Comparative Investigation of $\beta$- and $\gamma$-cyclodextrin as Ionophores in Potentiometric Based Sensors for Naltrexone

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The formation and developed of Polyvinyl chloride (PVC) membrane sensors for naltrexone (NALT) are examined. The electroactive elements contains molecular recognition components $\beta$- or $\gamma$-cyclodextrin as ionophores. Sensor 1 was fabricated using $\beta$- cyclodextrin, while sensor 2 was used $\gamma$-cyclodextrin in presence of potassium tetrakis (4-chlorophenyl)borate as ion additive, PVC as matrix and dioctylphthalate as plasticizer. The sensors show rapid, fixed and sub-Nernstian response (38 and 34 mV/decade) meantime a relative wide naltrexone dynamic range ($1 \times 10^{-2}$ - $5.8 \times 10^{-6}$ and $1 \times 10^{-2}$ - $4.0 \times 10^{-6}$ M), with detection limits of $5 \times 10^{-6}$, and $3.0 \times 10^{-6}$ M for $\beta$- or $\gamma$- cyclodextrin sensor, respectively. The optimum pH was in range of 2.0 - 7.0. The investigated sensors show a good selectivity for NALT with respect of different ions. The determination of 300 $\mu$g/ml of naltrexone appear a recovery value of 97.2% and 97.5%, respectively with mean RSD values of 1.7% and 2.0% for sensors 1 and 2. The examined sensors have been used for the assay of NALT in its dosage form. The outcome data for the assay of naltrexone in tablet using the investigated sensors are good convention with the published spectrophotometric procedure. Potentiometric titrations of naltrexone using the examined sensors have been carried out.

Keywords: Naltrexone HCl, $\beta$- and $\gamma$- cyclodextrin, PVC, Potentiometry.

1. INTRODUCTION

The basic purpose of naltrexone is the remediation of alcohol groggy and reduce drinking winery as well as working to reduce the effects of opiates, where it works to reduce the effects of delightful of narcotic drugs[1,2]. Naltrexone has any therapeutic benefit, except for the treatment of addiction.
Naltrexone resembles oxymorphone in its chemical synthesis and does not have the same properties of opiates. Chemical structure of naltrexone is similar to oxymorphone except that the methyl group on the nitrogen atom is changeling with a cyclopropylmethyl. Its chemical structure is: (5α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one [3] [Fig.1]. It’s a white crystal powder; that is soluble in water and is present as hydrochloride salt.

![Chemical structure of naltrexone](image)

**Figure 1.** Chemical structure of (A) naltrexone, (B) β- and (C) γ-cyclodextrin.

Various analytical methods reported for its assay include: spectrophotometry[4,5], spectrofluorimetry[6], amperometry[7], voltammetry[8], high performance liquid chromatography-ultraviolet (HPLC-UV)[9,10] HPLC-amperometry[11], HPLC-Mass detection (HPLC-MS)[12,13] and gas chromatography coupled with mass detection (GC-MS)[14,15]. Most of these methods involve complicated procedures, sample treatment, high price instruments and need a high qualified person.

Recently, there has been an extended energy to make exact illustrative methods which are streamlined for NALT assay in clinical and quality control Laboratory, due to the importance of naltrexone for treatment of addiction.

On the other hand, electrochemistry provided analytical instruments, which are characterized by low price and portability. PVC sensor being fundamental, fast, selective, reasonable, low energy consumption, wide dynamic range and have been applied to different areas[16-18].

To the best of our knowledge, up to date there is only one potentiometric sensor for NALT has been reported[19]. The cited method involves NALT-tetraphenylborate ion-associate as electroactive element for PVC membrane sensor[19]. The calibration range was 1×10^-3 - 1×10^-5 M with low limit of concentration of 5×10^-6 M for NALT.

