Tropical Journal of Pharmaceutical Research June 2020; 19 (6): 1139-1146
ISSN: 1596-5996 (print); 1596-9827 (electronic)
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Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v19i6.3

Original Research Article

Characterization and *in vitro* release study of artesunate-loaded microparticles prepared using crosslinked-chitosan and its derivatives

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Sent for review: 26 October 2019 *Revised accepted: 23 May 2020*

Abstract

Purpose: *To determine the effect of crosslinking on the physical characteristics, recovery, and release of artesunate-loaded chitosan and carboxymethyl chitosan microparticles.*
Methods: *The artesunate microparticles were prepared by means of ionic gelation-spray drying methods involving the use of a crosslinking agent i.e. tripolyphosphate for chitosan and $CaCl_2$ for carboxymethyl chitosan. The drug-polymer solution mixture was introduced into the crosslinker solution and stirred for two hours at 500 rpm prior to drying at a temperature of 100 °C, a pressure of 2 mbar and a flow speed of 6.0 mL/min. The resulting microparticles were subsequently evaluated for their morphology, physical state, drug content and in vitro drug release.*
Results: *The results showed that the type of chitosan and crosslinking affected particle shape, surface roughness, drug recovery, and drug release. The artesunate microparticles prepared with cross-linked polymer demonstrated a lower encapsulation efficiency due to the barriers presented by the crosslinking agents. The use of carboxymethyl chitosan increased the release rate of the artesunate from the microparticles by up to 1.2 times (16.78 mg/ml.min½), while chitosan decreased it 0.7 times (9.12 mg/ml.min½) compared to artesunate alone (13.54 mg/ml.min½).*
Conclusion: *The use of crosslinking agents and chitosan type affects the physical characteristics of artesunate in addition to its release rate from microparticles.*

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

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INTRODUCTION

Artesunate, an artemisinin derivate, constitutes an antimalarial drug effective against Plasmodium falciparum, even in cases of chloroquine-resistant parasites [1], but which demonstrates low drug solubility resulting in extremely limited drug bioavailability when administered orally. Artesunate is rapidly absorbed with peak plasma drug concentration occurring at 1.5, 2, and 0.5 h respectively after oral, rectal, or intramuscular administration, while drug elimination also occurs relatively rapidly with a half-life of 20 - 45 min [1-3]. Therefore, in

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order to achieve high antimalarial efficacy, the bioavailability of artesunate requires further improvement.

Chitosan is a natural cationic polysaccharide polymer widely employed to prepare microparticles, useful in modifying the solubility and stability of a drug. It provides certain ideal properties for drug carriers, such as mucoadhesiveness, biocompatibility, biodegradability, non-toxicity, and economy. Consequently, it can be used to produce microparticles with high levels of stability and low toxicity [5]. Carboxymethyl chitosan, a derivate of chitosan, has recently been developed since it possesses high aqueous solubility, strong gel-forming capacity, low toxicity, and high levels of biocompatibility [8].

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

The presence of a crosslinking agent can strengthen the mechanical strength of the microparticles, thus increasing the absorption of drugs into their matrices [13]. The microparticles can be dehydrated through the application of freeze dry or spray dry techniques to produce a dry mass of microparticles. Spray drying technique constitutes a convenient and reproducible method of producing a dry mass of drug solution or suspension in hot air flow.

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

EXPERIMENTAL

Materials

For the purposes of this study, artesunate was purchased from Hunan Goldliloo Pharmaceutical Co., Ltd. (Changsa, Hunan China). Chitosan was acquired 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, is a product of China Eastar Group Co., Ltd. (Shanghai, China). Calcium chloride $CaCl_2.2H_2O$ pro analysis (Merck), analytical grade pentasodium tripolyphosphate (TPP) was obtained from Nacalay Tesque. All reagents and solvents employed in this study were of the highest commercially available grade.

Preparation of artesunate microparticles

In this study, artesunate microparticles were prepared by means of ionic-gelation method employing the formula shown in Table 1. Firstly, artesunate was dissolved in ethanol. Chitosan and carboxymethyl chitosan were dissolved in acetic acid solution and water, respectively, through continuous stirring. These polymer solutions were subsequently added to the artesunate solution with the resulting mixture being introduced into the solution containing the crosslinking agent and agitated with a magnetic stirrer for two hours at 500 rpm. The mixtures were dehydrated using a spray dryer (SD-elementary spray dryer SD B09060019, Lab Plant Ltd., UK) with a nozzle diameter of 1.0 mm at an inlet temperature of 100°C, a pressure of 2 mBar and a flow speed of 6.0 mL/min. The microparticles prepared without a crosslinking agent were produced using the same method and served as the control groups.

Evaluation of particle size and morphology

The particle size and morphology of artesunate microparticles were evaluated by means of scanning electron microscopy (Inspect S50 Type FP 2017/12, FEI, USA). During the measuring process, the samples were coated with palladium gold.

