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Original Research Article

Nanocellulose crystals reinforced chitosan hydrogel loaded with artemether-lumefantrine to achieve a sustained release formulation

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ABSTRACT

Multiple dosing regimen is one of the factors driving poor adherence and the emerging resistance of parasites to artemisinin utilized in the treatment of malaria. Hence, a cellulose nanocrystal-reinforced chitosan hydrogel loaded with artemether-lumefantrine (AL) for sustained release of AL to achieve a once-daily dosing was developed. Various concentrations of cellulose nanocrystals (CNCs) of 0 - 2.5% were added to the artemether-lumefantrine (AL) chitosan solution to produce six hydrogel formulations. The drug-excipient compatibility and the effect of the CNC on the mechanical properties, swelling behavior, and *in vitro* release profile of the hydrogels were determined. The FTIR spectra revealed the presence of a -C=N stretching at 1546 cm-¹ indicating a successful cross-linking within the hydrogel. An increase in the concentration of CNC from 0 to 2.5% increased the maximum compression of the hydrogel from 26.1 ± 1.2 kPa to 52.6 ± 3.1 kPa. All the hydrogels exhibited increased swelling in an acidic medium (pH 2.01); an increase in CNC concentration caused an increase in the swelling of hydrogels. The 0.5% CNC-chitosan hydrogel released the highest amount of drugs (48.0 ± 3.56% and 38.0 ± 2.76% for artemether and lumefantrine respectively) after 12 h; an increase in the CNC concentration causes a decrease in the amount of artemether and lumefantrine released. The cellulose nanocrystals improved the mechanical strength, the swelling behavior and also exhibited a gradual and highest release of AL from the chitosan hydrogel with 0.5% CNC. Hence, the CNC-chitosan hydrogel can be useful in formulating sustained-release artemether-lumefantrine.

Keywords: artemisinin resistance, artemether-lumefantrine, cellulose nanocrystal, chitosan, hydrogel, sustained release.

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Introduction

Artemisinin-based combination therapies (ACT) are recommended by World Health Organization (WHO) as the first and second-line treatment for uncomplicated *P. falciparum* malaria and chloroquine-resistant *P. vivax* malaria.[1] In recent years, there have been reports from Africa of emerging parasite resistance to artemisinin. [1] Drug pressure has been identified as a key factor in the emergence of antimalarial drug resistance. This pressure is favoured by several factors including the use of counterfeit antimalarial medicine, inadequate prescription controls, and poor adherence to treatment regimens amongst others.[2] Poor adherence jeopardizes antimalarial effectiveness and control of malarial transmission as well as contributes to resistance.[3]

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Artemether-lumefantrine (AL) is the most administered antimalarial globally, being the first or second-line treatment in thirty African countries.[1] A 6-dose regimen to be taken over 3 days is the recommended course of treatment unlike other ACT's currently recommended by the World Health Organization for which 3 doses are taken over 3 days. The increase in the number of doses could affect patients' adherence to AL in routine health settings.[4] Simple dosing could improve adherence to antimalarial drug regimens, therefore, giving the fixed antimalarial combination medication artemether-lumefantrine (AL) once a day would increase adherence and reduce the chance of resistance selection.[5]

Chitosan is a biodegradable polymer obtained by deacetylation of chitin – a substance found in the shells of arthropods like crabs, shrimps, insects and produced by fungi and bacteria.[6] Chitosan-based drug delivery systems such as beads, films, sponges, hydrogels, microspheres, and nanoparticles have been developed to control the release of drugs for once-daily dosing and enhance the dissolution of poorly soluble drugs.[7,8] Also, the large amount of positively charged amino groups on the surface of chitosan allows for strong interactions with the mucosal membrane as a result reduces drug clearance and allows drugs to penetrate through the cell membrane, thereby improving drug absorption rate and bioavailability.[7] The above properties of chitosan make them suitable as drug carriers for artemether with low aqueous solubility (BCS class II) and lumefantrine with low aqueous solubility and low permeability (BCS class IV).

