BUKTI KORESPONDENSI ARTIKEL PADA JURNAL INTERNASIONAL BEREPUTASI DAN BERFAKTOR DAMPAK



Pengusul: Nadya Alfa Cahaya Imani, S.T., M.Eng.

Fakultas Teknik, Universitas Negeri Semarang Tahun 2024

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Bersama dengan surat ini, saya sertakan bukti korespondensi proses publikasi artikel pada Jurnal Internasional dengan judul "Preparation, Characterization, and Release Study of Nanosilica/Chitosan Composite Films", yang dimuat pada International Journal of Technology, edisi Vol 13 (2) Tahun 2022 halaman 444-453.

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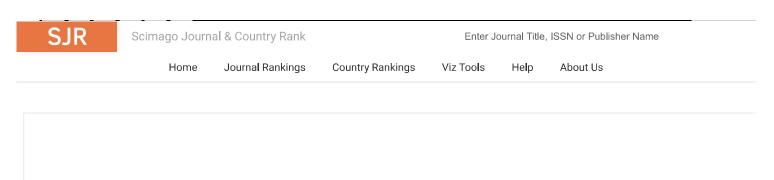
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Identitas Publikasi

Judul artikel	:	Preparation, Characterization, and Release Study of Nanosilica/Chitosan
		Composite Films
Penulis	:	Nadya Alfa Cahaya Imani, Yuni Kusumastuti, Himawan Tri Bayu Murti Petrus,
		Daniel Timotius, Nur Rofiqoh Eviana Putri, Mime Kobayashi
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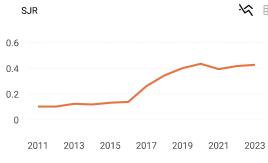
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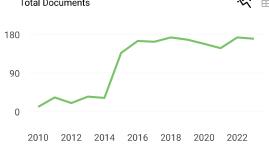
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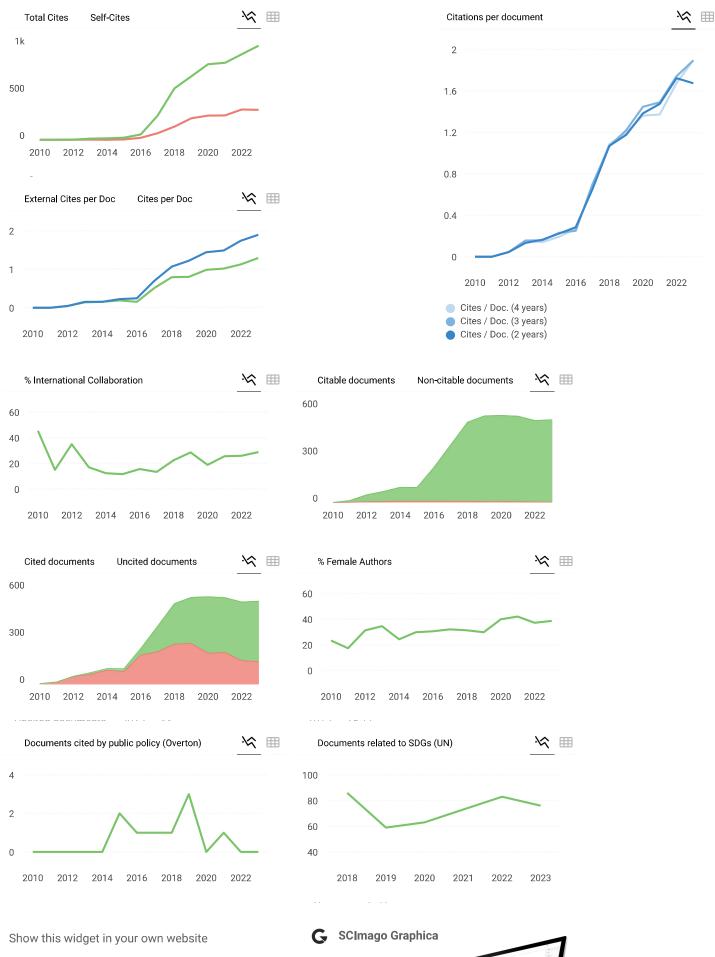
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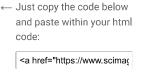
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We recommend that this manuscript be revised in order to proceed to peer review.

