Development of Chitosan-Coated PLGA-Based Nanoparticles for Improved Oral Olaparib Delivery: In Vitro Characterization, and In Vivo Pharmacokinetic Studies

Md. Khalid Anwer 1,*, Essam A. Ali 2, Muzaffar Iqbal 2, Mohammed Muqtader Ahmed 1, Mohammed F. Aldawsari 1, Ahmed Al Saqr 1, Ahmed Alalaiwe 1 and Gamal A. Soliman 3,4

1 Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia; mo.ahmed@psau.edu.sa (M.M.A.); moh.aldawsari@psau.edu.sa (M.F.A.); a.alsaqr@psau.edu.sa (A.A.S.); a.alalaiwe@psau.edu.sa (A.A.)
2 Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia; esali@ksu.edu.sa (E.A.A.); muziqbal@ksu.edu.sa (M.I.)
3 Department of Pharmacology and Toxicology, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia; g.soliman@psau.edu.sa
4 Department of Pharmacology, College of Veterinary Medicine, Cairo University, Giza 12211, Egypt
* Correspondence: m.anwer@psau.edu.sa

Abstract: Olaparib (OLP) is an orally active poly (ADP-ribose) polymerase enzyme inhibitor, approved for treatment for the metastatic stage of prostate, pancreatic, breast and ovarian cancer. Due to its low bioavailability, an increase in dose and frequency is required to achieve therapeutic benefits, which also results in associated toxicity in patients. In the current study, OLP-loaded poly (d,l-lactide-co-glycolide) (PLGA) nanoparticles (NPs) (OLP-PLGA NPs) and a coating of OLP-PLGA NPs with chitosan (CS) (OLP-CS-PLGA NPs) were prepared successfully in order to improve the dissolution rate and bioavailability. The developed OLP-PLGA NPs were evaluated for hydrodynamic particle size (392 ± 5.3 nm), PDI (0.360 ± 0.03), ZP (-26.9 ± 2.1 mV), EE (71.39 ± 5.5%) and DL (14.86 ± 1.4%), and OLP-CS-PLGA NPs, hydrodynamic particle size (622 ± 9.5 nm), PDI (0.321 ± 0.02), ZP (+36.0 ± 1.7 mV), EE (84.78 ± 6.3%) and DL (11.05 ± 2.6%). The in vitro release profile of both developed NPs showed a sustained release pattern. Moreover, the pharmacokinetics results exhibited a 2.0- and 4.75-fold increase in the bioavailability of OLP-PLGA NPs and OLP-CS-PLGA NPs, respectively, compared to normal OLP suspension. The results revealed that OLP-CS-PLGA NPs could be an effective approach to sustaining and improving the bioavailability of OLP.

Keywords: olaparib; PLGA; chitosan; dissolution; sustained release; bioavailability

1. Introduction

Poly (ADP-ribose) Polimerase (PARP) is an essential enzyme for maintaining genomic integrity, playing a crucial role in both DNA single-strand and double-strand break repairing pathways [1]. PARP inhibitors suppress cell proliferation and tumor growth by the disruption of the DNA repair process, which leads to the accumulation of single-strand DNA breaks and finally leads to double-strand DNA breaks [2]. Olaparib (OLP) is a first-in-class, orally active PARP inhibitor, approved for the treatment of metastatic prostate, pancreatic and breast cancers and the advanced stages of ovarian cancer [3]. It is a strong PARP 1 and 2 inhibitor, and research has shown that it may be used alone or in combination with platinum-based chemotherapy to reduce tumor development in mice xenograft models of human cancer [4,5].

Olaparib (OLP) is an approved oral drug that is rapidly absorbed after oral administration with peak plasma concentration (Cmax) achieved at 1.5 hr (Tmax). However, it has poor permeability and low solubility in aqueous solutions and therefore is classified
as a Class IV drug according to the BCS Class System (BCS) [6,7]. Although the absolute bioavailability of olaparib has not been reported in humans, it was low in experimental rats (11.7–17.2% for male and 19.2–29.6% for female) [8]. Due to its low bioavailability, a higher dose of olaparib is administered to the patient to enhance the therapeutic efficacy (the recommended dose of olaparib is 300 mg (total 600 mg) twice daily). However, large doses of OLP used in conventional therapy have been linked to serious adverse effects in patients, including hematological toxicity and toxicity in those with BRCA1/2 mutant ovarian cancer, according to recent research [9].