Fourier-transform infrared spectroscopy

In order to evaluate the physicochemical interaction between components of artesunate microparticles,

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

the Fourier-transform infrared (FTIR) spectra of samples were measured through the manufacture of 2 mg of pellet samples containing 300 mg of KBr. These pellets were subsequently analyzed at wavelengths from 4000-450 cm^{-1} using a Jasco FT-IR 5300 spectrophotometer (Easton MD, USA).

Differential thermal analysis

Differential thermal analysis was undertaken using differential thermal apparatus (DTA FP-65 P-900 Thermal, Mettler Toledo, USA). Approximately 5 mg of samples were placed in a closed crucible pan with measurement subsequently being performed at 50-300°C and a heating rate of 10°C per minute.

X-ray diffraction studies

X-ray diffraction analysis was conducted to determine the crystallinity of the artesunate microparticles. The samples were analyzed at room temperature using a Phillips X'Pert diffraction apparatus (X'Pert Analytical, Netherlands) featuring the following measurement elements: the X-ray X source, Cu metal target, Ni filter, 40 kV voltage, and 40 mA electrical current within the range of 2θ of 5-40°.

Drug content and recovery analysis

The drug content and percentage recovery of samples were determined using a UV-Vis spectrophotometer (Varian Cary® 50 UV-Vis, US). Approximately 10 mg of the samples were dissolved in ethanol to produce a 10 mL solution which was allowed to settled for two hours at room temperature prior to sonication for five minutes and subsequent settling for a second 60-minute period. At that point, 5 mL of the sample solution was pipetted and added to 2 mL of 0.1N NaOH. The mixture was heated to 60°C for a period of 60 minutes and allowed to cool to room temperature. Acetic acid solution was added to 10 mL of 20% v/v ethanol solution, with the absorbance being measured on three occasions by spectrophotometry at a maximum wavelength of λ 238 nm. The drug content of artesunate in the microparticles was then calculated as in Eq 1.

$$\text{Drug content (\%)} = W_{drug}/W_{microparticles} \times 100\% \quad \ldots (1)$$

Recovery of the drug was calculated as in Eq 2.

$$\text{Recovery (\%)} = W_{actual}/W_{theoretical} \times 100\% \quad \ldots\ldots (2)$$

In vitro release of artesunate microparticles

In order to determine the profile of artesunate released from microparticles, a drug release test was conducted using aquadest as the release medium. Samples equivalent to 5 mg of artesunate were weighed and incubated in 50 mL of aquadest before being placed in a water bath shaker at a temperature of 37 ± 0.5°C and an agitation speed of 120 rpm. At pre-determined intervals, samples of approximately 3 mL were collected and their concentration of artesunate analyzed using a UV-Vis spectrophotometer (Hewlett Packard (HP) 8452A Diode Array Spectrophotometer, USA).

Statistical analysis

All data relates to the three replicates and is presented as the mean ± SD. In order to evaluate the significance of difference, the data was subjected to analysis using a one-way ANOVA test followed by a Tukey post-hoc test where $p < 0.05$ which was considered statistically significant.

RESULTS

Particle size and morphology

In the course of 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 with surfaces coarser (Figure 1 A and C) than those of the cross-linked variety (Figure 1 B and D). There were artesunate crystal-like substances present on the surface of the nanoparticles as observed in the SEM pictures of

artesunate microparticles prepared with carboxymethyl chitosan polymers which incorporated the use of a crosslinking agent (Figure 1 C). This result indicated that the artesunate might not be absorbed into microparticle matrices.

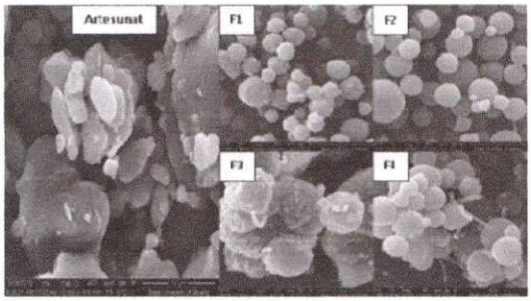

Figure 1: Scanning electron microscopy (SEM) photographs of artesunate, cross-linked chitosan-artesunate microparticles C-CL-AS (F1), non-cross-linked chitosan-artesunate microparticles C-AS (F2), cross-linked carboxymethyl chitosan-artesunate microparticles CM-CL-AS (F3), and non-cross-linked carboxymethyl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

FTIR spectra

The spectra of artesunate and TPP are shown in Figures 2A and 2B, respectively. In Figure 2C, the chitosan spectrum has a specific absorption band at a wavenumber of 3449 cm^{-1} experiencing both vibration and an amide bond derived from the carbonyl group (-C=O) at a wavenumber of 1655 cm^{-1}. This indicates the presence of the amine ($-NH_2$) and hydroxy group (-OH) of chitosan polymer. Due to the interaction with TPP (Figure 2B), the amide peak of chitosan observed at wavenumber of 1655 cm^{-1} disappeared, forming new peaks at 1643 cm^{-1} and 1566 cm^{-1} for C-CL-AS (Figure 2D). 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 the wavenumbers of 1645 cm^{-1} and 1554 cm^{-1} (Figure 2 E).

