Synthesis And Characterization Of Fe^0 @Chitosan/Cellulose Green Nanocomposite As Advanced Carrier For Ibuprofen Drug; Loading And Release Properties

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Research Article

Keywords: Zero-valent iron, Chitosan, Cellulose, Green nanocomposite, Ibuprofen carrier

Posted Date: March 3rd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1382820/v1>

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Abstract

Green nanocomposite of Fe^0 @chitosan/cellulose (Fe^0 @CH/CS) was synthesized utilizing the green extract of khaya senegalensis leaves and sugarcane bagasse as cellulose precursor. The composite was evaluated as an effective carrier for ibuprofen drug (IBF) considering its release and loading properties. The Fe^0 @CH/CS is of significant IBF loading capacity (553 mg/g) and the loading behavior can be directed by the values of the experimental variables. The loading of IBF into Fe^0 @CH/CS is in agreement with the classic Langmuir isotherm ($R^2 > 0.95$) and Pseudo-first order kinetic ($R^2 > 0.97$). This displays homogenous, physisorption, and a monolayer loading of IBF into Fe^0 @CH/CS. Based on the findings of the Monolayer model with one energy as advanced isotherm model, the Fe^0 @CH/CS structure is of 252.6 mg/g active receptors density and each receptor was occupied by two or three IBF ions ($n=2.18$) by multi-molecular mechanism. The determined IBF loading energy (4.81 kJ/mol) demonstrates the physical loading of the drug by Van-der Waals forces and/or hydrogen bonding. The Fe^0 @CH/CS structure is of significant release profiles as carrier for IBF which continued up to 260 h (gastric buffer) and 180 h (intestinal buffer). The studied release kinetics and the obtained diffusion exponent (0.58 (pH 1.2) and 0.48 (pH 7.4)) reflect the release of IBF from Fe^0 @CH/CS by complex diffusion and erosion mechanisms. The cytotoxicity tests declared the safe and biocompatible value of both Fe^0 @CH/CS and IBF loaded Fe^0 @CH/CS on the human bronchial epithelial cells.

1. Introduction

Inflammation as a health term refers to the biological responses of the organisms when affected by the different species of infections which commonly resulted in high damage impacts as compared to the essential infects [1, 2]. Several species of drugs were applied as anti-inflammation drugs including ibuprofen, azithromycin, and levofloxacin [3, 4]. Ibuprofen ($\text{C}_{13}\text{H}_{18}\text{O}_2$; IBF) is considered a long-term non-steroidal anti-inflammatory and antipyretic drug [5]. It is used for analgesic symptoms of pain and a variety of rheumatoid arthritis and musculoskeletal in addition to its value as medication for acute pain and fever for the children [5, 6]. The application of IBF suffers from some problems which are related to its low solubility, short half-life, low bioavailability, high permeability, and fast degradation [7]. Moreover, the overdosages are of certain adverse effects including nausea, dyspepsia, and diarrhea in addition to the gastrointestinal toxicity of its chemical structure [8]. It has a significant negative effect on the gastric mucus and reduces its resistance to acidic conditions in addition to its side effects on gastric and mucosal protective agents [9].

The interested researcher did their best to develop a new effective drug delivery system to enhance the release percentage, solubility, stability, bio-distribution properties, and specificity of the drug [9, 10]. This can reduce its hazardous side effects, improve therapeutic efficiency, and enhance patient compliance [8, 10, 11]. The properties which were recommended for the effective carriers are the significant biocompatibility, chemical inertness, mechanical strength, and high loading capacities in addition to the low fabrication cost [1, 12]. Therefore, developing enhanced IBF delivering systems to control the released

percentage and keep the drug concentration at the safe level was recommended strongly in the later periods [5, 9, 13]. Recently several products were assessed for this target as hydroxyapatite, MCM-41, titanium alloy, MOFs, biopolymer-based composites, and montmorillonite [8, 9, 13].

The natural polymer which can be extracted from the bio-resources as plants (starch, chitosan, and cellulose) and animal (collagen, albumin, and gelatin) were studied extensively as natural biopolymers of significant medical and health applications [14, 15, 16]. Such polymers are of excellent biocompatibility, chemical safety, availability, reactivity, and chemical affinities for the organic structures of the drug [12, 17, 18]. Among such biopolymers, cellulose and chitosan attracted great attention as promising materials in several industrial and medical industries [9, 19]. Cellulose is a known type of natural polysaccharide biopolymer composed structurally of anhydroglucose rings which are connected chemically with each other by β -1, 4 glycoside bonds [12, 20]. Cellulose is of significant availability as it is a valuable component in numerous green plants, agricultural wastes, and biomasses which can be extracted by facile and low-cost methods [21]. Technically, cellulosic materials are low-cost, non-toxic, stable, biocompatible, highly reactive, biodegradable, and highly heat resistant materials [17, 19, 22]. Additionally, it exhibits high chemical flexibility to be modified or integrated into numerous varieties of composites either with organic or inorganic materials [17, 23].

