Anastrozole as nanostructured lipid carriers

Anastrozole Loaded Nanostructured Lipid Carriers: Preparation and Evaluation

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Abstract

Anastrozole (ANZ) is considered a constituent of the fourth–generation of Non–steroidal aromatase blockers. ANZ has been used for hormone receptor positive breast cancer in postmenopausal women. The serious side effects of ANZ including, vaginal dryness, hot flashes, irritability, breast tenderness, and unstable circulation.

Nanostructured lipid carriers (NLCs) have recently emerged as a multifunctional platform for drug delivery in cancer therapy. Five formulae were composed of (200 mg of glyceryl monostearate, 40 mg of oleic acid, 1% (w/w) Tween 80, 1% (w/w) Poloxamer 407, 1% (w/w) soy lecithin, and Vitamin E Polyethylene Glycol Succinate.

The mean particle size, polydispersity index, zeta potential, entrapment efficiency, and loading capacity range of the optimum formula F05 (166±3.86 nm), (0.271±0.04), (-23.7±2.65 mV), (42.43±3.90%) and (1.23±0.35%) respectively that prepared by the same above composition but higher amplitude value (70%). The in-vitro drug leakage study demonstrated intact formula through 5 hours, with an approximately 78.37% of the drug was encapsulated, which exhibit an anomalous release mechanism.

Keywords: Breast cancer, Anastrozole (ANZ), Nanostructured lipid carriers (NLCs), Solvent Evaporation Technique and ultrasonication Technique.

Introduction

Due to patient preference, lower costs, proven effectiveness, lack of infusion-related discrepancies, and the opportunity of developing chronic treatment regimes, the use of oral anticancer drugs has increased during the last decade. The first factor that can increase dissolution and absorption is pharmaceutical modification or the physicochemical characteristics of the drug. Second, Pharmacological therapies can resolve physiological endogenous limitations by combining drugs with transporter protein inhibitors and/or pre-systemic metabolism enzymes (1).

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Anastrozole (ANZ) is a nonsteroidal benzylationazole with molecular formula: [C17H19N5]. ANZ is structurally related to letrozole, fadrozole and vorozole, with all being classified as azoles. It is class III as BCS (high solubility with low permeability). Appearance: white crystalline powder. Molecular weight: 293.37 Da. Density: 1.08 g/cm3. Melting point: 80–84 °C. Solubility: very slightly soluble in water (0.53 mg/ml at 25 °C); freely soluble in alcohol, methyl alcohol, acetone and in tetrahydrofuran, very soluble in acetonitrile. Practically insoluble in cyclohexane. The log P (octanol/water) is 1.58, indicating that it is a moderately lipophilic compound.

Anastrozole–loaded Nanostructured Lipid Carriers (ANZ-NLCs) were prepared by solvent evaporation method, briefly involves the addition of lipid mixture (solid and liquid) and drug in organic solvent that is then emulsified in an aqueous phase the addition rate of the melted lipid phase to the aqueous phase which was about (1 ml/min), in a dropwise manner then sonication used ice bath to decrease temperature of solution. After evaporation of the solvent, the lipid precipitates forming NLCs.

Materials and Methods

Materials

The following material were utilized in the present study with their suppliers: ANZ, Glyceryl monostearate (GMS), oleic acid (OA), Poloxamer 407 (P407), Vitamin E Polyethylene Glycol Succinate (E–TPGS), Lecithin from Soybean, Tween®80 and Cetyl palmitate (HyperChem®, Zhejiang, China). Miglyol®812 (IOI Oleo GmbH, Germany), Brij®-35 (Merck, Germany), Gelot-64 and Compritol 888®ATO (Gattefosse, France).

Preparation

ANZ–NLCs were prepared using the process of emulsion evaporation at a high temperature and solidification at a low temperature. The NLCs were made of 200 mg of glyceryl monostearate, 40 mg of oleic acid, 1% (w/w) Tween 80, 1% (w/w) Poloxamer 407, 1% (w/w) soy lecithin and Vitamin E Polyethylene Glycol Succinate.; under agitate at 1,000 rpm by magnetic stirrer (Staufen, Germany) in a water bath at 70 °C for 24 h. The obtained pre–emulsion was then sonicated by probe sonicator (for 5 min at (40-70 %) amplitude by probe sonicator (Misonix S–4000 Sonicator, USA) with a pulse of 8 sec on and 4 sec off using ice bath. Finally, the dispersion was cooled at 4.0 °C to solidify the lipid matrix and produce NLCs. The control blank NLCs were pre–pared similarly without adding ANZ.

