Formulation and characterization of artemether-loaded sodium alginate microcapsules

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INTRODUCTION

Malaria is a poverty-related disease and its mortality burden is high in Africa [1].

Abstract

Purpose: To increase the solubility of artemether (ART) in Transcutol® HP through microencapsulation in sodium alginate polymer to achieve sustained in vivo release.

Method: Graded concentrations of ART (0.00, 0.25, 0.50, 0.75, and 1.00 g) microcapsules were produced using Tween® 80 by the cold homogenization method at 24 x 1000 rpm for 15 min. Characterization based on yield, encapsulation efficiency (EE), particle size, pH stability, differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and in vivo release using Peter’s four-day suppressive protocol in Wistar mice infected with Plasmodium berghei, were determined.

Results: The results obtained indicate that 0.5 g ART-loaded microcapsules (AMC) showed the highest yield of 96.85 %. The EE of 88.3 % corresponded to 0.75 g ART-loaded microcapsules. DSC results revealed that there was a significant reduction in enthalpy in all the formulations compared to the crystalline drug, but no strong bond interaction occurred except for the blank microcapsules. The AMC1.0 showed high dose-dependent plasmodial growth inhibition of 88.75 % while AMC0.25 had the least (68.13 %).

Conclusion: The artemether microcapsules showed sustained release characteristics for oral delivery of artemether and therefore may reduce some of the adverse effects associated with high dose artemether therapy in conventional oral tablets.

Keywords: Malaria, Artemether, Transcutol® HP, Sustained-release, RBC count, Antiplasmodial activity
worldwide, with an approximation of 219 million incidents and 435 000 demises as of 2017 [2]. Recently, Nigeria is one of the ten highest burden countries in Africa reported to have increased cases of malaria. The country accounts for 25 % out of the 93 % of global malaria deaths in 2018 that was concentrated in 17 countries in the WHO African Region and India. Children under 5 years are the most susceptible group disturbed by malaria and account for 65 % of all the global malaria demises. [3]. The consequence of malaria is felt by the poor population of third world countries especially in Africa where the people cannot afford the expensive drugs. Due to parasite resistance, monotherapy has given way to artemisinin-combination therapies (ACTs).

Artemether (ART) is unique active drug therapy for the chloroquine-resistant and *Plasmodium falciparum* species of malaria. Artemether (ART) is a semi-synthetic (methyl ether) by-products of artemisinin obtained from a China plant *Artemisia annua*, where it exists as a sesquiterpene endoperoxide lactone, also recognised as dihydroartemisinin methyl ether. However, treatment failure has been reported which is due to poor bioavailability hindering therapeutic potency of the drug [4]. The poor bioavailability is as a result of the limited solubility of the drug [5].

The highly frequently used drug delivery route is the oral route because it possesses many advantages compared to other routes of drug administration. However, oral delivery of lipophilic drugs introduces a key disadvantage due to their low aqueous solubility which results in inadequate and variable bioavailability and gastrointestinal mucosal toxicity [6]. Poor oral bioavailability is the major reason for redesigning a drug such as ART to improve its permeability, solubility and dissolution to reduce its numerous side effects when administered orally. Additionally, the conventional regimens of artemether (injection, tablet and capsule) are associated with pain, degradation and loss of drug before it gets to its site of action leading to poor bioavailability [7]. Intervention based on novel drug delivery systems ensures greater pharmacological response, with lower doses and minimization of side effects.

To improve on the limitations of concern to ART, encapsulation has been proposed as an alternative approach [8]. Microencapsulation exists as a method whereby solid, liquid and gaseous materials are encapsulated in tiny capsules or microcapsules that discharges their content at a controlled rate over an extended period [9]. These microcapsule matrices protect the loaded labile substances against degradation and can defend the GIT mucosa from severe irritations of various drugs as well as conceivably offer sustained drug discharge and drug targeting [10]. Many research works on Artemether loaded microcapsules has been formulated and assessed for in vivo performance in maliariogenic mice [11,12].

The reason for the microcapsule formulation was to generate microcapsules where the oil (Transcutol) containing the drug is incorporated into the core of a polymer matrix (sodium alginate). This could result in greater encapsulation efficiency, % yield and regulated drug discharge as the drug melts in the oil and at the same time encapsulates in the polymer matrix; which could also lead to a lower crystallinity index (improved stability).

