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KARYA ILMIAH TAMBAHAN

	Jurnal Internasional bereputasi (terindeks pada database internasional bereputasi dan berfaktor dampak) (SJR > 0,10)		
	Judul	Jurnal, Volume	Keterangan
C22	Characterization and in vitro release study of artesunateloaded microparticles prepared using crosslinked-chitosan and its derivatives. (**Penulis ke 1** dari 5 penulis) **dan Corresponding Author** (**Retno Sari***, Meta Dian Feriza, Amani Syarahil, Andang Miatmoko, Dwi Setyawan)	Tropical Journal of Pharmaceutical Research.. Vol. 19, Issue. 6. June 2020 ISSN: 1596-9827 Hal: 1139-1146 http://dx.doi.org/10.4314/tjpr.v19i6.3 Penerbit: Pharmacotherapy Group https://www.tjpr.org/admin/12389900798187/2020_19_6_3.pdf **SJR 2019: 0,19; Q3;** **Coverage: 2009-2020**	1. Bukti korespondensi terlampir 2. Jurnal termasuk WoS (Lampiran C 01)

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Characterization and *in vitro* release study of crosslinked chitosan and chitosan-artesunate microparticles

Retno Sari*, Meta Dian F, Amani Syarahil, Andang Miatmoko, Dwi Setyawan

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga

*For correspondence: **Email:** retno-s@ff.unair.ac.id

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ABSTRACT

Artesunate is an antimalarial-drug and is effective for chloroquine-resistant malaria therapy. However, it has low bioavailability which affects the efficacy. Microparticles provide an effective system for improving the drug bioavailability since the size and morphology of the particles can be manipulated to enhance the drug solubility and bioavailability. Chitosan and its derivate have some ideal properties as drug matrices, such as mucoadhesive, biocompatible, biodegradable, and not toxic, thus they can be useful to generate microparticles with good stability and low toxicity for delivery of artesunate.

The aim of this study was to determine the effect of crosslinking on physical characteristics, drug recovery, and drug release from chitosan and carboxymethyl chitosan microparticles of artesunate. The artesunate microparticles were prepared by ionic gelation-spray drying methods with a crosslinking agent, tripolyphosphate for chitosan and $CaCl_2$ for carboxymethyl chitosan.

The results showed that the type of chitosan and crosslinking affected the particle shape, surface roughness, drug recovery, and the drug release. The artesunate microparticles prepared with cross-linked polymer had a lower encapsulation efficiency due to the barriers of the crosslinking agents. The use of carboxymethyl chitosan increased the release rate of artesunate from the microparticles

up to 1.3 times, while chitosan decreased it by 0.5 times. In conclusion, the use of crosslinking agents and the different types of chitosan affected the physical characteristics and release rate of the artesunate from microparticles.

Keywords: Artesunate, Chitosan, Carboxymethyl chitosan, Crosslinking, Microparticle, Drug release

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INTRODUCTION

Artesunate, an artemisinin derivate, is an effective antimalarial drug against Plasmodium falciparum, even for the chloroquine-resistant parasites [1]. However, artesunate has low drug solubility, thus produces low drug's bioavailability when it is administered orally. Artesunate is rapidly absorbed with a peak plasma drug concentration at 1.5, 2, and 0.5 hours after oral, rectal, and intramuscular administration, respectively, while the drug elimination also occurs very rapidly with a half-life of 20-45 minutes [1, 2, 3]. Therefore, for achieving high antimalarial efficacy, the bioavailability of artesunate still needs to be improved. Nowadays, microparticles have been widely developed for delivering drug since the particle size and the particle surface morphology can be easily manipulated to modify drug's solubility and stability [4]. They can also control and maintain drug release to achieve improved drug therapy effects and reduce its side effects. By using microparticles, drugs can be dissolved, entrapped, encapsulated, bonded, or dispersed on macromolecular matrices, such as polymers, and produced within sizes ranging from 10 to 1000 nm [4-7].

Chitosan is a natural cationic polysaccharide polymer that has been widely used to prepare microparticles. It provides some ideal properties for drug carrier, such as mucoadhesive, biocompatible, biodegradable, non-toxic, and inexpensive, thus it can be used for producing microparticles with good stability and low toxicity [5]. Chitosan is composed of copolymers i.e. a combination of glucosamine and N-acetylglucosamine which are obtained from the deacetylation process of chitin. It has weak alkaline property with pKa of 6.5 and high solubility in dilute acids. Moreover, chitosan has positive ions that easily interact with anionic compounds, such as sulfuric acid, citric acid, and tripolyphosphate.