Nanoparticles size distribution analysis

The particle size, PDI and Zeta (ζ)–Potential based standard deviations were recorded. Measurements were repeated to ensure that no aggregation of particles occurred.

Drug entrapment efficiency and drug loading capacity

The entrapment efficiency (EE%) and drug loading capacity (DL%) which corresponds to the percentage of ANZ encapsulated was determined indirectly by measuring the concentration of free ANZ in the NLCs. The amount of not trapped free drug was determined using an ultrafiltration technique. Briefly, 5.0 ml of ANZ–NLCs solution was placed in the upper chamber of Amicon® Ultra Centrifugal tube a molecular cut off size (MWCO) 10 kDa and centrifuged for 30 min at 5,000 rpm. The ultrafiltration containing the free drug and the concentration of unentrapped ANZ was determined by HPLC–analysis. The (EE%) and drug loading percent (DL%) were calculated using the equations:

\[ \text{EE} \% = \frac{w_f - w_d}{w_f} \times 100 \quad \ldots (1) \]
\[ \text{DL} \% = \frac{w_d}{w_f} \times 100 \quad \ldots (2) \]

Where:
\( w_f \) = weight total drug is the weight of initial drug used,
\( w_d \) = weight free drug is the weight of free drug detected in the supernatant after ultrafiltration of the aqueous dispersion and
\( w_l = \) weight lipid is the weight of lipid used.

Fourier Transform Infra–Red Spectroscopy (FTIR)

FTIR spectroscopy (FTIR– 8400S, Shimadzu, Japan) was used to study any possible interaction between ANZ and other excipients and to affirm the drug identity. The spectra were recorded for the pure drug, glyceryl monostearate, physical mixtures of drug and lipid. Each sample was weighed accurately and prepared in KBr disk. The spectrum was scanned over the frequency range of 4,000–400 cm\(^{-1}\) spectral resolution. Differential Scanning Calorimetry (DSC)

Any possible interaction between ANZ and other excipients used in the study during the methods of ANZ–NLCs preparation can be predicted by using DSC (DSC–60 plus, Shimadzu, Japan). The thermal analysis was performed on pure ANZ, glyceryl monostearate and lyophilized ANZ–NLCs. 5 milligrams of sample were placed in a standard aluminum pan. Then heated at a constant rate of 10 °C/min and scanned (30–300 °C) against an empty aluminum pan as a reference under a constant nitrogen purge.

Field Emission Scanning Electron microscope (FESEM)

FESEM (HITACHI S–4160, Japan) provides topographic and elementary information. The field-emission cathode in the electron gun of the scanning
Transmission Electron microscope Examination (TEM)

In order to verify the size results obtained by PCS, the morphology of NLCs-loaded NLCs was studied by a TEM, (Zeiss Libra 120 PLUS, Carl Zeiss GmbH. Germany). After diluting 20-fold with ultrapure water, the samples were stained with uranyl acetate before analysis (14).

In vitro leakage study

In vitro leakage study of ANZ–NLCs was performed using a modified dialysis membrane technique(15) in different pH media (1.2 and 6.8).

Dialysis membrane (Viskase Companies, USA) represented (donor compartment) with molecular weight cut off size (MWCO) 8000–12,000 Da, was previously soaked overnight with dissolution media. One milliliter of ANZ–NLCs formulation was sited in the dialysis membrane and knotted at individually ends.

The modified dialysis membrane technique containing ANZ–NLCs (1 ml) was then introduced into a 50 ml plastic sample test tube with screw cap containing 25 ml of media, which was stirred at 100±2 rpm using incubator shaker the temperature of the media was maintained at 37±0.5 ℃.

