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RESEARCH ARTICLE

Enhanced ibuprofen loading capacity of chitosan nanoparticles for prolonged release: A comprehensive study

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Abstract

Objectives. Oral administration of ibuprofen often requires much higher doses than the necessary therapeutic dose due to the low solubility and first-pass metabolism of this anti-inflammatory drug. In order to improve its solubility and bioavailability, orally administered ibuprofen can be encapsulated into chitosan nanoparticles. The release of ibuprofen from chitosan nanoparticles can be pH-controlled to increase drug delivery efficiency when passing through the gastrointestinal tract. While ionic gelation provides versatile nanochitosan synthesis, the impact of the chitosan-to-tripolyphosphate (CS/TPP) ratio on encapsulation efficiency (EE) and loading capacity (LC) of the ibuprofen-loaded chitosan nanoparticles (IBU-CSNPs), as well as their release behavior under various pH conditions, remains unexplored. The study aims to determine the appropriate CS/TPP ratio for the highest EE and LC, as well as to evaluate the morphology, release behavior, and degradability of the IBU-CSNPs under optimal conditions.

Methods. The effect of CS/TPP ratio on the EE and LC of nanoparticle-loaded ibuprofen is studied by comparing the total and free concentrations of the drug and the weights of the CSNPs and IBU-CSNPs. To elucidate the characteristic properties of the IBU-CSNPs prepared at the optimal CS/TPP ratio, in-depth characterization was performed, including their morphology, chemical structure, crystallinity profile, *in vitro* degradation, and release behavior. The release profile of the IBU-CSNPs is studied under simulated gastric fluid (SGF), intestinal fluid (SIF), and sequential conditions of SGF and SIF.

Results. EE and LC were found to be significantly enhanced by an appropriate 1 : 1 mg/mg ratio, reaching 77.70 ± 0.65% and 46.62 ± 0.39%, respectively. The fabricated IBU-CSNPs exhibit a spherical shape with a uniform size distribution of approximately 50–60 nm and accelerated degradation compared to the unadulterated chitosan nanoparticles under simulated gastrointestinal conditions. The synthesized IBU-CSNPs demonstrate remarkable acid resistance by a minimal drug release of 9.44% in SGF after 3 h. However, a sustained release pattern in SIF achieves an equilibrium cumulative release of 94.51% over 5 days. The elaboration of drug release kinetics using the Kopcha and Korsmeyer–Peppas models suggests erosion-controlled release in SGF and diffusion-controlled release with swellable ability in SIF.

Conclusions. The results represent valuable insights into the formulation of pH-responsive IBU-CSNPs for the controlled delivery of ibuprofen via oral administration.

Keywords

chitosan nanoparticles, ibuprofen, pH-controlled release, encapsulation efficiency, loading capacity

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НАУЧНАЯ СТАТЬЯ

Комплексное исследование способности наночастиц хитозана к пролонгированному высвобождению ибупрофена

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Аннотация

Цели. Пероральное применение ибупрофена часто требует значительно более высоких доз, чем необходимая терапевтическая доза, из-за низкой растворимости и быстрого метаболизма этого противовоспалительного препарата. Чтобы улучшить его растворимость и биодоступность, ибупрофен, вводимый перорально, может быть инкапсулирован в наночастицы хитозана. Для того, чтобы повысить эффективность доставки лекарства при прохождении через желудочно-кишечный тракт, можно регулировать высвобождение ибупрофена из наночастиц хитозана, контролируя pH. В то время как ионное гелеобразование обеспечивает универсальный синтез нанохитозана, влияние соотношения хитозана и триполифосфата (CS/TPP) на эффективность инкапсуляции и загрузочную способность наночастиц хитозана, содержащих ибупрофен (IBU-CSNPS), а также на их высвобождение при различных значениях pH, остается неизученным. Цель исследования — определить подходящее соотношение CS/TPP для получения наивысших значений инкапсуляции и загрузочной способности, а также оценить морфологию, характеристики высвобождения и способность к разложению IBU-CSNPS в оптимальных условиях.

Методы. Влияние соотношения CS/TPP на инкапсуляцию и загрузочную способность ибупрофена, содержащего наночастицы, изучают путем сравнения общей и свободной концентраций препарата и масс CSNP и IBU-CSNP. Для выяснения характерных свойств IBU-CSNPs, приготовленных при оптимальном соотношении CS/TPP, был проведен углубленный анализ, включающий их морфологию, химическую структуру, профиль кристалличности, разложение *in vitro* и поведение при высвобождении. Профиль высвобождения IBU-CSNPs изучался с помощью моделирования поведения IBU-CSNPs в желудочной и кишечной жидкостях, а также при последовательном введении в желудочную и кишечную жидкости.