Carboxymethyl chitosan is a chitosan derivate that has important properties as a drug carrier, i.e. high aqueous solubility, good gel-forming capacity, low toxicity, and good biocompatibility. Since

it is an amphiprotic molecule that contains carboxylic and primary amine groups with lots of free electron pairs, carboxymethyl chitosan can be used for many purposes [8].

In general, artesunate microparticles can be prepared by the bottom-up process of ionic gelation method, which is feasible and does not use any organic solvents [9]. However, this ionic gelation method requires polymeric matrices and a crosslinking agent. Tripolyphosphate (TPP) is a multivalent polyanion that is usually used to prepared microparticle of chitosan, resulted in the complexity of crosslinking between the negative carboxylic groups of sodium TPP and the positive primary amine groups of chitosan [10]. Meanwhile, carboxymethyl chitosan can be cross-linked with calcium chloride ($CaCl_2$) that releases negative ions in water. This process can be prepared by adding a low molecular weight of carboxymethyl chitosan with $CaCl_2$ solution [11]. However, $CaCl_2$ is a hygroscopic compound that adsorbs free water molecules in the air. Therefore, it requires a binary solution of water-ethanol at concentration within 10-90% as the solvent during the preparation process [12].

The presence of crosslinking agent can strengthen the mechanical strength of the microparticles, thus increasing the adsorption of drugs into the microparticles matrices [13]. The formation of microparticles using ionic gelation method is affected by several factors, such as the length of polymers, the amount of crosslinking agent, the molar ratio of polymer and crosslinking agent, the pH and temperature of the solution, the concentration of acetic acid solution used for polymer solubilization, temperature, and speed of mixing [14]. The microparticles can be dried using freeze dry or spray dry techniques to obtain dry mass of microparticles. Spray drying technique provides a convenient and reproducible method to produce dry mass of drug solution or suspension in the presence of hot air flow. Factors affecting the microparticles formation using this method are nozzle size, air flow rate, atomization pressure, and inlet temperature [15].

In this study, artesunate microparticles were produced using chitosan and carboxymethyl chitosan by bottom-up ionic gelation method and dried using spray drying technique at optimized parameters. Particle size and surface morphology were then determined to evaluate the physical characteristics of these microparticles.

EXPERIMENTAL

Materials

In this study, artesunate was purchased from Hunan Goldliloo Pharmaceutical Co., Ltd. (Changsa, Hunan China). Chitosan was bought from Biotech Surindo (Cirebon, Indonesia). Carboxymethyl

chitosan, which has a substitution degree of 81.9%, a deacetylation degree of 96.5%, and 1% of viscosity value, 22 mPas, was a product of China Eastar Group Co., Ltd. (Shanghai, China). Calcium chloride $CaCl_2.2H_2O$ pro analysis (Merck), pentasodium tripolyphosphate (TPP), (analytical grade) was obtained from Nacalay Tesque. All reagents and solvents used in this study were the highest grade available.

Preparation of artesunate microparticles

In this study, artesunate microparticles were prepared using ionic-gelation method using formula shown in Table 1. Firstly, artesunate was dissolved in ethanol. Chitosan and carboxymethyl chitosan were dissolved in acetic acid solution and water, respectively, with continuous stirring. Afterwards, these polymer solutions were added into the artesunate solution. The mixtures were then wisely dropped into solution containing crosslinking agent, and stirred using a magnetic stirrer at 500 rpm for 2 hours. The mixtures were then dried using a spray dryer (SD-elementary spray dryer SD B09060019, Lab Plant Ltd., UK) with a nozzle size of 1.0 mm at an inlet temperature of 100ºC and pressure of 2 bar with flow speed of 6.0 mL/min. The microparticles prepared without crosslinking agent were produced using the same method and used as the control groups.

Evaluation of particle size and morphology

Particle size and morphology of artesunate microparticles were evaluated with scanning electron microscopy (Inspect S50 Type FP 2017/12, FEI, USA). During the measurement, the samples were coated with palladium gold.

Fourier transform infrared spectroscopy

In order to evaluate the physicochemical interaction among components of artesunate microparticles, the Fourier transform infra-red (FTIR) spectra of samples were measured by making 2 mg of pellet samples with 300 mg of KBr. Those pellets then were analyzeded at wavelengths of 4000-450 cm^{-1} using Jasco FT-IR 5300 spectrophotometer (Easton MD, USA).