In the artesunate microparticles prepared with carboxymethyl chitosan, the infrared spectrum of carboxymethyl chitosan (Figure 3A) depicts a wide band at a wavenumber of 3443.35 cm^{-1} that indicates the presence of -OH or -NH groups. However, there were changes in 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, hydrogen bond formation between COO- of carboxymethyl chitosan and Ca^{2+} of $CaCl_2$ might occur which converts the hydrogen bond into carboxymethyl chitosan. In CM-AS, although the crosslink did not occur, changes in the 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 appeared as broad bands at the wavenumbers of 1416.47 cm^{-1} and 1647.44 cm^{-1}. However, the CM-CL-AS and CM-AS bands were in sharper relief than those of carboxymethyl chitosan and a shift could also be observed indicating that the -OH, -NH, and -COO groups are involved in bond formation within the microparticles.

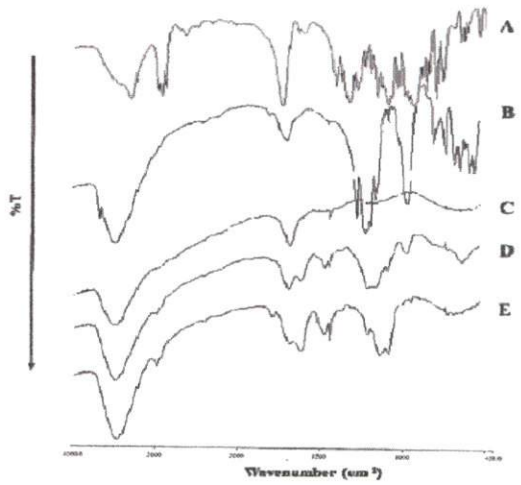

Figure 2: Infrared spectra of (A) artesunate, (B) TPP, (C) chitosan, (D) cross-linked chitosan-artesunate microparticles C-CL-AS, and (E) non-cross-linked chitosan-artesunate microparticles C-AS

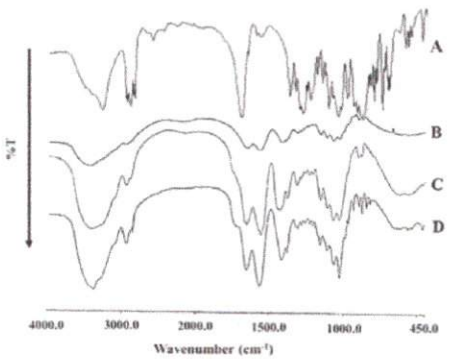

Figure 3: Infrared spectra of (A) artesunate, (B) carboxymethyl chitosan, (C) cross-linked carboxymethyl chitosan-artesunate microparticles CM-CL-AS, and (D) the non-cross-linked carboxymethyl

chitosan-artesunate microparticles CM-AS

Thermal properties

It has been shown that the thermograms of C-CL-AS and C-AS microparticles (Figures 4D and 4E) possessed patterns different to those of artesunate (Figure 4A), but similar to those of chitosan (Figure 4B). This indicates that microparticulate chitosan matrices containing artesunate had been formed. Moreover, the absence of an observable exothermic peak of artesunate in the thermograms of the artesunate microparticles signified that artesunate had been trapped in the microparticulate matrices. C-CL-AS and C-AS had sharp endothermic peaks which means that bond formation occurred between the crosslinking agent and chitosan or intramolecular chitosan bonds. The heating points of these microparticles, approximately 149.0 and 152.1°C for C-CL-AS and C-AS respectively, were higher than that of artesunate. In the artesunate-carboxymethyl chitosan microparticles, the thermograms of CM-CL-AS and CM-AS showed sharp endothermic peaks at 150.1 and 151.4°C respectively, (Figures 4F and G). This 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 carboxymethyl chitosan bond in CM-AS. Consequently, the energy required to heat the microparticles was higher, leading to sharpened endothermic peaks.