Cellulose nanocrystals (CNC) are derived from cellulose, the most abundant natural polymer on earth.[9] It possesses the advantageous qualities of cellulose, including non-toxicity, low density, and biodegradability.[9] Furthermore, it possesses a wide surface area, high tensile strength and stiffness, great colloidal stability, and potential for modification because of the abundance of surface hydroxyl groups.[10] Cellulose nanocrystals possess strong reinforcing potential when added into a polymer matrix and are a great material for creating high-performing nanocomposites.[11,12]

Hydrogels are a three-dimensional network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure due to chemical or physical cross-linking of individual polymer chains.[13] Hydrogels formed from polymers such as chitosan can be responsive to stimuli and show significant changes in their properties under external stimuli such as temperature, pH, light, ion changes, and redox potential.[14] Stimulus-responsive hydrogels loaded with multiple drugs show controlled and sustained drug release and can act as drug carriers.[14]

This research focuses on developing an artemether-lumefantrine-loaded chitosan-based hydrogel formulation reinforced with cellulose nanocrystals for improved mechanical properties and sustained release of artemether and lumefantrine.

Materials and Methods

Methods

Artemether and lumefantrine powders were obtained from Hennan Senyuan Biological Technology, China; medium molecular weight chitosan, glacial acetic acid, polysorbate 80, tetrabutyl ammonium hydrogen sulphate were purchased from Loba Chemie, India; cellulose nanocrystals obtained from corn cobs residue was produced in Pharmaceutical Technology Laboratory, University of Lagos; acetonitrile (HPLC grade) was purchased from Sigma-Aldrich, USA.

Preparation of artemether-lumefantrine loaded CNC-chitosan hydrogel formulation

A CNC-Chitosan hydrogel loaded with artemether-lumefantrine was prepared using a modified method reported by Udeni Gunathilake et al. [15] Chitosan solution (2% w/v) was prepared by dissolving 4 g of chitosan in 200 mL of 5% acetic acid solution. The mixture was stirred and sonicated for 10 minutes at a temperature of 25°C. The chitosan solution was filtered to remove undissolved or impure materials. Artemether (200 mg) and lumefantrine (1200 mg) were mixed with 100 mL of the chitosan solution at 350 rpm for 1 h. The CNC solutions were homogenized via ultrasonic bath (Acmesonic, Model C210, China) for 10 min to ensure that they were uniformly dispersed. Thereafter, the CNCs were added in different concentrations (0, 0.5, 1, 1.5, 2, and 2.5%) to 10 mL each of the drug-chitosan solution and stirred at 250 rpm for 2 min. Glutaraldehyde (0.2% v/v) was added to the drug-CNC-chitosan mixture, the mixture was stirred at 350 rpm at 25°C for 1 min and transferred into a 5 mL mold. This was allowed to set at room temperature for 24 h to produce the artemether-lumefantrine-loaded CNC-reinforced chitosan hydrogel. The hydrogel was repeatedly rinsed with distilled water to remove unreacted chemicals.

Characterization of artemether-lumefantrine loaded CNC-chitosan hydrogel formulation

Mechanical testing

Using a universal tensile tester (AGS-X, Shimadzu, Kyoto, Japan), compression tests were carried out to examine the mechanical properties of the hydrogels. The hydrogels were cut into disc shapes with a thickness of 11 mm and a diameter of 17 mm; the hydrogels were allowed to equilibrate in buffer solution at pH 7.4 for 30 h. Stress and strain responses were observed during the compressive strength tests at a rate of 0.5 mm per minute with a 500N load. Using Trapezium lite X software, strain and stress values were recorded until the point at which maximum breaking stress was approached.[15] The Young's modulus was calculated from the data obtained.