Differential thermal analysis

Differential thermal analysis was determined using the differential thermal apparatus (DTA FP-65 P-900 Thermal, Mettler Toledo, USA). About 5 mg of samples were put into a closed crucible pan. The measurement was then performed at 50-300ºC with a heating rate of 10ºC per minute.

X-ray diffraction studies

The X-ray diffraction analysis was conducted to determine the crystallinity of artesunate microparticles. The samples were analyzed using X'Pert Phillips diffraction apparatus (X'Pert analytical, Netherlands), carried out at room temperature with the measurement conditions as follows: the X-ray X source, Cu metal target, Ni filter, 40 kV voltage, and 40 mA electrical current in the range of 2θ of 5-40°.

Drug content and recovery analysis

The drug content and percent recovery of samples were determined using UV-Vis spectrophotometer (merk, Negara). About 10 mg of the samples were dissolved in ethanol to make a 10 mL sample solution, and then it was settled for two hours at room temperature. The sample was then sonicated for 5 minutes and settled again for 60 minutes. After that, about 5 mL of the sample solution was pipetted, and then added with 2 mL of 0.1N NaOH. The mixture was then heated at 60ºC for 60 minutes and cooled at room temperature. Acetic acid solution was added into 10 mL of 20% v/v ethanol solution. Afterwards, the absorbance was measured at the maximum wavelength, λ 238 nm by spectrophotometry method. The measurement was conducted in triplicates. The drug content of artesunate in the microparticles was then calculated using the following formula:

$$\textbf{\textit{Drug content}}\ (\%) = \frac{\textbf{\textit{amount of drug entrapped}}}{\textbf{\textit{amount of microparticles}}}\ \textbf{\textit{x}}\ \mathbf{100\%}$$

While, the percent recovery of drug was calculated as follows:

$$\textbf{Percent of recovery} = \frac{\textbf{\textit{actual drug amount}}}{\textbf{\textit{theoritical drug amount}}}\ \textbf{\textit{x}}\ \mathbf{100\%}$$

In Vitro drug release of artesunate microparticles

To determine the profile of artesunate released from microparticles, drug release test was carried out using aquadest as release medium. The samples, which were equivalent to 5 mg of artesunate, were weighed and incubated in a 50 mL of aquadest, and then placed on a water bath shaker at

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temperature of 37 ± 0.5°C with stirring speed of 120 rpm. At determined interval times, about 3 mL samples were collected, and the artesunate concentration was analyzed with UV-Vis spectrophotometer (Hewlett Packard (HP) 8452A Diode Array Spectrophotometer, USA).

Statistical analysis

All data are in triplicates and presented as the mean ± SD. To evaluate significance of difference, the data were analyzed by one-way ANOVA followed by Tukey's post-hoc test using SPSS Software v.17.0. with P <0.05 and < 0.01 were considered statistically significant.

RESULTS

Particle size and morphology

In this study, it has been shown that the type of chitosan polymers and the presence of crosslinking agents affected the surface morphology of artesunate microparticles (Figure 1 A - D). The use of chitosan polymers produced particles with smoother and more spherical surfaces (Figure 1 A) than those of carboxymethyl chitosan (Figure 1 C). The addition of crosslinking agent generated particles that has a coarser surface (Figure 1 A and C) than the cross-linked ones (Figure 1 B and D). There were artesunate crystal-like substances on the surface of nanoparticles as observed in the SEM pictures of artesunate microparticles that were prepared with carboxymethyl chitosan polymers using a crosslinking agent (Figure 1 C). This result indicated that the artesunate might not be adsorbed into the matrices of microparticles.

FTIR spectra

The spectra of artesunate and TPP are shown in Figure 2 A and B, respectively. In Figure 2 C, chitosan spectrum has specific absorption band at wavenumber of 3449 cm^{-1} experiencing vibration as well as amide bond derived from the carbonyl group (-C=O) at wavenumber of 1655 cm^{-1}. It indicates the presence of the amine ($-NH_2$) and hydroxy group (-OH) of chitosan polymer. Due to the interaction with TPP (Figure 2 B), the amide peak of chitosan observed at wavenumber of 1655 cm^{-1} was disappeared, forming new peaks at 1643 cm^{-1} and 1566 cm^{-1} for C-CL-AS (Figure 2 D). The loss of this peak can be triggered by the occurrence of crosslinking between phosphate ions and ammonium ions [16]. It can also be seen in the non-cross-linked chitosan microparticles (C-AS) at wavenumbers of 1645 cm^{-1} and 1554 cm^{-1} (Figure 2 E).