Chitosan is also a well-known biopolymer that is an essential component for numerous environmental, medical, and pharmaceutical applications especially as a drug carrier [9, 15, 18]. Chitosan is polyaminosaccharide polymer that is of several technical advantages and can be produced easily from the chitin component in different biogenic sources [18]. Technically, the chitosan chains are of high safety, high bioactivity, and biodegradability in addition to their high mechanical and adsorption properties [9, 24]. The predicted integration between cellulose and chitosan in a composite can result in a hybrid structure of high reactivity, enhanced morphology, high loading capacity, and controlled loading behavior. Additionally, the possible functionalization of such a hybrid structure with metal oxide of green properties can induce the impact of the used drug and the loading capacity of the final structure.

Among the green fabricated metals and metal oxides, zero-valent iron (Fe^0) and Fe_2O_3 NPs were investigated as innovative materials for biomedical industries, drug delivery systems, tissue repair applications, and hyperthermia [23, 25]. Such nanoparticles are of good dispersion properties, high stability, significant biocompatibility, high biodegradability, and nontoxicity [25, 26]. Therefore, the presented study involved a novel synthesis of cellulose, chitosan, and Fe^0 heterostructure ($\text{Fe}^0\text{@CH/CS}$) green extract of *khaya senegalensis* leaves and sugarcane bagasse as cellulose precursor. The $\text{Fe}^0\text{@CH/CS}$ structure was characterized as a potential carrier for IBF drug of enhanced loading and release properties. The loading studies involved investigation for the effect of the experimental variables as well as the mechanism considering the kinetic, classic isotherm, advanced equilibrium, and thermodynamic studies. Also, the release profiles were addressed for about 260 h at different release buffers and the release mechanism was studied based on the kinetic release modeling.

2. Experimental Work

2.1. Materials

The studied raw cellulose was extracted from sugarcane bagasse. Sodium hydroxide pellets (> 98%), potassium hydroxide pellets (> 85%), sulfuric acid (98%), acetic anhydride (98%), and sodium hypochlorite (5%) (Sigma-Aldrich Egypt) were used during the extraction of cellulose. Chitosan powder was delivered a commercial polymer (MW 120,000; 85%) and glacial acetic acid (Sigma- Aldrich Egypt, 99.8%) was used as a solvent for chitosan. Ferric chloride (%) and liquid extract of *khaya senegalensis* leaves were used during the synthesis of green zero-valent iron (Fe^0). Ibuprofen drug (98% purity; Sigma-Aldrich Egypt) was applied during the loading and release tests.

2.2. Synthesis of the carrier

2.2.1. Extraction of cellulose

The commercial sugarcane bagasse (SB) was cut into small pieces and dried in an open environment. After that, the sample was ground using a home hand blender to be within the size range from 50 μm to 100 μm . Then, 500 g of SB was immersed within NaOH solution (18 N) for 2 h at 170 °C as starting step. This was followed with bleaching step using $\text{NaClO}_2/\text{CH}_3\text{COOOH}$ mixture (5% w/v) at 70 °C and pH 5 for an additional 120 min. Then the bleached product was neutralized by washing and transferred treated with KOH solution (4% (w/v)) for 1 h at 80 °C to get rid of hemicellulose. The alkaline treated product was neutralized and bleached again (5% $\text{NaClO}_2 + \text{CH}_3\text{COOH}$) at 70 °C for 2 h. This was followed with acid leaching step (30% H_2SO_4) at 45 °C for 1 h in the existence of the sonication waves producing cellulose enrich fibers.

2.2.2. Chitosan/cellulose composite (CH/CS)

The synthesis of chitosan/cellulose composite was performed by facile dispersion of the extracted cellulose fibrous (5 g) within a chitosan solution. The chitosan gel was prepared by dissolving 5 g of chitosan powder within diluted acetic acid (0.1 M). The cellulose/chitosan solution mixture was left for 24 h under stirring at 500 rpm. After that, the resulted hybrid cellulose/chitosan structure was isolated, washed with distilled water, and finally dried for 12 h at 60 °C.

2.2.3. Synthesis of Fe^0 @chitosan/Cellulose nano-composite (Fe^0 @CH/CS)

The obtained CH/CS particles were ground to be within size range from 10 to 25 μm . After that 3 g of the CH/CS fractions were dispersed within 100 mL of ferric chloride solution (3 M). As a parallel step, the green extract was produced by boiling the *Khaya senegalensis* leaves (20 g in 100 mL water) for 5 min and after cool down to room temperature was added to the ferric chloride mixture in the presence of CH/CS fractions. The final mixture was left under string for 48 h at room conditions before extracting the

solid by filtration. The extracted solids were washed with distilled water carefully and dried at 60 °C overnight to be applied in the next steps.

2.3. Characterization techniques:

The crystalline properties were addressed considering the XRD patterns of the chitosan and cellulose components and the synthetic composite (Fe⁰@CH/CS) using X-ray diffractometer (PANalytical (Empyrean)). The chemical composition and the structural functional groups were addressed considering the FT-IR spectra (Fourier Transform Infrared spectrometer (FTIR – 8400S)). The morphology of the produced structure and its internal properties were assessed considering the SEM (Scanning-Electron Microscope (Gemini, Zeiss-Ultra 55)) and HRTEM (Transmission-Electron Microscope (JEOL-JEM2100)) images, respectively. The surface area of the Fe⁰@CH/CS composite as well as its porous structure was studied based on its measured N₂ adsorption/desorption curve using Beckman Coulter surface area analyzer (SA3100 type).