Then placed in the incubator shaker using dissolution media, the time interval for 0.1N HCl (pH 1.2) were 1 hour at intervals (5, 10, 15, 30, 45 and 60 min) then in phosphate buffer solution with (pH 6.8) for 4 hours at pre-determined time intervals (0.25, 0.5, 0.75, 1, 2, 3 and 4 hours) and replenished equivalent volume of fresh dissolution medium (16).

The sample was taken and analyzed to determine the amount of ANZ found, using an HPLC equipped with a UV detector at 215 nm. A cumulative amount of drug was calculated. The reported values are averages of three replicates.

Statistical Analysis

The outcomes of the experimental work are demonstrated as a mean of triplicate models ±SD and were examined in relation to the one-way analysis of variance (ANOVA) to determine if the changes in the applied factors are statistically significant at level of (P<0.05) and non-significant at level of (P>0.05) (17).

Results and Discussion

Screening of solid lipids

ANZ showed maximum solubility of (28±4.31 mg/g) in glyceryl monostearate (GMS) compared to other lipids being investigated as seen in figure (1). Therefore, GMS was selected as the solid lipid matrix in the formulation of NLCs because it has more potential to solubilize ANZ in comparison with other studied solid lipids.

Screening of liquid lipids

Oleic acid exhibits significantly higher ANZ solubility since it possesses the best solubilization capacity than other oils and this is due to the formation of hydrogen bonding between the carboxylic group of the fatty acids and the drug molecules (18).

Therefore, it was chosen as a liquid lipid for the formulation of ANZ–NLC. In general, lipophilic drugs are much more soluble in liquid lipids than in solid lipids (19) as shown in figure (2).
Screening of Surfactant and Co–Surfactant \( ^{(20)} \)

The solubility of ANZ in different surfactants and co–surfactants is presented in table (1). The basis for the selection of surfactant or co–surfactant was mainly dependent on the emulsification efficiency. Ease of emulsification was judged by the number of flask inversions required to yield homogenous mixtures and it was assessed visually \( ^{(21)} \).

<table>
<thead>
<tr>
<th>Type of Surfactant/Co–surfactant</th>
<th>No. of Inversions</th>
<th>% Transparency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myverol( ^{®} )</td>
<td>34</td>
<td>93.4</td>
</tr>
<tr>
<td>Tween( ^{®} ) 60</td>
<td>28</td>
<td>96.5</td>
</tr>
<tr>
<td>Tween( ^{®} ) 80</td>
<td>5</td>
<td>99.1</td>
</tr>
<tr>
<td>Span( ^{®} ) 20</td>
<td>43</td>
<td>94.5</td>
</tr>
<tr>
<td>Span( ^{®} ) 80</td>
<td>49</td>
<td>96.7</td>
</tr>
<tr>
<td>Poloxamer–407</td>
<td>7</td>
<td>98.1</td>
</tr>
<tr>
<td>Poloxamer–188</td>
<td>13</td>
<td>97.5</td>
</tr>
<tr>
<td>Soy Lecithin</td>
<td>9</td>
<td>98.7</td>
</tr>
<tr>
<td>E–TPGS</td>
<td>9</td>
<td>98.3</td>
</tr>
<tr>
<td>Brij( ^{®} )–35</td>
<td>19</td>
<td>86%</td>
</tr>
<tr>
<td>Gelot( ^{®} )–64</td>
<td>17</td>
<td>88%</td>
</tr>
</tbody>
</table>

Figure 2. Solubility of Anastrozole in Liquid Lipids, mean values ±SD (n=3).

Figure 3. The number of flask inversions for surfactants and co–surfactants required to yield homogeneous emulsion.
**Preparation of ANZ–NLCs**

Five formulas of Anastrozole–loaded Nanostructured Lipid Carriers (ANZ–NLCs) formulations have been proposed in the current study as a new oral controlled and sustained release delivery system to offer an enhancing therapeutic effect and decrease side effects prepared by Solvent evaporation technique plus ultrasonication.

This technique involves the addition of lipid mixture (solid and liquid) and drug in organic solvent that is then emulsified in an aqueous phase the addition rate of the melted lipid phase to the aqueous phase that was about 1ml/min, in a dropwise manner then sonication used ice bath to decrease temperature of solution. After evaporation of the solvent (overnight), the lipid precipitates forming NLCs\(^{(22)}\).

