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Original Research Articles

Formulation and development of a topical combination cream for arthritis management HTML (abstract.php?id=2879&aTitle=Formulation and development of a topical combination cream for arthritis management) | Fulltext (../admin/12389900798187/2020_19_6_1.pdf)

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

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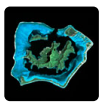

Formulation, in vitro evaluation and characterization of atorvastatin solid dispersion HTML (abstract.php?id=2880&aTitle=Formulation, in vitro evaluation and characterization of atorvastatin solid dispersion) | Fulltext (../admin/12389900798187/2020_19_6_2.pdf)

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),
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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),
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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*,
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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)

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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*,
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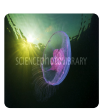

Effects of icariin and quercetin on high glucose-induced neuronal cell apoptosis HTML (abstract.php?id=2888&aTitle=Effects of icariin and quercetin on high glucose-induced neuronal cell apoptosis) | Fulltext (../admin/12389900798187/2020_19_6_10.pdf)

Mengqian Dong, *Ying Jin*, *Peifen Huang*, *Zhiyang Chen* (mailto:djnrs2@163.com),
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Shengu'an exerts anti-osteoporotic effect in rats via TGFβ1-Smad2/3 signal pathway, and enhancement of bone and cartilage metabolism HTML (abstract.php?id=2889&aTitle=Shengu) | Fulltext (../admin/12389900798187/2020_19_6_11.pdf)

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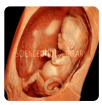

Hesperetin protects SH-SY5Y cells against 6-hydroxydopamine-induced neurotoxicity via activation of NRF2/ARE signaling pathways HTML (abstract.php?id=2890&aTitle=Hesperetin protects SH-SY5Y cells against 6-hydroxydopamine-induced neurotoxicity via activation of NRF2/ARE signaling pathways) | Fulltext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

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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),
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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*,
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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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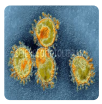

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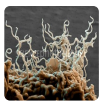

Designing dual inhibitors for the treatment of Alzheimer's disease as well as Type 2 diabetes mellitus via pharmacoinformatics approach: A step towards better medication for diabetes-associated neurological disorder HTML (abstract.php?id=2896&aTitle=Designing dual inhibitors for the treatment of Alzheimer's disease as well as Type 2 diabetes mellitus via pharmacoinformatics approach: A step towards better medication for diabetes-associated neurological disorder) | Fulltext (../admin/12389900798187/2020_19_6_18.pdf)

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Effect of doxycycline-bioglass treatment on calvarial bone defect in rats: A histological study HTML (abstract.php?id=2897&aTitle=Effect of doxycycline-bioglass treatment on calvarial bone defect in rats: A histological study) | Fulltext (../admin/12389900798187/2020_19_6_19.pdf)

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

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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)

Shazi Shakil (mailto:sfaruqi@kau.edu.sa), *Suzan M Attar*, *Adel M Abuzenadah*, *Omar Fathaldin*, *Rajaa Al-Raddadi*, *Mansour I Sulaiman*,
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Effect of polyphenol extract from Zanthoxylum bungeanum Maxim. on endocrine hormones and monoamine oxidase activity in a mouse model of climacteric depression HTML

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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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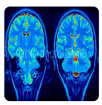

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Analysis of blood stream infections: Antimicrobial susceptibility and associated types of extended spectrum β-lactamases HTML (abstract.php?id=2903&aTitle=Analysis of blood stream infections: Antimicrobial susceptibility and associated types of extended spectrum β-lactamases) | Fulltext (../admin/12389900798187/2020_19_6_25.pdf)

Lorina I Badger-Emeka (mailto:lbadgeremeka@kfu.edu.sa), *Zainab Yaseen Al-Jaziri*, *Naheed Kausar*, *Nora Ahmad Al-Muhainy*, *Edric Estrella*,

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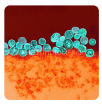