2.4. Fe⁰@CH/CS as carriers for Ibuprofen drug

2.4.1. The loading properties

The properties of Fe⁰@CH/CS were assessed based on several experimental variables including the loading pH (pH 2 up to pH 8) interval (1 h up to 24 h), drug concentration (100 up to 900 mg/L), and the Fe⁰@CH/CS dosage (20 mg up to 100 mg). The homogenization between the drug solutions and the Fe⁰@CH/CS particles was conducted using a vortex rotator. After the equilibration interval of each loading test, the Fe⁰@CH/CS particles were separated by filtration using Whitman filter paper and the filtrate samples were collected to detect the rest of IBF in the solutions. The remaining concentrations of IBF after the loading tests were measured by UV-Vis spectrophotometer (λ (max) = 222 nm) to calculate the loading capacity based on Eq. 1 [21]. All the tests were completed in triplicate form and the evaluated results were inserted as average values with a standard deviation of less than 3.2%.

$$\text{Loaded drug (mg/g)} = \frac{(\text{Initial concentration} - \text{Residual concentration}) \times \text{solvent volume}}{\text{Carrier weight}} \quad (1)$$

2.4.2. In-vitro release studies

The release profile of Fe⁰@CH/CS as a carrier for IBF was studied using two types of buffers of different pH (pH 1.2 (Gastric fluid) and pH 7.4 (Intestinal fluid)). The release tests were conducted by mixing certain quantities of IBF-loaded Fe⁰@CH/CS (100 mg/g) within 500 mL of the studied buffers for a total release interval of 120 h. The homogenization process between the IBF-loaded Fe⁰@CH/CS particles and the buffers was accomplished by the DISTEK dissolution apparatus considering the rotating speed of the vessels at 200 rpm. After that, regular samples (5 mL) were extracted from the buffers at regular intervals to determine the diffused IBF molecules using a UV-Vis spectrophotometer (λ (max) = 222 nm). Then the

extracted samples were re-incorporated again into the bulk buffers to preserve the volume during the release process. The measured concentrations of the diffused IBF were applied to calculate the release percentages according to Eq. 2 considering the average values of the tests as triplicate tests with a standard deviation less than 2.8%.

$$\text{Drug release(\%)} = \frac{\text{The amount of Released IBF}}{\text{Amount of loaded IBF}} \times 100 \quad (2)$$

2.5. In Vitro Cytotoxicity

The cytotoxicity properties of Fe⁰@CH/CS and IBF-loaded Fe⁰@CH/CS were studied considering their effect on the human bronchial epithelial cells (NL20) (American Type Culture Collection (ATCC)). This was accomplished to assess the value of the product during the treatment and reduction of the cytokine effects within the bronchial epithelial cells. The test was conducted by immersion of the cell lines within Ham's F12 medium of different components (hydrocortisone (500 ng/mL⁻¹), glutamine (2 mM), epidermal growth factor (10 ng/mL⁻¹), amino acid (0.1 mM), transferrin (1 mg/mL⁻¹), 5 mg/mL⁻¹ insulin, FBS (4%), and 5 mg/mL⁻¹ insulin.). The studied cells after that were seeded for 24 h using 24-well culture plates and then incubated for another 24 h within the growth medium without serum. Then, regular dosages of Fe⁰@CH/CS and IBF-loaded Fe⁰@CH/CS were mixed with the media for an incubation period of 24 h. This was followed by the removal step for the used media and the treated cells were incubated again in fresh media for 4 h in the existence of resazurin (5%). As a final step, the cell viability at the different dosages was determined based on the fluorescence signals which were obtained after the addition of the dye considering the measurement conditions at 590 nm emission and 544 nm excitation. The detected variations in the measured values were used to determine the relative values of cell viability considering the value of the fresh cells as 100%.

3. Results And Discussion

3.1. Characterization of the carrier

3.1.1. XRD analysis

The structural properties of the synthetic Fe⁰@CH/CS were evaluated considering its XRD pattern in comparison with the patterns of cellulose and chitosan (Fig. 1). The cellulose substrate was recognized as crystalline cellulose with its common peaks at 2 Theta angles of 14.6° (1 $\bar{1}$ 0), 16.6° (110), 22.7° (200), and 34.6° (004)) JCPDS card no 00-056-1718) (Fig. 1A). The integrated chitosan as a single component exhibits the common peaks of semi-crystalline chitosan (9.91° and 20.22°) [18] (Fig. 1B). The obtained pattern of Fe⁰@CH/CS still shows reduced humps for the cellulose identification peaks and well-recognized peaks at about 44.8° (110) and 65.3° (200) which characterize the crystalline zero-valent iron

(JCPDS: 006-0696) (Fig. 1C). Additionally, a single reduced peak for magnetite was detected at about 56.2° (JCPDS no. 19-0629) reflecting partial oxidation of the Fe^0 particles and suggesting an effective role for the polymers matrix in reducing the oxidation process (Fig. 1C).

