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Copper-amino acid/Carboxymethyl starch composite for controllable releasing of povidone-iodine

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Abstract

Povidone-iodine is identified as one of the widely applicable antiseptic reagents for treatment of skin infection and wound healing. Controllable releasing of povidone-iodine is extensively required for healing of chronic wounds. The release of povidone-iodine was systematically studied from the composites based on carboxymethyl starch (CMS). Currently, different ratios from copper precursor and L-aspartic acid (L-AA) were interacted with CMS to obtain Cu-L-AA@CMS composites. Increment the percentage of L-AA was reflected in clustering of dense masses from the desirable composite with highly crystalline/stable structural network. Regardless to pH conditions, Cu-L-AA(30%)@CMS composite showed the highest efficiency for controllable release of povidone-iodine, whereas, the release percentages were estimated to be 58%, 32% and 18% at pH 5, 7 and 9, respectively. The kinetic results revealed the impossibility of povidone-iodine releasing via diffusion/erosion for further support of the hypothesis of releasing via swelling process. Moreover, the release of povidone-iodine using column technique showed that the lowest release was estimated at using high rate of 6 mL/min. Besides the biocompatibility and biodegradability of the prepared Cu-L-AA@CMS composites, it showed the superiority for controllable release of povidone-iodine antiseptic reagent to regulate its beneficial effect in curing of the skin.

Keywords CMS, Cu, L-aspartic acid, Povidone-iodine, Controllable releasing, Kinetic

Introduction

The chemical modification of starch is carried out to overcome the shortcoming of pristine starch, such as: non-solubility in cold water, hard controlling for the viscosity after gelation, turbidity of aqueous solution/gel or the affinity for the retrogradation. The carboxymethyl starch (CMS) is known to be wide-scaled produced for many years. CMS is ascribed as an anionic starch derivative to be categorized as a biopolymer with superior performance in pharmaceutical, medical, cosmetic industry, food industry, environmental and many other industrial purposes [1]. The viscosity, rate of dissolution, clarity, film forming affinity, gelation temperature, pH and storage stabilization of CMS are extensively identified

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in dependent on the degree of substitution (DS) [2–5]. Commonly, CMS often is represented with a low DS value up to ca. 0.3. Some of the referred CMS properties can be substantially improved by increment the value of DS [1, 5]. Aspartic acid, or "aspartate," is known as a non-essential amino acid that is produced and exploited by the human body in two enantiomers; L-aspartic acid and D-aspartic acid. The L-configuration of amino acids is the dominant enantiomer that is applied in the protein production; thus, L-aspartic acid is by far the more common form. Whereas, D-aspartic acid is one of two well-known D-amino acids that is biosynthesized via the eukaryotes. L-aspartic acid is applied in biosynthesis protein and neurotransmission, also, D-aspartic acid is accompanied with the neurogenesis and the endocrine systems [6–8].

In addition to the bio-functionality of aspartic acid, it is widely applied in the food production, cosmetics, beverage industry, pharmaceutical production, and agricultural purposes [9]. Moreover, L-aspartic acid is exploited as a nutritional additive in both foods and beverages industries, but its primarily applied in combination with phenylalanine to prepare aspartame, that is applied as an artificial sweetener [10]. Aspartic acid is also applied for bolstering the immune functionalization and as a natural additive for the depression [9]. Its affinity for acting in the production of energy, resistance to fatigue, synthesis of RNA and DNA, and detoxification of liver makes it be broadly applied in the clinical purposes [9]. Moreover, it is applied as an intermediary additive in manufacturing of pharmaceutics and organic reagents, that serve as a building unit for active pharmaceutical component [9]. The utility of aspartic acid extensively increased with the consideration of its derivatives such as acetyl aspartic acid, that is used as an active component in the anti-aging cosmetic reagent that is targeting the wrinkle, skin lift, and firmness losing [11]. Also, aspartic acid is successfully applied for the production of poly-aspartic acid, that is superiorly act as a fertilizer synergist to increase the nitrogen absorption and crop yield [8]. Moreover, poly-aspartic acid hydrogel is a biodegradable super absorbent with exceptional water holding ability and is applicable in manufacturing of various amenities like engineered tissues, diapers and feminine products [12]. The ranging and deepness for the applicability of aspartic acid, particularly L-enantiomer, that has placed it on "the Department of Energy's Top Value Added Chemicals" from the biomass list [10].

Owing to the broad spectra of antibiotics, the antiseptic reagents could be considered as alternative to antibiotic reagents [13]. Povidone-iodine is a complex of iodine and povidone and that could be identified as one of highly reactive antiseptic laborer [14–16]. Povidone-iodine is known to be highly active against different pathogenic strains such as gram-negative and gram-positive bacterial species, fungi, protozoa and different viruses such as H1N1 influenza virus [14, 17]. Povidone-iodine (10%) is ascribed as a first antiseptic reagent for the treatment of skin infections and wound healing [17–19]. On the other hand, the deep and intense wound is known to take a long time for healing and burning with irregular in shape are difficult to be treated. There is still no suitable remedy for paining relief within wound dressing, and the marks that are seen on the skin after the wound healing are still unfavorable. Zhang et al. investigate the self-healing nanocomposites that were made of the wound centers, then quickly transported into an integrated hydrogel that could fill the wound site and could be separated, and eventually painless remove the wound site by the dissolution it in amino acids [20, 21]. Few reports were interested in preparation of hydrogels based on polysaccharides for controllable release of povidone-iodine. It was depicted that bio-macromolecular wound-dress based on sodium and potassium alginate was applied for controlled releasing of povidone-iodine [22]. Another report was interested in the synthesis of hydrogels of "carboxy-methyl cellulose/polyvinyl alcohol/gelatin" and cross-linked polyacrylamide to be exploitable for wound healing with controllable release of povidone-iodine [23]. Emam et al., investigated the control releasing of povidone-iodine from networked hydrogel based on pectin/carboxymethyl pullulan [24]. In another study [25], bioelastomer based on starch was also successfully applied for regulating the release of povidone-iodine. Immobilization of chitosan within poly-vinyl pyrrolidone for manufacturing of wound dress with controllable release of povidone-iodine was also reported [26]. Additionally, wound dress based on bacterial cellulose was most recently exploited for controllable releasing of povidone-iodine [27].