In the artesunate microparticles prepared with carboxymethyl chitosan, infrared spectrum of carboxymethyl chitosan (Figure 3 A) depicts a wide band at a wavenumber of 3443.35 cm^{-1} that indicates the presence of the -OH or -NH groups. However, there were spectral changes on the infrared spectra of the cross-linked microparticles (CM-CL-AS) and non-cross-linked microparticles (CM-AS) observed at this wavenumber. It has been reported that the formation of a pointed band indicates a change in the hydrogen bonds [17]. In the CM-CL-AS, there might be hydrogen bond formation between COO- of carboxymethyl chitosan and Ca^{2+} of $CaCl_2$, which converts the hydrogen bond to carboxymethyl chitosan. In CM-AS, although the crosslink did not occur, changes in IR spectra might be caused by the formation of intramolecular hydrogen bonds. In addition, band shifts also occurred in COO- groups with symmetric and asymmetric strains of carboxymethyl chitosan on the microparticles. In carboxymethyl chitosan, the COO- bands with symmetric and asymmetric strains were seen as broad bands at wavenumbers of 1416.47 cm^{-1} and 1647.44 cm^{-1}. However, the CM-CL-AS and CM-AS bands appeared sharper than those of carboxymethyl chitosan, and there was also a shift. It means that the -OH, -NH, and -COO groups are involved in the bond formation in the microparticles.

Thermal properties

It has been shown that the thermograms of C-CL-AS and C-AS microparticles (Figure 4 D and E) had different patterns from that of artesunate (Figure 4 A), but similar to that of chitosan (Figure 4 B). It indicates that microparticulate chitosan matrices containing artesunate have been formed. In addition, there was no exothermic peak of artesunate observed in thermograms of the artesunate microparticles. It indicates that artesunate has been trapped in the microparticulate matrices. C-CL-AS and C-AS have sharp endothermic peaks, which mean there is the bond formation between crosslinking agent and chitosan, or intramolecular chitosan bonds. The heating points of those microparticles were higher than that of artesunate, about 149.0 and 152.1°C for C-CL-AS and C-AS, respectively.

In the artesunate-carboxymethyl chitosan microparticles, the thermograms of CM-CL-AS and CM-AS show sharp endothermic peaks at 150.1 and 151.4°C, respectively (Fig. 4F and G). It may be due to the presence of the bond between the carboxylate groups of carboxymethyl chitosan and Ca^{2+} of $CaCl_2$ in CM-CL-AS and the intramolecular bond of carboxymethyl chitosan in CM-AS.

Consequently, the energy required for heating the microparticles was higher, thus leading to the sharpened endothermic peaks.

Crystal properties

The X-ray diffraction analysis was performed to determine the crystallinity of artesunate microparticles. The results showed that free artesunate had high crystallinity as indicated by intense and strong peaks at 2θ of 9, 12, 13, 15, 18, and 20° (Fig. 5A). Meanwhile, the diffraction peak of chitosan and carboxymethyl chitosan lay at 2θ of 20° with a weak intensity (Fig. 5B and C), indicates that they have low crystallinity. The diffractograms of artesunate-chitosan microparticles i.e. C-CL-AS and C-AS (Fig. 5F and G) show that no diffraction peak of artesunate appears when it is compared with the physical mixture. It means that the artesunate is entrapped and undergoes change on its crystalline structure in the artesunate-chitosan microparticles.

On the other hand, artesunate microparticles prepared with carboxymethyl chitosan i.e. CM-CL-AS and CM-AS no longer have any crystalline peaks of artesunate (Fig. 5H and I). These results indicate that there have been changes in artesunate crystal structures. In CM-CL-AS, a new crystalline peak formed at 2θ of 31° (Fig. 5H) that may be caused by the interaction between carboxymethyl chitosan and $CaCl_2$ forming a regular structure. Meanwhile, in CM-AS, several crystalline peaks were formed with low intensity at 2θ of 7, 9, and 10 ° (Fig. 5I).

Drug content and recovery

By using UV-Vis spectrophotometry method, the artesunate content was determined to measure drug content and percent recovery of artesunate in the microparticles. As shown in Table 2, the addition of the crosslinking agent decreased the encapsulation of artesunate. As the result, the contents of artesunate in the cross-linked chitosan and carboxymethyl chitosan-artesunate microparticles were smaller than those of the non-cross-linked microparticles.