3.1.2. FT-IR analysis

The FT-IR spectra of $\text{Fe}^0\text{@CH/CS}$ and IBF-loaded $\text{Fe}^0\text{@CH/CS}$ were assessed in comparison with the characteristic spectra of cellulose and chitosan (Fig. 2). For the cellulose, the main identification bands of its chemical groups were detected at 3450 cm^{-1} (OH groups), 2914 and 1367 cm^{-1} (-CH bearing groups), 1630 cm^{-1} (adsorbed water molecules), 1057 cm^{-1} (-C-O-C of pyranose ring), and 897 cm^{-1} (β -glycosidic linkages) [28] (Fig. 2A). For chitosan as separated components, the spectrum demonstrates the existence its chemical groups including O-H and or N-H (3423 cm^{-1}), -CH (2915 cm^{-1}), C = O (1637.2 cm^{-1}), C-N group (1402 cm^{-1}), and C-O (1040 cm^{-1}) [18] (Fig. 2B).

The spectrum of $\text{Fe}^0\text{@CH/CS}$ shows intensification in the observed bands around 3390 cm^{-1} , 2900 cm^{-1} , 1630 cm^{-1} , 1400 cm^{-1} , and 1045 cm^{-1} as compared to the reported bands for cellulose and chitosan (Fig. 2C). This demonstrates the overlap between the chemical groups of the two integrated organic components. Additionally, the considerable shifting in the positions of these bands suggested chemical interaction between chemical groups of cellulose and chitosan. The β -glycosidic linkage of cellulose was identified in the composite by a reduced and deviated band at 787.7 cm^{-1} (Fig. 2C). The detected small band at 669 cm^{-1} and 560 cm^{-1} (Fe-O) declare the partial oxidation of the Fe^0 iron particles which is in agreement with the XRD findings [25, 26] (Fig. 2C).

The inspected spectrum of the IBF loaded sample declared remarkable changes in both positions and intensities of the $\text{Fe}^0\text{@CH/CS}$ reported bands suggesting significant interaction with the chemical structure of the drug (Fig. 2D). Additionally, several new bands were detected related to the carbonyl group (1760 cm^{-1}) and the aromatic ring (700 cm^{-1} - 1500 cm^{-1}) of the IBFdrug [29] (Fig. 2D). Such observations confirm the effective entrapping of the IBF drug into $\text{Fe}^0\text{@CH/CS}$ composite as delivery system.

3.1.3. SEM and HRTEM analyses

The SEM images of the chitosan/cellulose composite (CH/CS) reflect the presence of the composite as tabular or cylindrical grains of smooth surface (Fig. 3A). The present grains are commonly agglomerated with each other in irregular forms which might be related to the integrated chitosan which acts as a matrix for the cellulose fibers (Fig. 3B). The HRTEM images confirm the detected morphology of CH/CS composite as tabular or rods-like grains (Fig. 3C). The tabular interconnected with each other by the chitosan matrix-forming porous structure (Fig. 3C). For the synthetic $\text{Fe}^0\text{@CH/CS}$ composite, the SEM images demonstrate the decoration of the CH/CS tabular grains with numerous micro/nanoparticles of the synthetic green Fe^0 particles (Fig. 3D). The same observations were observed clearly in the studied HRTEM images as the tabular particles of CH/CS composite were coated with the Fe^0 particles (Fig. 3E).

The previous findings confirm the formation of hybrid structure of chitosan, cellulose, and Fe⁰ with multifunctional active chemical groups and enhanced morphology.

3.2. IBF loading properties of Fe⁰@CH/CS

3.2.1. Effect of the loading variables

3.2.1.1. Effect of pH values

The influence of pH on the IBF loading capacity of Fe⁰@CH/CS was assessed from pH 2 up to 8. The other affecting variables were fixed at 20 °C as temperature, 400 mg/L as IBF concentration, 50 mL as IBF solution volume, 20 mg as carrier dosage, and 24 h as loading interval (Fig. 4A). The obtained IBF loading trends by Fe⁰@CH/CS declare a noticeable enhancement in the determined IBF capacities as the pH values increased from pH 2 up to pH 6 (Fig. 4A). This was followed by a noticeable declination in the recognized IBF loading capacity for the investigated pH values from pH 6 up to pH 8 (Fig. 4A). The observed faint IBF loading properties of Fe⁰@CH/CS at the low pH values were illustrated as a result of the hydrophobic and low solubility nature of the drug at the acidic conditions [30]. Therefore, the increment in the pH enhances the hydrophilic and solubility behaviors of IBF molecules to be in an ionic form which induces their loading into Fe⁰@CH/CS structure [9]. Beyond pH 6, the significant deprotonation of the Fe⁰@CH/CS effective chemical groups resulted in remarkable electrostatic repulsion with carboxylate groups of IBF which are of negative charges at these conditions [31, 32]. Therefore, pH 6 is the recommended value to attain the best IBF loading capacity (410 mg/g) by the synthetic Fe⁰@CH/CS composite (Fig. 4A).

3.2.1.2. Effect of IBF loading interval

The loading behavior of IBF into Fe⁰@CH/CS as a function of the experimental interval was followed from 1 h up to about 24 h. The other affecting variables were fixed at pH 6, 20 °C as temperature, 400 mg/L as IBF concentration, 20 mg as carrier dosage, and 50 mL as IBF solution volume (Fig. 4B). Generally, there is a significant enhancement in the actual IBF loading capacities with expanding the tested interval up to 12 h (395 mg/g) (Fig. 4B). After that, the determined IBF loading capacity slightly increased and appears to be nearly fixed up to 24 h (410 mg/g) displaying an equilibration state (Fig. 4B). The presence of numerous free and active loading receptors on the surface of Fe⁰@CH/CS during the initial loading intervals resulted in a strong increment in the IBF loading capacity at a fast rate [33]. The gradual occupation of the Fe⁰@CH/CS free receptors by the adsorbed IBF ions resulted in an observable reduction in the actual loading rate. This can be detected until the full occupation of all the present receptors with the IBF ions which demonstrates the IBF loading equilibration of Fe⁰@CH/CS.