Результаты. Найдено, что инкапсуляция и загрузочная способность IBU-CSNPs значительно повышаются при соотношении CS/TPP = 1 : 1 мг/мг, достигая 77.70 ± 0.65% и 46.62 ± 0.39% соответственно. Модельные наночастицы IBU-CSNPs имеют сферическую форму с равномерным распределением по размерам (приблизительно 50–60 нм) и ускоренным разложением по сравнению с наночастицами чистого хитозана в условиях, имитирующих желудочно-кишечный тракт. Синтезированные IBU-CSNPs демонстрируют значительную кислотоустойчивость благодаря минимальному высвобождению лекарственного средства — 9.44% в желудочной жидкости через 3 часа. Однако при длительном нахождении в кишечной жидкости достигается равновесное кумулятивное высвобождение в размере 94.51% в течение 5 дней. Кинетика высвобождения лекарственного средства с использованием моделей Копча и Корсмейера–Пеппаса предполагает высвобождение с контролем эрозии в желудочной жидкости и высвобождение со способностью к набуханию и контролем диффузии в кишечной жидкости.

Выводы. Полученные результаты представляют значительную ценность в разработке PH-чувствительных IBU-CSNPs для контролируемой доставки ибупрофена при пероральном приеме.

Ключевые слова

наночастицы хитозана, ибупрофен, высвобождение с регулируемым pH, эффективность инкапсуляции, несущая способность

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INTRODUCTION

Ibuprofen is a nonsteroidal anti-inflammatory drug that exerts nonselective inhibition on cyclo-oxygenase-1 and cyclo-oxygenase-2 to hinder the transformation of arachidonic acid into prostaglandins, which play a key role in pyrexia, inflammation, and pain sensation. Ibuprofen is predominantly administered orally at a dosage of 200–600 mg every 6 hours. However, the required dose for therapeutic effect is only about 20–30 mg/kg, which means that the oral dosage of ibuprofen is 10–20 times higher than the necessary therapeutic dose [1]. This is a drawback of oral ibuprofen usage owing to the low solubility (0.685 mg/mL at 37°C) [2] and the first-pass metabolism of the drug. Ibuprofen overdosage may result in some reported adverse effects, including gastrointestinal problems (heartburn, indigestion, nausea, and vomiting), uncommon metabolic acidosis, as well as rarely experienced effects on the central nervous system [3]. The low dissolution rate of ibuprofen contributes to its low bioavailability, even when administered at high oral doses. Many attempts have been made to formulate ibuprofen into topical products such as creams and gels as an alternative to oral administration. However, these alternatives also exhibit limited therapeutic concentration of ibuprofen because of its poor skin permeability [4].

An alternative strategy for enhancing the solubility of ibuprofen for oral administration is to encapsulate it into a nanoscale drug delivery system. By protecting the drug from bio-metabolism, the encapsulation of ibuprofen into nanoparticles improves absorption, as well as decreasing the frequency and dose of administration [5]. In general, nano-sized carrier systems having a large surface area have a significant advantage in improving the solubility of hydrophobic drugs. In order for the nanoparticles to be considered as suitable delivery systems, they must demonstrate suitable properties such as biodegradability, biocompatibility, and non-toxicity. For this reason, naturally derived polymers emerge as promising materials for the synthesis of ibuprofen-encapsulated nanoparticles. In recent years, chitosan has become a widely used bio-based polymer for the fabrication of nano-sized drug delivery systems. This is attributed to its distinctive chemical structure containing functional groups of the amino ($–NH_2$) and hydroxyl (–OH), as well as biocompatibility, mucoadhesion, and low toxicity. Under appropriate conditions, ibuprofen with the carboxylic group interacts with the chitosan chains through electrostatic interactions and hydrogen bonding between the functional groups of chitosan and ibuprofen, resulting in the entrapment of the drug within the polymeric matrix [6]. During the synthesis of ibuprofen-loaded chitosan nanoparticles (IBU-CSNPs), cross-linking agents are utilized in association with mechanical methods like ultra-sonication or homogenization to facilitate the formation of the nano-sized particles. In the case of chitosan nanoparticles, tripolyphosphate (TPP) is applied to promote the ionic gelation process via ionic interactions between the negatively charged TPP and positively charged chitosan groups in combination with mechanical stirring or homogenization-ultrasonication. IBU-CSNPs were successfully synthesized by following the ionic gelation method with TPP as the cross-linker and *in situ* loading of ibuprofen, achieving an encapsulation efficiency (EE) and loading capacity (LC) of 68.94 ± 1.61% and 28 ± 1.18%, respectively. The release of ibuprofen from the fabricated IBU-CSNPs reached an equilibrium state after 15 h with cumulative drug release (CDR) of 86.79 ± 1.02% and 77.27 ± 1.48% in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), respectively. The IBU release mechanism from the IBU-CSNPs is mainly driven by Fickian diffusion according to the Ritger–Peppas model [7]. Another study conducted by Olvera Rodríguez *et al*., which is focused on synthesizing IBU-CSNPs for pulmonary therapy, uses the same ionic crosslinking method with TPP but incorporating a post-loading approach for ibuprofen. After the formation of chitosan nanoparticles, these particles were dispersed in an ibuprofen solution, allowing the drug to diffuse into and anchor onto the chitosan nanoparticles via surface adsorption. This incubation method achieved a high EE of 80% across all tested drug concentrations (1000 mg/mL, 500 mg/mL, and 250 mg/mL). The particle size of IBU-CSNPs was found to range from 5 to 20 nm [8].