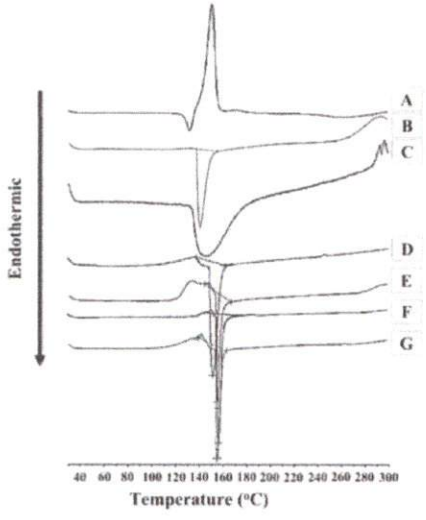

Figure 4: The thermograms of (A) artesunate, (B) chitosan, (C) carboxymethyl chitosan, (D) cross-linked chitosan-artesunate microparticles C-CL-AS, (E) non-cross-linked chitosan-artesunate microparticles C-AS, (F) cross-linked carboxymethyl chitosan-artesunate microparticles CM-CL-AS, and (G) non-cross-linked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

Crystal properties

An X-ray diffraction analysis was performed to determine the crystallinity of artesunate microparticles. The results showed that free artesunate possessed high crystallinity as indicated by intense and strong peaks at 2θ of 9, 12, 13, 15, 18, and 20° (Figure 5A). Meanwhile, the diffraction peak of chitosan and carboxymethyl chitosan, which lay at 2θ of 20° with weak intensity (Figures 5B and C), indicated low crystallinity. The diffractograms of artesunate-chitosan microparticles i.e. C-CL-AS and C-AS (Figures 5F and G) showed that no diffraction peak of artesunate appeared when compared with the physical mixture. This indicates that the artesunate was entrapped and underwent changes to 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 produced crystalline peaks of artesunate (Figures 5H and I). These results indicated the occurrence of changes in artesunate crystal structures. In CM-CL-AS, a new crystalline peak formed at 2θ of 31° (Figure 5H) possibly 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°C (Figure 5I).

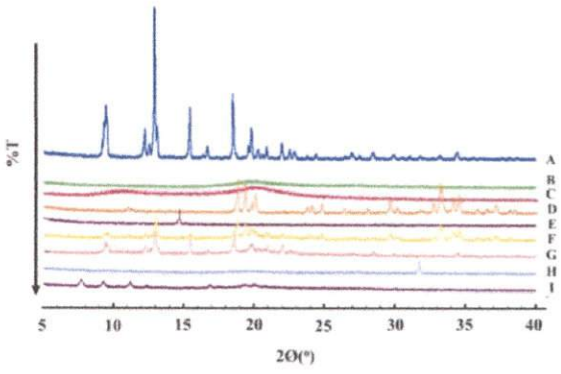

Figure 5: Diffractograms of (A) artesunate, (B) carboxymethyl chitosan, (C) chitosan, (D) tripolyphosphate, TPP, (E) calcium chloride $CaCl_2$, (F) cross-linked chitosan-artesunate microparticles C-CL-AS, (G) non-cross-linked chitosan-artesunate microparticles C-AS, (H) cross-linked carboxymethyl chitosan-artesunate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

Drug content and recovery

Through the application of UV-Vis spectrophotometry, the artesunate content was determined to measure the drug content and percentage recovery of artesunate in the microparticles. As shown in Table 2, the addition of the crosslinking agent reduced the encapsulation of artesunate. Consequently, the artesunate content in the cross-linked chitosan and carboxymethyl chitosan-artesunate microparticles was lower than that of the non-cross-linked microparticles.

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
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

In vitro drug release

The results showed that the artesunate released by microparticles prepared with chitosan was lower than the artesunate substance possibly owing to the low solubility of chitosan in water inhibiting drug release at a rate 9.12 ± 0.85 mg/ml.min^{½} lower than artesunate (Table 2).

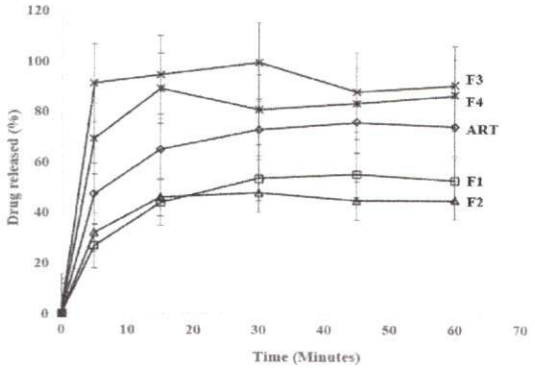

Figure 6: Release profiles of artesunate, cross-linked chitosan-artesunate microparticles, (F1), non-cross-linked chitosan-artesunate microparticles (F2), cross-linked carboxymethyl chitosan-artesunate micro-particles (F3), and non-cross-linked carboxymethyl chitosan-artesunate microparticles (F4) in aquadest at 37 ± 0.5°C. The measurement consisted of three replicates

The artesunate-carboxymethyl chitosan micro-particles experienced greater drug release than artesunate substances (Figure 6). There were no significant differences in artesunate release rates between non cross-linked and cross-linked artesunate-carboxymethyl chitosan microparticles (p= 0.057,) 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 1.2 times higher than that of artesunate which was 13.54 ± 0.36 mg/ml.min^{½}.