3.2.1.3. Effect of IBF concentration

The maximum IBF loading capacity of Fe⁰@CH/CS was studied by detecting the loading properties in the existence of different IBF concentrations (100 to 900 mg/L) (Fig. 4C). The other affecting variables were

fixed at pH 6, 20 °C as temperature, 24 h as loading interval, 20 mg as carrier dosage, and 50 mL as IBF solution volume. The recognized results display a strong increment in the values with testing the loading properties of Fe⁰@CH/CS using high concentrations of IBF up to 700 mg/L (Fig. 4C). This was reported in the literature as a result of the expected increase in the IBF driving forces with increasing the concentration. This enhances the diffusion properties of the dissolved IBF ions towards the free active loading receptors of Fe⁰@CH/CS which in turn improves the actual IBF loading results [15, 34]. The increase in the tested IBF concentration above 700 mg/L up to 900 mg/L is of slight impact on the measured IBF loading capacity of Fe⁰@CH/CS (Fig. 4C). Therefore, the equilibrium concentration during the loading of IBF into Fe⁰@CH/CS is 700 mg/L. After the equilibrium concentration, all the active receptors of the Fe⁰@CH/CS composite were occupied by the drug and attended its actual maximum capacity (526.2 mg/g) (Fig. 4C).

3.2.1.4. Effect of Fe⁰@CH/CS quantities

Testing the loading properties of IBF using different quantities of Fe⁰@CH/CS was accomplished from 20 mg up to 100 mg as an essential factor to control the IBF loaded dosages (Fig. 4D). The other affecting variables were fixed at pH 6, 20 °C as temperature, 24 h as loading interval, 400 mg/L as IBF concentration, and 50 mL as IBF solution volume. The IBF loading percentages using Fe⁰@CH/CS enhanced significantly by 41%, 63.4%, 82.6%, 96.8%, and 100% with increasing its quantities in the tests by 20 mg, 40 mg, 60 mg, 80 g, and 100 mg, respectively (Fig. 4D). This was illustrated as a result of the strong increase in the availability of the Fe⁰@CH/CS active loading receptors with increasing its quantity as well as the interaction interface between the drug solution and the composite particles [33].

3.2.2. Loading mechanism

3.2.2.1. Kinetic studies

The Intra-Particle diffusion curve in addition to both Pseudo-First and Pseudo-Second order models were studied to illustrate the IBF loading reactions into Fe⁰@CH/CS carrier (Table.S1). Considering the observed segments in the Intra-Particle diffusion curve, the IBF loading process into Fe⁰@CH/CS involved three essential mechanisms and did not control only by the diffusion behaviour of the drug ions (Fig. 4E). The first segment in the curve reflects the loading of IBF by surficial adsorption mechanism depending on the present free receptor sites on the surface of Fe⁰@CH/CS carrier [34] (Fig. 4E). This was followed by another segment which reflects the saturation of the surficial receptors with the IBF ions and the operation of the layered adsorption processes as the dominant loading mechanism [35] (Fig. 4E). The last segment which represents the equilibrium portion of the curve reflects the dominance of molecular association and/or interionic processes as the effective loading mechanisms [36].

Considering the fitting results, the values of both Chi-squared (χ^2) and determination coefficient (R^2) reflect the operation of the IBF loading reactions into Fe⁰@CH/CS according to the kinetic properties of the Pseudo-First order model (PF) (Fig. 4F; Table.1). This suggested controlling impact for the

physisorption mechanisms during the loading of IBF ions into Fe⁰@CH/CS carrier. However, the reported good agreement with Pseudo-Second order kinetics demonstrates considerable effects for some chemisorption mechanisms during the loading process as chemical complexation (Fig. 4F; Table.1) [36, 37].

Table.1. The theoretical parameters of the studied the kinetic models, the equilibrium models, Van't Hof formula, and the release kinetic models.

Model	Parameters	
Pseudo-first-order	$K_1 \text{ (min}^{-1}\text{)}$	0.291
	$q_e \text{ (Cal) (mg/g)}$	409.6
	R^2	0.99
	χ^2	0.18
Pseudo-second-order	$k_2 \text{ (g mg}^{-1} \text{ min}^{-1}\text{)}$	5.12×10^{-4}
	$q_e \text{ (Cal) (mg/g)}$	463
	R^2	0.96
	χ^2	1.12
Isotherm models		
Langmuir	$q_{\max} \text{ (mg/g)}$	544.5
	$b \text{ (L/mg)}$	0.0026
	R^2	0.94
	χ^2	2.31
	R_L	0.04–0.79
Freundlich	$1/n$	0.623
	$k_F \text{ (mg/g)}$	10.66
	R^2	0.88
	χ^2	3.67
D-R model	$\beta \text{ (mol}^2\text{/KJ}^2\text{)}$	0.0096
	$q_m \text{ (mg/g)}$	517.5
	R^2	0.96
	χ^2	1.89
	$E \text{ (KJ/mol)}$	7.2