One key benefit of the ionic gelation for the synthesis of chitosan nanoparticles is the ease with which their characteristics, including particle size, EE, LC, and release behavior, may be adjusted by manipulating technological parameters such as chitosan-to-TPP (CS/TPP) ratio, pH, temperature, and velocity of chitosan and TPP mixing [9]. However, to the best of our knowledge, no study has evaluated the influence of the CS/TPP ratio on the EE and LC of IBU-CSNPs to suggest the appropriate IBU-CSNPs synthesis condition for enhanced drug encapsulation. Moreover, the existing works have only investigated the release kinetics of IBU-CSNPs in batches of SGF and SIF without examining the release profile under conditions of sequential pH change.

In the present study, batch experiments are performed to fabricate IBU-CSNPs with varying CS/TPP ratios from 1 : 0.25 to 1 : 3 (mg/mg) to assess the impact of this parameter on the drug LC of the nanoparticles and figure out the appropriate synthesis condition. Additionally,

various properties of morphology, chemical structure, crystallinity, and degradability of the IBU-CSNPs under the determined synthesis condition are comprehensively analyzed. The *in vitro* drug release profile of the IBU-CSNPs in different simulated environments is investigated by employing diverse mathematical models of zero order, first order, Higuchi, Kormeyer–Peppas, and Kopcha.

2. MATERIALS AND METHOD

2.1. Materials

Chitosan with a molecular weight of 158 kDa and a degree of deacetylation of above 80% was supplied by *Vietnam Food* (Vietnam). Ibuprofen (IBU, ≥98%) and phosphate-buffered saline (PBS) were obtained from *Sigma-Aldrich*, USA. Dialysis Flat Tubing with a molecular weight cut-off of 14000 kDa was supplied by *Frey Scientific*, USA. Acetic acid (CH_3COOH, 99.5%), lactic acid (85.5–90%), hydrochloric acid (HCl, 36%), sodium tripolyphosphate (TPP, 56–60%), and ethanol (99.5%) were purchased from *Xilong*, China. In order to prepare solutions, distilled water was utilized.

2.2. Preparation of chitosan nanoparticles loaded with ibuprofen (IBU-CSNPs)

Chitosan is firstly dissolved in 1% acetic acid solution under continuous stirring to prepare a chitosan solution of 3.75 mg/mL. An ibuprofen solution of 1.25 mg/mL is also prepared by dissolving ibuprofen in 70% ethanol. Next, 1 mL of ibuprofen solution is added to the chitosan solution and a mixture is stirred in 15 min at 800 rpm. Finally, an aqueous TPP solution is added dropwise to the CS/IBU mixture under stirring at 800 rpm for 1.5 h until an opalescent suspension is obtained. The formulation of IBU-CSNPs with varying TPP concentrations is presented in Table 1. The CSNPs without loading ibuprofen are prepared by following the same procedure.

Table 1. Experimental design of synthesizing IBU-CSNPs

CS/TPP ratio, mg/mg	Final concentration		
	Chitosan, mg/mL	TPP, mg/mL	Ibuprofen, mg/mL
1 : 0.25	3.00	0.75	1.00
1 : 0.5		1.50	
1 : 1		3.00	
1 : 2		6.00	
1 : 3		9.00	

2.3. Characterization

Following synthesis, both CSNPs and IBU-CSNPs were evaluated for their morphologies using field emission scanning electron microscopy (FE-SEM, *Hitachi*, S-4800, Japan). The samples were coated with thin Pt layers before measurement. Chemical structure of ingredients (chitosan, ibuprofen, TPP) and synthesized nanoparticles (CSNPs and IBU-CSNPs) were studied by Fourier-transform infrared spectroscopy (FTIR, Alpha II, *Bruker*, Germany). FTIR spectra were plotted in the wavenumber range of 600–4000 cm^{-1} at a resolution of 4 cm^{-1}. The crystallinity profile of the individual ingredients, CSNPs, and IBU-CSNPs was obtained by utilizing X-ray diffraction (XRD, *Bruker*, D8 Advance). The specimens are ground into fine powder and investigated for their XRD spectra in the range of 5°–80° (2θ).