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 consisted of two formulas for each polymer, one using crosslinking and the other without cross-linking agent at a drug-polymer ratio (w/w) of 2:5. As shown in Figure 2, the infrared spectra of the artesunate-chitosan particulate system indicated the occurrence of bonding between phosphate ions and ammonium ions evident from the loss of amide bonds by chitosan at the wave number of 1655 cm^{-1} and the new peaks which appeared at 1645 and 1554 cm^{-1}. In the artesunate-carboxymethyl chitosan particulate system, the infrared spectra also experienced a resulting change, namely; a larger band with a change in the hydrogen bond occurring at a wave number of 3443.35 cm^{-1}.

The results of thermal analysis using a Differential Thermal Analyzer (DTA) showed that the thermogram pattern of the artesunate-chitosan and artesunate-carboxymethyl chitosan particulate systems differed from each of the forming materials. Furthermore, during the evaluation of the X-ray diffraction systems of artesunate-chitosan and artesunate-carboxymethyl chitosan, the diffraction peaks of artesunate were not visible in contrast to those of the physical mixture. This suggests that the artesunate was entrapped and underwent changes to the crystalline structure in the microparticle system. The results of the morphological test of particulate systems using SEM indicated that the artesunate-chitosan particulate system was more spherical in shape than the artesunate-carboxymethyl chitosan particulate system. However, with cross-linking, both systems possessed a similar morphology which featured a rougher surface when compared to the non-crosslinked microparticles. The formation of an artesunate-chitosan and

artesunate-carboxymethyl chitosan particulate system produced particles of smaller size compared to those of artesunate which were heterogeneous in size.

The percentage of artesunate recovery from the crosslinked artesunate-chitosan particulate system (F1) was 73.79 ± 1.80%, while the non-crosslinked system (F2) was 75.43 ± 0.85%. In contrast, 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 these results, it was evident that crosslinking inhibits drug entrapment because the system has less space within which to entrap the artesunate. Statistical analysis of an independent t-test on the artesunate-chitosan particulate system showed that cross-linking had no significant effect on artesunate entrapment (p=0.226), whereas in the artesunate-carboxymethyl chitosan particulate system there were significant differences between the crosslinked and non-crosslinked systems (p= 0.001).

The artesunate release test of 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 the crosslinked and non-crosslinked systems was lower than that of artesunate, while both the crosslinked and non-crosslinked particle with carboxymethyl chitosan experienced a higher release rate compared to the other formula (Table 2). Since chitosan swells rather than dissolves in water, it inhibits drug release. In the case of water-soluble carboxymethyl chitosan, this produces a solubilization effect resulting in increased drug dissolution.

The results of this study indicated that the formation of artesunate microparticles of crosslinked chitosan and carboxymethyl chitosan had a contrasting effect on the artesunate release rate, although both systems had a similar effect by decreasing drug crystallinity.

CONCLUSION

The use of crosslinking agents and different types of chitosan was undertaken to determine the properties of chitosan microparticles as carriers of artesunate. The results suggest that the presence of crosslinking agent reduced artesunate loading efficiency and its release from chitosan microparticulate matrices. The use of carboxymethyl chitosan, in place of chitosan, affected spherical morphology, drug entrapment and drug release. However, their combined use shows promise as a method of achieving modified delivery of artesunate for improved malaria therapy.

DECLARATIONS

Acknowledgement

This work was funded by a DIPA-Competitive University Research Grant awarded by Airlangga University in 2016.

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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Current Issue

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Md Shafayat Hossain (mailto:shafayatbd@gmail.com), *Md Abdullah Shamim*, *Md Saifuzzaman*, *Md Attiquzzaman*, *Md Golam Hossain*, *Obayed Raihan*,

http://dx.doi.org/10.4314/tjpr.v19i6.1 (http://dx.doi.org/10.4314/tjpr.v19i6.1)

Formulation, in vitro evaluation and characterization of atorvastatin solid dispersion HTML (abstract.php?id=2880&aTitle=Formulation, in vitro evaluation and characterization of atorvastatin solid dispersion) | Fulltext (../admin/12389900798187/2020_19_6_2.pdf)

Asif Iqbal, *Md Shafayat Hossain* (mailto:shafayatbd@gmail.com), *Md Abdullah Shamim*, *Monirul Islam*, *Md Abu Talha Siddique*,

http://dx.doi.org/10.4314/tjpr.v19i6.2 (http://dx.doi.org/10.4314/tjpr.v19i6.2)