According to the above-mentioned information, the requirement of controllable release for antiseptic reagents is extensively considered for the wound-healing purpose. The represented approach is designed for exploiting the advantageous characters in combination for both CMS and L-aspartic acid in the form of Cu-L-AA@CMS composite for controllable release of povidone iodine. Cu-L-AA@CMS composite was primarily synthesized via coordinative interaction between copper as central metal and L-AA & CMS as ligands. The chemical composition and topographical features of Cu-L-AA@CMS composite were investigated via infrared and scanning microscope, energy dispersive X-ray. The release behavior of Povidone-iodine from the synthesized Cu-L-AA@CMS composites was systematically studied at different pH. The kinetic parameters for the controllable release were estimated via different models and the mechanism of release with the aid of Cu-L-AA@CMS composite was predicted according to the represented data.

Experimental session

Materials

Corn starch [$(C_6H_{10}O_5)n$, from Sigma-Aldrich], Mono-chloro-acetic acid [$ClCH_2COOH$, ≥99%], Copper nitrate [$Cu(NO_3)_2.3H_2O$, ≥99.5%], L-aspartic acid [$HO_2CCH_2CH(NH_2)CO_2H$, L-AA], Sodium hydroxide [NaOH, pellets, ≥97.0%], 2-propanol [C_2OH_7, 99.9%] and Povidone-iodine (PI, 10%), Poly(vinylpyrrolidone)–Iodine complex [povidone-iodine, PVP-I, $C_6H_9ONI_2$] were all purchased from Sigma-Aldrich and were all used as received.

Methods

Synthesis of CMS

The carboxymethylation reaction of starch was performed in an organic-aqueous medium as reported in literature [24, 28]. In brief, 10 gm of starch was mixed with 30 mL of 2-propanol in round flask with two-necked and then the flask equipped with the mechanical stirrer. The mixture was stirred for 20 min at room temperature for good dispersion, followed addition of 20 mL of an NaOH solution (2 M) drop wisely and the reaction is proceeded under stirring for an additional 30 min. Afterwards, 25 g of monochloroacetic acid was added step-wisely and the temperature of reaction mixture was raised to 70 °C under continuous stirring. After 5 h, the obtained carboxymethyl starch (CMS) was collected by centrifugation at 5000 rpm for 15 min, followed by neutralization. At the end, the obtained CMS was lyophilized prior to using.

Synthesis of Cu-L-AA@CMS composite

In 100 mL beaker there were 1.0 g of L-AA that dissolved in 50 mL of double-distilled water (DDw) at 500 rpm stirring with occasional addition of 1 M NaOH solution. L-AA was completely dissolved, then the pH of solution was adapted up to 7.0, using 1 M HCl solution. 1 g CMS was added to above solution. Then, the aqueous solutions of Cu (II) nitrate containing stoichiometrically 1:1 mol ratio of Cu (II) ions with respect to L-AA were added dropwise into different L-AA solutions at pH 7 and stirred at 750 rpm till mixing for 12 hours. Therefore, blue coloured solid assemblies that formed during the reaction were filtered and washed sequentially with water, water-ethanol (1:1 v/v), and water, then dried and stored in closed tubes until further usage.

Characterization and analysis

The chemical composition of the synthesized CMS, Cu-L-AA and Cu-L-AA@CMS were investigated via FTIR "attenuated total reflection-Fourier transform infrared spectroscopy, ATR-FTIR, Jasco FT/IR 6100", that is in connection with "a detector of deuterated triglycine sulfate; TGS" and the accessories "ATR unit with Golden Gate diamond crystal". The absorption spectral data were detected at 500–4000 cm^{-1}, using "resolution of 4 cm^{-1} with 1 cm^{-1} scanning interval and smoothed with 15 points". Geometry and topographical features of the prepared Cu-L-AA@CMS composites were identified via the microscopic images of "high resolution scanning electron microscopy; HRSEM, SEM Quanta FEG 250 with field emission gun, FEI Company – Netherlands". The elemental composition of the prepared samples was also identified via the collected data of "surface Energy dispersive X-ray spectroscopy; EDX, EDAX AMETEK analyzer", that is connected to the microscope. The change in the crystallinity degree due to the coordinative complexing of CMS with Cu-L-AA was identified via the collected data of "diffraction of X-ray; XRD, using X'Pert MPD diffractometer; Philips". The diffraction angle (2θ) was estimated at ambient conditions (3.0° – 60.0°), via "Cu as monochromator; Kα X-radiation and λ = 1.5406 Å".

Povidone-iodine loading

Typically, 42.0 mg of Povidone-Iodine was put into 100 mL of ultra-pure water and left to dissolve in an ultrasound bath for 40 min. Then 70 mg of CMS, Cu-L-AA(10%)@CMS, Cu-L-AA(20%)@CMS and Cu-L-AA(30%)@CMS were added to the above flask. The reaction flasks were covered with aluminum foil to eliminate any photo-induced reactions and placed on stirring plates to keep the sample immersed. To determine the percentage of the pesticide loaded onto the samples, the pesticide concentration that remained in the solution was measured with UV-VIS spectrometer (shmiadzu pc 2400) multiple times during the incubation period.

Povidone-iodine release

Various samples of MCS, Cu-L-AA(10%)@CMS, Cu-L-AA(20%)@CMS and Cu-L-AA(30%)@CMS, with povidone-iodine were incubated at 37 °C under different pH conditions (phosphate-buffered saline (PBS), pH 5, pH 7 and pH 9). The speed of vibration of the used shaker was set as 100 rev/min at constant-temperature. The released solution (1.0 mL) was removed from the dissolving medium at predetermined intervals and replaced with an equivalent volume of fresh PBS solution. UV-visible spectrophotometer was used to measure the pesticide release quantity. Five rounds of each release experiment were conducted.