In vitro drug release

The results showed that the artesunate released from microparticles prepared with chitosan was lower than artesunate substance. This may be due to the low solubility of chitosan in water, thus inhibiting drug release with the release rate 9.12 ± 0.85 mg/ml.min^{½} lower than artesunate (Table 2).

The artesunate-carboxymethyl chitosan microparticles had greater drug release than artesunate substances (Figure 7). There were no significant differences of artesunate release rates between non cross-linked and cross-linked artesunate-carboxymethyl chitosan microparticles, which were 14.43 ± 1.27 mg/ml.min^{½} and 16.78 ± 0.93 mg/ml.min^{½}, respectively. However, the drug release rate of cross-linked artesunate-carboxymethyl chitosan microparticles was 1.3 times higher than artesunate.

DISCUSSION

This study was conducted to determine the effect of crosslinking on drug characterization and release from the artesunate particulate system using chitosan and chitosan derivate namely carboxymethyl chitosan.

The particulate system was made in two formulas for each polymer, using crosslinking and without cross-linking agent with drug ratio : polymer was 2 : 5. From Figure 2, the infrared spectra of the artesunate-chitosan particulate system showed the occurrence of bonding between phosphate ions and ammonium ions which is indicated by the loss of amide bonds from chitosan at the wave number of 1655 cm^{-1} and new peaks appeared at 1645 and 1554 cm^{-1}. In the artesunate-carboxymethyl chitosan particulate system, the infrared spectra also showed a change in the resulting spectra, namely a more band which showed a change in the hydrogen bond that occurred at wave number 3443.35 cm^{-1}.

The results of thermal analysis using Differential Thermal Analyzer (DTA) showed that the thermogram pattern of the artesunate-chitosan and artesunate-carboxymethyl chitosan particulate systems was different from each of the forming materials. Furthermore, in the evaluation of X-ray diffraction systems of artesunate-chitosan and artesunate-carboxymethyl chitosan, the diffraction peaks of artesunate did not appear when compared to the physical mixture. This suggests that the artesunate is entrapped and undergoes changes in the crystalline structure in the microparticles system. The results of the morphological test of particulate systems using SEM showed that the artesunate-chitosan particulate system had a more spherical shape than the artesunate-carboxymethyl chitosan particulate system. But with cross-linking, both of them showed the similar morphology which is rougher surface when compared to the non-crosslinked microparticles. The formation of an artesunate-chitosan and artesunate-carboxymethyl chitosan

particulate system produces particles of smaller size compared to artesunate with heterogeneous size.

The percentage of artesunate recovery from the crosslinked artesunate-chitosan particulate system (F1) was 73.79 ± 1.80 % and the non-crosslinked system (F2) was 75.43 ± 0.85 %. Whereas the drug recovery of the crosslinked artesunate-carboxymethyl chitosan particulate system and non-crosslinked system were 74.56 ± 1.94 and 92.31 ± 2.31 %, respectively. Based on those results, it was known that crosslinking inhibits drug entrapment. This is because, without crosslinked, the system has more space to entrapped the artesunate. The statistical analysis of the independent t-test on the artesunate-chitosan particulate system showed that cross-linking did not have a significant effect on artesunate entrapment, whereas in the artesunate-carboxymethyl chitosan particulate system shows that there was significant differences between the crosslinked system and non-crosslinked system.

The artesunate release test from the particulate system was carried out to determine the effect of the polymer and crosslinking on the artesunate release rate. The drug release rate of the artesunate-chitosan particulate system for crosslinked and non-crosslinked system were lower than artesunate, whereas the particle with carboxymethyl chitosan both crosslinked and non-crosslinked particle had higher release rate compared to other formula (Table 2). Since chitosan is insoluble in water but swelling, it causes drug release inhibition. In case of carboxymethyl chitosan that is soluble in water, it gives solubilization effect on increasing drug dissolution.

So that the results of this study indicated that the formation of artesunate microparticles of crosslinked chitosan and carboxymethyl chitosan had opposite effect on artesunate release rate even though both system had similar effect on decreasing drug crystallinity.

CONCLUSION

The use of crosslinking agents and different types of chitosan prepare artesunate microparticles has been undertaken has been to determine the properties of microparticles of artesunate as a carrier for artesunate, an antimalarial drug. The results suggest that the presence of crosslinking agent reduced artesunate loading efficiency and its release from chitosan microparticulate matrices. Instead of chitosan, the use of carboxymethyl chitosan affected the spherical morphology, drug entrapment and drug release. However, the use of their combinations is promising for achieving modified delivery of artesunate for improved malaria therapy.