Solid phase extraction and LC-MS/MS quantification of ibandronate in human plasma HTML (abstract.php?id=2904&aTitle=Solid phase extraction and LC-MS/MS quantification of ibandronate in human plasma) | Fulltext (../admin/12389900798187/2020_19_6_26.pdf)

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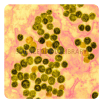

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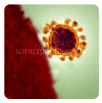

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Leptin and systemic lupus erythematosus: A comprehensive review HTML (abstract.php?id=2908&aTitle=Leptin and systemic lupus erythematosus: A comprehensive review) | Fulltext (../admin/12389900798187/2020_19_6_30.pdf)

Amal H Uzrail (mailto:auzrail@zu.edu.jo), *Lubna Swellmeen*,

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Archives

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Original Research Article

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

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

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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 ºC, 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

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 100ºC, 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 50-300ºC and a heating rate of 10ºC 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 60ºC 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.

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

Recovery of the drug was calculated as in Eq 2.

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

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.

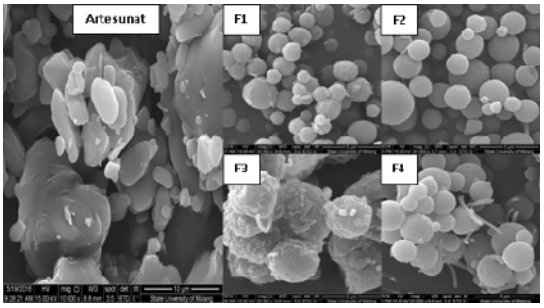

Figure 1: Scanning electron microscopy (SEM) photographs of artesunate, cross-linked chitosan-artesunate microparticles C-CL-AS (F1), non-cross-linked chitosan-artesunate microparticles C-AS (F2), cross-linked carboxymethyl chitosan-artesunate microparticles CM-CL-AS (F3), and non-cross-linked carboxymethyl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

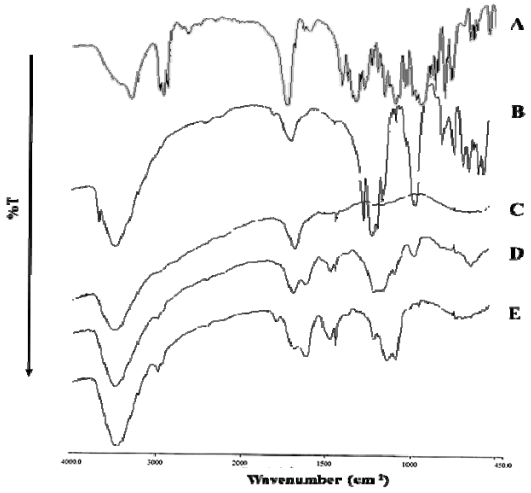

Figure 2: Infrared spectra of (A) artesunate, (B) TPP, (C) chitosan, (D) cross-linked chitosan-artesunate microparticles C-CL-AS, and (E) non-cross-linked chitosan-artesunate microparticles C-AS

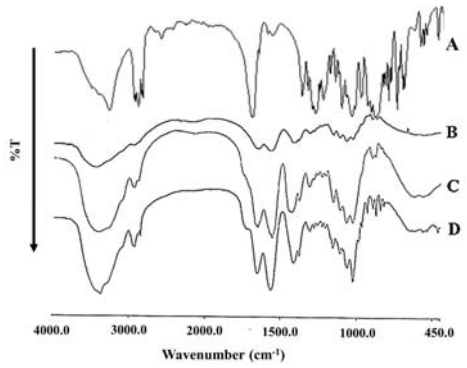

Figure 3: Infrared spectra of (A) artesunate, (B) carboxymethyl chitosan, (C) cross-linked carboxymethyl chitosan-artesunate microparticles CM-CL-AS, and (D) the non-cross-linked carboxymethyl

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.