Mathematical modelling of povidone-iodine release

In order to suit the release profiles, three phases were identified based on the slopes of the profiles. These stages included the Higuchi, Ritger-Peppas, zero-order, and first-order equations. For each release profile, Origin software was used to fit a linear or nonlinear curve. The cumulative release percentage at time *t* is defined as.

$$Q_t=(M_t/M_\infty)\times 100\% \quad \text{Eq. (1)}$$

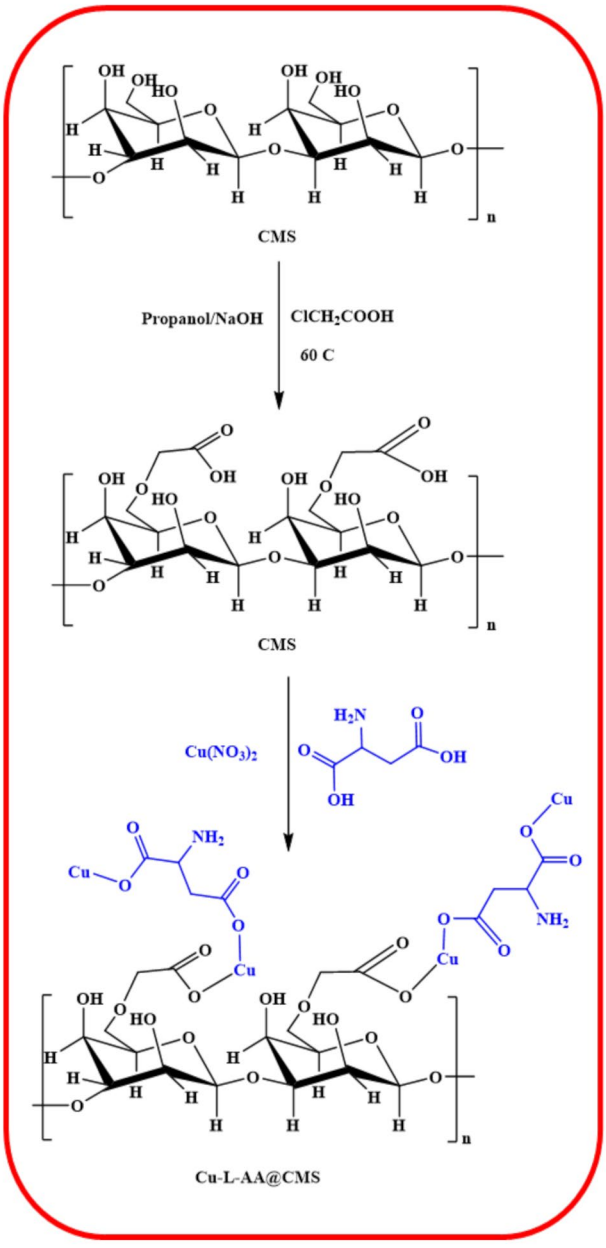

Fig. 1 Preparation scheme of Cu-L-AA@CMS composite

where M_t is the cumulative amount of pesticide released at time t and M_∞ is the total amount released.

Model	Equation	Parameters
Zero-order	$Q_t = Q_0 + k(t - t_{0)}$	Q_t, k, t
First-order	$Q_t = Q_0 + (1 - e^{-k(t-t_0)}$	Q_t, k, t
Higuchi	$Q_t = Q_0 + k(t - t_0)^{1/2}$	Q_t, k, t
Kormeyer–Peppas	$Q_t = kt^n$	Q_t, k, t, n

Column experiments

Using prepared materials, a column descendant flow reactor was used to conduct the release investigation. The column had 43 mL capacity and measured 3×60 mm. First, a column containing 100 mg of pesticide-containing samples was added. Next, 100 milliliters of ultrapure water were fed straight from the top of the column at varying flow rates of 2, 4, and 6 milliliters per minute at room temperature and neutral pH.

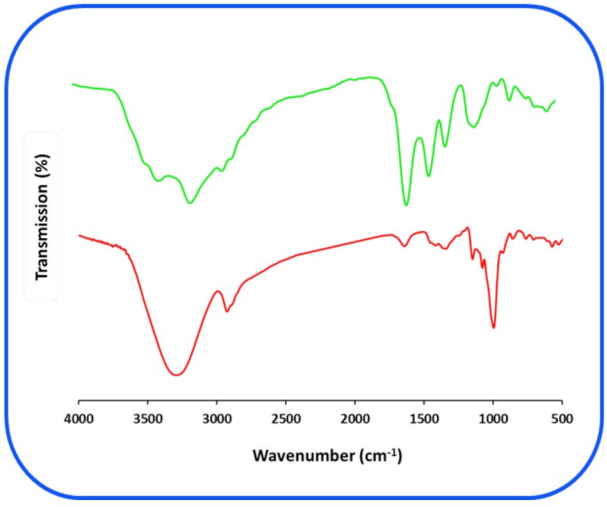

Fig. 2 Infrared spectra for the synthesized CMS

Results and discussion

Synthesis of Cu-L-AA@CMS composite

The reaction mechanism for synthesis of Cu-L-AA@CMS from CMS and L-AA was schematically presented in Fig. 1. It could be hypothesized that, carboxymethylation of starch was supposed to be performed via the interaction of native starch with chloro-acetic acid, while, electrophilic substitution reaction is supposed to take a place on the terminal hydroxyl groups (C6) on the glucose building units of starch. Afterwards, copper nitrate was exploited as a copper precursor for coordinative interaction with CMS & L-AA to prepare the as-required Cu-L-AA@CMS composite, whereas, both of bidentate CMS (carboxyl and hydroxyl groups) and tridentate L-AA (carboxyl, hydroxyl and amino groups) acted as superior and ligands with highly accessible chelating groups.