Swelling behaviour at different pH

The swelling ratio of the hydrogel formulations was determined in buffer solutions at pH 2.01, 7.00, and 10.00. The hydrogels were divided into discs and allowed to dry at room temperature until they achieved a consistent weight before the swelling test. The hydrogels were submerged in buffer solutions (pH values 2.01, 7.0, and 10.0) at 37°C. At a 30-minute interval up until each hydrogel sample attained a constant weight, the samples were taken out of the buffer solution, dried with a paper towel, and weighed. The percent swelling ratios of the hydrogels were calculated using equation 1.[16]

$$Swelling\ ratio\ (\%) = \frac{Wt1 - Wt2}{Wt2}\ x\ 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ 1$$

Where Wt_1= weight of swollen gel and Wt_2=weight of initial gel

FTIR studies

The drug-polymer interaction was investigated using Fourier transform infrared (FTIR) spectroscopy. The artemether-lumefantrine (drug), drug-loaded CNC-chitosan hydrogel, CNC-chitosan hydrogel and chitosan hydrogel were subjected to FTIR studies. The samples were dispersed in KBr pellets and compressed into discs; the disc was placed in the light path and the spectrum was scanned at 400 – 4000cm^{-1} using a spectrophotometer (Cary 630, USA).

In vitro drug release and kinetics study

The dissolution of the hydrogel was carried out using the paddle apparatus (Agilent Dissolution Apparatus 708-DS, USA) according to the dissolution testing protocol for sustained release dosage forms outlined in the USP 2011.[17] The release of artemether and lumefantrine from three formulations containing 0.5%, 1.5% and 2.5% CNC respectively were determined. For quantification of artemether, each formulation was placed in 900 mL of distilled water that had been equilibrated to 37°C, and the setup was operated at a paddle speed of 100 rpm for 12 h. Aliquot samples (5 mL) were taken at predetermined time intervals (1h, 3h, 6h and 12h), filtered through a 0.45 µm syringe filter and subsequently analyzed by HPLC (Agilent Technologies L200 series, USA). Similarly, for lumefantrine, each formulation was placed in 900 mL of 0.1N HCl containing 1% polysorbate 80 and the apparatus was operated at 100 rpm for 12 h. Aliquot samples (5 mL) were withdrawn at 1, 3,6 and 12 h intervals, filtered through a 0.45 µm filter, and analyzed using HPLC (Agilent Technologies L200 series, USA). The *in vitro* release data for artemether and lumefantrine was analyzed using KinetDS 3.0 rev. 2010 software (Krakow, Poland) and fitted into different kinetic models such as zero order, first order, and Korsmeyer-peppas to determine the mechanism of release of the drug from the hydrogel formulation.

Statistical analysis

The data obtained were expressed as mean ± standard deviation. All data was analyzed statistically by one-way analysis of variance (ANOVA). A p-value < 0.05 was considered significant.

Results and Discussion

Mechanical properties

The stress-strain values at the point of fracture of the AL-loaded chitosan hydrogels with varying CNC concentrations are presented in Figure 1 while the maximum stress and Young's modulus obtained for the formulations is represented in Figure 2. The magnitude of stress increased with an increase in CNC concentration of the hydrogel at a given strain (Figure 1); this demonstrates an enhanced mechanical property with increasing content of CNC. The stress-strain curve is non-linear at 30-40% strain level for both the drug-loaded chitosan hydrogel (0% CNC) and the drug-loaded CNC-chitosan hydrogels with plastic deformation occurring in all the hydrogels at strain greater than 40% (Figure 1). The improved mechanical strength of the hydrogel is further demonstrated by the Young's modulus (Figure 2). The Young's modulus measures the stiffness of the polymeric materials used to prepare the hydrogel. The lesser the value of the Young's modulus, the less stiff the material and the lesser its ability to withstand mechanical stress and vice versa.[18] The Young's modulus of the AL-loaded hydrogel formulation increased from 0.71 to 1.15 kPa with an increase in CNC concentration from 0.5 to 2.5% resulting in enhancement of the mechanical strength of the formulation. Hydrogels with low mechanical strength may fragment after repetitive gastric contractions.[19] The improved mechanical strength of the hydrogel would enable it to withstand pressure during gastric contraction and prolong the gastric retention time. The AL-loaded chitosan hydrogel without CNC exhibited the lowest maximum stress of 26.1 ± 1 kPa (Figure 2). There is a sharp increase in maximum stress with the addition of 0.5% CNC to 31.4 ± 1 kPa. This is in line with the work done by Yadav et al. [20] with chitosan composite films reinforced CNC where there was an increase in maximum stress values of up to 4% CNC. In a similar work by Wu et al.[21] the addition of nanofibrillar cellulose (NFC) to chitosan films significantly increased its maximum stress by up to 12 times. The maximum stress of the AL-loaded CNC-chitosan hydrogel increased from 31.4 ± 1 to 50.8 ± 3 kPa with increasing CNC concentration from 0.5 to 2.5% which is about a two-fold increase from that of AL-loaded chitosan hydrogel. The improvement in maximum stress might be attributed to the strong hydrogen bonding between the CNC and the chitosan matrix which allows for efficient stress transmission.[15]