DECLARATIONS

Acknowledgement

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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Table 1: Composition of artesunate microparticles

Code	Amount (mg)				
	Chitosan	***TPP***	***Carboxymethyl chitosan***	***$CaCl_2$***	***Artesunate***
F1	100	80	-	-	40
F2	100	-	-	-	40
F3	-	-	100	50	40
F4	-	-	100	-	40

Table 2: Drug content, drug recovery, and release rate of artesunate (n=3)

Code	Drug content (%)	Drug recovery (%)	Release rate ($mg/ml.min^{½}$)
Artesunate	-	-	13.54 ± 0.36
F1	13.42 ± 0.33	73.79 ± 1.80	9.12±0.85

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F2	21.55 ± 0.24	75.43 ± 0.85	10.05 ± 0.73
F3	15.69 ± 0.41	74.56 ± 1.94	16.78 ± 0.93
F4	26.37 ± 0,66	92.31 ± 2.31	14.43 ± 1.27

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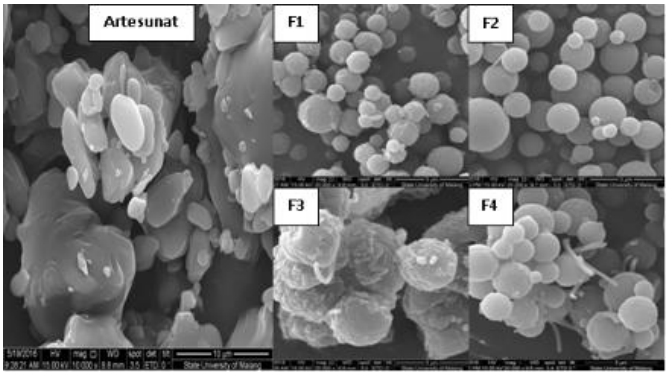

Figure 1: Scanning electron microscopy (SEM) photograps of artesunate, cross-linked chitosan-artesunate microparticles, C-CL-AS (F1), non-cross-linked chitosan-artesunate microparticles, C-AS (F2), cross-linked carboxymethyl chitosan-artesunate microparticles, CM-CL-AS (F3), and non-cross-linked carboxymethyl chitosan-artesunate microparticles, CM-AS (F4)

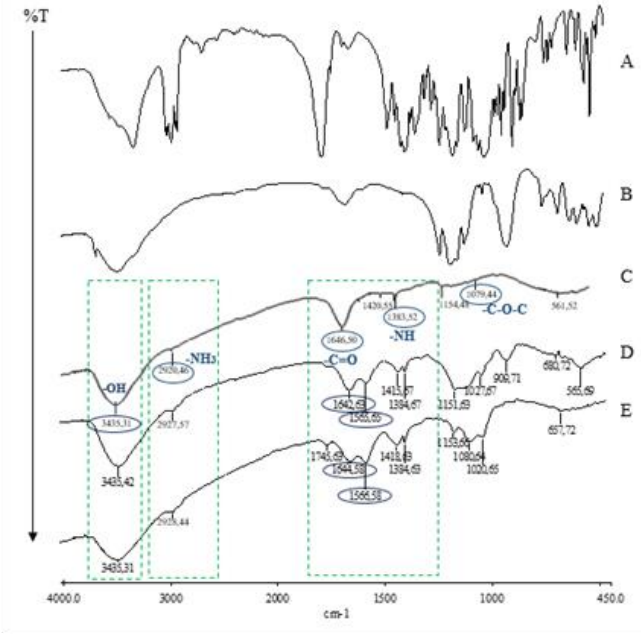

Fig. 2. Infrared spectra of (A) artesunate, (B) TPP, (C) chitosan, (D) cross-linked chitosan-

artesunate microparticles, C-CL-AS, and (E) non-cross-linked chitosan-artesunate microparticles, C-AS.