Model	Parameters	
Monolayer model of one energy	n	2.18
	Nm (mg/g)	252.6
	Q_(sat) (mg/g)	553
	ΔE (kJ/mol)	4.81
Thermodynamics		
ΔG° (kJ mol ⁻¹)	293.15	-15.94
	303.15	-16.40
	313.15	-16.78
	323.15	-17.07
	333.15	-17.43
ΔH° (kJ mol ⁻¹)		-5.28
ΔS° (J K ⁻¹ mol ⁻¹)		36.5
Release kinetics		
Models	Determination coefficient	
	pH 1.2	pH 7.4
Zero-order model	0.70	0.57
First order model	0.94	0.98
Higuchi model	0.80	0.90
Hixson-Crowell model	0.88	0.94
Korsmeyer-peppas model	0.90	0.90

3.2.2.2. Equilibrium modeling

3.2.2.2.1. Classic equilibrium models

The equilibrium behaviours of the IBF loading reactions into Fe⁰@CH/CS were assessed considering the assumptions of Freundlich, Langmuir, and Dubinin–Radushkevich (D-R) isotherm models (Table.S1). The values of χ^2 , as well as R^2 , demonstrate higher agreement with the Langmuir equilibrium properties rather than the equilibrium behaviour of Freundlich isotherm (Fig. 5A; Table.1). Such fitting findings suggested monolayer loading of the IBF ions on the surface of Fe⁰@CH/CS by the numerous homogeneously

distributed active loading receptors [24]. Moreover, the reported values of the RL fitting parameter (< 1) displays the favourable loading process of the IBF ions into $\text{Fe}^0\text{@CH/CS}$ with a theoretical Q_{max} of 540 mg/g (Table.1). The fitting parameters of the D-R model as the Gaussian energy are of valuable indications about the properties of the IBF loading process into $\text{Fe}^0\text{@CH/CS}$ (Fig. 5A; Table.1) [37, 38]. The value of Gaussian energy (6.45 KJ/mol) suggested the physisorption of IBF ions by the active groups of $\text{Fe}^0\text{@CH/CS}$ which is in agreement with the kinetic findings (Table.1) [34].

2.2.2.2. Advanced equilibrium studies

To make a deep illustration about the IBF loading process into $\text{Fe}^0\text{@CH/CS}$, an advanced equilibrium model (Monolayer model of one energy) based on the statistic physics theory was studied the nonlinear fitting process with the equation of the model (Fig. 5B). The addressed fitting parameters are the number of loaded IBF ions per each receptor site (n), the present active loading receptor density (N_m), the IBF loading capacity of $\text{Fe}^0\text{@CH/CS}$ at the saturation state (Q_{sat}), and the IBF loading energy (ΔE) (Table.1). Based on the value of the n parameter (2.18), the IBF molecules were loaded into the receptors of $\text{Fe}^0\text{@CH/CS}$ as two or three ions per receptor. Moreover, this value suggested the loading of IBF in vertical/non-parallel orientation on the surface of $\text{Fe}^0\text{@CH/CS}$ by a multi-molecular mechanism [39, 40]. The active loading receptors density (N_m) of $\text{Fe}^0\text{@CH/CS}$ during the loading of IBF ions is 252.2 mg/g and the loading capacity of the composite at saturation (Q_{sat}) is 553 mg/g. Such equilibrium findings demonstrate the significance of $\text{Fe}^0\text{@CH/CS}$ as a carrier for IBF drugs with remarkable loading capacity.

The value of IBF loading energy into $\text{Fe}^0\text{@CH/CS}$ carrier was estimated according to Eq. 4 in which the presented symbol donate the IBF loading energy (ΔE), gas constant (R), temperature (T), the solubility of IBF (S), and concentration of dissolved IBF at the half-saturation state (C).

$$\Delta E = RT \ln \left(\frac{S}{C} \right) \quad (6)$$

The value of IBF loading energy is 4.81 kJ/mol and within the identified limit of physical mechanisms including hydrogen bonding (< 30 kJ/mol), van der Waals forces (4–10 kJ/mol), and dipole bonding forces (2–29 kJ/mol) [40].

3.2.2.3. Thermodynamic properties

The thermodynamic functions of the IBF loading reactions by $\text{Fe}^0\text{@CH/CS}$ were studied considering the experimental temperature range from 20 °C up to 60 °C. The other affecting variables were fixed at pH 6, 20 mg as carrier dosage, 24 h as loading interval, 400 mg/L as IBF concentration, and 50 mL as IBF solution volume. The values of both entropy (ΔS°) and enthalpy (ΔH°) were obtained as fitting parameters for the linear regression fitting with Van't Hof equation (Eq. 4) (Fig. 6). However, the values of

Gibbs free energy (ΔG^0) at the experimentally studied loading temperature were calculated based on Eq. 3 (Table.1) [33]:

$$\ln(K_c) = \frac{\Delta S^0}{R} - \frac{\Delta H^0}{RT} \quad (3)$$

$$\Delta G^0 = -RT \ln K_c \quad (4)$$

The calculated ΔG^0 values within the temperature range from 293 K up to 33 K are of negative signs which display the spontaneous and favorable loading of IBF into $\text{Fe}^0\text{@CH/CS}$ as a carrier (Table.1). Additionally, the estimated value of ΔH^0 as a fitting parameter with a negative sign confirms the exothermic properties of the occurred reactions during the loading of IBF into $\text{Fe}^0\text{@CH/CS}$ (Table.1). The estimated positively signed value of ΔS^0 display considerable enhancement in the randomness of the IBF loading reactions as a function of the tested temperature.