You must respond to this revise and resubmit request before **15 Feb 2021**, after which point we will presume that you have withdrawn your submission from International Journal of Technology (IJTech) Online System.

Yours sincerely,

Dr. Nyoman Suwartha nsuwartha@eng.ui.ac.id Managing Editor International Journal of Technology (IJTech) p-ISSN: 2086-9614 e-ISSN: 2087-2100 https://ijtech.eng.ui.ac.id/

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Dear Dr. Yuni Kusumastuti

The editorial boards are delighted to inform you that your paper has been accepted to be published in IJTech next Volume 13 issue 2, April 2022.

We have carried out the necessary layout and editing of your manuscript. Prior to publication, we need your final proof and copyright of the paper.

Here are notes from the editor:

- 1. Please provide the corresponding author's telephone and fax number (if any)
- 2. Check the decimal values in abstract
- 3. Revise and add unit on page 722
- 4. In the acknowledgment add a number of contract grant and year (if any)

Please make all revisions to the one file final manuscript that we sent (We do not accept another file),

Enclosed please find the copyright form and the paper for a final check and please confirm that the article is ready for printing.

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On behalf of editorial boards, we want to express to you and your collaborators our deep appreciation for your contribution to IJTech.

We look forward to receiving the copyright form and proofs at your earliest convenience.

Yours sincerely,

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- 2. Dr. Yuni Kusumastuti
- 3. Dr. Himawan Tri Bayu Murti Petrus
- 4. Mr. Daniel Timotius
- 5. Mrs. Nur Rofiqoh Eviana Putri
- 6. Dr. Mime Kobayashi

Greetings from Depok!

On behalf of the Editorial Board, I am pleased to inform you that your article entitled **Preparation**, **Characterization**, **and Release Study of Nanosilica/Chitosan Composite Films** has been published online in *Volume 13 Issue 2, Apr 2022*. You can check the online version at: https://ijtech.eng.ui.ac.id/ issue/77

The articles are available to be accessed and downloaded free of charge. The hardcopy version is being printed and one copy will be delivered to the corresponding author.

Thank you for your contribution to IJTech and we look forward to a good collaboration in the next future.

Yours sincerely,

Prof. Mohammed Ali Berawi Editor in Chief International Journal of Technology (IJTech) p-ISSN: 2086-9614 e-ISSN: 2087-2100 https://ijtech.eng.ui.ac.id/

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International Journal of Technology 13(2) 444-453 (2022) Received February 2021 / Revised February 2021 / Accepted March 2021

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Preparation, Characterization, and Release Study of Nanosilica/Chitosan Composite Films

Nadya Alfa Cahaya Imani¹, Yuni Kusumastuti^{2*}, Himawan Tri Bayu Murti Petrus^{2,3}, Daniel Timotius², Nur Rofiqoh Eviana Putri², Mime Kobayashi⁴

¹Department of Chemical Engineering, Faculty of Engineering, Universitas Negeri Semarang, Sekaran Campus, Gunungpati, Semarang, 50229, Indonesia

²Department of Chemical Engineering, Faculty of Engineering, Universitas Gadjah Mada, Sleman, Yogyakarta, 55281, Indonesia

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Abstract. The development of film materials that can control the release of drugs is needed to create a smart drug delivery system. This paper reports the properties and kinetic studies of film models made of chitosan and nanosilica. Nanosilica was directly incorporated into the chitosan solution to modify and enhance the properties of the composites as potential drug carriers. Fourier transform infrared spectroscopy results acknowledge the successful fabrication of chitosan/nanosilica composite films. Wettability tests showed that the inclusion of nanosilica could make the film more hydrophilic by incorporating up to 5 wt%. The effective diffusion coefficients obtained by mathematical modeling were in the range of 10^{-6} cm²/min. Based on the kinetic studies, the powerlaw model is the most suitable model to explain the mechanism of drug released from composite films with k_K values ranging from 0.3552 to 0.4279, the value of *n* in the range of 0.3103 to 0.3955, and the value of R^2 in the range of 0.9008 to 0.9411. The overall result concludes that these chitosan/nanosilica composite films have great potential to be used as materials for drug carriers.