Drug encapsulation in biodegradable polymer-based nanoparticles (NPs) has received a lot of attention in the fabrication of novel drug delivery systems (DDS) for a variety of drug entities. Biodegradable polymer-based NPs may improve solubility and bioavailability and minimize non-selective drug toxicity by increasing the drug dissolving rate as well as drug permeability across lipid-based biological membranes [10–14].

In order to manufacture nanoparticles (NPs) for the administration of hydrophobic molecules, the US Food and Drug Administration (FDA) has approved a biocompatible and biodegradable polymer known as poly (lactic-co-glycolic acid) (PLGA) [15]. However, PLGA-based NPs have a negative surface potential, which reduces their mucoadhesive properties and reduces the absorption of the drug. The burst effect of PLGA-based NPs causes their inability to accumulate the drug at the target location, which restricts their therapeutic applicability. Due to the mucoadhesive characteristics of chitosan (CS), it facilitates the interaction with negatively charged membranes and mucosa, promoting adhesion and retention of the drug. Additionally, CS has the capacity to relax the intestinal epithelium’s tight junction, increasing permeability. Because of their positive surface charge and increased mucoadhesion and cellular absorption, attempts have been undertaken to develop CS-coated PLGA NPs [16–18]. In our previous study, apremilast- and rivaroxaban-loaded PLGA NPs were developed successfully as intended for sustained release and bioavailability improvement and the enhanced antitumor activity of brigatinib-loaded PLGA NPs against non-small-cell lung cancer cell lines [19–21]. In order to address OLP’s limited oral bioavailability, we developed nano-formulations of OLP using PLGA and chitosan polymers. It was anticipated that a lower dosage schedule would prolong drug release, improve bioavailability, and improve site specificity.

2. Materials and Methods

2.1. Materials

From “Mesochem Technology” in Beijing, China, OLP was bought. The suppliers of PLGA, chitosan (CS), and Polyvinyl alcohol (PVA) were “Sigma Aldrich, St. Louis, MO, USA”. As received, all other chemicals and solvents were utilized.

2.2. Development of OLP-Loaded PLGA Nanoparticles and CS-Coated PLGA NPs

A single method of emulsification and evaporation was used to develop OLP-loaded PLGA NPs [19]. In order to prepare the oil phase, OLP (30 mg) was first solubilized in DMSO and added to a previously produced polymeric solution of PLGA (100 mg) in dichloromethane (4 mL). Separately, an aqueous phase containing PVA (8 mL, 0.5 percent w/v) was prepared (Table 1). Using a syringe, the aqueous phase was added at a rate of 0.5 mL/min into the oil phase and emulsified under probing sonication. On a magnetic stirrer operating at 150 rpm, the organic solvent was evaporated for 6 h. After high-speed centrifugation, the OLP-loaded PLGA NPs were recovered and freeze-dried three times using deionized water. The synthesis of OLP-loaded CS-coated PLGA NPs followed a similar process, with the exception of adding chitosan to an aqueous phase that included PVA (0.5 percent, w/v) in 1 percent v/v acetic acid (Table 1).
Table 1. Composition of nanoparticles.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>OLP (mg)</th>
<th>PLGA (mg)</th>
<th>CS (mg)</th>
<th>PVA (%w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLP-PLGA NPs</td>
<td>30</td>
<td>100</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>OLP-CS-PLGA NPs</td>
<td>30</td>
<td>100</td>
<td>50</td>
<td>0.5</td>
</tr>
</tbody>
</table>

2.3. Measurement of Hydrodynamic Particle Size, PDI and Zeta Potential

The OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs were evaluated for mean hydrodynamic particle size, PDI, and ZP. The mean particle size and PDI of a freshly formed dispersion were determined by “Malvern zetasizer (ZEN-3600, Malvern Instruments Ltd., Westborough, MA, USA)” and then appropriately diluted with distilled water before being put into a plastic disposable cuvette. The same procedure was adopted, except that a glass electrode cuvette was used for ZP measurement [22,23].