**EXPERIMENTAL**

**Materials**

Artemether powder (Hangzhou Dayangchem Co. Limited, China), sodium alginate (Marine Hydrocolloids, Kochi, India), Transcutol® HP (Gattefossé, St Priest, France), Tween® 80 (Polysorbate 80) (Qualichem, China). All other reagents were used as procured without further processing.

**Animals**

All animal experiments were performed following the National Institute of Health guideline on the principles of laboratory animal care (National Institutes of Health publication 85-23, revised 1996) [13] and were approved by the Institution Animal Care and Use Committee of the University of Nigeria Nsukka (approval no. FPSRE/UNN/18/00036). Male albino adult Wistar mice (35) were bought, accommodated and nourished to acclimatize to the laboratory setting. *Plasmodium berghei* was hosted by donor mice obtained from the Department of Pharmacology and Toxicology animal house in the University of Nigeria.

**Preparation of microcapsules**

Cold homogenization method was adopted. Some 32 mL of Transcutol HP was added to a beaker and separately loaded with graded concentrations of artemether (0.0, 0.25, 0.5, 0.75, and 1 g). Sodium alginate (1.8 % w/w) was dissolved in deionized water after which polysorbate 80 (2 % w/w) was inserted into the mix. Afterwards, the aqueous phase was added into the oil phase and exposed...
to homogenization (Ultra Turrax, T18 basic, IKA Germany) at high shear of 24 × 1000 rpm for 15 min to generate a dispersion which separated into lower (colloidal sediment) and upper (supernatant liquid) parts. By decanting off the upper fluid, the microcapsules were recovered and stored securely at room temperature.

**Determination of yield and encapsulation efficiency**

The microcapsules yield from each batch was determined by linking the weight of the formulation gotten to the absolute weight of the components (W2 and W3) used in the formulation, as seen in Eqn 1.

\[ Y(\%) = \left( \frac{W1}{W2+W3} \right) \times 100 \]  

where W1 = weight of formulated microcapsules (g), W2 = weight of added drug (g), and W3 = weight of Transcutol and surfactant (g).

Encapsulation efficiency (EE) was determined by calculating the amount of artemether in the microcapsules using spectrophotometric method. The supernatant from the formulation of the microcapsules was assayed spectrophotometrically (UNICO-3102, England) at 255.4 nm. Briefly, some 2 mL aliquot of the dispersion was combined with 2 mL of deionized water, after which it was placed in the refrigerator at 4 °C for 5 min, followed by centrifugation at 3000 rpm for 20 min.

The 1 mL measure of the supernatant from the dispersions was processed by derivatization with 25 mL volume of 1N HCl and heated at 80 °C for 30 min in a water bath. The treated tests were then diluted to 100 ml with de-ionised water before absorbance readings. The drug encapsulation efficiency (EE) of the ART-loaded microcapsules was calculated using Eq 2.

\[ EE(\%) = \frac{ADL}{TDL} \times 100 \]  

where ADL = actual drug loading, and TDL = theoretical drug loading.

**Determination of pH, and stability studies**

Determination of the short-term stability of the microcapsules necessitated exposure to time-dependent pH analysis. The pH of the dispersion was resolved by employing a validated pH meter (pH/ion meter S220, Mettler Toledo multimeter analyser, Switzerland). After calibration with pH standards (pH 4 and 7), the electrode component was rinsed, paper-dried and immersed into the dispersions and each time, triplet readings were recorded, after 1 week of formulation following storing at ambient temperature for 1 and 3 months of preparation.

**Differential scanning calorimetry**

The level of crystallinity and polymorphism of excipients and microcapsule formulations were evaluated. An appropriate quantity (~ 4 - 8 mg) was weighed in an aluminium pan, heated in a differential scanning calorimeter (STAR SW 13.00, Mettler Toledo, Switzerland) from 60 to 300 °C at 10 °C/min under continuous nitrogen flux (10 ml/min). The DSC criteria, such as temperature onset, maximum peak, and enthalpy were produced after baseline correction with an empty aluminium pan which served as reference.

**Fourier transforms infrared spectroscopy**

The affinity of the micro-capsule formulations, pure drug and polymer matrix was determined by utilising a Shidmazu FTIR 8300 spectrophotometer (Shidmazu, Tokyo, Japan). Briefly, KBr (0.4 g) was weighed, ground into powder, mixed with 0.001 g of the test sample and moulded into a disc. The disc was inserted into the sample compartment of the instrument to generate the IR spectrum.