Swelling behaviour

The swelling property of the AL-loaded hydrogel with varying CNC concentrations at acidic, neutral, and basic media is presented in Figure 3. The swelling behaviour of all hydrogel formulations is pH dependent; an increase in the pH caused a reduction in the swelling of all the hydrogels as the least and highest swelling ratio was observed in the alkaline (pH 10) and acidic (pH 2.01) medium respectively (Figure 3). At each pH investigated, the addition of CNC to the AL-loaded chitosan hydrogel caused an increase in the swelling of the formulation; also, an increase in the CNC concentration resulted in an increase in swelling of the hydrogel at all the studied pH. This may be attributed to the hydrophilic property of the CNC which enables water uptake and in turn causes an increase in swelling of the hydrogels with increasing CNC concentration. A time-dependent increase in swelling ratio followed by a decrease up to 0% will dissolve the hydrogels. All the AL-loaded chitosan hydrogels with or without CNC exhibited a greater than 100% swelling ratio on migration from pH 10 to pH 2.01 (Figure 3). This further confirmed the pH-sensitive nature of chitosan hydrogel and its suitability for drug delivery and release in the stomach environment.[16]

FTIR study

The FTIR spectra of artemether-lumefantrine, chitosan hydrogel, CNC-chitosan hydrogel, and the AL-loaded CNC-chitosan hydrogel are represented in Figure 4. The major peaks in the FTIR of the CNC-chitosan hydrogel loaded with AL did not exhibit significant changes when compared to the FTIR of the drug and excipients.

In the chitosan hydrogel, spectrum (Figure 4), the absorption peak showed that the peaks assigned to the N-H and O-H stretching vibrations are located at 3340 cm^{-1} indicating the presence of N-H and O-H vibrations; peaks at 2910 cm^{-1} and 1635 cm^{-1} is due to the C-H asymmetric stretching and the C=O stretching vibrations present in the formulation. A peak at 1548 cm^{-1} represents the stretching vibration of C=N which is formed when the amino groups of chitosan interact with the aldehyde group of glutaraldehyde, thus confirming the crosslinking of chitosan with glutaraldehyde to produce the hydrogel. The FTIR spectra of CNC and chitosan are similar because of the chemical similarities between cellulose and chitosan. [15] The FTIR spectra of the CNC-chitosan hydrogel showed peaks that corresponded to the CNC and chitosan hydrogel, no new peaks or shifts were observed suggesting that the cellulose nanoparticles were physically added. Characteristic peaks were observed in the artemether-lumefantrine spectrum at 1601, 1506, 1274, and 1152 cm^{-1} (Figure 4). This corresponds to the aromatic C-O stretching, the C-O-C stretching, and the stretching vibrations of the benzene ring C=C vibrations, respectively.[22] The distinctive peaks do not exhibit a significant shift in AL-loaded CNC-chitosan hydrogel, indicating the absence of any drug-excipient chemical interaction. As a result, the drug's functional groups were not altered and as such the drug did not undergo any chemical modification during the preparation of the formulation. Therefore, the FT-IR analysis confirms the presence of artemether-lumefantrine in the drug-loaded hydrogel and its compatibility with the excipients.