FTIR spectral mapping

Infrared spectral maps were analyzed for starch before and after carboxymethylation in order to show the chemical changing attributed to the chemical modification with interaction with chloroacetic acid, while, the collected FTIR spectral data were represented in Fig. 2. Native starch is shown with characteristic absorbance bands at 3292, 2903, 1627, 1393/1307 and 997 cm^{-1}, referring to OH stretching, aliphatic asymmetric stretching CH_2, O-C-O stretching, C-O stretching and OH bending, respectively [29–31]. On the other hand, all of

the observed bands of were retained with blue shifting owing to carboxymethylation, however, the characteristic bands of OH & CH_2 aliphatic were observed with lower intensity, in contrast to the corresponding bands of O-C-O & C-O were shown with higher intensity. In addition to, a new specific band was estimated at 1579 cm^{-1} that is characteristic for C=O. Therefore, it could be depicted that, FTIR spectral data could confirm the successive carboxymethylation of starch under the performed conditions in the current approach [32].

SEM & EDX data

The topographical features of Cu-L-AA@CMS composites prepared with different percent of L-AA can be identified from the microscopic images in Fig. 3. From the plotted micrographs, it could be clarified that, rod-like structures were viewed in Fig. 3a for Cu-L-AA@CMS composite prepared with 10% L-AA. Whereas, increment of L-AA percentage up to 20% (Fig. 3b) & 30% (Fig. 3c) was reflected in denser masses to be seen in the microscopic images. This could reflect the superior affinity of L-AA as a tridentate chelating agent for clustering of denser masses of the as-demanded composite. On the other hand, the estimated data of the elemental analysis of EDX reflect that, regardless to the L-AA percentage, the significant signals of carbon, nitrogen, oxygen and copper were obviously estimated that is corresponds to the chemical composition of the as-prepared Cu-L-AA@CMS composites.

Controllable release of povidone-iodine

Povidone-iodine is well-known to be highly applicable antiseptic reagent for treatment of skin infections, however, its controllable release is highly demanded for regulation and maximizing its benefit. Herein, the affinity of Cu-L-AA@CMS composite as a supporting template for controllable releasing of povidone-iodine was monitored and approved at different pH. Figure 4 represents a schematic diagram for the affinity of Cu-L-AA@CMS composite as a supporting template for successive uploading of povidone-iodine via dipole-dipole interaction of iodine with copper as a central metal in Cu-L-AA@CMS composite. The release of povidone-iodine was estimated by in mg/g and by percentage (%). Figure 5 represents the plotted data for the efficiency of Cu-L-AA@CMS composites in accordance to the percentage of L-AA, to act as a supporting template for uploading povidone-iodine. The data showed that, increment of the percentage for L-AA in the prepared Cu-L-AA@CMS composite resulted from 10 to 20% and up to 30%, was reflected in more efficient loading of povidone-iodine, as the estimated data of uploading efficiency percentage were 48%, 68% & 95%, respectively. This could be attributed to the superior effect of higher percentage for L-AA (30%) as a tridentate chelating agent in successive clustering of dense masses for Cu-L-AA@CMS composite to act in uploading of higher amounts from povidone-iodine as previously mentioned in the interpretation of microscopic data. Figure 6b, c& d represents the estimated data for releasing efficiency percentage

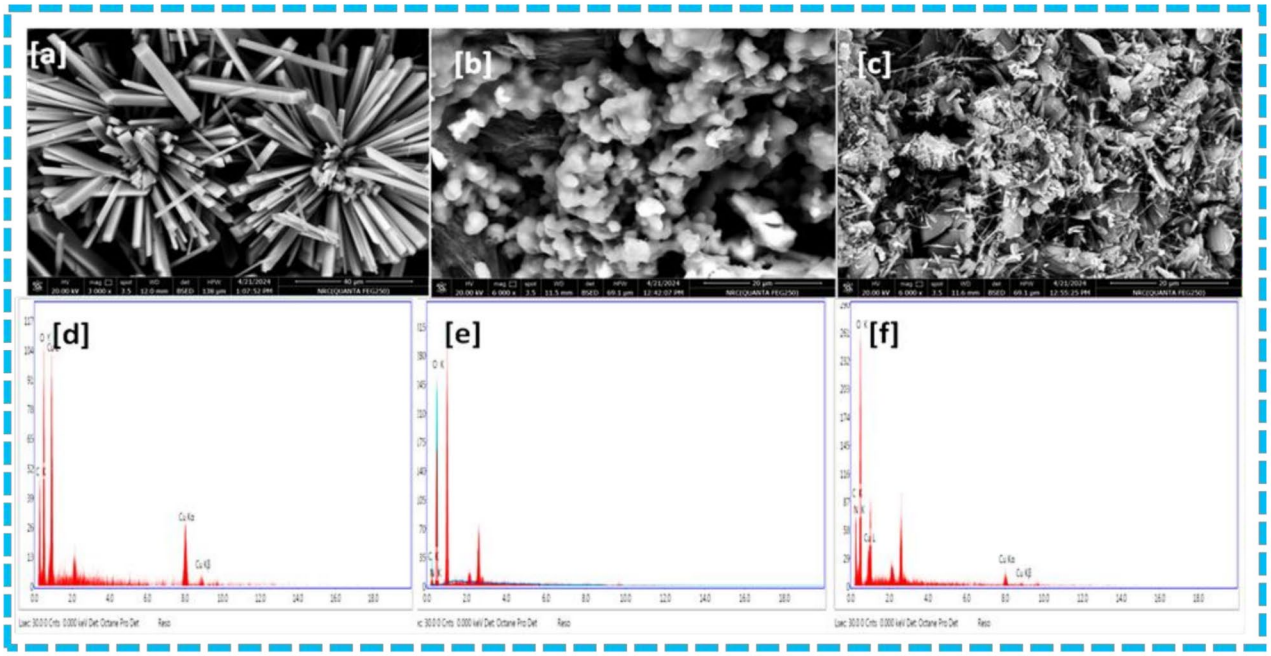

Fig. 3 Micrographs and EDX analysis for the synthesized Cu-L-AA@CMS composite; [**a**] Cu-L-AA(10%)@CMS, [**b**] Cu-L-AA(20%)@CMS and [**c**] Cu-L-AA(30%)@CMS