**Evaluation of in vivo anti-plasmodial activity of artemether micro-capsules**

The in vivo anti-plasmodial activity was considered using a 4-day suppressive test procedure (Peters 4 day suppressive test) [14]. Thirty albino Wistar mice procured from the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka was used for the investigation and were cared-for on food and water as desired. Briefly, the animals were divided into 7 groups (1-7) of 5 animals each, weighed and clearly marked to avoid any mix-up. The animals were injected intraperitoneally by inoculating with 0.2 mL of donor mice blood suspension (donor mice blood diluted with normal saline) on the first day. Group 1 was treated with 5 mg/kg of artemether (as positive control). Groups 2-5 were treated with micro-
capsule dispersions of artemether coded as AMC0.25, AMC5.0, AMC7.5 and AMC1.0 respectively containing 0.25, 0.5, 0.75 and 1.0 g artemether). Group 6 was treated with the drug-free (unloaded) micro-capsule whereas Group 7 was infected but not treated (negative control). Treatments of the formulations were given once daily for 3 days after 24 h post-infection. After which, the animals were subjected to red blood cell count (RBC) and parasitaemia count. The RBC count was determined using haemocytometer method. This method is realised by preparing a mixture of 0.1 mL of animal’s blood and 0.9 mL of Hayems solution which is placed in a charged counting chamber whereby the cells were counted as n and multiplication of n by 10,000 was expressed in cells/mm³ [10]. The parasitaemia count was determined by tail-bleeding the mice and preparing blood smears on microscope slides, subsequently, fastened with methanol and marked with Giemsa. The parasitemia number was determined by viewing under the microscope and taking the count thrice and the average calculated. The antimalarial activity was evaluated using equation 3 [6]:

\[
\% GI = \frac{(PNC-PTS)}{PNC} \times 100 \quad \text{……… (3)}
\]

where \( \% GI = \) percentage growth inhibition, \( PNC = \) parasitaemia of negative control and \( PTS = \) parasitaemia of test sample.

### Statistical analysis

All the data established were demonstrated as mean ± standard deviation. Statistical significance was determined using Students t-test, with \( p < 0.05 \) considered statistically significant.

### RESULTS

#### Yield and encapsulation efficiency

The yield of the different batches is presented in Table 1 which shows that the micro-capsule yield was high (51.35 - 96.85%). AMC5.0 had the highest yield (96.85 %) while AMC0.25 had the lowest yield (51.35 %). This corresponds to the microcapsule formulations containing 0.5 and 0.25 g of artemether, respectively. In other words, the microcapsule encapsulated artemether to a large extent. In terms of EE (%), AMC0.75 had the highest value of 88.3 % (Table 1). The order in decreasing EE was AMC 0.75 > AMC0.5 > AMC0.25 > AMC1.0 corresponding to 88.30 > 85.46 > 76.62 > 64.11 %.

### Morphology and particle size

The particle size of the microcapsules was between 5.33 and 9.23 μm. The photomicrographs are shown in Figure 1. The highest particle size was that of the batch loaded with 0.5 g of artemether (AMC0.5) while the lowest was the batch containing 1g of artemether (AMC01.0). This shows that particle size increased with the efficiency of drug encapsulation since AMC0.5 batch of microcapsule contained as high as 85 % artemether whereas AMC0.75 contained a lower amount of artemether (64 %).

### Formulation stability

The results of the pH test carried out post formulation of microcapsule dispersions (1 week, 1 and 3 months) of the drug-loaded microcapsules and unloaded microcapsule showed mean pH range of 8.44 ± 0.22 to 9.62 ± 0.11, 8.71 ± 0.96 to 9.22 ± 1.89, 8.58 ± 0.05 to 9.28 ± 0.09, 8.72 ± 0.02 to 9.82 ± 0.07, and 8.72 ± 0.02 to 9.82 ± 0.07 relative to AMC0.25, AMC0.5, AMC0.75, AMC1.0 and AMC unloaded, respectively. An insignificant increase in pH of the formulations was observed. In other words, the formulations were stable at room temperature. It can be inferred that AMC0.5 was the most stable of the formulations as it showed a little change in pH between the 1st and 3rd months.