3.3. In-vitro release profiles

The release properties of IBF from $\text{Fe}^0\text{@CH/CS}$ were studied considering two release buffers (gastric fluid (pH 1.2) and intestinal fluid (pH 7.4)) (Fig. 7A). The recognized IBF release rates within the two buffers are of fast properties during the initial intervals of the release process (Fig. 7A). After that, the IBF diffusion rates shows remarkable slow behaviors, and the recognized rates declined significantly until attending an equilibration state of fixed IBF release values by the ending of the release interval (Fig. 7A). The detected fast IBF release rates with starting the process are credited to the abrupt and significant desorption of the drug ions from the surficial receptors of $\text{Fe}^0\text{@CH/CS}$ [41]. After that, the release of IBF became restricted to the loaded ions which are of strong bonds with the active groups of $\text{Fe}^0\text{@CH/CS}$ in addition to the deep entrapped ions within the matrix of CH/CS matrix [12, 42].

Within the studied gastric buffer (pH 1.2), the release of IBF ions continued up to 260 min without attending the complete diffusion of the loaded drug dosage (Fig. 7A). 50% of the loaded IBF dosage was diffused after 30 h and 91% as the maximum diffused percentage was detected after 260 min (Fig. 7A). Within the intestinal buffer (pH 7.4), the release of IBF from $\text{Fe}^0\text{@CH/CS}$ is of faster properties than the gastric buffer (Fig. 7A). 50% and 95% of the IBF dosage were diffused from $\text{Fe}^0\text{@CH/CS}$ after 20 h and 100 h, respectively, and the complete IBF diffusion (100%) was detected after 180 h (Fig. 7A). The recognized fast IBF release properties from $\text{Fe}^0\text{@CH/CS}$ at the basic buffer (intestinal (pH 7.4)) was assigned to the high solubility of IBF at this pH as compared to the acidic pH values [43]. The high solubility of IBF induces the migration and diffusion of the structure of $\text{Fe}^0\text{@CH/CS}$ into the release buffer. On the other hand, at the acidic pH value (pH 1.2), the IBF is of poor solubility and accumulates in its molecular form which reduces the release efficiency [8, 43].

Generally, the synthetic carriers that are of controlled release properties were recommended. For some cases, the synthetic carriers that are of abrupt IBF release properties are highly effective to liberate the loaded dosage within a short interval according to the required therapeutic value. In other cases,

developing carriers of slow and continuous IBF release properties is preferred to keep the drug at the recommended limit for long intervals [33, 44]. Therefore, the green synthesized Fe⁰@CH/CS is a valuable structure to be used as a delivery system of controlled and enhanced IBF loading and release properties based on the experimental conditions.

3.4. Release kinetics

The IBF release kinetics from Fe⁰@CH/CS reflects the affecting mechanism during the release reactions. The kinetic properties were studied based on the recognized linear fitting results with Zero-order (Z-O) (Eq. 5), First-order (F-O) (Eq. 6), Higuchi (H-U) (Eq. 7), Hixson-Crowell (H-C) (Eq. 8), and Korsmeyer-Peppas (K-P) models (Eq. 9) [12].

$$W_t - W_0 = K_0 \cdot t \quad (5)$$

$$\ln(W_\infty / W_t) = K_1 \cdot t \quad (6)$$

$$W_t = K_h t^{1/2} \quad (7)$$

$$W_o^{1/3} - W_t^{1/3} = K_{HC} t \quad (8)$$

$$W_t / W_\infty = K_p t^n \quad (9)$$

The kinetic properties of the Zero-order (Z-O) model involved the release of IBF according to constant rate without considerable influence for the IBF dosage as a loaded drug [45]. The release kinetics that follows the First-order (F-O) properties assumes a significant effect for the loaded IBF dosage during the release reactions [43]. The release of IBF according to the Higuchi (H-G) kinetic demonstrates a controlling effect for diffusion processes according to six parameters during the reaction. The controlling parameter are (1) the loading of IBF at a concentration higher than the released concentration, (2) there is only one direction along it the IBF drug can be diffused, (3) the IBF diffusion is constant during the process, (4) the actual diameter of IBF grains should be smaller than the actual thickness of Fe⁰@CH/CS grains, (5) the detected solubility and swelling value of Fe⁰@CH/CS are of significant effect on the IBF release rate, and (6) the loaded IBF as a drug is remarkable sink properties [32, 45]. The release of IBF based on the Hixson-Crowell (H-C) model suggests an essential effect for the erosion mechanisms during the release processes considering the significant impact of both the Fe⁰@CH/CS diameter and its surface area [46]. The kinetic hypothesis of the K-P model suggested the dominant effects of both diffusion and erosion mechanisms during the IBF release process from Fe⁰@CH/CS [47].