Characterization and in vitro release study of artesunate-loaded microparticles prepared using crosslinked-chitosan and its derivatives HTML (abstract.php?id=2881&aTitle=Characterization and in vitro release study of artesunate-loaded microparticles prepared using crosslinked-chitosan and its derivatives) | Fulltext (../admin/12389900798187/2020_19_6_3.pdf)

Retno Sari (mailto:retno-s@ff.unair.ac.id), *Meta Dian Feriza*, *Amani Syarahil*, *Andang Miatmoko*, *Dwi Setyawan*,

http://dx.doi.org/10.4314/tjpr.v19i6.3 (http://dx.doi.org/10.4314/tjpr.v19i6.3)

Aloperine attenuates high glucose-induced oxidative injury in Schwann cells via activation of NRF2/HO-1 pathway HTML (abstract.php?id=2882&aTitle=Aloperine attenuates high glucose-induced oxidative injury in Schwann cells via activation of NRF2/HO-1 pathway) | Fulltext (../admin/12389900798187/2020_19_6_4.pdf)

Yiran Chen, *Tieming Ma* (mailto:TiemingMadkl@163.com), *Zhimin Wang*, *Lianqun Jia*, *Xiaoqing Zhang*, *Qingxuan He*, *Sijia Liu*,

http://dx.doi.org/10.4314/tjpr.v19i6.4 (http://dx.doi.org/10.4314/tjpr.v19i6.4)

LncRNA gas5 regulates granulosa cell apoptosis and viability following radiation by x-ray via sponging miR-205-5p and Wnt/?-

catenin signaling pathway in granulosa cell tumor of ovary HTML (abstract.php?id=2883&aTitle=LncRNA gas5 regulates granulosa cell apoptosis and viability following radiation by x-ray via sponging miR-205-5p and Wnt/?-catenin signaling pathway in granulosa cell tumor of ovary) | Fulltext (../admin/12389900798187/2020_19_6_5.pdf)

Yan Li, *Xing Ma*, *Jun Li*, *Saifei He*, *Juhua Zhuang*, *Guoyu Wang*, *Ying Ye*, *Wei Xia* (mailto:weixia1911@163.com),

http://dx.doi.org/10.4314/tjpr.v19i6.5 (http://dx.doi.org/10.4314/tjpr.v19i6.5)

Trigonoside II mitigates sepsis-induced myocardial injury via reduction in oxidative stress and regulation of TLR-4/NF-kβ inflammatory pathway HTML (abstract.php?id=2884&aTitle=Trigonoside II mitigates sepsis-induced myocardial injury via reduction in oxidative stress and regulation of TLR-4/NF-kβ inflammatory pathway) | Fulltext (../admin/12389900798187/2020_19_6_6.pdf)

Fengru Wang, *Lili Wu*, *Qun Liang* (mailto:liangqun1@sina.com),

http://dx.doi.org/10.4314/tjpr.v19i6.6 (http://dx.doi.org/10.4314/tjpr.v19i6.6)

Effect of polyphenol extract from Zanthoxylum bungeanum Maxim. on endocrine hormones and monoamine oxidase activity in a mouse model of climacteric depression HTML (abstract.php?id=2900&aTitle=Effect of polyphenol extract from Zanthoxylum bungeanum Maxim. on endocrine hormones and monoamine oxidase activity in a mouse model of climacteric depression) | Fulltext (../admin/12389900798187/2020_19_6_22.pdf)

Aiying Song, *Qiang Zhang*, *Xiaoqing You*, *Xiangni Zou*, *Xiao Han*, *Yu Li* (mailto:aneesa@qau.edu.pk), *Yin Tang*,

http://dx.doi.org/10.4314/tjpr.v19i6.22 (http://dx.doi.org/10.4314/tjpr.v19i6.22)

Pristimerin attenuates sepsis-induced lung injury by regulating nuclear factor kappaB/high-mobility group box 1 pathway HTML (abstract.php?id=2885&aTitle=Pristimerin attenuates sepsis-induced lung injury by regulating nuclear factor kappaB/high-mobility group box 1 pathway) | Fulltext (../admin/12389900798187/2020_19_6_7.pdf)

Xiao Wang (mailto:362550125@qq.com), *Lei Huang*, *Peng Li*,

http://dx.doi.org/10.4314/tjpr.v19i6.7 (http://dx.doi.org/10.4314/tjpr.v19i6.7)

Morphine pretreatment reduces myocardial ischemia-reperfusion injury in heart failure rats via GSK-3β/Cx43 signaling proteins and apoptosis-related gene, Bcl-2/Bax HTML (abstract.php?id=2886&aTitle=Morphine pretreatment reduces myocardial ischemia-reperfusion injury in heart failure rats via GSK-3β/Cx43 signaling proteins and apoptosis-related gene, Bcl-2/Bax) | Fulltext (../admin/12389900798187/2020_19_6_8.pdf)