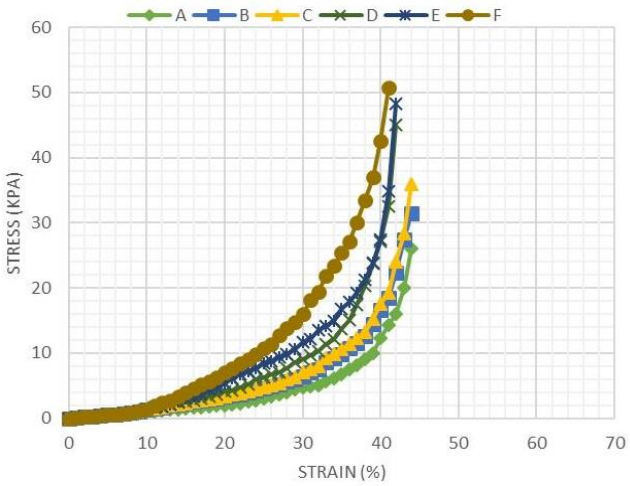

Figure 1: Stress-strain curves at point of fracture of artemether-lumefantrine loaded chitosan-CNC hydrogel
where A, B, C, D, E, F represent 0%, 0.5%, 1%, 1.5%, 2% and 2.5% CNC respectively.

In vitro release study

The *in vitro* release data of artemether and lumefantrine from the CNC-chitosan hydrogel formulations is presented in Figures 5 and 6 respectively. The formulation containing 1.5% and 2.5% CNC released a similar amount of artemether over 12 h with an initial release of 19±2% and 18±2% respectively at 1 h and a total of 35±2% and 38±3% were released after 12 h respectively (Figure 5). On the other hand, for the 0.5% CNC formulation, a higher amount of artemether was released at 1h (30±1%) and 12 h (48±4%) than the amount of artemether released

when higher concentrations of CNC were utilized. Although formulations containing higher amounts of CNC exhibited an increased swelling rate, there was a decrease in the amount of artemether released from the chitosan hydrogels (Figure 3). This finding might be due to the formation of a strong intermolecular force and rigid hydrogel structure by CNC as demonstrated by the increase in stiffness (depicted by the Young's modulus) which will delay degradation and subsequent release of the drug.[23]

An increase in CNC concentration caused a decrease in the initial amount of lumefantrine at 1 h (Figure 6). However, at the end of 12 h, the amount of lumefantrine released from 0.5% and 2.5% CNC formulations were comparable (32.2±1.0 % versus 30.7±1.1 %) whereas the 1.5% CNC formulation released the least amount of lumefantrine at 12 h (18.5±2.3%) (Figure 6). In the 0.5% CNC formulation, there was a steady increase in the amount of lumefantrine released from 16.4±1.3% at 1 h up to 32.3±1.0% at 12 h. Conversely, the 2.5% CNC formulation released only 1.2±1.9% of lumefantrine in the first 6 h followed by a burst release up to 28.9±2.3% after 9 h. This formulation may not be suitable for artemether-lumefantrine delivery because an initial release of an appreciable amount of the drug followed by a steady release is desirable for a sustained release formulation. Generally, the 0.5% CNC formulation exhibited a gradual release as well as the maximum amount of artemether and lumefantrine after 1h h. There exists the possibility for further release of the drugs from the hydrogel if time was extended beyond the 12 h of this study as evidenced by similar studies by Nnamani et al., in which the dissolution study yielded a percentage cumulative release of 86.9 % and 71.4% for artemether and lumefantrine respectively in simulated gastric fluid.[24]

The release kinetics of artemether and lumefantrine in the CNC-reinforced chitosan hydrogel formulation are presented in Tables 1 and 2 respectively. The release of both artemether and lumefantrine from the CNC-chitosan hydrogel followed a Kosmeyer-Peppas release kinetics (0.9944-0.9960 for artemether (Table 1) and 0.9873 – 0.9956 for lumefantrine (Table 2)) via a super case II transport mechanism (n >1) which suggests the breakdown of the polymer matrix to allow for drug permeation and erosion.[25]