### Statistical analysis

All the data established were demonstrated as mean ± standard deviation. Statistical significance was determined using Students t-test, with \( p < 0.05 \) considered statistically significant.

### RESULTS

#### Yield and encapsulation efficiency

The yield of the different batches is presented in Table 1 which shows that the micro-capsule yield

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Yield (%)</th>
<th>Encapsulation efficiency (%)</th>
<th>Particle size (µm)</th>
<th>Melting point (°C)</th>
<th>Enthalpy (-mW/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC0.25</td>
<td>51.35</td>
<td>67.62</td>
<td>21</td>
<td>88.16</td>
<td>19.98</td>
</tr>
<tr>
<td>AMC0.5</td>
<td>96.85</td>
<td>85.46</td>
<td>20</td>
<td>98.50</td>
<td>14.13</td>
</tr>
<tr>
<td>AMC0.75</td>
<td>80.20</td>
<td>88.30</td>
<td>21</td>
<td>88.16</td>
<td>19.98</td>
</tr>
<tr>
<td>AMC1.0</td>
<td>72.45</td>
<td>64.11</td>
<td>18</td>
<td>75.55</td>
<td>0.82</td>
</tr>
<tr>
<td>AMC0.0</td>
<td>65.90</td>
<td>-</td>
<td>14</td>
<td>87.94</td>
<td>31.34</td>
</tr>
<tr>
<td>ART</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>86.96</td>
<td>87.51</td>
</tr>
</tbody>
</table>

*Key: AMC0.25, AMC0.5, AMC0.75, and AMC1.0 represents microcapsule batches with 0.25, 0.5, 0.75 and 1g of artemether, AMC unloaded (AMC0.0) represents microcapsule-free of artemether, respectively*
After 1 week of formulation, AMC0.0 (drug-free) had similar pH as other formulations; perhaps showing that the pH of the formulation is not dependent on ART incorporation.

Figure 1: Photomicrographs of alginate microparticles. **Key:** AMC0.0, AMC0.25, AMC0.5, AMC0.75, AMC0.10 correspond to Phase-contrast images (A, C, E, G, I) and light microscope images (B, D, F, H and J) respectively representing drug-free and ART-loaded microcapsules

**Thermal characteristics**

DSC is an analytical tool used to detect and study the thermal behaviour of materials. The summary of the DSC results is shown in Table 1. All formulations showed decreases in enthalpy when compared to pure ART. Higher enthalpy suggests more crystalline matrix and consequently low encapsulation efficiency while lower enthalpy suggests a more disordered matrix (amorphous) which is suitable for enhanced drug loading (Figure 3). AMC0.0 (drug-free) had the highest enthalpy (-31.34mW/mg) compared to the drug-loaded formulations. AMC0.25 and AMC0.75 had the same enthalpy (-19.98mW/mg) while AMC1.0 had the lowest enthalpy (-0.82mW/mg) showing that increase in the concentration of the drug did not affect enthalpy values of the microcapsules. The enthalpy values of sodium alginate, Transcutol and Tween® 80 were 24.29, -26.76 and -0.74 mW/mg respectively.

Figure 2: DSC thermograms of the pure samples

Figure 3: DSC thermograms of the formulations. **Key:** AMC0.25, AMC0.5, AMC0.75 and AMC1.0 represents microcapsule batches with 0.25, 0.5, and 1g of artemether, AMC unloaded (AMC0.0) represents microcapsule-free of artemether, respectively

**FTIR spectra**

The FTIR spectrophotometer was used to establish if there is an incidence of interaction between the excipients and pure sample of ART. The FTIR spectrum of artemether (Figure 4 and 5) displayed major peaks at 3499.16 (O-H bond), 2940.6 (C-H stretch), 2858.51 (-CH3- bond bending) and 1756.30 (C=O vibration) cm⁻¹, respectively. The FTIR spectrum of the pure
sodium alginate polymer showed characteristic peaks at 3570.26 (O-H stretching), 2959.5 (C-H bond vibration) and 1721.32 (C=O vibration) cm⁻¹, respectively whereas FTIR spectrum of pure Transcutol showed characteristic peaks at 3510.5 (O-H bond vibration), 2941.65 (C-H bond stretching) and 1748.34 (carboxylic acid C=O vibration) cm⁻¹, respectively. Tween® 80 showed characteristic peaks at 3489.20 (O-H bond stretching), 2921.78 (C-H bond vibration) and 1748.34 (C=O vibration) cm⁻¹, respectively.