2.4. EE and LC of chitosan nanoparticles

The opalescent suspensions of the chitosan nanoparticles with increasing TPP concentration were centrifuged at 13000 rpm (16058g) for 30 min. The precipitated IBU-CSNPs were then resuspended in 70% ethanol to solubilize the nanoparticles and remove unbound ibuprofen. The suspensions were further centrifuged at 13000 rpm (16058g) for another 30 min. Finally, the collected IBU-CSNPs were washed with water and dissolved in an HCl solution of 0.02 M for more than 1 day to completely release ibuprofen from the nanoparticles. The ibuprofen concentration in the media was analyzed using a UV–Vis spectrophotometer (UV–Vis, Model 754, *Stech International*, United Kingdom) at 222 nm. The EE and LC of the IBU-CSNPs are determined by Eqs. (1) and (2):

$$\mathrm{EE}(\%) = \frac{C_\mathrm{T} - C_\mathrm{F}}{C_\mathrm{T}} \times 100\%, \quad (1)$$

$$\mathrm{LC}(\%) = \frac{W_\mathrm{L}}{W_\mathrm{N}} \times 100\%, \quad (2)$$

where C_T and C_F (mg/mL) are total and free concentrations of ibuprofen in the CSNPs suspensions, respectively; W_L and W_N (g) are weight of ibuprofen loaded in CSNPs and the weight of nanoparticles, respectively.

2.5. *In vitro* ibuprofen release kinetics of the IBU-CSNPs

The IBU-CSNPs were studied *in vitro* release profile under different pH conditions by applying the analysis membrane method [10]. In particular, 1.5 mL of the IBU-CSNPs suspension was added into the tied dialysis

tube. For the drug release, three mediums of simulated gastric fluid (SGF, pH 1.2), simulated intestinal fluid (SIF, pH 6.8), and simulated biological fluid (SBF, pH 7.4) were prepared. Furthermore, ibuprofen release capacity from nanoparticles was evaluated in sequential release with a medium of pH 1.2 for the first 3 h [11, 12] and then moved to pH 6.8 for the next 12 days [13]. The equipped dialysis tube is immersed into 25 mL of each media to release the drug from the nanoparticles into the environment through the membrane. The CDR is calculated at different time intervals using a UV–Vis Spectrophotometer at 222 nm. The release kinetics of the IBU-CSNPs are studied by using mathematical models of zero order (Z-O), first order (F-O), Higuchi (H), and Korsmeyer–Peppas (K–P) as presented in Eqs. (3)–(7) [14]. In order to determine the appropriate release mechanism, the most suitable model for the release behavior of the IBU-CSNPs was identified.

Zero-order model (Z-O):

$$\frac{M_t}{M_\infty} = k_0 t\,, \tag{3}$$

First-order model (F-O):

$$\ln\left(\frac{M_t}{M_\infty}\right) = k_1 t\,, \tag{4}$$

Higuchi model (H):

$$\frac{M_t}{M_\infty} = k_H \sqrt{t}\,, \tag{5}$$

Korsmeyer–Peppas model (K–P):

$$\frac{M_t}{M_\infty} = k_{KP} t^n\,, \tag{6}$$

Kopcha model:

$$\frac{M_t}{M_\infty} = A\sqrt{t} + Bt\,, \tag{7}$$

where $\frac{M_t}{M_\infty}$ is the fractional amount of the drug released at time t (h); k_0, k_1, k_H, k_{KP}, A, and B are constants of the corresponding models. Besides, n is the diffusion exponent indicating the release mechanism (K–P model).

2.6. Degradability of the CSNPs and IBU-CSNPs

The degradability of the nanoparticles with and without ibuprofen was evaluated in a sequentially pH-changing experiment. In particular, the particles were incubated in the SGF solution (pH 1.2) for 3 h and then transferred to the SIF environment (pH 6.8) during the remaining period. The degradability of the nanoparticles is determined by their dry weight difference before and after incubation as described in Eq. (8).

$$\text{Degradability}(\%) = \frac{W_0 - W_t}{W_0} \times 100\%\,, \tag{8}$$

where W_0 and W_t are respectively the weight of the IBU-CSNPs initially and at the time t (h).

3. RESULTS AND DISCUSSION

3.1. EE and LC of the IBU-CSNPs

Following the synthesis process, IBU-CSNPs were successfully fabricated and homogenously suspended as a milky suspension (Fig. 1). The opacity of the samples was observed to progressively increase with a decrease in the CS/TPP ratio: in particular, the suspensions with the CS/TPP ratios of 1 : 2 and 1 : 3 (mg/mg) show particle aggregation at the bottom of the beaker. As the TPP concentration increases, the extent of the repulsive electrostatic interactions between the IBU-CSNPs reduces, resulting in the compression of the double electrical layer and a reduction in the zeta potential of the nanoparticles [15]. Consequently, aggregation is promoted, leading to a declined colloidal stability of the IBU-CSNPs. Previous studies have also shown that forming weak bonds between chitosan and TPP by adjusting the CS/TPP ratio helps prevent aggregation [16, 17].

