL$^{-1}$)</td>
<td>0.58</td>
<td>0.31</td>
</tr>
<tr>
<td>LOQ ($\mu$g·mL$^{-1}$)</td>
<td>1.94</td>
<td>1.04</td>
</tr>
<tr>
<td>Linearity range</td>
<td>2.00–100.00</td>
<td>2.00–100.00</td>
</tr>
<tr>
<td>Intercept ($a$)</td>
<td>0.47</td>
<td>4.52 × 10$^{-2}$</td>
</tr>
<tr>
<td>Slope ($b$)</td>
<td>1.58</td>
<td>2.54</td>
</tr>
<tr>
<td>Correlation coefficient ($r$)</td>
<td>0.9996</td>
<td>0.9995</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.9993</td>
<td>0.9990</td>
</tr>
<tr>
<td>$S_a^d$</td>
<td>0.76</td>
<td>1.47</td>
</tr>
<tr>
<td>$S_b^d$</td>
<td>1.33 × 10$^{-2}$</td>
<td>2.59 × 10$^{-2}$</td>
</tr>
<tr>
<td>$S_{y/x}^d$</td>
<td>1.51</td>
<td>2.92</td>
</tr>
<tr>
<td>$S_%{y/x}$</td>
<td>0.85</td>
<td>1.02</td>
</tr>
<tr>
<td>$F^d$</td>
<td>13,950.26</td>
<td>9,567.56</td>
</tr>
<tr>
<td>Significance $F$</td>
<td>4.64 × 10$^{-17}$</td>
<td>3.06 × 10$^{-16}$</td>
</tr>
</tbody>
</table>

$^a$ Calculated as (mean% recovery ± RSD%) from synthetic mixtures of different ratios ($n = 9$). $^b$ Calculated as mean% recovery from standard addition method at three concentration levels ($n = 9$). $^c$ Calculated as mean RSD% from synthetic mixtures at different ratios ($n = 9$). $^d$ $S_a$ is standard deviation of intercept, $S_b$ is standard deviation of slope, $S_{y/x}$ is standard deviation of residuals, and $F$ is variance ratio.

LOD: limit of detection; LOQ: limit of quantitation.

Into two 100 mL volumetric flasks, weights containing 15/225 and 5/40 mg TCC/ETXB were transferred from the powdered tablets of higher and lower components ratio, respectively.

For each flask, 60 mL volume was added from HPLC-grade methanol, followed by 30-min sonication. Then, methanol was completed till the mark and the solution was filtered. From each filtrate, 1 mL volume was diluted to 10 mL with distilled water. Finally, two tablet extracts were obtained containing 15/225 and 5/40 $\mu$g·mL$^{-1}$ TCC/ETXB at the higher and lower tablet ratios, respectively. Steps were then followed as described in the last section, entitled “Construction of calibration curves”.

### 3 Results and discussion

#### 3.1 MEKC method development

##### 3.1.1 Optimization of capillary electrophoresis conditions

Various attempts were made to separate TCC/ETXB mixtures effectively in CE. Initially, capillary zone electrophoresis (CZE) mode using acetate buffer (10, 20, 50, and 100 mM) of pH 4.7 and phosphate buffer (10, 20, 50, and 100 mM) of pH 7.4 were sequentially attempted. Separated, but deformed peaks for the binary mixture. Borate buffer (10, 20, 50, and 100 mM) of pH 9.2 as well as 50 mM borate buffer were also attempted at several pH values. TCC/ETXB binary mixtures were not resolved; overlapping peaks appeared in each trial. Finally, CZE mode was excluded throughout the cited assay.

MEKC mode was attempted by addition of SDS above its CMC. Phosphate buffer of 10–20 mM with 25 or 50 mM SDS, and borate buffer of 10 mM with 25 or 50 mM SDS were used for trials. Both buffers achieved two well-resolved peaks for the binary mixture. Borate-buffered SDS trials had the privilege of a shorter run time than phosphate-buffered ones and were consequently selected.

Analytes’ separation and quantification, by applying MEKC mode, were ultimately overwhelmed by differing parameters. Experimentally changeable parameters were carefully studied: the pH and the concentration of the used buffer, the concentration of the chosen surfactant SDS, capillary length, applied voltage, injection volume, and detection wavelength [15].
3.1.1 pH and concentration of the buffer

TCC has a highly basic pKa value of 12.74 while ETXB has a pKa of 4.5. Ascending serial of pH levels of borate buffer (7, 8, 9, 10, and 11) was attempted. Significant lengthening of peaks’ migration time was observed at pH values of 10 and 11. Lower pH values resulted in similar electropherograms. Borate buffer at pH 9.2 was optimal, seeking the maximum buffer capacity.