ANZ–NLCs formulas (F01–F05) were prepared by solvent evaporation technique. The evaluation parameters of the prepared ANZ–NLCs formulas.

The procedure involves preparing low pressure NLCs. The organic solvent is the chemical that is used to dissolve the chemotherapy drug while the resulting precipitated drug–loaded NLCs can be dried without the need to further prepare NLCs at elevated temperatures\(^{(23)}\). Besides, this process is limited by the presence of residual toxic substances in the final product which can lead to systemic toxic symptoms after administration.

**Particle Size Distribution and Polydispersity Index (PDI)**

The formula of ANZ–NLCs that prepared, particle sizes were within the sub–micron level as shown in table (2). Particle size determination has a crucial rule in lipid nanoparticles characterization, due to its effect on:

- The stable NLCs would also ensure longer shelf-life and less noxiousness. Site-specific NLCs; precisely those suggested should have a diameter of 50–300 nm for increasing cellular absorption as chemotherapy agent carriers\(^{(24)}\).

- For NLC carriers with 100 nm or less size the low permeability and retention effect enhances the round-trip time of the efflux transporter, epithelial reticuloendothelial barrier. The drug pharmacokinetics; target tissue distribution, elimination and clearance, a particle size ≤100 nm was found to be optimum for intestinal absorption of NLCs due to these reasons, particle size serves as an important feature for NLCs.

**Zeta (ζ)–potential Analysis**

The determination of zeta (ζ)–potential values of the prepared ANZ–NLCs formulation is a significant parameter in the evaluation of the system stability on long-term storage. It measures the electrical potential at the particle shear plane, the higher the (ζ)–potential value the more stable the colloidal system due to higher repulsion between close and similarly charged particles inhibiting particle aggregation.

**Table 2. Mean Particle Size (PS), Polydispersity Index (PDI) and (ζ)–potential of Different ANZ Loaded Nanostructured Lipid Carriers, mean ± SD, (n=3)**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Particle Size</th>
<th>±SD</th>
<th>PDI</th>
<th>±SD</th>
<th>ZP</th>
<th>±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F01</td>
<td>271</td>
<td>3.4</td>
<td>0.307</td>
<td>0.03</td>
<td>−18</td>
<td>2.52</td>
</tr>
<tr>
<td>F02</td>
<td>226</td>
<td>1.25</td>
<td>0.298</td>
<td>0.02</td>
<td>−16</td>
<td>3.51</td>
</tr>
<tr>
<td>F03</td>
<td>213</td>
<td>2.16</td>
<td>0.289</td>
<td>0.02</td>
<td>−21</td>
<td>3.06</td>
</tr>
<tr>
<td>F04</td>
<td>171</td>
<td>0.94</td>
<td>0.28</td>
<td>0.01</td>
<td>−23.1</td>
<td>1.37</td>
</tr>
<tr>
<td>F05</td>
<td>166</td>
<td>3.86</td>
<td>0.271</td>
<td>0.04</td>
<td>−23.7</td>
<td>2.65</td>
</tr>
</tbody>
</table>

**Drug entrapment efficiency and drug loading capacity**

The entrapment efficiency (EE%) means the percentage of drug successfully incorporated into the lipid matrix of the nanoparticles compared to the whole drug amount added during the lipid nanoparticles formulation process.

While, loading capacity of drug (DL%) refers to the drug percentage incorporated into the lipid nanoparticles relative to the total weight of the lipid matrix.