Keywords: Chitosan; Composite Film; Drug delivery system; Kinetic model; Nanosilica

1. Introduction

Medicine is an important component of human healthcare as it is a way to provide therapeutic or healing effects for various diseases (Whittam et al., 2016). Conventionally, drugs have been administered to the body through the gastrointestinal tract, rectal injection, or directly into a vein (Batchelor and Marriott, 2013). These methods are inherently less effective because, at each time of administration, a large dose of the drugs has to be given for the drugs to reach the target locations (Wen et al., 2015). Drug administration must be repeated and often cause side effects. Side effects can be allergies or systemic poisoning caused by reactions between the drugs and stomach fluids or the patient's blood. To avoid repeated drug administrations to patients so as to minimize the

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possibility of poisoning caused by excessive drug doses, a drug delivery system that can deliver controlled drug release is needed.

One of the most studied drug delivery systems is the use of a polymer film (thin membrane layer). This form of film has the advantage of being flexible in how it is administered to the body (Chan et al., 2019; Hatanaka et al., 2019). The drug delivery system in the form of films usually uses polymers from natural materials (biopolymers) as the matrix because these materials have biocompatible properties (properties where a material does not cause rejection reactions by the human immune system that detect and attack foreign objects), are biodegradable (the ability of a material to be degraded inside the body), and are nontoxic (Chan et al., 2019; Kalantari et al., 2019; Samadian et al., 2020). One biopolymer that has been gaining attention for this purpose is chitosan. Chitosan is a natural polysaccharide and a derivative of chitin, which can be found in the exoskeleton of shelled animals (crustaceans) (Sedaghat et al., 2017). This compound has antibacterial properties, is nontoxic, and is easy to modify, so it is often chosen to be used for various applications in the fields of food, textiles, waste treatment, agriculture, and health (Revathi and Thambidurai, 2017; Mohamed et al., 2018; Kamdem et al., 2019; Si et al., 2019). Chitosan is also a polymer that has a positive charge (polycation), which makes it good to be used as a matrix for drug delivery systems in the form of a film because it will increase the adhesive properties (ability to stick) of the film (Krisanti et al., 2020; Singh et al., 2020). In its application as a film for drug delivery, like other biopolymers, chitosan has a disadvantage that it is easy to swell; that is, swelling occurs when the film is in a liquid system. This swelling can cause discomfort when the patient uses this film-shaped drug release system. In addition, a high swelling rate will trigger an initial burst release (rapid drug release at the beginning) (Ammar et al., 2009). Therefore, efforts are needed to modify the film from this material to improve its characteristics, especially for applications as a delivery system of drugs or other components.

One way to increase the ability of chitosan film as a drug delivery system is by adding inorganic materials. According to Uragami et al. (2002) and Kusumastuti et al. (2017), the formation of an organic-inorganic film could create a vastly functional materials by combining the film-forming properties of organic polymers and the stability and strength of inorganic compounds. Furthermore, the potential use of organic/inorganic composites as biomaterials in tissue engineering has been reported by Kusumastuti et al. (2018). Also, research conducted by Liu et al. (2019) reported that the addition of an inorganic material, namely nanosilica, can decrease the percentage swelling of the chitosan film and increase the tensile strength of the film. Nanosilica is used because this material has properties such as nontoxic, large drug loading capacity, easy to modify, and biocompatible (Bharti et al., 2015). Another similar study was also conducted by Wu et al. (2019), where mesoporous silica was obtained from tetraethyl orthosilicate and it was added to chitosan for making films, which are able to be applied for food packaging application. The results of the study showed that the prepared hybrid films can slow the release of curcumin and have good antimicrobial activity.