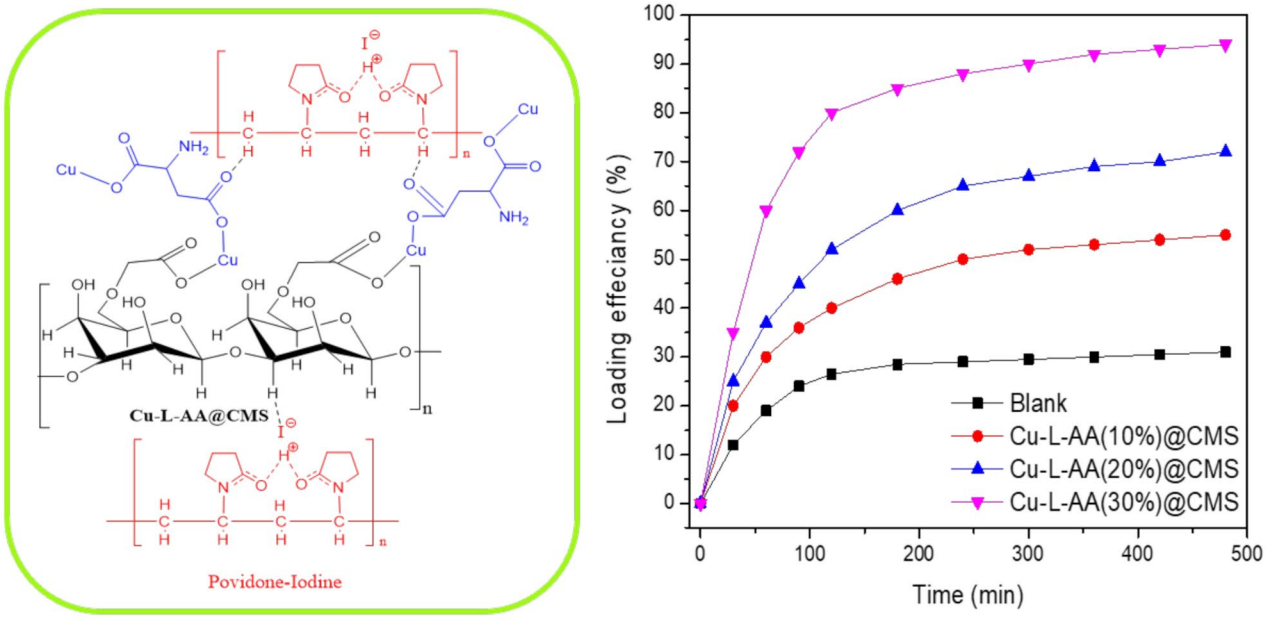

Fig. 4 Loading of povidone-iodine onto Cu-L-AA@CMS composite

of Cu-L-AA@CMS composites at different pH, to show that, for all of the examined Cu-L-AA@CMS composites, the release efficiency percentage was not significantly affected by changing pH from 5 (Cu-L-AA(30%)@CMS; release efficiency percentage 27%) to 9 (Cu-L-AA(30%)@CMS; release efficiency percentage 29%), however, it was observably decreased in case of pH 5. Moreover, regardless to pH conditions, Cu-L-AA(30%)@CMS composite shows the highest efficiency for controllable release of povidone-iodine, whereas, release efficiency percentage was estimated to be 58%, 32% &18% at pH 5, 7 &9, respectively.

Kinetic and releasing mechanism

The release of povidone-iodine from the synthesized Cu-L-AA@CMS composites was kinetically reported to predict the releasing mechanism. In this approach, two kinetic models were studied for releasing of povidone-iodine including zero order, first order, Higuchi, and Korsmeyer-Peppas, as shown in Fig. 6. For zero & first ordered kinetic model, log of povidone-iodine release percent in the as-prepared composites was plotted versus the releasing time (Fig. 6a **& b**). In case of Higuchi model, the povidone-iodine release percentage was figured out with the square root of release time (Fig. 6c).

Figure 6d represents the data derivatized from Korsmeyer-Peppas model, whereas, log of povidone-iodine release amount is plotted with log of time. All of the kinetic key factors for all models (k_1, k_H, n, k_{kp} and R^2) were estimated and tabulated in Table 1. From the estimated data in Table 1, the liberation of povidone-iodine from the used composites fits to the first ordered model and Cu-L-AA(30%)@CMS was shown the favorable fitting, due to the best linearity with the highest estimated coefficients correlation (R^2=0.97). This fitting shows that povidone-iodine release is mostly dependent on the amounts of povidone-iodine uploaded onto the applied composite.

The estimated data of the release rate constant (k_1) approved that; releasing of povidone-iodine from Cu-L-AA(30%)@CMS (3.28×10^3 min^{-1}) is significantly faster than that from Cu-L-AA(10%)@CMS (3.48×10^3 min^{-1}) and CMS was exhibited with the fastest rate of release (3.67×10^3 min^{-1}) for povidone-iodine. Releasing of povidone-iodine was closer to Higuchi model ($R^2\geq0.88$), that indicates the rational inert rate of dispersion at longer release duration, referring to the square root of releasing duration [33, 34]. By comparing with the estimated parameters of Cu-L-AA(30%)@CMS, Higuchi rate contestant (K_H) for Cu-L-AA(20%)@CMS are considerably higher. Cu-L-AA(30%)@CMS showed the lowest K_H (2.21 $mg.min^{-0.5}$) which affirmed its slowest dispersion rate at longer duration. Moreover, the collected results were demonstrated a quite well-fitting to Krosmeyer-Peppas modelling ($R^2\geq0.95$) and the evaluated exponential *n* values for Cu-L-AA@CMS were in range of 3.44–3.31.