**In vivo anti-plasmodial activity**

Fig. 6 shows that Group 1 which received pure ART sample had a percentage growth inhibition of 79.75%, whereas the mice groups that received formulation batches of AMC0.25, AMC0.5, AMC0.75, AMC1.0 and AMC0.0 (drug-free or placebo) respectively demonstrated percentage plasmodial growth inhibitions of 68.23, 82.10, 85.94, 88.75% and 27.26%. However, Group 7 mice which received no treatment (at all) had 0% growth inhibition. This shows that all batches of artemether-loaded microcapsules showed significantly higher hindrance to plasmodial growth than ART alone and/or the drug-free microcapsules except for batch AMC0.25.

**Figure 4:** FTIR spectra of pure samples. **Key:** A, B, C, and D represents artemether, sodium alginate, Transcutol, and tween 80, respectively

**Figure 5:** FTIR spectra of ART-microencapsulation formulations. **Key:** A (AMC0.25), B (AMC0.5), C (AMC0.75), and D (AMC1.0) represents microcapsule batches with 0.25, 0.5, 0.75, and 1g of artemether, respectively

**Figure 6:** Antimalarial activity of artemether-loaded sodium alginate microcapsules. **Key:** ART = artemether; AMC = artemether microcapsule containing graded drug concentrations (0.25, 0.5, 0.75 and 1.0 g); MC = microcapsule; untreated = rats infected with malaria but not treated
Table 2: Parasitaemia, RBC count and growth inhibition after administration of microcapsules

<table>
<thead>
<tr>
<th>Group</th>
<th>Parasitaemia (%)</th>
<th>RBC count (x10^6 cells/mm^3)</th>
<th>Growth inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (+ve control)</td>
<td>5.4</td>
<td>5.19±0.73</td>
<td>79.75</td>
</tr>
<tr>
<td>2</td>
<td>8.5</td>
<td>4.68±0.72</td>
<td>68.13</td>
</tr>
<tr>
<td>3</td>
<td>4.8</td>
<td>5.15±0.25</td>
<td>82.10</td>
</tr>
<tr>
<td>4</td>
<td>3.6</td>
<td>4.94±0.38</td>
<td>85.94</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>5.47±0.25</td>
<td>88.75</td>
</tr>
<tr>
<td>6 (placebo)</td>
<td>19.4</td>
<td>4.24±0.98</td>
<td>27.26</td>
</tr>
</tbody>
</table>

Key: Group 1 was treated with the pure artemether sample; Groups 2-5 were treated with Batches A to D containing graded doses of the microcapsules (0.25, 0.5, 0.75, 1 g), respectively; Group 6 was treated with the unloaded microcapsules whereas Group 7 was infected but not treated (at all)

DISCUSSION

The yield of the drug determined the content of microcapsules formed at the end of the formulation as well as the quantity of polymer consumed during the preparation process [15]. The percentage yield indicated that the technique employed in the formulation of the microcapsules was reliable and reproducible. Increasing the concentration of ART increased the EE up to 0.75 g, beyond which there was a reduction in EE, perhaps due to the saturation of spaces available for entrapment within the sodium alginate polymer. The findings of the particle size analysis applied on both the loaded and unloaded microcapsules stored at room temperature showed that the microcapsules were within the micrometre range as shown in Table 1. In other words, an increase in the dose of ART had no effect on EE and yield. The result of particle size correlated with the results of encapsulation efficiency and yield.

Based on the results, increased concentration of ART can be said to not affect formulation pH. The insignificant increase in pH indicates slight or no damage to the drug or constituents of the formulation. Higher enthalpy suggests more crystalline matrix and consequently low encapsulation efficiency while lower enthalpy suggests a more disordered matrix (amorphous) which is suitable for enhanced drug loading. However, the presence of sodium alginate and Transcutol in the formulation decreased the crystallinity (thereby decreasing the enthalpy) of the drug. Lower enthalpy and crystallinity index might probably trigger retention of the entrapped drug over time [16].