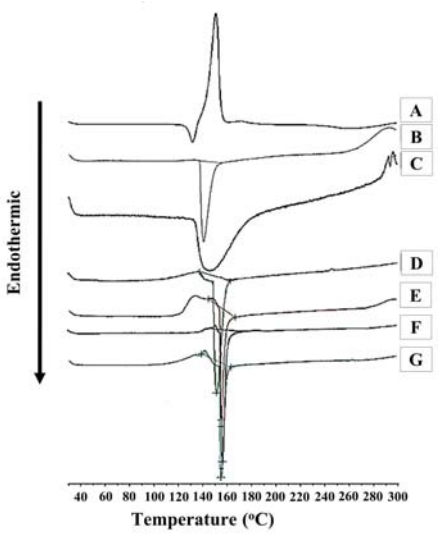

Figure 4: The thermograms of (A) artesunate, (B) chitosan, (C) carboxymethyl chitosan, (D) cross-linked chitosan-artesunate microparticles C-CL-AS, (E) non-cross-linked chitosan-artesunate microparticles C-AS, (F) cross-linked carboxymethyl chitosan-artesunate microparticles CM-CL-AS, and (G) non-cross-linked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

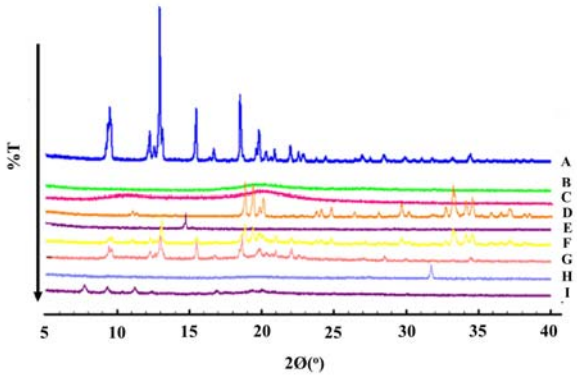

Figure 5: Diffractograms of (A) artesunate, (B) carboxymethyl chitosan, (C) chitosan, (D) tripolyphosphate, TPP, (E) calcium chloride $CaCl_2$, (F) cross-linked chitosan-artesunate microparticles C-CL-AS, (G) non-cross-linked chitosan-artesunate microparticles C-AS, (H) cross-linked carboxymethyl chitosan-artesunate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

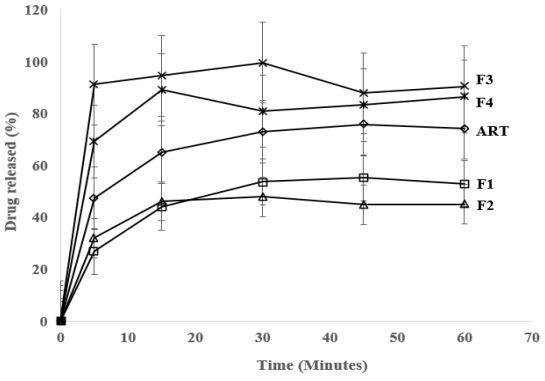

Figure 6: Release profiles of artesunate, cross-linked chitosan-artesunate microparticles, (F1), non-cross-linked chitosan-artesunate microparticles (F2), cross-linked carboxymethyl chitosan-artesunate micro-particles (F3), and non-cross-linked carboxymethyl chitosan-artesunate microparticles (F4) in 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

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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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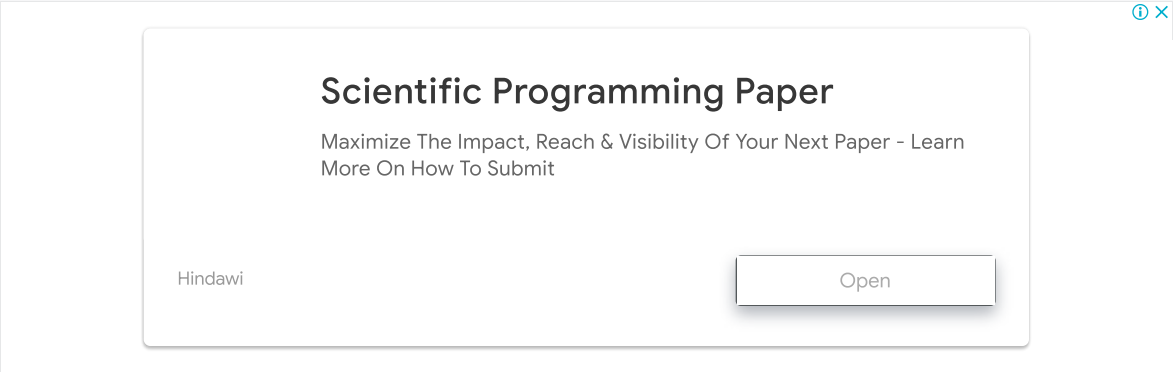