Xuelian Zhu, *Zhihai Geng*, *Xi Han*, *Xianfeng Xin* (mailto:g84613@163.com),

http://dx.doi.org/10.4314/tjpr.v19i6.8 (http://dx.doi.org/10.4314/tjpr.v19i6.8)

Amygdalin protects apoptosis of retinal ganglionic cells in glaucoma rats by regulating the expressions of anti- and pro-apoptotic proteins HTML (abstract.php?id=2887&aTitle=Amygdalin protects apoptosis of retinal ganglionic cells in glaucoma rats by regulating the ex<x>pressions of anti- and pro-apoptotic proteins) | Fulltext (../admin/12389900798187/2020_19_6_9.pdf)

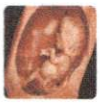
Xiaoli Zeng, *Hongbin Lv* (mailto:BertaJoycecid@yahoo.com), *Xuewen Huang*,

http://dx.doi.org/10.4314/tjpr.v19i6.9 (http://dx.doi.org/10.4314/tjpr.v19i6.9)

Effects of icariin and quercetin on high glucose-induced neuronal cell apoptosis HTML (abstract.php?id=2888&aTitle=Effects of icariin and quercetin on high glucose-induced neuronal cell apoptosis) | Fulltext (../admin/12389900798187/2020_19_6_10.pdf)

Mengqian Dong, *Ying Jin*, *Peifen Huang*, *Zhiyang Chen* (mailto:djnrs2@163.com),

http://dx.doi.org/10.4314/tjpr.v19i6.10 (http://dx.doi.org/10.4314/tjpr.v19i6.10)



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http://dx.doi.org/10.4314/tjpr.v19i6.11 (http://dx.doi.org/10.4314/tjpr.v19i6.11)

Hesperetin protects SH-SY5Y cells against 6-hydroxydopamine-induced neurotoxicity via activation of NRF2/ARE signaling pathways HTML (abstract.php?id=2890&aTitle=Hesperetin protects SH-SY5Y cells against 6-hydroxydopamine-induced neurotoxicity via activation of NRF2/ARE signaling pathways) | Fulltext (../admin/12389900798187/2020_19_6_12.pdf)

Jing Li, *Yue Liu*, *Li Wang*, *Zhaowei Gu*, *Zhigang Huan*, *Hui Fu*, *Qishuai Liu* (mailto:QishuaiLiufjk@163.com),

http://dx.doi.org/10.4314/tjpr.v19i6.12 (http://dx.doi.org/10.4314/tjpr.v19i6.12)

expression levels of reactive oxygen species, NF-κBp65 and TGF-β1 and their correlations in bronchopulmonary dysplasia in neonatal rats HTML (abstract.php?id=2891&aTitle=ex<x>pression levels of reactive oxygen species, NF-κBp65 and TGF-β1 and their correlations in bronchopulmonary dysplasia in neonatal rats) | Fulltext (../admin/12389900798187/2020_19_6_13.pdf)

Xin Wang, *Meng Sun*, *Chan Wang*, *Youning Zheng*, *Yaying Cheng* (mailto:dsmf5x@163.com),

http://dx.doi.org/10.4314/tjpr.6.13 (http://dx.doi.org/10.4314/tjpr.6.13)

In vitro comparative assessment of the inhibitory effects of single and combined spices against glucose-synthesizing enzymes HTML (abstract.php?id=2892&aTitle=In vitro comparative assessment of the inhibitory effects of single and combined spices against glucose-synthesizing enzymes) | Fulltext (../admin/12389900798187/2020_19_6_14.pdf)

Temitayo Esther Adeyeoluwa, *Fatai Oladunni Balogun*, *Anofi Omotayo Tom Ashafa* (mailto:ashafaaot@ufs.ac.za),

http://dx.doi.org/10.4314/tjpr.v19i6.14 (http://dx.doi.org/10.4314/tjpr.v19i6.14)

Effect of anti-CIRP antibody on inflammatory response, tumor formation and abdominal aortic aneurysm in rats HTML (abstract.php?id=2893&aTitle=Effect of anti-CIRP antibody on inflammatory response, tumor formation and abdominal aortic aneurysm in rats) | Fulltext (../admin/12389900798187/2020_19_6_15.pdf)

Yuqing Wang (mailto:muvm3w@163.com), *Lantao Lu*, *Weiyan Li*, *Shuntong Gu*,

http://dx.doi.org/10.4314/tjpr.v19i6.15 (http://dx.doi.org/10.4314/tjpr.v19i6.15)

Resveratrol protects the retina from I/R injury by inhibiting RGCS apoptosis, glial activation and expression of inflammatory factors HTML (abstract.php?id=2894&aTitle=Resveratrol protects the retina from I/R injury by inhibiting RGCS apoptosis, glial activation and ex<x>pression of inflammatory factors) | Fulltext (../admin/12389900798187/2020_19_6_16.pdf)