Figure 2 illustrates the EE and LC of the IBU-CSNPs with decreasing CS/TPP ratio from 1 : 0.25 to 1 : 3 mg/mg; in other words, increasing TPP concentration from 0.75 to 9.00 mg/mL. Overall, both EE and LC of the IBU-CSNPs tend to grow as the CS/TPP ratio declines from 1 : 0.25 to 1 : 1 (mg/mg), followed by a decrease in both criteria with a further reduction in the CS/TPP ratio

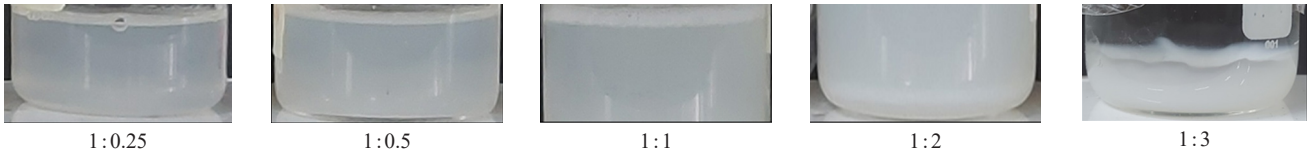


Fig. 1. Images of IBU-CSNPs fabricated from different CS/TPP ratios

to 1 : 3 (mg/mg). The highest EE and LC of the fabricated nanoparticles are respectively 77.70% and 46.62% at the CS/TPP ratio of 1 : 1 (mg/mg). Under this synthesis condition, the drug LC of the IBU-CSNPs in this work is almost 2 times higher than that fabricated by Balde *et al.* (EE and LC of 68.94% and 28%, respectively) [7].

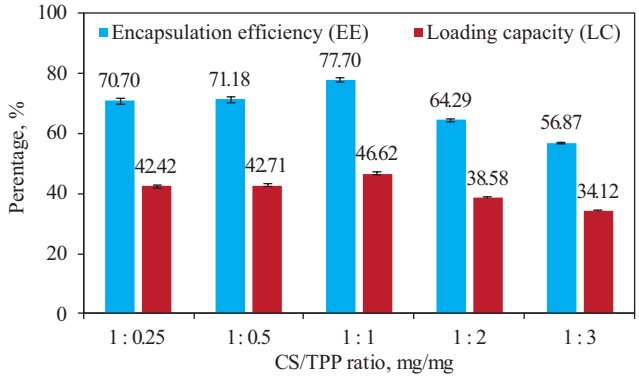


Fig. 2. Drug loading performance of the IBU-CSNPs with varying CS/TPP ratios

As can be seen from Fig. 2, an increase in the TPP concentration results in a higher cross-linking density of the IBU-CSNPs and a smaller nanoparticle size, permitting more IBU to be encapsulated within the nanoparticle core. The increased concentration of TPP also enhances the stability of the IBU-CSNPs colloids. Therefore, both EE and LC of the IBU-CSNPs achieve the highest values at the CS/TPP ratio of 1 : 1 (mg/mg). However, the stability of the nanoparticles diminishes as the CS/TPP ratio decreases to 1 : 2 and 1 : 3 (mg/mg) due to particle aggregation to significantly reduce the possibility for the ibuprofen-chitosan interactions and the entrapment of the drug within the cross-linked network of the nanoparticles. Consequently, there is a substantial decline in both EE and LC of the IBU-CSNPs down to 56.87% and 34.12% in the given order at the CS/TPP ratio of 1 : 3 (mg/mg).