Based on the estimated fitting degrees, the IBF release results are of strong agreement with the First-order model (F-O) as compared to the Zero-order model (Z-O) (Fig. 7B and C; Table.1). Therefore, the IBF release behavior depends essentially on the loaded concentration of IBF. The recognized IBF results also are of significant agreement with both the Higuchi model and Hixson-Crowell release kinetic models (Fig. 7D and E; Table.1). This suggested the release of IBF from Fe⁰@CH/CS into the studied buffers by both diffusion

and erosion mechanisms. Such findings were supported by the detected excellent fitting with Korsmeyer-Peppas (K-P) model (Fig. 7F). The obtained diffusion exponent as fitting parameter ((0.58 (pH 1.2) and 0.48 (pH 7.4)) declared the release of IBF by anomalous release behavior (non-Fickian transport reaction) (Table.1). This also confirms the operation of erosion and diffusion mechanisms during the IBF release processes from $\text{Fe}^0\text{@CH/CS}$ carrier [33].

3.5. Cytotoxicity properties

The cytotoxicity effects of $\text{Fe}^0\text{@CH/CS}$ and IBF-loaded $\text{Fe}^0\text{@CH/CS}$ on the Human bronchial epithelial cells were assessed considering the tested dosages from 100 $\mu\text{g/mL}$ up to 300 $\mu\text{g/mL}$. Considering the determined values of cell viability based on the performed MTT assay tests, the synthetic $\text{Fe}^0\text{@CH/CS}$ particles, as well as the IBF-loaded product, are of remarkable biocompatibility and safety be used as a delivery system. The measured cell viability percentages using 300 $\mu\text{g/mL}$ as the maximum dosages of $\text{Fe}^0\text{@CH/CS}$ and IBF-loaded $\text{Fe}^0\text{@CH/CS}$ are 92.7% and 89.2%, respectively.

Conclusion

The synthetic $\text{Fe}^0\text{@CH/CS}$ green nanostructure was synthesized as a potential carrier for IBF drug with a loading capacity of 553 mg/g. The IBF loading process is of homogenous, physisorption, and monolayer properties based on the representative equilibrium (Langmuir) and kinetic (Pseudo-First order) models. Considering the advanced isotherm studies (Monolayer model of one energy), the IBF drug was loaded in a vertical orientation as two or three ions per loading site by a multi-molecular process. The IBF loading energy (4.81 kJ/mol) donated physical loading mechanisms (Van-der Waals forces and/or hydrogen bonding). The synthetic $\text{Fe}^0\text{@CH/CS}$ structure exhibits continued and slow-release behavior for about 260 h at pH 1.2 and 180 h at pH 7.4. The IBF release kinetics and the obtained diffusion exponent (0.58 (pH 1.2) and 0.48 (pH 7.4)) reflects complex diffusion/erosion release mechanisms. Both $\text{Fe}^0\text{@CH/CS}$ (300 $\mu\text{g mL}^{-1}$; cell-viability 92.7 %) and IBF loaded $\text{Fe}^0\text{@CH/CS}$ (300 $\mu\text{g mL}^{-1}$; cell-viability 89.2 %) are of safe effects on the human bronchial epithelial cells.

Declarations

ACKNOWLEDGMENT

The authors acknowledge Researchers Supporting Project number (RSP-2021/149), King Saud University, Riyadh, Saudi Arabia.

Ethical Approval

The manuscript does not include experimental studies on any animal or human data

Consent to Participate

Not applicable

Consent to Publish

Not applicable

Authors Contributions

The authors contribute equally in preparing the material, designing the experimental section, interpreting the results, and writing the manuscript

Competing Interests

The authors declare that there is no conflict in interest

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Table

Table S1 is not available with this version.

Figures

Figure 1

XRD pattern of cellulose (A), chitosan (B), and synthetic Fe⁰@CH/CS (C)

Figure 2

FT-IR spectra of cellulose (A), chitosan (B), synthetic Fe⁰@CH/CS (C), and IBF loaded Fe⁰@CH/CS (D)

Figure 3

SEM of synthetic chitosan/cellulose composite (A and B), HRTEM of synthetic chitosan/cellulose composite (C), SEM of synthetic Fe⁰@CH/CS composite (D and E) (red arrow refers to the loaded Fe⁰ particles), and HRTEM of synthetic Fe⁰@CH/CS (F)

Figure 4

Effect of pH values on the loading of IBF into Fe⁰@CH/CS (A), effect of time interval on the loading of IBF into Fe⁰@CH/CS (B), effect of IBF concentration on the loading capacity of Fe⁰@CH/CS (C), effect of the Fe⁰@CH/CS dosages on the loading efficiency of IBF (D), the Intra-Particle diffusion curve of IBF loading results (E), and fitting of the IBF loading results with the different kinetic models (F)

Figure 5

Fitting of the IBF loading results with the different equilibrium models (A), and fitting of the IBF loading results with Monolayer model o one energy (B)

Figure 6

Fitting of the IBF loading results with Van't Hof equation

Figure 7

The release profiles of IBF from Fe⁰@CH/CS (A), fitting of the IBF release results with Zero-order model (B), fitting of the IBF release results with First-order model (C), fitting of the IBF release results with Higuchi model (D), fitting of the IBF release results with Hixson-Crowell model (E), and fitting of the IBF release results with Korsmeyer–Peppas model (F)