2.4. Measurement of Drug Entrapment Efficiency (%EE) and Drug Loading (%DL)

The EE was measured in an indirect manner. A freshly made NPs dispersion was centrifuged for 10 min at 15,000 rpm and the amount of free OLP was determined in the supernatant by UV/Vis method at 264 nm. The DL was quantified by dissolving 10 mg of lyophilized NPs in 5 mL of methanol by sonication, then this was suitably diluted with distilled water and analyzed. The %EE and %DL were estimated using the following equations.

\[
\%EE = \frac{\text{Initial drug added in NPs} - \text{Free drug in supernatant}}{\text{Initial drug added in NPs}} \times 100
\]

\[
\%DL = \frac{\text{Drug measured in NPs}}{\text{Weight of NPs}} \times 100
\]

2.5. DSC Spectral Analysis

The thermal properties of pure OLP, PLGA, chitosan, and their developed nanoparticles were investigated using DSC “(DSC N-650; Scinco, Liguria, Italy)”. The samples under investigation (5 mg each) were pressed into hermetically sealed aluminum pans, and kept in sample holders, heated at temperatures ranging from 50 to 250 °C with a heating rate of 10 °C/min under a constant supply of nitrogen gas with a flow rate of 20 mL/min.

2.6. FTIR Studies

By using the KBr technique, the FTIR spectra of pure OLP, PLGA, chitosan, OLP-loaded CS-PLGA NPs, and OLP-loaded PLGA NPs were collected. Crystalline KBr was added to the samples, and the combination was subsequently crushed into clear pellets using a portable compression device. The thin transparent sample film enclosed in the die was attached to the sample holder and scanned in the range of 400–4000 cm⁻¹ “(Jasco, V750, FTIR spectrophotometer, Philadelphia, PA, USA)”. Peaks at the fingerprint area were analyzed, and the addition/absence of peaks was looked at for potential functional group interactions between the drug and excipients. Then, spectrums were collaged and presented for a study of compatibility.

2.7. Morphology of Nanoparticles

Scanning electron microscopy (SEM, Hitachi equipment) was used to examine the morphology of OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs. The nanoparticle suspensions were cold centrifuged at 15,000 rpm, 4 °C for 10 min, and then the supernatant was removed and the sediment pellet was dried under vacuum. The dried samples were attached to a metal stub, sputter-coated with chrome, and viewed for SEM images.
2.8. In Vitro Drug-Release Studies

The drug-release studies of prepared NPs were performed in a phosphate buffer (pH 7.4). The NPs (equivalent to 10 mg OLP) were dispersed in 10 mL of dissolution media (Phosphate buffer pH 7.4) in a dialysis bag [24,25], dipped into a beaker containing dissolution media (40 mL) and kept in a biological shaker “(LBS-030S-Lab Tech., Jeju, Korea)” at 37 °C and 100 rpm. An amount of 1 mL of aliquots was withdrawn at certain time intervals and replaced with an equal volume of fresh media solution. The amount of drug was quantified by UV at 264 nm.

2.9. Bio-Analytical Method

The pharmacokinetic analysis of olaparib was performed by the validated UPLC-MS/MS method. The concentration of olaparib was measured using baricitinib as an internal standard (IS). Both analyte and IS were separated on the Acquity HILIC column and the quantification was performed using an ion transition of 435.14 > 361.18 for analyte and 372.07 > 251.14 for IS, respectively. Both chromatographic and mass spectrometry parameters were optimized to achieve the best responses.

2.10. Pharmacokinetic Studies

In experimental rats, freshly prepared nanoparticles “(OLP-PLGA NPs and OLP-CS-PLGA NPs)” were compared to pure OLP solution in terms of pharmacokinetic characteristics. The fifteen male Wistar albino rats were received from the “Animal Care Centre, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkhafji”. All animals were kept in appropriate cages and allowed to access free food and water as per internationally recommended conditions. The Research Ethics Committee, Prince Sattam Bin Abdulaziz University (Approval number: SCBR-030-2022), accepted the study protocol. In addition, the experiment was carried out in accordance with international standards for the care and use of animals in scientific research. The animals were divided into three group (n = 5): In the first group, a normal OLP suspension (20 mg/kg) suspended in 0.5% carboxy methyl cellulose was administered and was treated as the normal control, whereas the second and third groups received “OLP-PLGA NPs and OLP-CS-PLGA NPs”, respectively. All animals fasted overnight prior to the drug administration, and blood samples were taken pre-dose, 0.25, 0.5, 1, 2, 4, 8, and 24 h afterwards. In order to obtain plasma samples, all blood samples were centrifuged for 5 min at 4000 rpm. The plasma samples were then harvested and kept in deep freezers (80 ± 10 °C) pending UPLC-MS/MS analysis.