3.2. Characteristics of the IBU-CSNPs

3.2.1. Chemical-crystalline profile and morphology of the IBU-CSNPs

In order to analyze the chemical structure of the fabricated nanoparticles, FTIR spectra of the chitosan nanoparticles both with and without encapsulating ibuprofen and components (chitosan, TPP, and ibuprofen) are illustrated in Fig. 3a. Characteristic absorption bands appearing in the range of 3000–3500 cm^{-1} are attributed to hydroxyl and amino groups of chitosan chains. The strong bands at 1642, 1555, and 1240 cm^{-1} are assigned to vibrations of C=O stretching, N–H bending and C–N stretching in the given order. The significant intensity in the peak at 1035 cm^{-1} indicates the presence of C–O–C linkages in the chitosan chains [14]. For TPP, the peaks at 1076 and 1208 cm^{-1} refer to the P=O linkages, whereas the band at 1126 cm^{-1} is attributed to P–O–R bonds in the phosphate groups [18]. Ibuprofen is characterized by the peaks at 1708 and 2955 cm^{-1}, which present functional groups of carboxylic acid and hydroxyl. There is a strong absorption bond found at 1230 cm^{-1} indicating the C–O–C bonds in the structure of ibuprofen. The aromatic ring in the ibuprofen structure is characterized by the two absorption bands at 1458 and 1506 cm^{-1}. Moreover, the rocking vibrations of CH_2 and CH_3 linkages are correspondingly identified at 776 and 933 cm^{-1} [7]. The lack of a characteristic peak at 1708 cm^{-1} in the spectrum of IBU-CSNPs corresponding with the carboxylic acid of ibuprofen indicates interactions between the drug and the polymeric matrix of the chitosan nanoparticles. Additionally, the absorption bands at the remaining peaks of ibuprofen are not intense in the IBU-CSNPs spectrum, further confirming the successful encapsulation of the ibuprofen in the network of the nanoparticles [7].

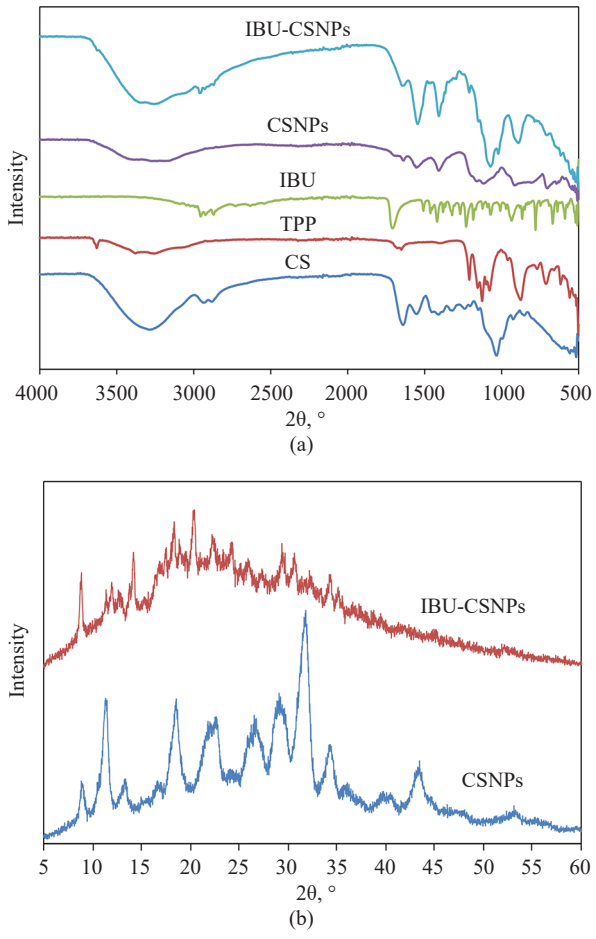


Fig. 3. FTIR (a) and XRD spectra (b) of CSNPs and IBU-CSNPs

The XRD analysis of the crystalline profile of the nanoparticles both with and without loaded ibuprofen is illustrated in Fig. 3b. According to the previous work, the neat chitosan exhibited diffraction peaks at 11.9° and 20°, whereas pure TPP showed various peaks at 19.05°, 19.77°, 33.60°, and 34.49° [19]. However, these characteristic peaks of chitosan and TPP are absent in the XRD pattern of CSNPs; instead, new multiple peaks appear at 11.5°, 13.4°, 18.6°, 22.7°, 26.6°, 29.2°, 31.8°, 34.4°, and 43.5°. This finding indicates that the interactions between the oppositely charged groups of chitosan and TPP cause the change in the packing structure of the chitosan chains. Moreover, there is a greater extent of chain bonding in the nanoparticles resulting from the cross-linking between chitosan and TPP. The previous work presented the XRD pattern of pure ibuprofen containing the diffraction peaks at 19.4°, 21.6°, 26.8°, 28.4°, and 33.2° [7]. In this study, the lack of signals at these peaks in the XRD spectrum of IBU-CSNPs demonstrates that the drug is encapsulated within the cross-linked network of the nanoparticles.

The morphology and particle size of the IBU-CSNPs are presented in Fig. 4. The uniform spherical shape of the IBU-CSNPs together with a smooth surface and nano size in the range of 50–60 nm confirms the success in the synthesis of the nanoparticles encapsulating hydrophobic ibuprofen. As already mentioned, the nano size of the chitosan-based delivery system increases its surface area, thus enhancing the efficiency of drug encapsulation within the polymer network and improving the solubility of hydrophobic drugs like ibuprofen.