Comparing the spectra of all formulated microcapsules with pure artemether revealed that the main peaks were sustained. This was confirmed in the AMC0.0 (free drug) spectrum. The observed spectra were not dependent on surfactants or manufacturing processes, signifying that these criteria did not change the bonds formed by the drug or the matrix. Since the characteristic peaks noticed in the pure drug and polymer matrix were still preserved in the spectra of the different formulations, it could be established that no strong chemical bond or contact leading to the development of entirely new compounds transpired. Consequently, artemether was successfully incorporated into the sodium alginate microcapsules without changes in structure. The result shows that all batches of artemether-loaded microcapsules showed significantly higher hindrance of plasmodial growth than ART alone and/or the drug-free microcapsules except for batch AMC0.25.

The increased concentration of ART yielded significant plasmodial inhibition when compared to that of the negative control (placebo). This agrees with earlier observation [17] that decreased bioavailability of ART was due to its low aqueous solubility. Additionally, it has been reported that administration of fatty meal increases absorption and bioavailability of ART.

It follows that solubilising ART in Transcutol, a liquid lipid (oil) rather than solid lipid increased its solubility. This microcapsule technique borrowed the concept of nanostructured lipid carrier to generate particles that their oil is absorbed into the foundation of the polymer and the drug solubilized in the oily core. These findings are in collaboration with Kasongo et al [18] and Varshosaz et al [19,20] that the observed high yield, encapsulation efficiency, steady polymorphic conversion and reduced crystallinity index (higher stability) expectedly controlled ART release as the drug dissolved in the oil and concurrently encapsulated in the polymer.

Therefore, the formulation of ART microcapsules using Transcutol and sodium alginate has increased the bioavailability of ART and also protected the encapsulated artemether against degradation in the stomach pH of 1.2 since the entire formulation had pH in the range of 8.4 - 9.8. The pH range of the formulations suggests that they would bypass the stomach (pH 1.2) to release inside the distal part of the small intestine. This perhaps would correct the wide absorption (GIT and kidney), distribution, rapid metabolism and clearance from the body may...
potentially reduce contra-indication in those with serious liver and kidney diseases, haematopathy (e.g., leucopenia or thrombocytopenia) and porphyria. Additionally, the many negative effects such as nausea, vomiting, skin eruption, elevated SGPT, and SGOT due to large doses (100 mg b.d) could also be corrected by the single daily dose of 5 mg. This agrees with our earlier report on artemether-lumefantrine loaded liquisolid sustained-release compact tablets formulated as an alternate-day regimen for malaria treatment to improve patient compliance which employed only 4 mg of ART. In consonance, this affirms that the clinical efficacy and pharmacokinetics of ART are dependent on the formulation [21,22].

The RBC counts of the treated mice were identical to those treated with the test formulations (Table 2), even though the group treated with pure artemether had a low plasmodial suppression. AMC1.0 and AMC0.75 showed the greatest antimalarial activity with growth inhibition of 88.75 and 85.94 % respectively. The once-daily dosing of microcapsule formulations of ART shows great potentials as sustained-release formulations, hence improving patient compliance. This shows that all batches of artemether-loaded microcapsules showed significantly greater hindrance of plasmodial growth than the individual ART and/or the drug-free microcapsules except for batch AMC0.25.

CONCLUSION

The findings of this study show that the introduction of Transcutol and sodium alginate into artemether-loaded microcapsule increases the bioavailability of the drug, as evident in the parasitaemia reduction by the formulation administered to mice, when compared to the reference drug. Furthermore, the findings show that artemether microcapsules attained sustained release ability, and therefore, could be given by once-daily dosing. Thus, once-daily dosing of artemether will not only improve the side effect profile of the drug but also improve patient compliance, and minimize increase in resistance.

DECLARATIONS

Acknowledgement

The authors appreciate the assistance of Projex Laboratory for particle size analysis.

Conflict of interest

No conflict of interest associated with this work.

CONTRIBUTION OF AUTHORS

We declare that this work was done by the authors named in this article and liabilities about claims relating to the content of this article be borne by the authors. The study was conceived and designed by Petra O Nnamani, while the laboratory work was done by Obialunanma C Metu and Uwakwe Simone Onoja. The data were analysed by John Ogbonna, Petra O. Nnamani, Adaeze C. Echezona and Obialunanma C. Metu. The work is written by Obialunanma C. Metu and Adaeze C. Echezona and proofread by Paul A. Akpa, Ifeanyi Nzekwe, Godswill Onunkwo, Anthony

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