**Formulas** groups from (F01–F05) that were prepared by emulsification method to other formula mentioned in table (3) entrapment efficiency % some drawbacks are lower than those that are prepared by HPH: prefer using solvents that are not organic (e.g. hexane, petroleum ether) and use microwave irradiation rather than pressure. The lipid mixture is blended into a cool aqueous phase with emulsifiers. More often in scientific writing, faster cooling and stirring must take place in order to crystallize an emulsion and evaporate solvents.
Table (3): the entrapment efficiency percentage and loading capacity of drug percentage, mean ± SD, (n=3)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Entrapment Efficiency %</th>
<th>±SD</th>
<th>Loading Capacity %</th>
<th>±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F01</td>
<td>46.48</td>
<td>2.55</td>
<td>1.31</td>
<td>0.23</td>
</tr>
<tr>
<td>F02</td>
<td>53.63</td>
<td>1.95</td>
<td>2.29</td>
<td>0.10</td>
</tr>
<tr>
<td>F03</td>
<td>44.56</td>
<td>2.45</td>
<td>1.14</td>
<td>0.175</td>
</tr>
<tr>
<td>F04</td>
<td>38.79</td>
<td>5.05</td>
<td>1.29</td>
<td>0.025</td>
</tr>
<tr>
<td>F05</td>
<td>42.43</td>
<td>3.9</td>
<td>1.23</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectral analysis is useful in determining the compatibility of drugs and excipients since such compatibility is the primary criteria in the selection of excipients. Whether there is any change in drug molecule during the preparation of nanostructured lipid carriers, FTIR is done. The standard FTIR of ANZ, The FTIR of pure ANZ and physical mixture are shown in figures (4, 5 and 6), respectively.

Figure (5) for pure ANZ showed characteristic peaks at: 3,444–3,432 cm⁻¹ representing aromatic nitrile, 2,235–2,245 cm⁻¹ representing aliphatic C≡N stretch of nitrile, and 1,605–1,272 cm⁻¹ representing C=N hetero aromatic stretching.

The FTIR spectra of formulation with GMS showed no interface between the drug itself and the excipients used; both the drug and the excipient peaks were identified; both the drug and the excipient peaks were identified and interpreted in the spectra (25).

The FTIR spectrum in figure (6) for physical mixture and drug loaded NLCs, showed the spectra confirmed the absenteeism of any chemical interaction between the drug, GMS, and OA. However, no shifting of the characteristic peaks was observed and these peaks appeared at their positions as shown in their individual spectra that confirmed no interaction among the components.

The aforementioned characters ensure that the ANZ chemical integrity and the molecular structure are not changed during the preparation process. Thus, FTIR spectroscopy further validated the compatibility between ANZ and lipids, surfactant and co-surfactant even after the formulation that shown in figure (7) (26).

Figure 4. Standard Fourier Transform Infrared Spectroscopy of ANZ (27).

Figure 5. Fourier Transform Infrared Spectroscopy (FTIR) of pure ANZ.
Figure 6. Fourier Transform Infrared Spectroscopy (FTIR) of physical mixture ANZ: GMS (1:1).

Figure 7. Fourier Transform Infrared Spectroscopy (FTIR) of excipients A: TW80; B: P407; C: OA; D: Lecithin; E: Vitamin E–TPGS; F: GMS.

Differential Scanning Calorimetry (DSC)
Thermal behavior of pure ANZ, pure GMS, GM: OA, the physical mixture of GMS: ANZ, lyophilized ANZ–NLCs and lyophilized ANZ–NLCs with mannitol are depicted in figure (8). The DSC thermogram (figure (8 A)) of pure ANZ profiles a sharp endothermic peak at 82.29 °C corresponding to its melting, indicating its crystalline anhydrous state which was consistent with the findings of published papers.

The DSC curve (figure (8 D)), reveals that the ANZ and GMS mixture (1:1) shows no extra peak when compared to DSC curve of ANZ (figure (8 A)), GMS alone (figure (8 B)) and physical mixture of GM: OA (figure (8 C)) and. Therefore, the ANZ and GMS combination is compatible.

The physical mixture of ANZ and GM showed nearly the same thermal behavior as the individual components, indicating that there was no interaction among the drug and NLCs in the solid state.

The absence of the endothermic peak of the drug at 82.29 °C in the DSC of its NLCs suggests that the ANZ existed in an amorphous.
Figure 8. Differential scanning calorimetry thermogram of (A): pure ANZ; (B): glyceryl monostearate (GM); (C): Physical mixture of GM: OA (1:1); (D): Physical mixture of GM: ANZ (1:1).

Field Emission Scanning Electron microscope (FESEM)

The FESEM study was carried out to get the information about the morphology of the ANZ–NLCs. The condition of the FESEM imaging specimen should be either conductive or grounded to prevent accumulation of electrostatic charge on the surface. The figure (9) of the optimized formula (F05) reveals almost all spherical shapes and the size of ANZ–NLCs was within the nanometer range.