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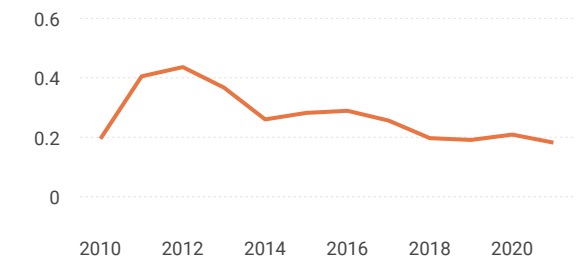

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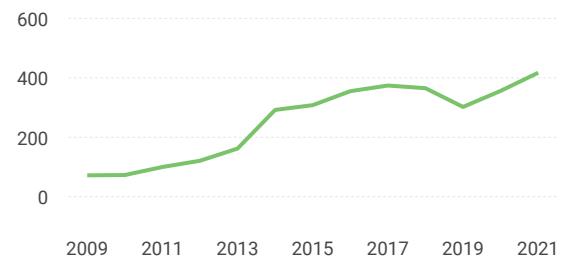

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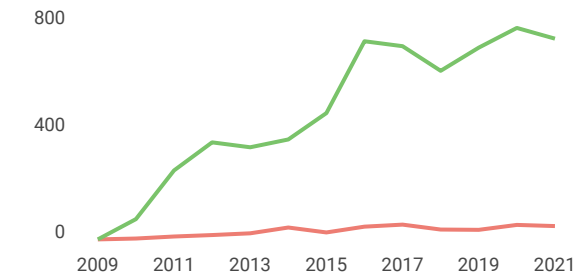

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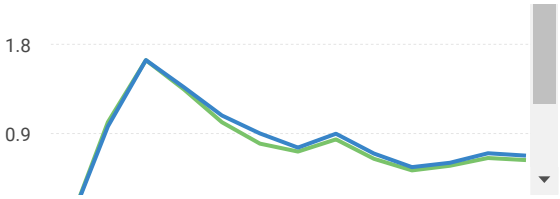

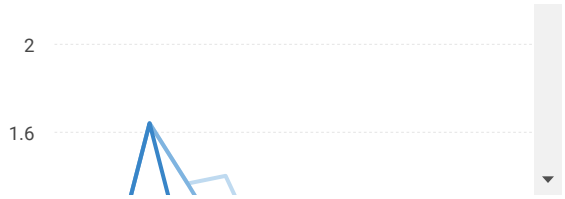

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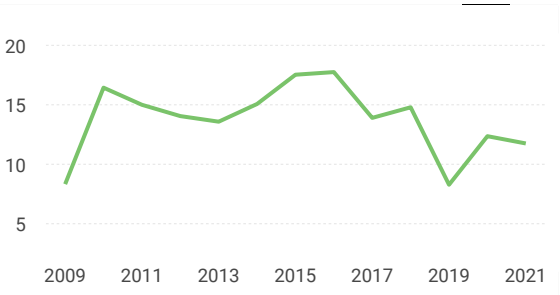

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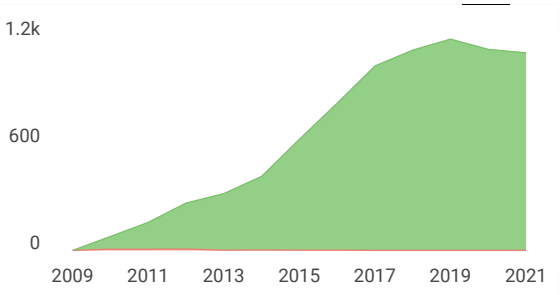