2.11. Pharmacokinetic and Statistical Analysis

Using “WinNonlin software, Pharsight Co., Mountain View, CA, USA,” the non-compartment model was used to determine the pharmacokinetic parameters. The findings of all parameters were provided as mean standard deviation (SD). Calculations were made for the C_{max}, T_{max}, elimination half-life (T_{1/2}), elimination rate constant (kz), mean residence time (MRT), and AUC [(AUC_{0–24}) (AUC_{0–∞})].

2.12. Statistical Analysis

“One-way ANOVA using Dunnett’s multiple comparison test. However, an unpaired t-test was used for the statistical evaluation of pharmacokinetic parameters. The Prism GraphPad InStat software (version 8) was used for statistical analysis, and p < 0.05 was considered significant”.

3. Results and Discussion

3.1. Measurement of Hydrodynamic Particle Size, PDI and Zeta Potential

OLP-loaded PLGA NPs and OLP-CS-PLGA NPs were prepared by the single emul- sification method. The particle properties of the produced NPs were assessed, and the hydrodynamic particle size, PDI, and ZP were determined to be 392 ± 5.3 nm (Figure 1), 0.360 and −26.9 ± 2.1 mV for OLP-loaded PLGA NPs and 622 ± 9.5 nm (Figure 1), 0.321
and +36.1 ± 1.7 mV for OLP-CS-PLGA NPs, respectively (Table 1). The chitosan coating on PLGA nanoparticles had an effect on the size and ZP of the particles [26]. Negative ZP values were produced by the carboxylic group that was present on the PLGA polymer’s surface [27]. However, the ZP of OLP-loaded CS-PLGA NPs was shown to be positive because the NPs’ surface contained a chitosan amino group [28]. These findings suggested that the CS had been effectively coated onto PLGA NPs. Ionic adsorption may allow CS-coated PLGA NPs to interact with the negatively charged cell membrane, resulting in increased cellular uptake [29].

Figure 1. Mean hydrodynamic particle size of “OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs” measured by the DLS technique.

3.2. Measurement of Drug Entrapment Efficiency (%EE) and Drug Loading (%DL)

Table 2 displays the percentages of EE and DL values. Without a chitosan coating, the OLP-loaded PLGA NPs had an EE value of 71.39 ± 5.5%. However, the entrapment of OLP was found to be 84.78 ± 6.3% in OLP-loaded CS-PLGA NPs. During the synthesis of OLP-loaded PLGA NPs, the formation of NPs took place between the interface of the organic and aqueous phase, and some drug molecules diffused out into the aqueous phase, which resulted in low entrapment efficiency [30,31]. Meanwhile, OLP-loaded CS-PLGA NPs showed higher EE (84.78 ± 6.3%) because they prevent the leakage of the drug due to the chitosan coating [32]. However, with OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs, %DL was measured as 14.86 ± 1.4% and 11.05 ± 2.6%, respectively. The DL value of OLP decreased because the total mass of NPs increased by the addition of the chitosan polymer in LP-loaded CS-PLGA NPs.

Table 2. Prepared NPs’ particle size, PDI, ZP, and encapsulation efficiencies.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Hydrodynamic Particle Size (nm ± SD)</th>
<th>PDI</th>
<th>ZP (mV)</th>
<th>EE (%)</th>
<th>DL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLP-PLGA NPs</td>
<td>392 ± 5.3</td>
<td>0.360 ± 0.03</td>
<td>−26.9 ± 2.1</td>
<td>71.39 ± 5.5</td>
<td>14.86 ± 1.4</td>
</tr>
<tr>
<td>OLP-CS-PLGA NPs</td>
<td>622 ± 9.5</td>
<td>0.321 ± 0.02</td>
<td>+36.0 ± 1.7</td>
<td>84.78 ± 6.3</td>
<td>11.05 ± 2.6</td>
</tr>
</tbody>
</table>