Figure 7 also represents the studying of release percentage of povidone-iodine from the applied composites using column technique in different rates (2 mL/min, 4 mL/min & 6 mL/min), whereas, Fig. 7a, b and c are plotted for the estimated by exploiting Cu-L-AA(10%)@CMS, Cu-L-AA(20%)@CMS and Cu-L-AA(30%)@CMS. The plotted data showed that, regardless to the type of the

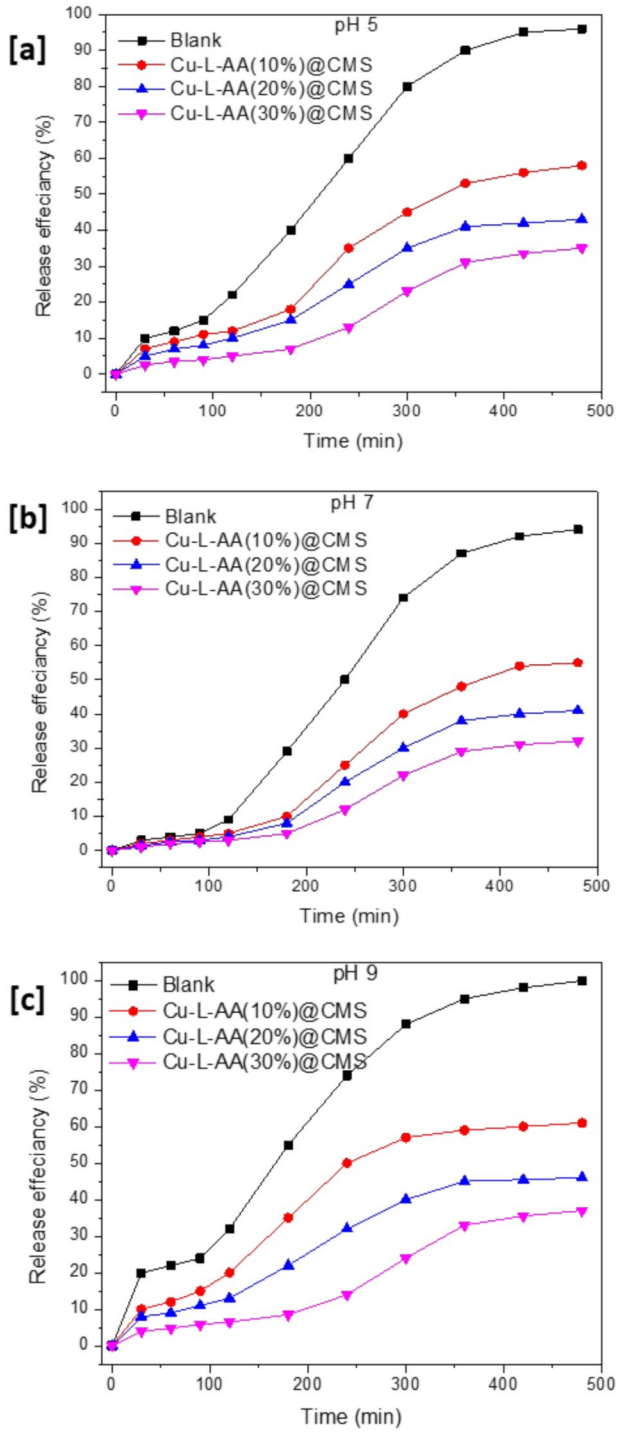

Fig. 5 Release of povidone-iodine from Cu-L-AA@CMS composite at different pH; [**a**] at pH 5, [**b**] at pH 7 and [**c**] at pH 9

exploited composite, the lowest values of release percentage were estimated at rate of 6 mL/minutes. Moreover, after 500 min, the lowest release percentage of povidone-iodine was evaluated at 6mL/minutes using Cu-L-AA(30%)@CMS to be 14%, while, Cu-L-AA(10%)@CMS is shown with the double value of release percentage compared to that of Cu-L-AA(30%)@CMS (28%).

In accordance to literature [35], the mechanism of releasing for any material from a certain polymeric network may be performed through either chemical or physical pathway "solute diffusion, degradation of material or swelling of polymer matrix". Povidone-iodine was supposed to be formerly diffused within the matrix of the as-exploited Cu-L-AA@CMS composite via physical deposing within the network pores that suggested the release mechanism to be more relevant for the composite swelling. Whereas, the central copper of the exploited composite could be chemically bonded with povidone via dipole-dipole interaction [36–38]. Therefore, the mechanism of povidone-iodine release from the prepared composite was hypothesized to be physically proceeded. The significant difference in the release of povidone between the three prepared composites confirmed the superior role of L-AA in preparation of more efficient composite for the most controllable affinity of povidone-iodine release. The lowest estimated value of releasing percentage for Cu-L-AA(30%)@CMS affirmed this hypothesis. Moreover, *n* values in Krosmeyer-Peppas model (3.44–3.31) can assign for the impossibility of povidone-iodine releasing via diffusion/erosion [35, 39] to be further supporting the hypothesis of releasing via swelling process. In summarization, the slowest release of povidone-iodine from Cu-L-AA(30%)@CMS was obtained to achieve the controllable release process.