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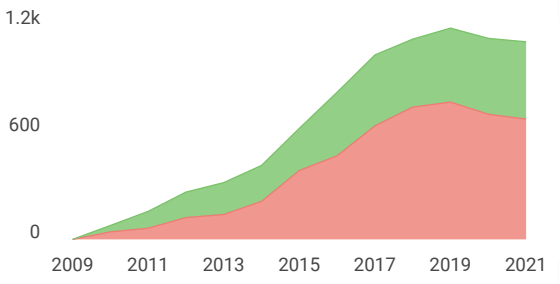

Tropical Journal of Pharmaceutical Research

Q3 Pharmaceutical Science

best quartile

SJR 2021 0.18

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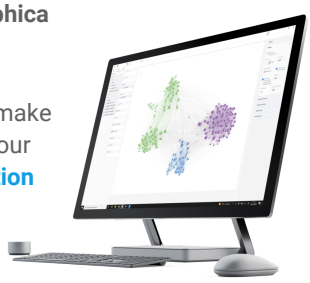

Metrics based on Scopus® data as of April 2022

S **Sari Yusuf** 1 year ago

Is the Tropical Journal of Pharmaceutical Research still being covered by scimago n 2021?

reply

Source details

Tropical Journal of Pharmaceutical Research

Open Access

Scopus coverage years: from 2009 to Present

Publisher: University of Benin

ISSN: 1596-5996 E-ISSN: 1596-9827

Subject area: Pharmacology, Toxicology and Pharmaceutics: Pharmaceutical Science | Medicine: Pharmacology (medical)

Source type: Journal

CiteScore 2021
0.9

SJR 2021
0.182

SNIP 2021
0.248

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CiteScore | CiteScore rank & trend | Scopus content coverage

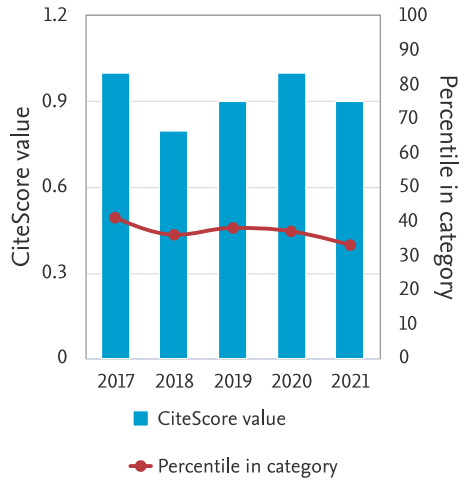
Export content for category

CiteScore rank 2021

In category: Pharmaceutical Science

	Rank	Source title	CiteScore 2021	Percentile
☆	#114/171	Tropical Journal of Pharmaceutical Research	0.9	33rd percentile
☆	#1	Advanced Drug Delivery Reviews	22.3	99th percentile
☆	#2	OpenNano	21.9	99th percentile
☆	#3	Nano Today	18.8	98th percentile
☆	#4	Journal of Controlled Release	15.7	97th percentile
☆	#5	Advanced healthcare materials	15.2	97th percentile
☆	#6	Artificial Cells, Nanomedicine and Biotechnology	13.6	96th percentile
☆	#7	Journal of Pharmaceutical Analysis	13.1	96th percentile
☆	#8	Asian Journal of Pharmaceutical Sciences	13.0	95th percentile
☆	#9	Nanomedicine: Nanotechnology, Biology, and Medicine	12.0	95th percentile
☆	#10	Journal of Pharmaceutical Investigation	11.3	94th percentile
☆	#11	International Journal of Nanomedicine	10.9	93rd percentile