Cyclodextrins can form a stable complex with many variety of ionic substances to form host-guest inclusion complexes. Cyclodextrins are a very significant class of compound that is used in electrochemical studies which depends basically on the reactions in solution as well as on the surface of electrodes. Preparation of PVC membrane sensors using CDs as electroactive materials is consider a new research area for electrochemical sensors particularly in pharmaceutical analysis[20-23].
The proposed sensors evaluates the applicability of using β-CD and γ-CD as ionophore as a new active material for construct PVC sensors for naltrexone which aim to improve both selectivity and sensitivity. The investigated study offered two new sensors for NALT. Sensor 1 is based on β-CD and sensor 2 is based on γ-CD as ionophore embedded on PVC membrane. Both sensors are examined and optimized for the determination of naltrexone in its pharmaceutical formulation.

2. EXPERIMENTAL

2.1. Apparatus

All measurements were carried out at 25 ± 1 °C unless otherwise stated using WTW (pH/mV) meter (model 523) with NALT membrane sensors in coupling with an Orion double junction calomel electrode as reference. Measurement of pH was made using Ross glass pH electrode (Orion 81-02) for all pH measurements.

2.2. Reagents and materials

All chemicals used were of analytical reagent class unless otherwise stated and doubly distilled water was used in all measurements. PVC powder of high molecular weight, dibutyl sebacate, dioctyl phthalate, o-nitrophenyl octylether, tetrahydrofuran (THF) of purity > 99 % were gained from Aldrich Chemical Company. Naltrexone HCl was acquired from Sigma Chemical Company, Germany. KTpClPB, β-CD and γ-CD, were acquired from BDH, Chemical Ltd. Deltrexone (Manufactured by Delta Pharmaceuticals Co., Egypt). The stock solution of 1×10^{-2} M NALT was prepared in water by dissolving the exact amount of NALT. Five working NALT standards were prepared (1×10^{-2} - 1×10^{-6} M ) by suitable dilution. Buffer solution of pH 3.5 was prepared from mixture of 0.05M sodium acetate with acetic acid.

2.3. Construction of the proposed sensors

Portion of five mg of β-CD or γ-CD and five mg of potassium tetrakis(4-chlorophenyl)borate were mixed with 190 mg PVC powder, 350 ml of plasticizer (DBS or DOP or NPOE) and 5 ml THF in glass Petri dishes. The sensing membranes have been constructed, after all component mixed well and allow it to volatilize overnight. The master membrane formed were cutting and pasting the body of the electrode using solution of THF[24,25]. Electrode bodies were a tube made of glass with a hose connected to a suitable plastic tube, connected with the membrane and filled with reference solution (NALT and KCl). Ag/AgCl was used as internal reference electrode. The working sensors were conditioned during soaking in a solution of 1×10^{-2} M NALT for 1 h.
2.4. Procedure

Insert the electrodes (PVC membrane sensors in coupling with reference electrode) into the electrochemical cell, containing 9 ml of acetate buffer, with continuous stirring. Added 1 ml aliquot of NALT solution to cover the final concentration of NALT range from $1 \times 10^{-2}$ to $1 \times 10^{-6}$M. Recorded the potential (E, mV) against -log[concentration]. Measure the potential of the unknown concentration, from the reconstructed graph, then calculate the unknown concentration.

2.5. Determination of naltrexone in its dosage form

Ten tablets of detrexone (50 mg) were powdered and totally blended in a mortar. An exact blended powder equal to one tablet (50 mg) of naltrexone was transmitted to a 100 ml beaker and soluble in water by sonication for about ten min. The above solution was carry into 100 ml measuring flask, diluted with water. Transfer exactly 5.0 ml of the previous solution into measuring flask (50 ml), adjusted pH using acetate buffer of pH 3, then completed with water to the mark. Measure the potential of this solution using NALT-PVC membrane sensors, after the potential reading was stable for ($\pm 0.3$ mV/min). Calculate the unknown concentration form the previous calibration graph.

On the other hand, the potential of unknown concentration was calculated using standard addition technique [26] by measuring the potential of unknown concentration, then added 1 ml of standard solution and again measure the related potential. The potential difference was used to determine the unknown concentration.

Reconstituted powder: A laboratory made mixture powder containing 25 mg of NALT in addition to different combination of tablets formulation. The accuracy of the prepared powder was examined by measuring its recovery.