Herein, film as a drug delivery system was prepared by mixing chitosan and nanosilica powder. Curcumin, which is known to have potential as an anticancer drug, was used as a model drug for drug release. Nanosilica addition aimed to modify the structure of the chitosan film so that it can increase resistance to control the speed of drug release. In this study, we report the properties of the films that have been made and investigated their potential as a controlled drug delivery system. Furthermore, we also report mathematical modeling and kinetic studies of drug release from the film. Thus, a simple thin-film model can be obtained and used to foresee the drug release profile of a system for wound dressing.

2. Methods

2.1. Materials

Chitosan with low-molecular-weight specifications (75–85% degree of deacetylation) and nanosilica (SiO₂) powder (10–20 nm) were purchased from Sigma Aldrich. Acetic acid glacial (100% w/w) was obtained from Merck, Germany. Phosphate-buffered saline (PBS), pH 7.4, was supplied by the Faculty of Dentistry, Universitas Gadjah Mada, Indonesia.

2.2. Chitosan–Nanosilica Solution Preparation

Low-molecular-weight chitosan was dissolved in a 1% (v/v) acetic acid water solution to make a 1% (w/v) chitosan solution. The mixture was stirred in a closed container at room temperature for 3 h. A certain amount of nanosilica powder (PC: film with 0% by weight of nanosilica/weight of chitosan; CSD25: film with 2.5% weight of nanosilica/weight of chitosan; CSD50: film with 5% weight of nanosilica/weight of chitosan; CSD75: film with 7.5% weight of nanosilica/weight of chitosan; CSD100: film with 10% weight of nanosilica/weight of chitosan) was mixed in the solutions and stirred at room temperature for 4 h (Imani, 2018).

2.3. Drug Loading

Curcumin, according to the concentration calculation (20% weight of curcumin/weight of chitosan), was stirred in Tween 80 (70% by weight of Tween 80/weight of chitosan). The solution was stirred at room temperature until it became homogeneous. The film matrix solution was poured onto the curcumin/Tween 80 solution and stirred again for 3 h in a closed container. The solution was then poured into a 11-cm-diameter polyethylene (PE) petri dish with a volume of 5 mL/petri dish and dried for 48 h at 30°C (Timotius et al., 2020).

2.4. Film Characterization

The procured samples were characterized using Fourier transform infrared (FTIR) spectroscopy (Shimadzu IR Prestige-21) in the wavenumber ranged between 4000–400 cm⁻¹. Changes in functional groups were observed by comparing the spectra of prepared films with those of pure components. Surface area and pore diameter and intensity analyses were carried out using a surface area analyzer instrument (NOVA series, Quantachrome).

2.5. Drug Release Test

Prepared films were cut using a 1.25-cm-diameter punch. They were immersed in 20 mL of PBS solution. Periodically, the sample solution was taken using a pipette and was analyzed using a spectrophotometer (Genesys-20) at a wavelength (λ max) of 421 nm for absorbance measurement (Hazra et al., 2015). Each analyzed solution was returned to the original solution so that the total volume of the sample solutions remained the same.