CiteScore trend



☆	Rank	Source title	CiteScore 2021	Percentile
☆	#12	Expert Opinion on Drug Delivery	10.4	93rd percentile
☆	#13	Drug Delivery	10.2	92nd percentile
☆	#14	Journal of Nanobiotechnology	10.2	92nd percentile
☆	#15	European Journal of Pharmaceutics and Biopharmaceutics	9.7	91st percentile
☆	#16	International Journal of Pharmaceutics	9.6	90th percentile
☆	#17	Phytomedicine	9.6	90th percentile
☆	#18	Bioconjugate Chemistry	9.4	89th percentile
☆	#19	Molecular Pharmaceutics	9.2	89th percentile
☆	#20	Journal of Drug Targeting	8.8	88th percentile
☆	#21	European Journal of Pharmaceutical Sciences	8.4	88th percentile
☆	#22	Apoptosis : an international journal on programmed cell death	8.3	87th percentile
☆	#23	Drug Delivery and Translational Research	8.3	86th percentile
☆	#24	Marine Drugs	8.1	86th percentile
☆	#25	Advanced Therapeutics	7.5	85th percentile
☆	#26	Pharmaceutical Research	7.4	85th percentile
☆	#27	Journal of Liposome Research	7.2	84th percentile
☆	#28	Journal of Natural Products	7.1	83rd percentile
☆	#29	Drug Metabolism and Disposition	7.0	83rd percentile
☆	#30	IEEE Transactions on Nanobioscience	6.9	82nd percentile
☆	#31	Saudi Pharmaceutical Journal	6.8	82nd percentile
☆	#32	Journal of Pharmaceutical and Biomedical Analysis	6.8	81st percentile
☆	#33	Cancer Nanotechnology	6.8	80th percentile
☆	#34	Drug Design, Development and Therapy	6.6	80th percentile
☆	#35	Bioorganic and Medicinal Chemistry	6.5	79th percentile
☆	#36	RSC Medicinal Chemistry	6.5	79th percentile
☆	#37	AAPS PharmSciTech	6.4	78th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#38	AAPS Journal	6.3	78th percentile
☆	#39	Journal of Drug Delivery Science and Technology	6.3	77th percentile
☆	#40	Planta Medica	6.2	76th percentile
☆	#41	Journal of Pharmaceutical Sciences	6.1	76th percentile
☆	#42	BioImpacts	6.1	75th percentile
☆	#43	Advanced Pharmaceutical Bulletin	6.1	75th percentile
☆	#44	Pharmaceutics	6.0	74th percentile
☆	#45	Drug Testing and Analysis	6.0	73rd percentile
☆	#46	Sustainable Chemistry and Pharmacy	5.9	73rd percentile
☆	#47	Molecules	5.9	72nd percentile
☆	#48	Drug Development and Industrial Pharmacy	5.9	72nd percentile
☆	#49	Critical Reviews in Therapeutic Drug Carrier Systems	5.5	71st percentile
☆	#50	International Journal of Pharmaceutics: X	5.4	71st percentile
☆	#51	Archiv der Pharmazie	5.4	70th percentile
☆	#52	Therapeutic Delivery	5.4	69th percentile
☆	#53	Pharmaceutical Development and Technology	5.4	69th percentile
☆	#54	Journal of Microencapsulation	5.3	68th percentile
☆	#55	Scientia Pharmaceutica	5.3	68th percentile
☆	#57	Journal of Cardiovascular Translational Research	5.2	66th percentile
☆	#58	Journal of Texture Studies	5.2	66th percentile
☆	#59	Bioengineering and Translational Medicine	5.2	65th percentile
☆	#60	Research in Social and Administrative Pharmacy	5.1	65th percentile
☆	#61	Journal of Aerosol Medicine and Pulmonary Drug Delivery	5.1	64th percentile
☆	#62	Pharmaceutical Nanotechnology	5.0	64th percentile
☆	#63	Bioorganic and Medicinal Chemistry Letters	5.0	63rd percentile
☆	#64	Pharmaceutical Biology	4.8	62nd percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#65	International Journal of Genomics	4.6	62nd percentile