Table 1: *In vitro* release kinetic parameters for artemether from samples of AL-Chitosan hydrogel containing different CNC concentrations

CNC concentration	Zero-order		First order		Kosmeyer-peppas		
	R^2	K	R^2	K	R^2	K	n
0.5	0.6407	12.5623	0.3020	5.6522	0.9944	7.1484	1.0790
1.5	0.7749	14.6528	0.3095	5.2147	0.9955	5.1691	1.0657
2.5	0.7660	13.2341	0.3105	5.3215	0.9960	5.4706	1.0685

Table 2: *In vitro* release kinetic parameters for lumefantrine from samples of AL-Chitosan hydrogel containing different CNC concentrations

Sample	Zero-order		First order		Kosmeyer-peppas		
	R^2	K	R^2	K	R^2	K	n
0.5	0.7663	14.7265	0.3091	5.6542	0.9956	4.7367	1.0620
1.5	0.7591	12.5685	0.3086	5.4218	0.9954	2.6164	1.0362
2.5	0.7995	15.2472	0.4405	5.0146	0.9873	8.1089	9.9509

Conclusion

The Artemether – lumefantrine loaded CNC- chitosan hydrogel with enhanced mechanical strength was successfully developed. The AL-loaded CNC-chitosan hydrogel formulations are pH-sensitive and swell considerably in an acidic medium, this property coupled with the improved mechanical strength makes it suitable for drug delivery to the stomach. However, an increase in CNC concentration reduced the amount of AL released. The 0.5% CNC hydrogel formulation released a steady and maximum amount of 48 and 32.3% artemether and lumefantrine respectively. The Artemether and lumefantrine were successfully incorporated into the CNC-reinforced chitosan hydrogel for sustained release of multiple drugs. The new artemether-lumefantrine hydrogels could help reduce dosing frequency due to the possibility of a once-daily dosage regimen. This can in turn solve the problem of adherence and by extension potentially delay or reverse the looming resistance to the mostly used artemisinin combination therapy.

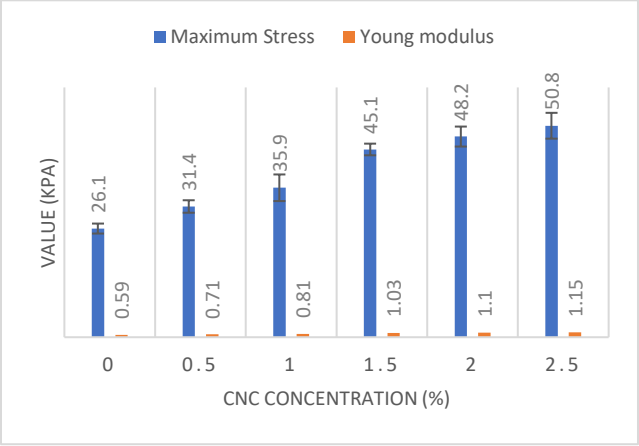

Figure 2: Maximum stress and Young's modulus of artemether-lumefantrine loaded hydrogel with varying CNC concentration

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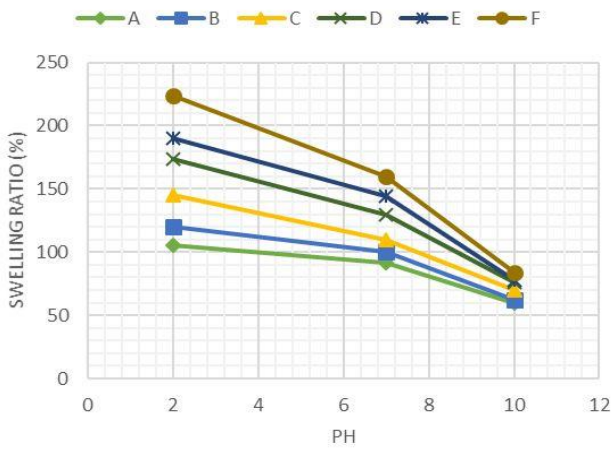

Figure 3: Swelling behavior of AL-loaded CNC-chitosan hydrogels at alkaline (pH 10), neutral (pH 7) and acidic (pH 2) medium where A, B, C, D, E and F represent batches of AL-chitosan hydrogen containing 0%, 0.5%, 1%, 1.5%, 2% and 2.5% respectively.