2.6. Kinetic Study

The diffusion process in drug release was modeled using the mathematical equation and conditions proposed by Timotius et al. (2020), as shown in Equation 1:

$$\frac{\partial^2 C_A}{\partial x^2} = \frac{1}{D_{ef}} \frac{\partial C_A}{\partial t}$$
(1)

In addition to the mathematical modeling that has been compiled, four mathematical models are also used to represent the mechanism of drug released from the film matrix, namely zero order (Equation 2), first order (Equation 3), Higuchi (Equation 4), and Korsmeyer Peppa or often called the power-law model (Equation 5) (Dash et al., 2010).

$$C_t = C_0 + k_z t \tag{2}$$

$$C_t = C_0 e^{-k_f t} \tag{3}$$

$$\frac{C_t}{C_\infty} = k_H t^{1/2} \tag{4}$$

$$\frac{C_t}{C_{\infty}} = k_K t^n \tag{5}$$

where C_t is the cumulative concentration of the drug released at time t, C_0 is the initial amount of the drug, C_{∞} is the amount of drug at the equilibrium state, and k is constant for the kinetic model (k_z , zero order; k_f , first order; k_H , Higuchi; k_K , power law).

3. Results and Discussion

3.1. FTIR Characterization Analysis

The existence of interactions between materials in the film was analyzed by FTIR spectroscopy. The spectra produced from chitosan, nanochitosan, curcumin, and chitosan/silica films that have been loaded with curcumin are shown in Figure 1. Changes in the peaks in the obtained FTIR spectra were observed. Chitosan used has a distinctive vibration from its functional groups, namely a large vibration area at 3100–3600 cm⁻¹, which imply the existence of O–H and/or N–H bonds; a peak at 2877 cm⁻¹, which suggest the presence of C–H alkyl bonds; a peak at 1651 cm⁻¹, which represents C=O stretch and N–H deformation in primary amine groups; and a peak at 1558 cm⁻¹, signaling the presence of C–N stretching and N–H deformation in secondary amine groups (Liu et al., 2019).

In nanosilica, Si–O–Si is linear, which is shown by the presence of stretching vibrations in the area at 1080–1200 cm⁻¹, Si–OH is shown with a peak at 964 cm⁻¹, and Si–O is shown by the existence of a peak at 474 cm⁻¹. The addition of nanosilica to the film matrix causes changes in the resulting film spectra. The shifts from 1651 and 1558 cm⁻¹ to 1629 and 1563 cm⁻¹ indicate a possible interaction in the form of hydrogen bond formation between the hydroxyl groups of the nanosilica and the amine groups present in chitosan. Meanwhile, the change of a peak at 1090 cm⁻¹ to a large area vibration from 1100 to 1180 cm⁻¹ may be due to the arrangement of the –Si–O–C bond produced by the reaction between the silanol groups of nanosilica and the carbonyl groups in chitosan and Si–O–Si stretching. In addition, a peak at 474 cm⁻¹ also appeared, which indicates the presence of Si–O bonds in the chitosan/nanosilica film. Furthermore, from the results of FTIR characterization on curcumin, typical vibrations of curcumin can be seen as a peak at 1512 cm⁻¹, which indicates the presence of C=O bonds, and there is also C–O enol, which is indicated by a peak at 1280 cm⁻¹. In the spectrum of prepared film, peaks at 1512 and 1280 cm⁻¹ were observed, thus confirming the presence of curcumin in the hybrid film.

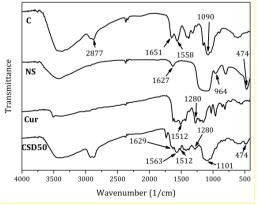


Figure 1 FTIR spectra for chitosan (C), nanosilica (NS), curcumin (Cur), and prepared film (CSD50)

3.2. Surface Observation

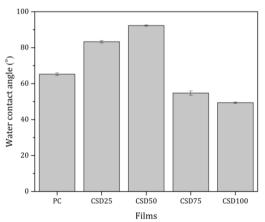
Brunauer–Emmett–Teller (BET) surface area analysis was carried out to compare the surface area of a film made of chitosan alone and a chitosan/nanosilica hybrid film. The addition of nanosilica has an impact on increasing the surface area of the film (Table 1). The surface area of a film made of chitosan alone (PC) was $6.93 \text{ m}^2/\text{g}$ while that of CSD50 was $8.522 \text{ m}^2/\text{g}$, with a 23.0% increase. At the same time, the average pore size of the film decreased from 40.7 to 35.95 Å with the addition of nanosilica. The results indicate that the addition of nanosilica creates a film that has more pores but in small sizes. Changes in the pore structure of the film will affect the film's properties such as mechanical strength and permeability. The decrease in pore size increases the tensile strength of a film and slows diffusion of the retained liquid due to the barrier effect (Fahim et al., 2015a, 2015b).