☆	#66	Current Drug Delivery	4.6	61st percentile
☆	#67	Acta Pharmaceutica	4.5	61st percentile
☆	#68	International Journal of Cosmetic Science	4.5	60th percentile
☆	#69	Drug Metabolism and Pharmacokinetics	4.5	59th percentile
☆	#70	Journal of Pharmacy and Pharmaceutical Sciences	4.4	59th percentile
☆	#71	Profiles of Drug Substances, Excipients and Related Methodology	4.3	58th percentile
☆	#72	Cosmetics	4.2	58th percentile
☆	#73	Current Pharmaceutical Biotechnology	4.2	57th percentile
☆	#74	Recent Advances in Drug Delivery and Formulation	4.1	57th percentile
☆	#75	Pharmaceuticals	4.0	56th percentile
☆	#76	Pharmaceutical patent analyst	3.7	55th percentile
☆	#77	Biological and Pharmaceutical Bulletin	3.7	55th percentile
☆	#78	Clinical Pharmacology in Drug Development	3.6	54th percentile
☆	#79	Journal of managed care & specialty pharmacy	3.6	54th percentile
☆	#80	Journal of Pharmaceutical Innovation	3.4	53rd percentile
☆	#81	International Journal of Clinical Pharmacy	3.3	52nd percentile
☆	#82	Biopharmaceutics and Drug Disposition	3.1	52nd percentile
☆	#83	Current Nanoscience	3.1	51st percentile
☆	#84	Pharmacy Practice	2.8	51st percentile
☆	#85	Open Medicinal Chemistry Journal	2.8	50th percentile
☆	#86	Drug Metabolism Letters	2.7	50th percentile
☆	#87	International Journal of Pharmacy Practice	2.6	49th percentile
☆	#88	Journal of Asian Natural Products Research	2.6	48th percentile
☆	#89	Statistics in Biopharmaceutical Research	2.5	48th percentile
☆	#90	Canadian Pharmacists Journal	2.4	47th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#91	Journal of Advanced Pharmaceutical Technology and Research	2.3	47th percentile
☆	#92	Journal of Liquid Chromatography and Related Technologies	2.3	46th percentile
☆	#93	Letters in Drug Design and Discovery	2.2	45th percentile
☆	#94	Pharmacia	2.1	45th percentile
☆	#95	Research Results in Pharmacology	2.0	44th percentile
☆	#96	Journal of Pharmacy and Pharmacognosy Research	1.6	44th percentile
☆	#97	Journal of Excipients and Food Chemicals	1.6	43rd percentile
☆	#98	Acta Pharmaceutica Sciencia	1.5	42nd percentile
☆	#98	International Journal of Applied Pharmaceutics	1.5	42nd percentile
☆	#100	Dissolution Technologies	1.5	41st percentile
☆	#101	Pharmaceutical Sciences	1.5	41st percentile
☆	#102	Turkish Journal of Pharmaceutical Sciences	1.5	40th percentile
☆	#103	JACCP Journal of the American College of Clinical Pharmacy	1.4	40th percentile
☆	#104	Beni-Suef University Journal of Basic and Applied Sciences	1.4	39th percentile
☆	#105	AAPS Advances in the Pharmaceutical Sciences Series	1.4	38th percentile
☆	#106	Pakistan Journal of Pharmaceutical Sciences	1.2	38th percentile
☆	#107	Current Pharmaceutical Analysis	1.2	37th percentile
☆	#108	Annales Pharmaceutiques Francaises	1.1	37th percentile
☆	#109	Indian Journal of Pharmaceutical Sciences	1.1	36th percentile
☆	#110	Journal of Pharmaceutical Negative Results	1.0	35th percentile
☆	#111	Jordan Journal of Pharmaceutical Sciences	1.0	35th percentile
☆	#112	Drug Delivery Letters	1.0	34th percentile
☆	#113	Pharmakeftiki	0.9	34th percentile
☆	#114	Tropical Journal of Pharmaceutical Research	0.9	33rd percentile
☆	#115	Fabad Journal of Pharmaceutical Sciences	0.8	33rd percentile