In accordance with the FESEM image of the ANZ–NLCs, Samples with a spherical shape and good dispersion were found to be uniform of the NLCs which was also shown in TEM.

Figure 9. FESEM Micrographs of ANZ–NLCs (F05) at different powers of magnification.
Visualization by Transmission Electron microscope (TEM)

Transmission electron microscope (TEM) was increasingly used to examine materials on the nanoscale. It uses electrons, which have a shorter wavelength than light, which makes the resolution of a particle microscope to be a thousand times better\(^\text{(29)}\).

The TEM study was done in order to provide more insight about the morphology and size of the optimized formula (F05). The micrographs of examined ANZ-NLCs (figure (10)) revealed that the prepared nanoparticles were almost spherical with smooth morphology. appeared contrast light surroundings indicated to PEG, well dispersed and separated on the surface. Such analysis results are in agreement with the results produced by FESEM.

The average droplets size \(\approx 100\) nm\(^\text{(30)}\) with no phase separation was observed. According to the imaging analysis, the most important result of the electron microscope study was the absence of clearly identifiable oil droplets in the NLCs samples that may result from separated oil phase\(^\text{(31)}\).

The diameters were calculated by using the TEM method at a microscopic level, which was vastly different to the findings of the nanosizer’s research. It might be that the methods used are really different, and it is due to the different systems used, and then the different processes used for preparing the samples, which lead to the different results.

In the first case, the size recognition of NLCs was carried out using a laser in a water solvent; in this case, lipid nanoparticles. Millions of TEMs were stained with the high-affinity staining process, which stained any free water and even some of the hydrated water. When expressing the sizes of NLCs resulting from TEM, it implies that these sizes might be greatly lesser than their real diameters\(^\text{(32)}\). Theoretically, the size of a particle is difficult to determine as the particle’s shape can differ from particle to particle. In order to obtain one particle from its mean area, the particles themselves must form a regular spherical shape that cannot be possible to obtain in nature\(^\text{(33)}\).

\[\text{Figure 10. Transmission Electron Microscopy (TEM) Micrographs of ANZ–NLCs.}\]

In vitro Leakage ANZ Study

HCl (pH 1.2) to stimulate acidic environment of stomach and phosphate buffer (PB) in (pH 6.8) to stimulate small intestine environment.

The in vitro leakage display profiles of ANZ exhibited drug leakage-free behavior in a physiological environment: figure (11): showed cumulative amount of ANZ in pH (1.2) media, in the gastric environment during the first 60 min. corresponding to transit through the stomach, only the 7.91% of the F05, was released. Thus, the developed NLCs remain intact in 0.1 HCl. Therefore, NLCs prevent degradation of the encapsulated drug and can be promising carriers for the transport of a large amount of ANZ into the intestine; the same observations were got by Piazzini et al\(^\text{(34)}\).

\[\text{Figure 11. The cumulative ANZ amount from (F01–F05) in 0.1N HCl (pH=1.2) at 37 ^\circ C.}\]
Figure (12) showed cumulative amount of ANZ from (F05) in pH (6.8) media, in simulated intestinal environment ratio of about 13.72 % at 4 hours. These results suggest that, following the gastrointestinal tract transit, 78.37% of ANZ remains encapsulated in NLCs, allowing greater intestinal absorption\(^{\text{58}}\).

Figure 12. The cumulative ANZ amount from (F01–F05) in PB (pH=6.8) at 37 °C.

Conclusion

Depending on the obtained data from our present study, one can conclude the following points:

The Anastrozole (ANZ) is suitable to be formulated as a Nanostructured Lipid Carrier (NLCs) delivery system.

FESEM and TEM studies showed an almost spherical particle shape with no particle’s aggregation. While the FTIR and DSC studies showing compatibility between the drug and other formula excipients, and the drug was perfectly encapsulated within the lipid matrix and existed in the amorphous state.

The leakage behavior of ANZ–NLCs from the nanostructured lipid carrier’s displays pH–sensitive release. The release kinetic modelling shows an anomalous drug release mechanism (non–Fickian).

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References