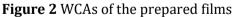
Table 1 Sumr	nary of surface ar	ea analysis
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Sample	Total surface area (m²/g)	Pore size (Å)		
РС	6.93	40.7		
CSD50	8.522	35.95		

3.3. Wettability

The effect of blending nanosilica on the hydrophobic/hydrophilic properties of the chitosan films was assessed by measuring the contact angles between water droplets and the surface of the films. Smaller angles mean that the films have hydrophilic properties, and greater angles mean reduced hydrophilic properties, or it can be called more hydrophobic (Dwivedi et al., 2017). The results of the water contact angle (WCA) measurements are presented in Figure 2. From the bar chart in the figure, it can be said that the addition of nanosilica in an amount of 5% by weight of nanosilica/weight of chitosan (CSD50) increases the WCA value of the film from $65.2 \pm 1.4^{\circ}$ to $93.05 \pm 0.35^{\circ}$.





The statistical analysis using analysis of variance (ANOVA) showed less than 0.05 in probability value for each individual sample. The presence of silica in the film showed a significant difference. However, increasing the amount of silica further to 7.5% (CSD75) or 10% (CSD100) by weight of nanosilica/weight of chitosan resulted in smaller WCA values ($55.55 \pm 1.25^{\circ}$ or $50.1 \pm 0.6^{\circ}$, respectively) when compared with PC (0% nanosilica). Basically, silica, including the one in nanosized scale, should be hydrophilic due to the presence of an OH group in the silanol group. In CSD25 and CSD50, the presence of the group is decreased as a result of interaction with chitosan. However, in CSD75 and CSD100, the excessive amount of silica makes it difficult for the solution to be homogeneous. The nanosilica tends to form aggregates with similar molecules. The aggregate formation will

cause an increase in the number of –OH groups, leading to more hydrophilic properties (Rallini and Kenny, 2017).

3.4. Drug Release Profiles and Kinetic Studies

Using curcumin as a model, drug release tests were performed to confirm the effectiveness of the prepared films in holding the drug and controlling drug release rates. All films made of chitosan and nanosilica mixture showed slower drug release compared with a film made of chitosan alone (Figure 3). The results show a profile where the drug will be gradually released over time, and for a certain period, the release will be sustained at constant rates. The profile is influenced by several factors, namely by components of the drug carrier matrix, pH of the solution, and temperature (Barleany et al., 2020). Statistical analyses using ANOVA showed a significant difference in the mixing variable of the amount of nanosilica in the film matrix on the cumulative amount of drug released.

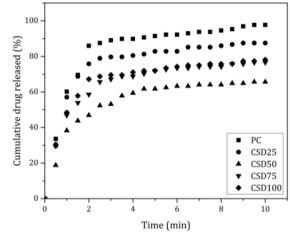


Figure 3 Release profile of drug from films

Sample	D_{ef}	H_A
PC	1.031×10^{-5}	$6.1767 imes 10^3$
CSD25	$9.9372 imes 10^{-6}$	$6.1456 imes 10^{3}$
CSD50	4.1935×10^{-6}	6.1102×10^{3}
CSD75	$7.7981 imes 10^{-6}$	$6.1525 imes 10^3$
CSD100	8.0042×10^{-6}	6.1398×10^3

The data for the effective diffusion value of each prepared film are shown in Table 2. The effective diffusivity coefficient values for all films containing nanosilica are lower than those of the films without the addition of nanosilica (PC). This decrease is possibly because the addition of nanosilica made the structure of the film tighter, thus giving it more resistance and making it more difficult for the drug in the middle area of the film to be released. However, the optimal decrease occurred only in CSD50; the effective diffusion value at the addition of a higher amount of nanosilica, namely in CSD75 and CSD100, started to increase again, but still smaller than that of PC. This is possibly because the nanosilica tends to form aggregates with similar molecules and the excessive amount of nanosilica in the film makes the matrix solution not homogeneous so that there is a gap in the film obtained and the drug can come out faster.