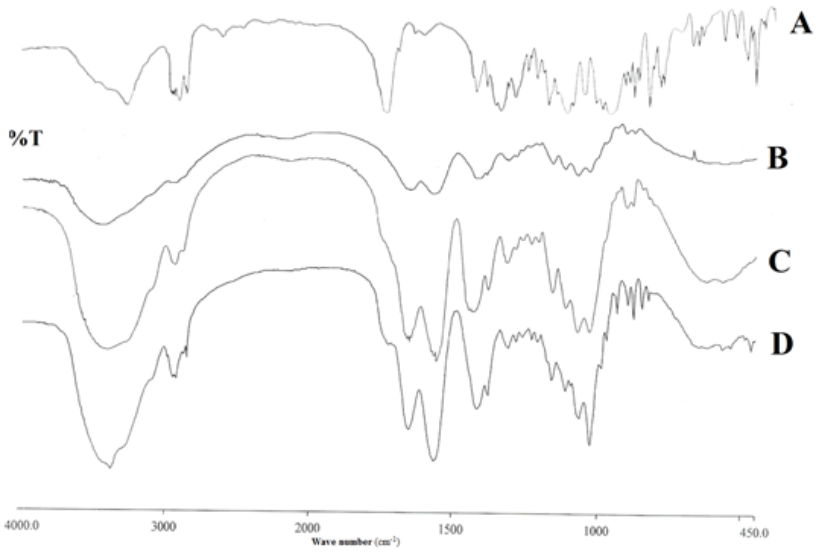

Figure 3: Infrared spectra of (A) artesunate, (B) carboxymethyl chitosan, (C) cross-linked carboxymethyl chitosan-artesunate microparticles, CM-CL-AS, and (D) the non-cross-linked carboxymethyl chitosan-artesunate microparticles, CM-AS

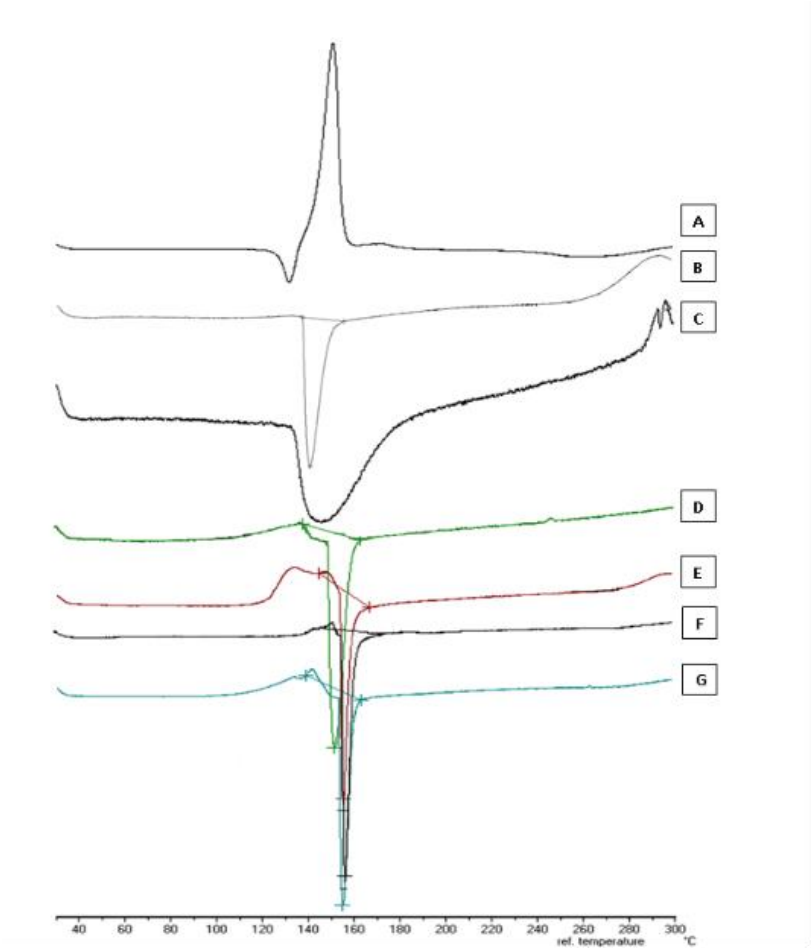

Figure 4: The thermograms of (A) artesunate, (B) chitosan, (C) carboxymethyl chitosan, (D) cross-linked chitosan-artesunate microparticles, C-CL-AS, (E) non-cross-linked chitosan-artesunate microparticles, C-AS, (F) cross-linked carboxymethyl chitosan-artesunate microparticles, CM-CL-AS, and (G) non-cross-linked carboxymethyl chitosan-artesunate microparticles, CM-AS.