3.3. DSC Spectral Analysis

In order to understand the crystalline or amorphous nature of nanoparticles, DSC spectral analyses were carried out. The DSC spectra of pure OLP, PLGA, chitosan, OLP-loaded CS-PLGA NPs and OLP-loaded PLGA NPs are presented in Figure 2. Pure OLP showed a pronounced endothermic peak at 217.56 °C [33], indicating that the substance is crystalline. At 58 °C and 282 °C, respectively, broad endothermic and exothermic peaks of PLGA and chitosan were seen [34]. The sharp endothermic peak of OLP disappeared from
both formulations of OLP-loaded CS-PLGA NPs and OLP-loaded PLGA NPs, which might be due to the entrapment of OLP in the polymeric nanocarrier.

Figure 2. Comparative DSC spectra of pure OLP and their developed nanoparticles.

3.4. FTIR Studies

Figure 3 displays the FTIR spectra of OLP, PLGA, CS, and their developed nanoparticles. The sample of pure OLP demonstrated the characteristic peaks at 3171 cm\(^{-1}\) (\(-\text{N-H-}\) str), 3011 cm\(^{-1}\) (\(-\text{C-H-}\) str), 2909 cm\(^{-1}\) (cyclo alkane str), 1666 cm\(^{-1}\) (\(-\text{C=O}\) str), and 810 cm\(^{-1}\) (C-F str). A distinctive peak for the PLGA polymer may be seen at 1753 cm\(^{-1}\) (\(-\text{C=O}\) str of aliphatic polyester) [30]. Chitosan (CS) has large peaks in its FTIR spectra at 3509 cm\(^{-1}\), which are ascribed to \(-\text{NH}_2\)- and \(-\text{OH-}\) vibrations, as well as at 1654 cm\(^{-1}\) and 1498 cm\(^{-1}\), which are assigned to the \(-\text{CONH}_2\) and \(\text{NH}_2\) groups, respectively [35,36]. OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs’ FTIR spectra did not reveal any obvious drug peaks, although certain chitosan and PLGA characteristic bands could be recognized. This clearly indicates the encapsulation of OLP in the nanocarrier [22].
3.5. Morphology of Nanoparticles

The SEM images of OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs showed a homogenous population of smooth and spherical particles [24], with difference in size due to the surface coating of chitosan. The measured size of nanoparticles by the SEM technique were similar to those obtained by DLS (Figure 4).

Figure 3. Comparative FTIR spectra of pure OLP and their developed nanoparticles.
3.6. In Vitro Drug Release Studies

It was reported that the conjugate showed faster drug release in an acidic region (pH 5.0), likely due to the condition of cancerous cells, than in normal cell conditions (pH 7.4) [25]. In this study, the experiments were performed at pH 7.4. The release profiles of pure OLP, OLP-PLGA NPs and OLP-CS-PLGA NPs were tested in a phosphate buffer at pH 7.4 (Figure 5). In dissolution media, the free OLP drug was rapidly and completely released (within 24 h). However, both OLP-PLGA NPs (64%) and OLP-CS-PLGA NPs (52%) showed an initial burst drug release in the first 2 h. The initial burst release of OLP from both NPs could be due to the surface of the adsorbed drug [36–40]. The release was sustained for 72 h in both OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs to enhance the efficacy of the drug. However, due to the charge attraction between OLP and chitosan in OLP-loaded CS-PLGA NPs, this exhibited a more sustained release of the drug in comparison to OLP-loaded PLGA NPs [28]. Data obtained from in vitro release studies of OLP-PLGA NPs and OLP-CS-PLGA NPs were fitted into various kinetic models. The R^2 values of OLP-PLGA NPs were: zero order (0.6776), first order (0.8808), Higuchi model (0.8753), Korsmeyer–Peppas (0.8341). On the other hand, the R^2 values of OLP-CS-PLGA NPs were: zero order (0.7428), first order (0.9122), Higuchi model (0.9127), Korsmeyer–Peppas (0.8834), respectively. The highest R^2 values in both formulations indicated that Higuchi model release kinetics were the best fitted model [19].
3.7. In Vivo Pharmacokinetic Study