3. RESULTS AND DISCUSSION

The inclusion complexation and the molecular recognition are of recently interest in host-guest and supramolecular chemistry which offer a favorable approach to chemical sensing. The response of electrochemical sensors based on ionophore is usually decided by the molecular interaction tendency between guest (analyte) and host (ionophore, CD)[27].

$\beta$- and $\gamma$-cyclodextrin has the capability to construct an inclusion complex with many guest molecules such as naltrexone, because its bore hydrophobic inside and hydrophilic out-side, which allow to form inclusion complex. The mechanism are based different approach: hydrophobic interactions, formation of hydrogen bonds, and van der Waals force[28]. The size of the chemical structure of cyclodextrin bore is appropriate with the size of the guest (NALT).

It has been found that the presence of potassium tetrakis(4-chlorophenyl)borate to the membrane composition is important to enhance the selectivity[29,30] where the ionophore is neutral and addition of KTpCIPB is increase the ionic site of the
membrane. A one to one ratio of ionic site (KTpCTPB) and ionophore was found to progress sensor selectivity and sensitivity.

It can be deduce that, the response mechanism of the PVC membrane sensors based on either β- or γ- cyclodextrin ionophore is based on the formation of inclusion complex, through hydrophobic interactions, formation of hydrogen bonds, and van der Waals force. The ionophore shows strong ability towards NALT ions and the addition of KTpCIPB to the membrane composition modify the neutral characteristic of the ionophores and to its ionic behavior.

3.1. Effect of plasticizer

Naltrexone PVC sensors with different plasticizer were tested in order to determine its characteristics in different plasticizer. Two ionophores (β-CD or γ-CD) were investigated as sensing materials for the developed of PVC membrane sensor for NALT. The obtained ionophores were tested with the respect of different plasticizer (DOP, DBS and NPOE) to give three remarkable blends with each ionophore were attempted. It is doubtlessly comprehended that the structure of PVC based sensors is mandatory step to use of a plasticizer which works as a fluidizer permit unclear degeneration and spread transportability of the ionophore inside the PVC membrane. PVC membrane based of β-CD or γ-CD with three plasticizers namely: DBS or DOP or NPOE was set up to be all fitting and perfect conceivable center individuals for NALT-PVC sensors. In certification, DOP was seen to be the perfect reachable go between for β-CD or γ-CD PVC sensors. In this way for all drawing closer work, dioctyl phthalate was used.

3.2. Effect of hydrogen ion concentration and signal response.

The signal response for naltrexone was examined in different pH mediums. The pH value of the naltrexone solution was controlled using dil. HCl or NaOH solution. The NALT-PVC sensor was inserted into naltrexone concentration of 1×10⁻³ and 1×10⁻⁴M and the (E, mV) of the test solution was measured related to the change of pH. The measured potential (E, mV) was plotted against pH values. Figure 2 show that the slope (E, mV) per tenfold concentration interval is constant (~ 38.0 ± 0.5 or 34.5.0 ± 0.5 for β-CD, or γ-CD respectively) in the pH range of 2 - 7 (Fig.2). At alkaline solution of pH > 7.0, due to the progressive increase in the concentration of the un-protonated species of naltrexone, the potential is decreased.

Response time [31] is outlined as the time required for the electrode to reach stable reading value, after equilibration of the electrode in different concentration of NALT (10 fold) either increase or decrease. At higher NALT concentration, the response time is less compared with lower concentration of NALT. It was found that 25s for NALT concentration ≥1×10⁻³M and ≤ 30 s for 1×10⁻⁴M NALT concentration. The reproducibility of the NALT-membrane sensors is about ± 0.3 mV per 10 fold from one-day to another. The age limit of the sensor is approximately one and half month, through that period the potential reading or slope of the electrode is constant only change is about ±1 mV/ decade. Also, the age limit of the master membrane for more than one month the potential reading is reproducible.
3.3. Effect of interferences

Some organic and inorganic ions were tested to study their effect on the electrode response. The selectivity coefficient $K_{A,B}^{pot}$ were certified according to IUPAC recommendations using either separate solution or mixed solution method [31,32]. The results obtained in acetate buffer are shown.
in Table 1. In respect of many related ions, selectivity for NALT appears to be a more selectivity to naltrexone.