3.2.2. Degradability of the IBU-CSNPs

Degradability is one of the crucial properties of drug delivery systems due to limiting the release behavior of the active compound and the toxicity potential of the material to the human body. In this work, the degradability of the synthesized nanoparticles is evaluated in the *in vitro* condition of simulated oral administration. Figure 5 depicts the degradability rate of CSNPs and IBU-CSNPs over time along with the images of the nanoparticles captured under microscopy as presented in Fig. 6. During the initial 3-h period in an acidic environment, the nanoparticles exhibit low degradation with the respective degradability of 3.93 and 6.40% for CSNPs and IBU-CSNPs. Figure 6b also shows that there is no significant change in the morphology of the IBU-CSNPs clusters after 3-h immersion in SGF. According to the previous study by Lin *et al*. [20], it was found that CS/TPP polyelectrolyte complex gel microspheres completely degraded within 2 h at pH 1.4. In contrast, both CSNPs and IBU-CSNPs in this work exhibit effective acid resistance. This can be attributed to the dense cross-linking within the polymeric matrix of the nanoparticles via the strong electrostatic interactions between the protonated amino groups of chitosan under an acidic environment and the negatively charged

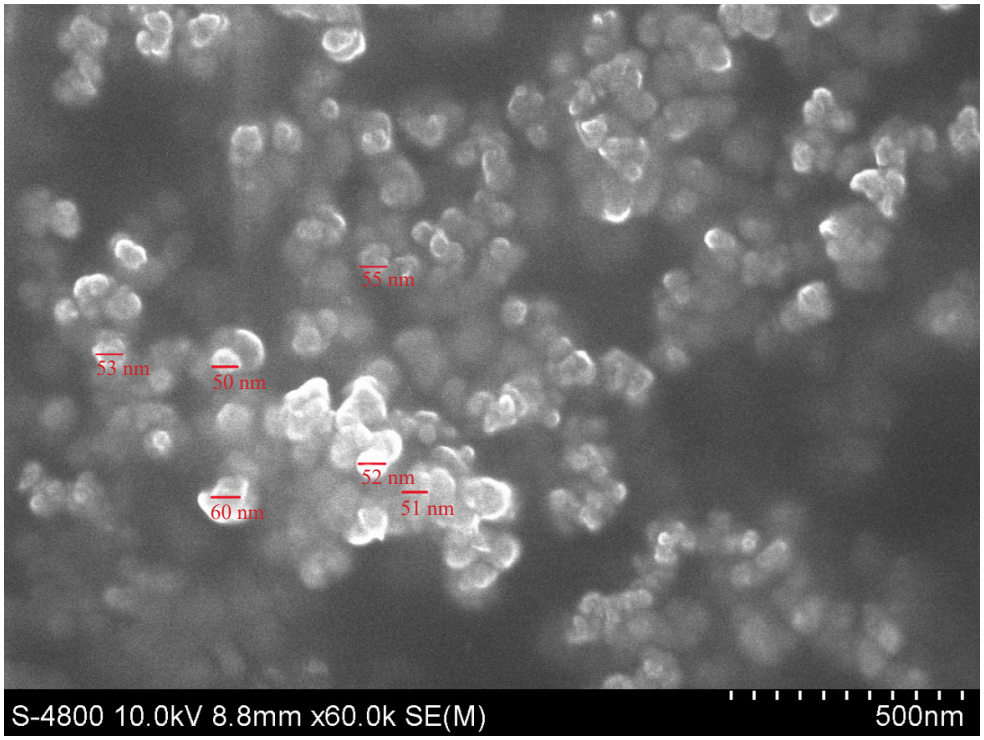


Fig. 4. Morphology of the IBU-CSNPs synthesized at a CS/TPP ratio of 1 : 1 (mg/mg)

phosphate groups of TPP. The high stability witnessed in SGF demonstrates the ability of the IBU-CSNPs to withstand the harsh conditions of the stomach and protect the drug from first-pass metabolism.