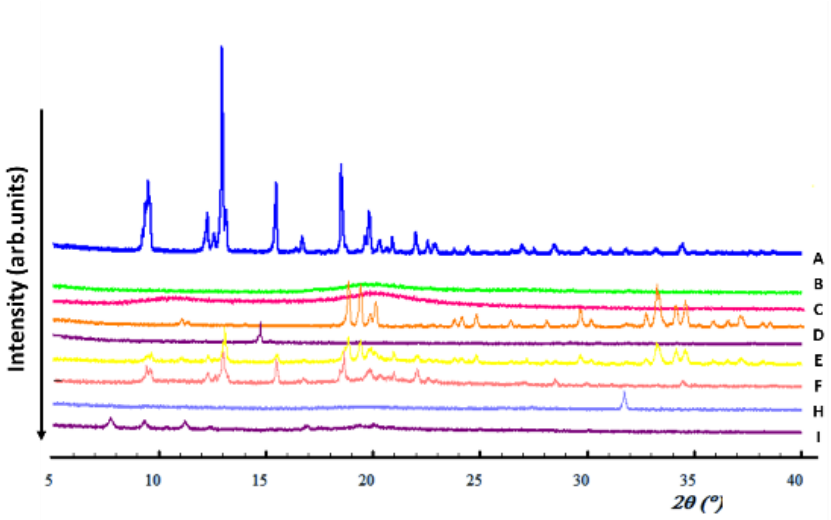

Fig. 5. The diffractograms of (A) artesunate, (B) carboxymethyl chitosan, (C) chitosan, (D) tripolyphosphate, TPP, (E) calcium chloride, $CaCl_2$, (F) cross-linked chitosan-artesunate microparticles, C-CL-AS, (G) non-cross-linked chitosan-artesunate microparticles, C-AS, (H)cross-linked carboxymethyl chitosan-artesunate microparticles, CM-CL-AS, and (I) non-cross linked carboxymethyl chitosan-artesunate microparticles.

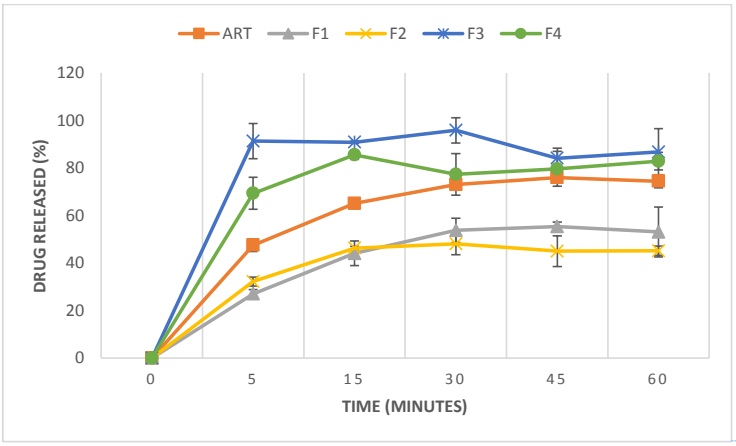

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Figure 6: Release profiles of artesunate, cross-linked chitosan-artesunate microparticles, (F1) and the non-cross-linked chitosan-artesunate microparticles (F2), cross-linked carboxymethyl

chitosan-artesunate microparticles (F3), and non-cross-linked carboxymethyl chitosan-artesunate microparticles (F4) in aquadest at 37 ± 0.5°C. The measurement was in triplicates.

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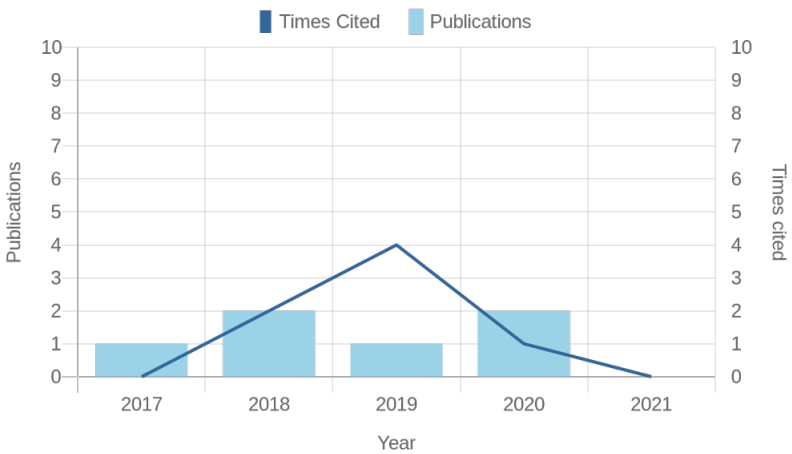

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