Table 1. Selectivity coefficients of NALT-PVC sensors.

<table>
<thead>
<tr>
<th>Interferent, J</th>
<th>( K_{NALT,B} )</th>
<th>( K_{NALT,B} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Na}^{+} )</td>
<td>( 2.3 \times 10^{-3} )</td>
<td>( 2.9 \times 10^{-3} )</td>
</tr>
<tr>
<td>( \text{K}^{+} )</td>
<td>( 1.2 \times 10^{-2} )</td>
<td>( 2.0 \times 10^{-3} )</td>
</tr>
<tr>
<td>( \text{Ca}^{2+} )</td>
<td>( 4.6 \times 10^{-3} )</td>
<td>( 2.1 \times 10^{-3} )</td>
</tr>
<tr>
<td>( \text{Zn}^{2+} )</td>
<td>( 5.8 \times 10^{-3} )</td>
<td>( 2.5 \times 10^{-3} )</td>
</tr>
<tr>
<td>( \text{Co}^{2+} )</td>
<td>( 3.0 \times 10^{-3} )</td>
<td>( 2.5 \times 10^{-3} )</td>
</tr>
<tr>
<td>( \text{Fe}^{2+} )</td>
<td>( 4.4 \times 10^{-3} )</td>
<td>( 4.4 \times 10^{-3} )</td>
</tr>
<tr>
<td>Magnesium Stearate (^b)</td>
<td>( 8.3 \times 10^{-3} )</td>
<td>( 2.0 \times 10^{-3} )</td>
</tr>
<tr>
<td>Glucose (^b)</td>
<td>( 8.3 \times 10^{-3} )</td>
<td>( 2.3 \times 10^{-3} )</td>
</tr>
<tr>
<td>Lactose monohydrate (^b)</td>
<td>( 8.1 \times 10^{-3} )</td>
<td>( 2.1 \times 10^{-3} )</td>
</tr>
<tr>
<td>Starch (^b)</td>
<td>( 8.1 \times 10^{-3} )</td>
<td>( 2.3 \times 10^{-3} )</td>
</tr>
<tr>
<td>Microcrystalline (^b) cellulose</td>
<td>( 8.0 \times 10^{-3} )</td>
<td>( 2.2 \times 10^{-3} )</td>
</tr>
</tbody>
</table>

\(^a\)separate and \(^b\)mixed solution method, respectively.

3.4. Sensors characteristics

According to IUPAC guide line [32], the general characteristics of the NALT sensors based on the use of \( \beta \)-CD or \( \gamma \)-CD ionophore; DOP as a plasticizer and PVC matrixes were certified. The data in Table 2 presented the general properties of the proposed sensors. The least squares equations extracted from the calibration curve as the following form:

\[
E (\text{mV}) = S \log [\text{NALT}] + \text{Intercept}
\]

where \( E \) is the potential of the sensor / mV, \( S \) slope (38.0 ± 0.5, and 34.5 ± 0.5 mV for \( \beta \)-CD or \( \gamma \)-CD, respectively) and intercept (91.0 ± 0.5 and 60.0 ± 0.5 for \( \beta \)-CD or \( \gamma \)-CD, respectively).

Table 2. General properties of NALT-PVC sensors.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NALT-( \beta )-CD</th>
<th>NALT-( \gamma )-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibration range</td>
<td>( 5.8 \times 10^{-6} ) - ( 1 \times 10^{-2} )</td>
<td>( 4 \times 10^{-6} ) - ( 1 \times 10^{-2} )</td>
</tr>
<tr>
<td>Slope (mV/decade)</td>
<td>( 38 \pm 0.4 )</td>
<td>( 34.5 \pm 0.4 )</td>
</tr>
<tr>
<td>Intercept (mV)</td>
<td>( 91 \pm 0.4 )</td>
<td>( 60.0 \pm 0.4 )</td>
</tr>
<tr>
<td>Correlation coefficient, (r)</td>
<td>0.996</td>
<td>0.995</td>
</tr>
<tr>
<td>Lower limit of detection (LOD), M</td>
<td>( 5.0 \times 10^{-6} )</td>
<td>( 3.0 \times 10^{-6} )</td>
</tr>
<tr>
<td>Lower limit of quantification (LOQ), M</td>
<td>( 5.8 \times 10^{-6} )</td>
<td>( 4.0 \times 10^{-6} )</td>
</tr>
<tr>
<td>Response time for ( 1 \times 10^{-3} ) M, s</td>
<td>( 25 \pm 0.6 )</td>
<td>( 25 \pm 0.6 )</td>
</tr>
<tr>
<td>pH range</td>
<td>2 - 7</td>
<td>2 - 7</td>
</tr>
</tbody>
</table>
3.5. Validity of the NALT-Sensors