Conclusion

Currently, Cu-L-AA@CMS composite was prepared to be successfully exploited in controllable release of povidone iodine. Cu-L-AA@CMS composite was primarily synthesized via coordinative interaction between copper as central metal and L-AA & CMS as ligand. Three composites with different percentage of L-AA (10%, 20% & 30%) were currently prepared for studying the effect of L-AA on the affinity of the prepared composite for controllable release of povidone-iodine. The chemical composition and topographical features of the prepared Cu-L-AA@CMS composites were investigated via infrared and scanning microscope, energy dispersive X-ray. The release behavior of povidone-iodine from the synthesized Cu-L-AA@CMS composites was systematically studied at different pH. For all of the examined Cu-L-AA@CMS composites, the release efficiency percentage was not significantly affected by changing pH from 5 (Cu-L-AA(30%)@CMS; release efficiency percentage 27%) to 9 (Cu-L-AA(30%)@CMS; release efficiency percentage 29%), however, it was observably decreased in case of pH 5. Moreover, regardless to pH conditions, Cu-L-AA(30%)@CMS composite showed the highest efficiency for controllable release of povidone-iodine, whereas, release efficiency percentage

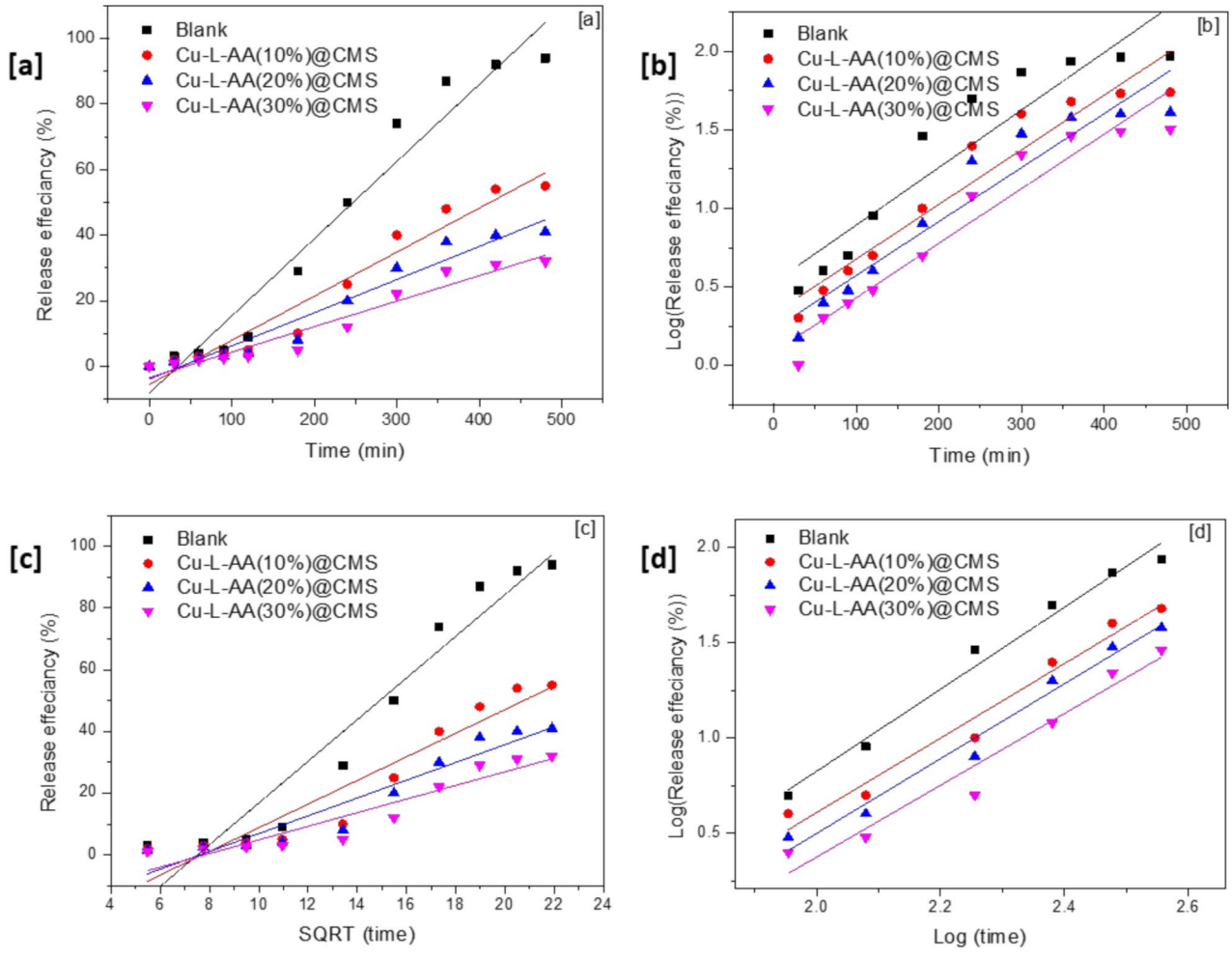

Fig. 6 Kinetic of povidone-iodine from Cu-L-AA@CMS composite; [**a**] zero order, [**b**] first order, [**c**] Higuchi model and [**d**] Korsmeyer-Peppas model

Table 1 Pparameters of the release Kinetic of povidone-iodine from Cu-L-AA@CMS composite

Sample	Parameter	Blank	Cu-L-AA(10%)@CMS	Cu-L-AA(20%)@CMS	Cu-L-AA(30%)@CMS
Zero order	$K_0 \times 10^3$ (mg.min^{-1})	235.26	134.30	101.09	77.61
	Q_0 (mg)	8.12	5.47	3.9	3.4
	R^2	0.95	0.92	0.95	0.91
First order	$K_1 \times 10^3$ (min^{-1})	3.67	3.48	3.44	3.28
	Q_1 (mg)	0.53	0.33	0.23	0.08
	R^2	0.97	0.97	0.98	0.97
Higuchi	K_H (mg. min$^{-0.5}$)	6.75	3.83	2.88	2.21
	R^2	0.93	0.90	0.91	0.88
Korsmeyer-Peppas	K_k (min^{-n})	2.16	1.96	1.92	1.88
	n	3.49	3.44	3.40	3.31
	R^2	0.98	0.97	0.97	0.95

was estimated to be 58%, 32% &18% at pH 5, 7 &9, respectively. The kinetic parameters for the controllable releasing were estimated via different models and the mechanism of releasing with the aid of Cu-L-AA@CMS composite was predicted according to the represented data. The data revealed that; increment in the percentage of L-AA was reflected in clustering of dense masses from the desirable composite with highly crystalline/stable structural network. Moreover, the significant difference in the release of povidone between the three prepared composites confirmed the superior role of L-AA in preparation of more efficient composite for the most controllable affinity of povidone-iodine release. The lowest estimated value of release percentage for Cu-L-AA(30%)@CMS affirmed this hypothesis. Moreover, *n* values in Krosmeyer-Peppas model (0.049–0.077) can assign for the impossibility of povidone-iodine release via diffusion/erosion for further support to the hypothesis of releasing via swelling process. In summarization, the slowest release of povidone-iodine from Cu-L-AA(30%)@