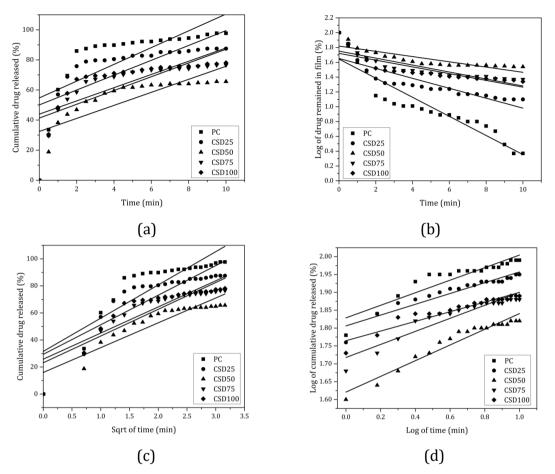


Figure 4 Linear fitting of drug release using the (a) zero-order model, (b) first-order model, (c) Higuchi model, and (d) power-law model

In addition to fitting mathematical models that have been compiled, the drug release results were also compared with several known release kinetic models, namely the zero-order, first-order, Higuchi, and power-law models. Data and calculation results using each model are shown in Figure 4 and Table 3. Based on the figures and the R^2 data, the drug release trend of the samples produced in this study is the closest to the power-law model. The R^2 value shown in comparison with the power-law linear model ranges from 0.9008 to 0.9411, where the CSD50 has the highest number. The power (n) values reported for all films are less than 0.5. The n value in this power law illustrates the mechanism of drug release from the film. If n < 0.5, then the release mechanism involves Fickian diffusion, which means that solvent diffusion is much more dominant than the polymer chain relaxation process in the film matrix (Bruschi, 2015).

Commla	Zero order		First order		Higuchi		Power law		
Sample	k_z	R^2	<i>k</i> _f	R^2	k_{H}	R^2	kк	п	R^2
РС	0.2114	0.5101	0.4921	0.8736	0.3977	0.7462	0.4503	0.4525	0.8551
CSD25	0.0191	0.5001	0.2926	0.7362	0.3601	0.7376	0.4279	0.3955	0.9008
CSD50	0.0138	0.6253	0.0469	0.7335	0.2605	0.8446	0.3552	0.3103	0.9411
CSD75	0.0164	0.5750	0.1199	0.7484	0.3092	0.8079	0.3935	0.3533	0.9159
CSD100	0.0168	0.5241	0.1406	0.6947	0.3174	0.7619	0.3995	0.3602	0.9091

Table 3 Parameter for kinetics of release models

4. Conclusions

Composite films made of nanosilica and chitosan have been successfully prepared by varying the ratio of the amount of nanosilica to chitosan. The addition of nanosilica to the film matrix up to 5% by weight of nanosilica/weight of chitosan increased the hydrophobic properties of the film. However, higher nanosilica content led to smaller WCA values or more hydrophilic films. Performance tests on drug release show that all films containing a mixture of nanosilica have higher drug-retaining ability than films made only with chitosan. The calculation results show that the effective diffusion values of chitosan/nanosilica films are in the range of 4.1935×10^{-6} to 9.9372×10^{-6} cm²/min and the most suitable drug release mechanism follows the power-law model with R^2 value ranging from 0.9008 to 0.9411. From the results, it can be stated that chitosan and nanosilica composites have great potential to be used as materials for drug carriers. However, further study of the optimal methods and conditions for film formation is needed to make this controlled drug delivery system even more effective.

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