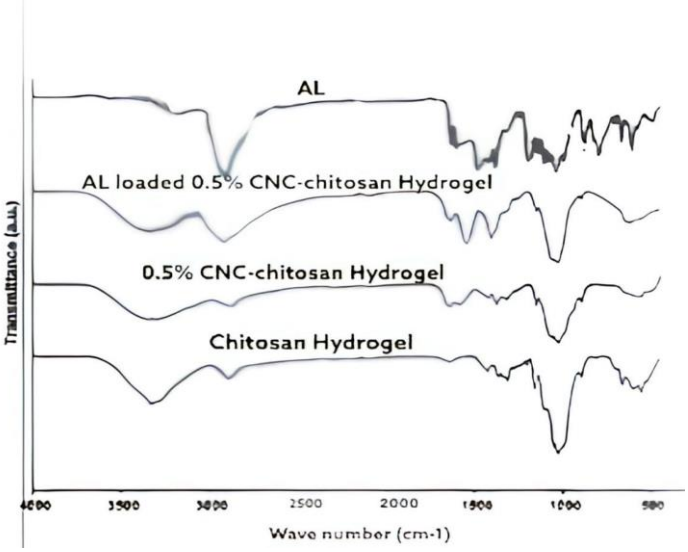

Figure 4: FTIR spectra of chitosan hydrogel, 0.5% CNC-chitosan hydrogel and AL loaded 0.5% CNC-chitosan hydrogel and AL powder.

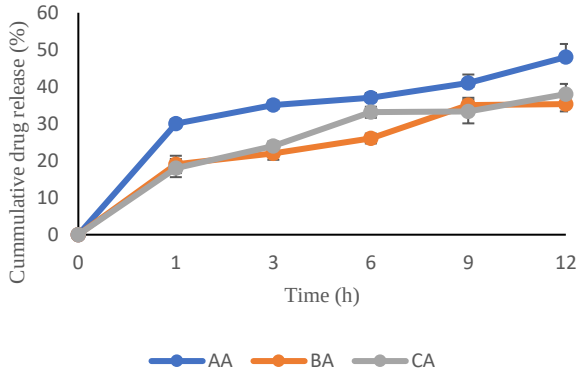

Figure 5: *In vitro* release of artemether from AL-CNC-chitosan hydrogel where AA, BA and CA represent AL-chitosan hydrogel containing 0.5, 1.5, and 2.5% CNC respectively

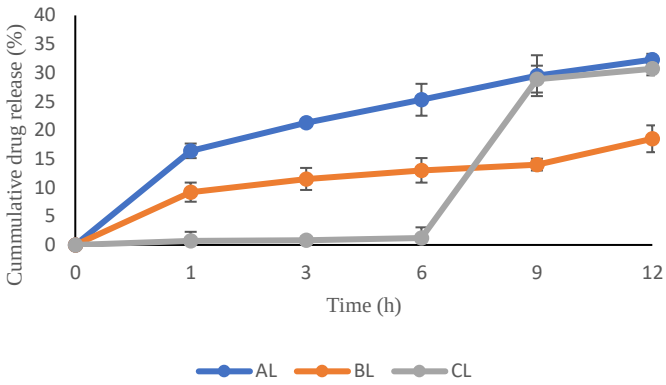

Figure 6: *In vitro* release of lumefantrine from AL-CNC chitosan hydrogel where AL, BL and CL represent AL-chitosan hydrogel containing 0.5, 1.5 and 2.5% CNC respectively.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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