3.5.1. Quantification Limit and detection limit

For every point in the calibration curve was tested five times, averaged each point, then was plotted against concentration. The link between potential and concentration is logarithmic form \( X = S \log [\text{NALT}] + Y \), \( X \) is the potential \( E \), mV, \( S \) is the slope, and \( Y \) is the intercept and \( r \) is the correlation coefficient.

In the pH range of 2-7, the sensors show a calibration range of \( 1 \times 10^{-2} \) to \( 5.8 \times 10^{-6} \) and \( 1 \times 10^{-2} \) to \( 4.0 \times 10^{-6} \) M for \( \beta \)-CD or \( \gamma \)-CD, respectively. According IUPAC guidelines the LOQ and LOD were assessed, which is of \( 5 \times 10^{-6} \) and \( 3 \times 10^{-6} \) for sensor 1 and 2 respectively (Fig. 3).

![Figure 3](image)

**Figure 3.** Calibration curve of NALT membrane sensors.

3.5.2. Recovery

At the recommended pH medium (pH 3.5). The recovery of NALT was calculated which is the measured value divided to added value multiplied by 100. The assay of recovery according the next equation.

\[
\text{Recovery} \% = \left( \frac{\text{found concentration}}{\text{added concentration}} \right) \times 100
\]

The average recovery of 300 \( \mu \)g/ml of NALT was found to be 97.2 and 97.5\% , on the other hand RSD value was 1.70 and 2.0\% for sensor 1 and 2 respectively (Table 3).
3.5.3. Accuracy and Precision

The accuracy and precision of the suggested method were investigated [33] by carrying out the assay of NALT at 300µg/ml during the day and in several three days. The five replicate were subject to estimate the intra-day and inter-day precision. Linear models were extracted from the calibration graphs to determine the unknown samples. Accuracy % was determined as closeness of the measured to the added concentration. Precision was expressed as RSD%. The accuracy of the proposed method was larger than 97.0%, while the RSD% value was smaller than 2.2%. Results are summarized in Table 3.

Table 3. Precision survey of the developed PVC membrane sensors.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Naltrexone (300µg/ml)*</th>
<th>Naltrexone (300µg/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intra day</td>
<td>Inter days</td>
</tr>
<tr>
<td></td>
<td>NALT-β-CD</td>
<td>NALT-γ-CD</td>
</tr>
<tr>
<td>R %</td>
<td>97.2</td>
<td>97.5</td>
</tr>
<tr>
<td>R.S.D %</td>
<td>1.7</td>
<td>2.0</td>
</tr>
<tr>
<td>E %</td>
<td>2.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Slope</td>
<td>38.0 ± 0.5</td>
<td>34.0 ± 0.5</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.998</td>
<td>0.997</td>
</tr>
</tbody>
</table>

* Medium of five repetitions .
* R%, recovery %; RSD , relative standard deviation %, and E is error%

3.5.4. Ruggedness

The ruggedness of the suggested procedure was examined [33] by investigate the proposed method using two various operators and two various machines in various days. The obtained results show that the suggested procedure is able to producing results with great effectively and skillfully. The RSD value was less than 2.2% were noticed for the assay in the same day and in different days.