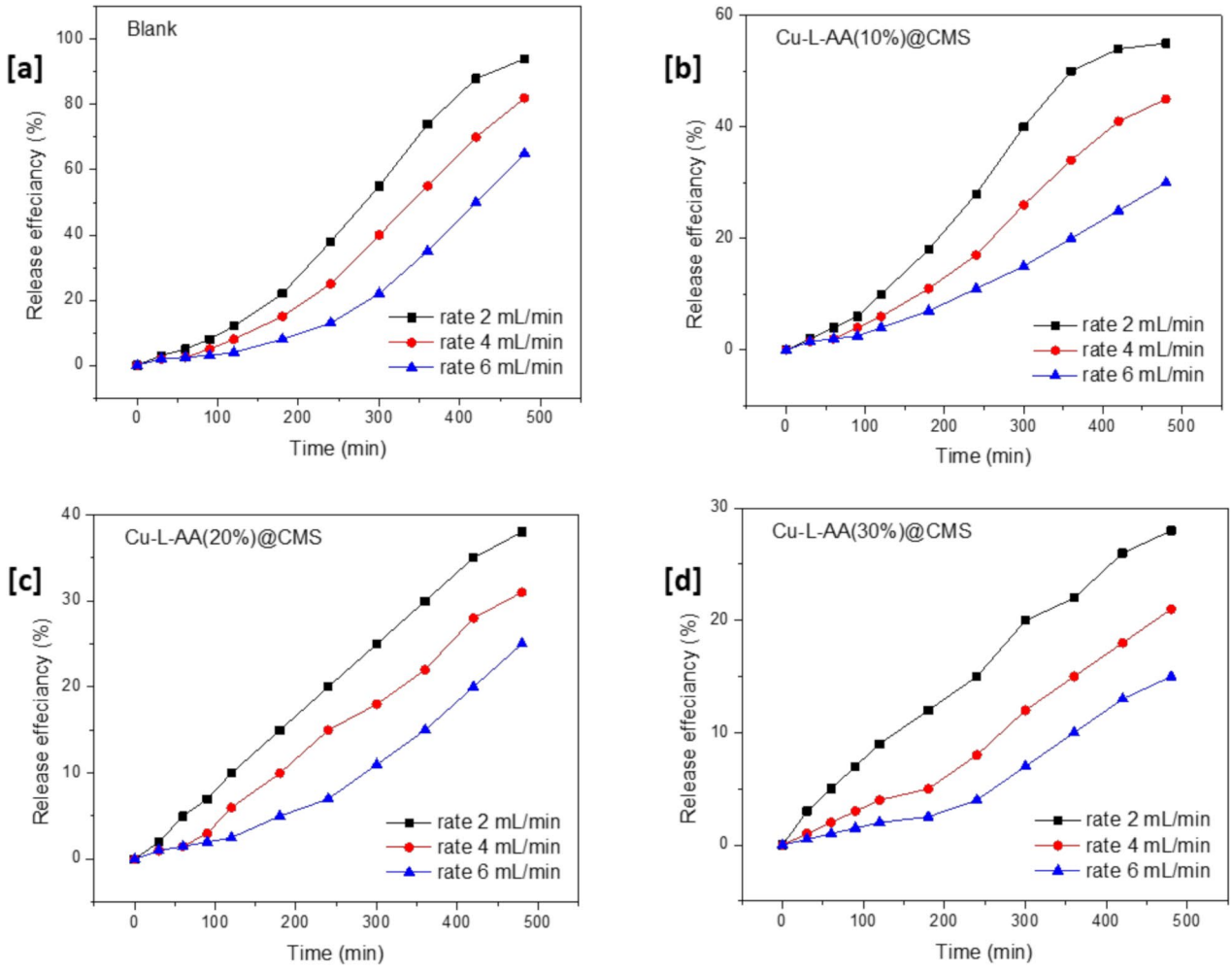

Fig. 7 Release of povidone-iodine from Cu-L-AA@CMS composite using column through different rates; [**a**] blank, [**b**] Cu-L-AA(10%)@CMS, [**c**] Cu-L-AA(20%)@CMS and [**d**] Cu-L-AA(30%)@CMS

CMS was obtained to achieve the controllable release process. Beside the biocompatibility and biodegradability of the prepared composites, it showed the superiority for controllable release of povidone-iodine antiseptic reagent to regulate its beneficial effect in the skin curing. The controllable release behavior of the prepared composite makes it advantageously applicable for drug delivery systems for other skin surficial purposes.

Author contributions

Moataz Morad, Seraj O. Alzahrani: Conceptualization, Methodology, Software, Writing- Original draft preparation. Albandary Almahri, Ibrahim S. S. Alatawi: Data curation, Writing- Original draft preparation. Formal analysis, Investigation. Kamelah S. Alrashdi, Kholood M. Alkhamis, Hatun H. Alsharief: Formal analysis, Investigation, Software, Validation. Writing- Reviewing and Editing. Nashwa M. El-Metwaly: Supervision; Revision.

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Data availability

All relevant data are within the manuscript and available from the corresponding author upon request.

Declarations

Ethical approval

Not applicable.

Consent to participate

All authors participated directly in the current research work.

Consent to publish

The authors agree to publish the article under the Creative Commons Attribution License.

Competing interests

The authors declare no competing interests.

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