Rank	Source title	CiteScore 2021	Percentile
#116	Journal of Pharmacy Technology	0.8	32nd percentile
#117	Journal of Medicinal and Chemical Sciences	0.8	31st percentile
#118	Indonesian Journal of Pharmacy	0.7	31st percentile
#119	Farmatsiya i Farmakologiya	0.7	30th percentile
#120	Thai Journal of Pharmaceutical Sciences	0.7	30th percentile
#121	Acta Poloniae Pharmaceutica	0.6	29th percentile
#122	Journal of Advanced Pharmacy Education and Research	0.6	28th percentile
#123	Drug Development and Registration	0.6	28th percentile
#124	Journal of Chinese Pharmaceutical Sciences	0.6	27th percentile
#125	Pharmacy Education	0.5	27th percentile
#126	Chinese Traditional and Herbal Drugs	0.5	26th percentile
#127	Yakugaku Zasshi	0.5	26th percentile
#128	Iranian Journal of Pharmaceutical Sciences	0.5	25th percentile
#129	Ankara Universitesi Eczacilik Fakultesi Dergisi	0.5	24th percentile
#130	American Pharmaceutical Review	0.5	24th percentile
#131	Current Trends in Biotechnology and Pharmacy	0.5	23rd percentile
#132	Chinese Pharmaceutical Journal	0.5	23rd percentile
#133	Korean Journal of Pharmacognosy	0.5	22nd percentile
#134	International Journal of Drug Delivery Technology	0.4	21st percentile
#135	Korean Journal of Medicinal Crop Science	0.4	21st percentile
#136	European Journal of Parenteral and Pharmaceutical Sciences	0.4	20th percentile
#137	Revista Cubana de Farmacia	0.4	20th percentile
#139	Journal of China Pharmaceutical University	0.4	19th percentile
#140	Tropical Journal of Natural Product Research	0.4	18th percentile
#141	U.S. Pharmacist	0.4	17th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#142	Revista de Ciencias Farmaceuticas Basica e Aplicada	0.3	17th percentile
☆	#143	Indian Drugs	0.2	16th percentile
☆	#143	SA Pharmaceutical Journal	0.2	16th percentile
☆	#145	BioPharm International	0.2	15th percentile
☆	#146	Bulletin of Pharmaceutical Sciences. Assiut	0.2	14th percentile
☆	#147	ONdrugDelivery	0.2	14th percentile
☆	#148	Pharmaceutical Technology	0.2	13th percentile
☆	#149	Pharmaceutical Technology Europe	0.2	13th percentile
☆	#150	Anti-Obesity Drug Discovery and Development	0.1	12th percentile
☆	#151	Klinicka Farmakologie a Farmacie	0.1	11th percentile
☆	#151	Pharmaceutical Care and Research	0.1	11th percentile
☆	#153	Drug Development and Delivery	0.1	10th percentile
☆	#154	Arhiv za Farmaciju	0.1	10th percentile
☆	#155	Journal of International Pharmaceutical Research	0.1	9th percentile
☆	#156	Journal of Medical Pharmaceutical and Allied Sciences	0.1	9th percentile
☆	#157	Drug Delivery System	0.1	8th percentile
☆	#158	Pharmaceutical Outsourcing	0.1	7th percentile
☆	#159	Chinese Journal of Pharmaceutical Biotechnology	0.1	7th percentile
☆	#160	Farmaceutski Glasnik	0.1	6th percentile
☆	#161	Farmacja Polska	0.0	6th percentile
☆	#162	Drugs and Clinic	0.0	5th percentile
☆	#163	Pharmacy Times	0.0	4th percentile
☆	#164	PZ Prisma	0.0	4th percentile
☆	#165	Drug Topics	0.0	2nd percentile
☆	#165	Egyptian Pharmaceutical Journal(Egypt)	0.0	2nd percentile
☆	#165	European Pharmaceutical Law Review	0.0	2nd percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#165	Frontiers in Clinical Drug Research - CNS and Neurological Disorders	0.0	2nd percentile
☆	#165	Frontiers in Clinical Drug Research - HIV	0.0	2nd percentile
☆	#165	GMP Review	0.0	2nd percentile
☆	#165	Manufacturing Chemist	0.0	2nd percentile

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