The concentration of borate buffer (adjusted at pH 9.2) was studied at ascending levels (10, 20, 30, 40, and 50 mM). Lower concentrations (10 and 20 mM) gave broadened peaks for ETXB. Better results were obtained at higher borate concentrations. Optimal peak shapes and reasonable migration times were achieved by the 40 mM borate buffer at pH 9.2.

3.1.2 Concentration of the surfactant (SDS)

Migration time is directly proportional to the added SDS concentration. Beyond its CMC (8 mM), SDS was added in different concentrations: 15, 20, 25, 30, and 35 mM in separate CE runs. Again, peak broadening was obtained at trials of lower concentrations. For satisfactory results, the 30 mM SDS was selected.

3.1.3 Type and concentration of organic modifier

Methanol and ACN were tried as organic modifiers. However, ACN resulted in distorted peaks. On the other hand, methanol is considered a greener and more economic solvent. Generally, the maximum content of any organic solvent to stabilize micelles is 20–30%. In addition, higher or lower methanol percentages resulted in unacceptable resolution or poor precision; respectively. Therefore, methanol was employed at a concentration of 20% (v/v).

3.1.4 Length of the capillary

In simple words, the use of a 25 cm capillary achieved reasonable run time for assay of the studied binary mixture. This was significantly observed after the use of a 50 cm capillary that increased the run time without gaining any additional privilege.

3.1.5 Applied voltage

Changing the applied voltage and retesting (10, 15, 20, 25, and 30 kV) for successive CE runs was attempted. Voltage is inversely proportional to migration time (related to electroosmotic flow). Although migration times were longer, resolution was quite acceptable, a voltage of 30 kV was the one of the choice.

3.1.6 Time of injection

Hydrodynamic injection, at a constant pressure of 50 mbar, was applied by varying the injection time (starting 5–18 s). The longer the injection time, the higher the peaks of the analytes. Optimal injection time of this assay was 16 s, compromising the targeted sensitivity and peaks’ symmetry.

3.1.7 Wavelength of detection

DAD has the ability of developing electropherograms at more than one wavelength for the same run. Various wavelengths were tried. However, response recorded at 210 nm could achieve the maximum sensitivity without peaks’ distortion (Figure 2). Moreover, DAD confirmed peak purity for both analytes.

3.2 Double A_max spectrophotometric method

The UV-absorption spectra of TCC and ETXB aqueous solutions showed continuous spectral overlap through the 210–310 nm range (Figure 3a). This hindered the direct simultaneous determination of both drugs. TCC showed a broad distinct peak of \( \lambda_{\text{max}} \) 373 nm; heavy spectral absorbance readings of the major component, ETXB, diminished beyond 315 nm. Solution of binary drug mixture in Figure 3a was 10-fold diluted with distilled water. The diluted solution was rescanned through the same wavelength range (Figure 3b). Latter scan disclosed an absorption maximum of ETXB at 282 nm at which zero absorbance was recorded for TCC.

Many solvents were tried, such as ACN, methanol, and distilled water. However, the latter was selected as it is the greenest solvent ever. Moreover, none of the other solvents presented a significant advantage over water regarding spectral characteristics of both TCC and ETXB.
3.3 Method validation

Both proposed MEKC and spectrophotometric methods were successfully validated following ICH recommendations [14].

3.3.1 Selectivity

Selectivity was evaluated through analysis of synthetic TCC/ETXB mixtures of different ratios, including both ratios of the commercial tablets (1:15 and 1:7.5). Following

Figure 2: Typical MEKC electropherograms of standard mixtures of (a) 40 and 40 μg·mL⁻¹, (b) 5 and 37.5 μg·mL⁻¹, and (c) 5 and 75 μg·mL⁻¹ of TCC and ETXB, respectively. Simulating the ratios of 1:1, 1:7.5, and 1:15 of formulations.
triplicate analysis by both the proposed methods, mean percentage errors for both drugs did not exceed 2% (Table 1). Thus, the proposed methods proved to be free from cross-interference between the studied combined drugs.

3.3.2 Accuracy

The accuracy of both methods was investigated by applying standard addition approach. Powdered tablets were spiked with each component, separately, at three levels (80%, 100%, and 120% of label claim). Extraction, filtration, and dilution were carried out. Following triplicate analysis by both the proposed methods, the resulting mean percentage recoveries guaranteed excellent accuracy (Table 1).

3.3.3 Precision

Precision was assessed from triplicate analysis of synthetic mixtures (previously mentioned in section 3.3.1), on the same day and in different days. Intra-day and inter-day RSD% values did not exceed the acceptable limit (2%) (Table 1).