The pharmacokinetic profile of the pure OLP suspension, OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs is depicted in Figure 6, and the values of the pharmacokinetic parameters are listed in Table 3. The increase in the \( C_{\text{max}} \) value of OLP-loaded PLGA NPs was highly significant \((p < 0.01)\) in comparison to the pure OLP suspension, whereas its exposure was extremely significant \((p < 0.001)\) for OLP-loaded CS-PLGA NPs without any change in the \( T_{\text{max}} \) value. Similarly, the \( \text{AUC}_{0-24} \) values for OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs were significant \((p < 0.01)\) and extremely significant \((p < 0.001)\), respectively, higher than the pure suspension of OLP solution. However, the increase in \( \text{AUC}_{0-\infty} \) values of OLP-loaded PLGA NPs was not comparable to the pure suspension. The bioavailability of OLP was enhanced by 2 and 4.75 times in OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs, respectively, which was significantly higher compared to previously reported work by [41–43], who developed a nanoliposhpere and nanosuspension of OLP. This agrees with the data reported by Badran MM, 2018, and Kashyap S, 2019, which showed that CS-coated PLGA NPs showed a tremendous increase in the bioavailability of the targeted drugs [41,44]. The \( T_{1/2} \) (h) and MRT of CS-coated PLGA NPs was significantly \((p < 0.05)\) higher than the pure OLP suspension; however, these changes were insignificant in the case of OLP-loaded PLGA NPs which means that CS layers increased the sustained release effects of PLGA NPs and promoted their resident time in plasma [45]. The above results indicate that CS-coated PLGA NPs have shown better pharmacokinetic parameters than the OLP-loaded PLGA NP nanoparticles, ensuring a better sustained effect of the OLP.

![Figure 6. Comparative in vitro pharmacokinetic profile of pure OLP and their developed nanoparticles.](image-url)
Table 3. Pharmacokinetic parameters after single oral dose of pure OLP suspension, OLP-PLGA NPs
and OLP-CS-PLGA NPs administration (1 mg/kg in rats).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>OLP Suspension Mean ± SD, (n = 5)</th>
<th>OLP-PLGA NPs Mean ± SD, (n = 5)</th>
<th>OLP-CS-PLGA NPs Mean ± SD, (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>36.38 ± 7.24</td>
<td>110.93 ± 18.28 **</td>
<td>263.13 ± 24.25 ***</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>$AUC_{0-24}$ (ng.h/mL)</td>
<td>217.11 ± 11.01</td>
<td>435.27 ± 135.30 *</td>
<td>1131.34 ± 47.66 ***</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/mL)</td>
<td>225.35 ± 11.42</td>
<td>455.70 ± 147.36</td>
<td>1354.76 ± 208.37 ***</td>
</tr>
<tr>
<td>$K_{\text{el}}$ (h)</td>
<td>0.14 ± 0.02</td>
<td>0.17 ± 0.06</td>
<td>0.08 ± 0.03 *</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>5.05 ± 0.11</td>
<td>4.40 ± 1.42</td>
<td>10.05 ± 3.93 *</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>6.90 ± 0.12</td>
<td>5.93 ± 1.69</td>
<td>11.98 ± 5.21 *</td>
</tr>
</tbody>
</table>

Relative Bioavailability (%): 100 200 475

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

4. Conclusions

OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs were synthesized for the improved bioavailability of OLP. Chitosan was successfully coated on the surface of OLP-loaded PLGA NPs, which was confirmed by particle size and zeta potential studies. The coated formulations (OLP-loaded CS-PLGA NPs) showed larger particle sizes and positive zeta potentials. In vitro studies indicated that OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs showed a sustained release pattern in comparison to a pure OLP suspension. The improved (2 times) and extremely high (4.75 times) bioavailability of OLP-loaded PLGA NPs and OLP-loaded CS-PLGA NPs, respectively, was observed in comparison to free drug suspension. Moreover, OLP-loaded CS-PLGA NPs have shown higher $T_{1/2}$ and MRT than the OLP-loaded PLGA NPs nanoparticles ensuring better sustained effect of the OLP. Based on these findings, it can be said that OLP-loaded CS-PLGA NPs are a useful and potentially effective chemotherapeutic delivery system.


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Institutional Review Board Statement: The Study was conducted after approval of Research Ethics Committee, Prince Sattam Bin Abdulaziz University (Approval number: BERC 003-03-21; dated: March 2021).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.
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