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http://dx.doi.org/10.4314/tjpr.v19i6.16 (http://dx.doi.org/10.4314/tjpr.v19i6.16)

Antioxidant and anti-diabetic effects of caffeic acid in a rat model of diabetes HTML (abstract.php?id=2895&aTitle=Antioxidant and anti-diabetic effects of caffeic acid in a rat model of diabetes) | Fulltext (../admin/12389900798187/2020_19_6_17.pdf)

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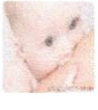

Designing dual inhibitors for the treatment of Alzheimer's disease as well as Type 2 diabetes mellitus via pharmacoinformatics approach: A step towards better

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Mona Mokhtarian, *Mohammad Reza Nourani*, *Nasrin Esfahanizadeh* (mailto:n_esfahanizadeh@yahoo.com),

http://dx.doi.org/10.4314/tjpr.v19i6.19 (http://dx.doi.org/10.4314/tjpr.v19i6.19)

Anti-diabetic effect of a monoamine oxidase inhibitor (tranylcypromine) in rats with poorly-controlled blood glucose levels: A potential and novel therapeutic option for diabetes HTML (abstract.php?id=2898&aTitle=Anti-diabetic effect of a monoamine oxidase inhibitor (tranylcypromine) in rats with poorly-controlled blood glucose levels: A potential and novel therapeutic option for diabetes) | Fulltext (../admin/12389900798187/2020_19_6_20.pdf)

Jingying Qiu, *Chengjiang Li*, *Zhichun Dong*, *Jing Wang* (mailto:wjing0525@163.com),

http://dx.doi.org/10.4314/tjpr.v19i6.20 (http://dx.doi.org/10.4314/tjpr.v19i6.20)

Identification of a putative anti-rheumatoid arthritis molecule by virtual screening HTML (abstract.php?id=2899&aTitle=Identification of a putative anti-rheumatoid arthritis molecule by virtual screening) | Fulltext (../admin/12389900798187/2020_19_6_21.pdf)

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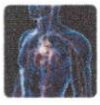

Synergistic hypolipidemic and hypoglycemic effects of mixtures of Lactobacillus nagelii/betanin in a mouse model HTML (abstract.php?id=2901&aTitle=Synergistic hypolipidemic and hypoglycemic effects of mixtures of Lactobacillus nagelii/betanin in a mouse model) | Fulltext (../admin/12389900798187/2020_19_6_23.pdf)

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Lorina I Badger-Emeka (mailto:lbadgeremeka@kfu.edu.sa), *Zainab Yaseen*

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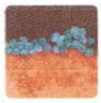

Solid phase extraction and LC-MS/MS quantification of ibandronate in human plasma HTML (abstract.php?id=2904&aTitle=Solid phase extraction and LC-MS/MS quantification of ibandronate in human plasma) | Fulltext (../admin/12389900798187/2020_19_6_26.pdf)

Moustapha E Moustapha, Sherif A Abdel-Gawad (mailto:sagawad@yahoo.com),
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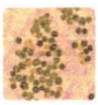
Ahmad A Almeman (mailto:meman@qu.edu.sa),
http://dx.doi.org/10.4314/tjpr.v19i6.27 (http://dx.doi.org/10.4314/tjpr.v19i6.27)

Review Articles



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Manal Ali Buabeid, Nihal Abdalla Ibrahim, Zelal Jaber Kharaba, Muhammad Ihtisham Umar, Ghulam Murtaza (mailto:gmdogar356@gmail.com),
http://dx.doi.org/10.4314/tjpr.v19i6.28 (http://dx.doi.org/10.4314/tjpr.v19i6.28)

Current application of metabolomics in the elucidation of processing mechanisms used in Chinese materia medica: A review HTML (abstract.php?id=2907&aTitle=Current application of metabolomics in the elucidation of processing mechanisms used in Chinese materia medica: A review) | Fulltext (../admin/12389900798187/2020_19_6_29.pdf)

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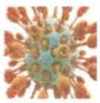

Leptin and systemic lupus erythematosus: A comprehensive review HTML (abstract.php?id=2908&aTitle=Leptin and systemic lupus erythematosus: A comprehensive review) | Fulltext (../admin/12389900798187/2020_19_6_30.pdf)

Amal H Uzrail (mailto:auzrail@zu.edu.jo), *Lubna Swellmeen*,
http://dx.doi.org/10.4314/tjpr.v19i6.30 (http://dx.doi.org/10.4314/tjpr.v19i6.30)

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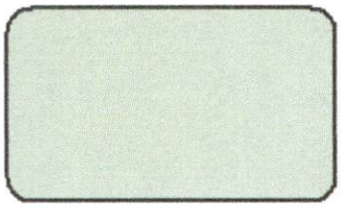

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