3.3.4 Linearity and range

Serial dilutions for each of the studied drugs were analyzed by the described MEKC and spectrophotometric procedures within concentration ranges listed in Table 1. Under the previously chosen experimental parameters, there were good linearity proportionalities between the recorded signals (peak area or A) and TCC or ETXB concentration levels. Correlation coefficients (r) were ≥0.999. Moreover, linearity ranges covered TCC and ETXB in their tablet ratio, 1:15 and 1:7.5. The rest of the linearity parameters were computed [16,17]. As shown in Table 1, the rest of the statistical parameters were computed, and all were found to be acceptable to fulfill linearity as a fundamental validation parameter.

3.3.5 LODs and LOQs

As MEKC is a chromatographic technique, LODs and LOQs were calculated as the concentrations with S–N ratio of 3:1 and 10:1, respectively. In the spectrophotometric method, (S/n/b) was multiplied by 3 and 10 to determine LODs and LOQs, respectively. LODs and LOQs for TCC and ETXB are listed in Table 1, showing high sensitivities of both suggested methods.
3.3.6 Robustness

The robustness of the MEKC method was evaluated as in selectivity and precision; synthetic mixtures were prepared at different TCC/ETXB ratios. However, slightly intended variations in the experimental conditions were made during triplicate analysis. Both borate buffer and SDS concentrations were changed by ±2 mM, while pH was susceptible to ±0.2 variation. Methanol percentage in BGE and detection wavelength was changed by ±2% (ν/ν) and nm, respectively. Moreover, various methanol lots were tried. Only one parameter was varied each time. For both TCC and ETXB, the calculated RSD% values of peak areas and retention times were low enough to conclude that small unintentional changes of the methods’ experimental conditions do not affect its reliability (Table 2).

3.4 Assay of pharmaceutical dosage forms

Both 4/60 and 80/60 mg TCC/ETXB tablet extracts, prepared in section 2.5, were analyzed in five replicates using the proposed methods. Mean percentage recovery, SD, and RSD% values were calculated. They were satisfactory to prove the absence of cross-interference from the co-formulated commercial excipients (Table 3). As an additional investigation in MEKC, no interfering peaks appeared in electropherograms of TCC/ETXB tablet extracts. Moreover, the purity of TCC and ETXB peaks were checked by DAD. Spectra of tablets extracts and reference solutions were superimposed. All of these indicated high accuracy, precision, and selectivity of the proposed methods for commercial tablets assay at both higher (1:15) and lower (1:7.5) TCC/ETXB ratios.

Table 3: Assay of TCC and ETXB in their combined tablets using the proposed methods (n = 5)

<table>
<thead>
<tr>
<th>Laboratory-prepared tablets</th>
<th>MEKC</th>
<th>Double A&lt;sub&gt;max&lt;/sub&gt; spectrophotometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCC</td>
<td>ETXB</td>
<td>TCC</td>
</tr>
<tr>
<td>Mean%</td>
<td>100.59</td>
<td>100.59</td>
</tr>
<tr>
<td>recovery ± SD</td>
<td>± 0.69</td>
<td>± 0.98</td>
</tr>
<tr>
<td>RSD%</td>
<td>0.69</td>
<td>0.98</td>
</tr>
</tbody>
</table>

4 Conclusions

Two novel analytical methods were developed for simultaneous determination of TCC and ETXB at their challengeable tablet ratios. The first one presents the first attempt to adopt MEKC-DAD for assay of TCC/ETXB commercial tablets. It could compromise between the required resolution and high sensitivity. The developed MEKC method has the advantage of simple operation and cheapness (requiring just few milliliters of BGE and inexpensive capillaries relative to HPLC columns). The second method depends on measuring each drug at its maximum wavelength. The minor component, TCC, was determined at a distant maximum where spectrum of the major component, ETXB, showed no overlap. TCC contribution was, then, eliminated along the whole spectrum by a ten-fold dilution. Finally, the major component, ETXB, was freely measured at its normal maximum. This approach is considered the first direct spectrophotometric proposal to resolve such mixture at all tablet ratios. Spectrophotometric method represents a suitable straightforward and affordable alternative, where no analytical laboratory lacks spectrophotometer instrumentation even in the developing countries. Both developed MEKC and spectrophotometric methods successfully overcame TCC/ETXB challengeable ratios in their tablets in selective, accurate, and precise manner. Meanwhile the former method is highly sensitive than the latter, in addition to chromatographic separation and green manner. Results recommend their application for routine industrial analysis of TCC/ETXB tablets.

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Conflict of interest: Authors state no conflict of interest

Data availability statement: The files used to support the data findings of this study are available from the corresponding author on request.

References