3.5.5. Robustness

The robustness of the suggested method was examined [33] during studying the pH and response period that influence the electrode signal. The obtained results under experimental parameter conditions appear that the suggested procedure is fairly robust. The pH value must be control and the pH value was from 2.0 - 7.0. The optimum value was 3.5 and was controlled using acetate buffer.
3.6. Application of NALT-PVC sensors

The recovery of an accurate amount of NALT in aqueous solution was tested as first step to assay of the NALT in its dosage form. The assay of the pure amount in the range of 3.7-377.0 ppm in five replicate by the proposed method were tested. An average recovery of 99.8 and 100.93% with RSD value of 1.77 and 1.66% for β- and γ-CD sensor, respectively. The obtained data are summarized in Table 4.

Table 4. Assay of naltrexone using NALT-β- and NALT-γ-CD sensors.

<table>
<thead>
<tr>
<th>Added (µg/ml)</th>
<th>NALT-β-CD, *</th>
<th>NALT-γ-CD, *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>SD a</td>
</tr>
<tr>
<td>3.7</td>
<td>97.0</td>
<td>0.2</td>
</tr>
<tr>
<td>33.7</td>
<td>103.0</td>
<td>2.0</td>
</tr>
<tr>
<td>337.7</td>
<td>99.5</td>
<td>1.0</td>
</tr>
<tr>
<td>3377.7</td>
<td>99.7</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Where , a standard deviation, b relative standard deviation %, R( recovery %), E( error%)

* Average of 5 repetitions

An accurate amount of NALT drug in a synthetic laboratory powder was tested, to test the suggested methods. The recovery percentage was 98 % or 98.5% with an average RSD of 1.7 for β-CD or γ-CD respectively.

Moreover, the assay of NALT in its dosage form show an average recovery of 98.0% or 98.5% with RSD value of 1.7% or 1.6% for β-CD or γ-CD, respectively. Results are presented in Table 5.

Table 5. Assay of naltrexone using NALT-β- and γ-CD sensors.

<table>
<thead>
<tr>
<th>Tested form</th>
<th>NALT (certified, value)</th>
<th>Developed method*</th>
<th>Spectrophotometry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NALT-β-CD R,% (RSD, %)</td>
<td>NALT-γ-CD R,% (RSD, %)</td>
</tr>
<tr>
<td>Reconstituted powder</td>
<td>25 mg</td>
<td>97.5 (1.8)</td>
<td>97.5(1.6)</td>
</tr>
<tr>
<td>Detrexone Tablet</td>
<td>50 mg</td>
<td>97.0 (1.7)</td>
<td>98.0(1.6)</td>
</tr>
</tbody>
</table>

*Average of five repetitions.

The assay of NALT by the proposed method was compared with reported spectrophotometric[6], results are presented in Table 5. The obtained data are in adequate convention with the published procedure. The spectrophotometric method is based on oxidation of
NALT with excess amount of Ce(IV) in acid medium, followed by determination the remaining amount of Ce(IV) by reaction with methyl orange and monitoring the absorbance at 510 nm[6]. The obtained results are presented in Table 5. The obtained data proves that the suggested PVC membrane sensors are in comparable with spectrophotometric method with regard to accuracy and precision.

3.6.1. Application of NALT-PVC sensors in potentiometric titration

The examined sensors have been tested as indicator sensor in some potentiometric titration reaction. For example reaction of NALT with NaTPB as precipitation titration reaction. Titration graph has been shown in (Fig.4) using β- and γ- CD PVC sensors. Nalterxone is react with NaTPB in 1:1 ratio with a potential inflection of about 150 mV for β- and γ- CD sensors, respectively. From the results it is clear the method is highly sensitive.

![Figure 4](image-url)  
**Figure 4.** Potentiometric titration of 2.5 ml of $1 \times 10^{-2}$ M NALT against 0.01M sodium-TPB by NALT-PVC sensors.

4. CONCLUSION

Beta- or γ-cyclodextrin as neutral ionophore, dioctylphthalate, KTpCIPB as an anionic additive and PVC matrix have been developed as PVC membrane sensors for naltrexone. In the pH range 2-7, the sensors appear a high selective and sensitive with sub-Nernstian response for naltrexone. A wide dynamic range for naltrexone has been appearing for β- or γ-cyclodextrin. The suggested
method shows a good accuracy and precision. The investigated sensors have been used as indicator sensors for the assay of naloxone using precipitation titration reaction.

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**References**


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