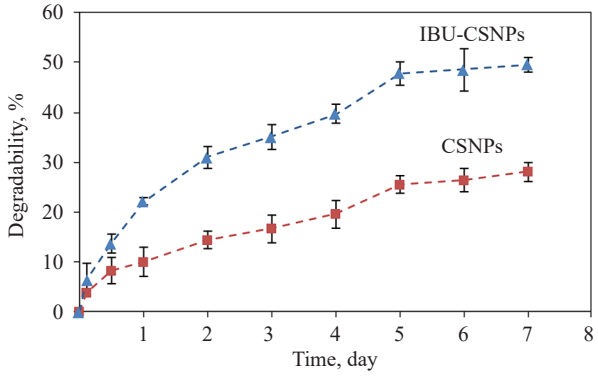


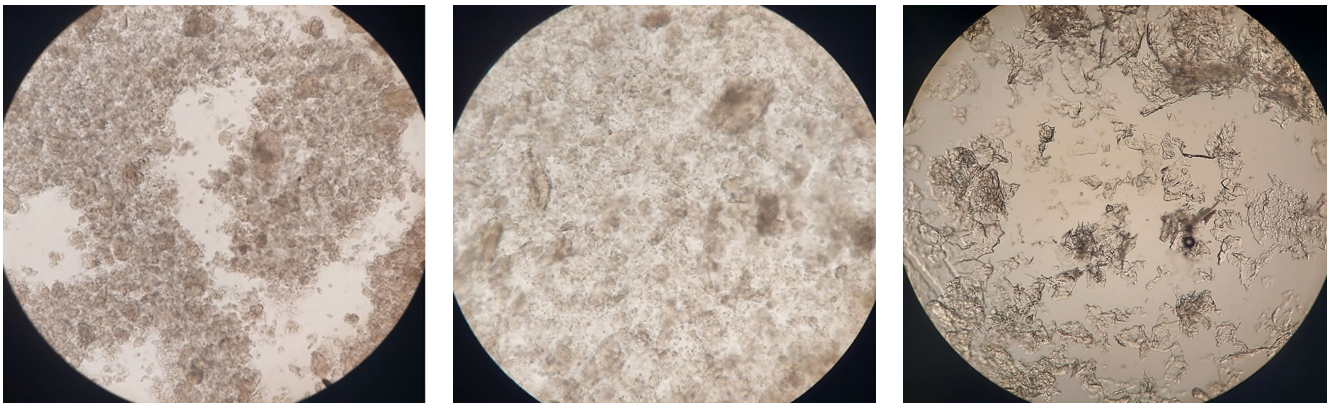
Fig. 5. Degradability of CSNPs with and without encapsulating ibuprofen under sequential pH change conditions (SGF at pH 1.2 for 3 h, followed by SIF at pH 6.8 for the remaining duration)

When the experimental environment changes to SIF, the degradation of the nanoparticles occurs more prominently with the corresponding degradability of 28.03% and 49.62% after 7 days for CSNPs and IBU-CSNPs. The looser structure of the polymeric matrix resulted from the partial deprotonation of chitosan chains, while the high solubility of ibuprofen in a neutral environment (pH 6.8) contributes to the weakening of the interactions between the drug and chitosan chains, promoting the diffusion of drug molecules from the nanoparticles. As a result, voids and porous channels are created within the structure of the nanoparticles, allowing the penetration of the environment fluid and causing more deprotonation of chitosan. Therefore, the degradation of IBU-CSNPs is considerably greater than that of CSNPs at the same time interval. Figure 6c demonstrates the evident degradation of IBU-CSNPs clusters in the SIF characterized by the presence of discrete fragments with various morphologies.

3.3. *In vitro* release kinetics of the IBU-CSNPs

The release kinetics of IBU-CSNPs under different simulated fluid conditions are depicted in Fig. 7. The equilibrium release state of IBU-CSNPs in all investigated environments is achieved after 5 days with approximately the entire ibuprofen-loaded content being released from the nanoparticles. In particular, at the same time point of 1 day after exposure to the environment, the CDR of the IBU-CSNPs in SGF and SIF is 23.13% and 67.58% in the given order. These values are all lower than the CDR reported in the study by Balde *et al*. (around 80%) [7]. Therefore, the as-fabricated IBU-CSNPs exhibit prolonged ibuprofen release demonstrated by their slow release rate in comparison with the previous work.

The distinct release behavior of the IBU-CSNPs among the environments indicates the pH-responsive release capability of the synthesized delivery system. In particular, the SIF condition strongly promotes the ibuprofen release from the nanoparticles, whereas the SGF environment inhibits the diffusion of drug molecules into the medium (Fig. 7a), similar to the findings in the degradation assessment. The maximum ibuprofen concentration is achieved after 4 days and 2 days in respective environmental pH values of 1.2 and 6.8. The specific maximum drug concentration is correspondingly 28.48 and 27.36 mg/L (Fig. 7b). In comparison with previous studies, the pattern of the ibuprofen concentration in the aqueous media over time is similar to the drug concentration-time profile of a sustained release delivery system [21, 22]. Moreover,



(a) (b) (c)

Fig. 6. Alteration in the morphology of IBU-CSNPs before the experiment (a), after 3h-immersion in SGF (b), and the next 5-day cultivation in SIF (c)

the therapeutic concentration range for ibuprofen analgesic and anti-inflammatory effects is approximately 10–50 mg/L [23]. According to the experimental data, the ibuprofen concentration in the SIF reaches 20.55 mg/L and remains within the therapeutic window of ibuprofen until the 12th day. While IBU-CSNPs in SGF also exhibit a similar trend in the drug release behavior, the therapeutic concentration is only achieved on the 2nd day from the beginning.

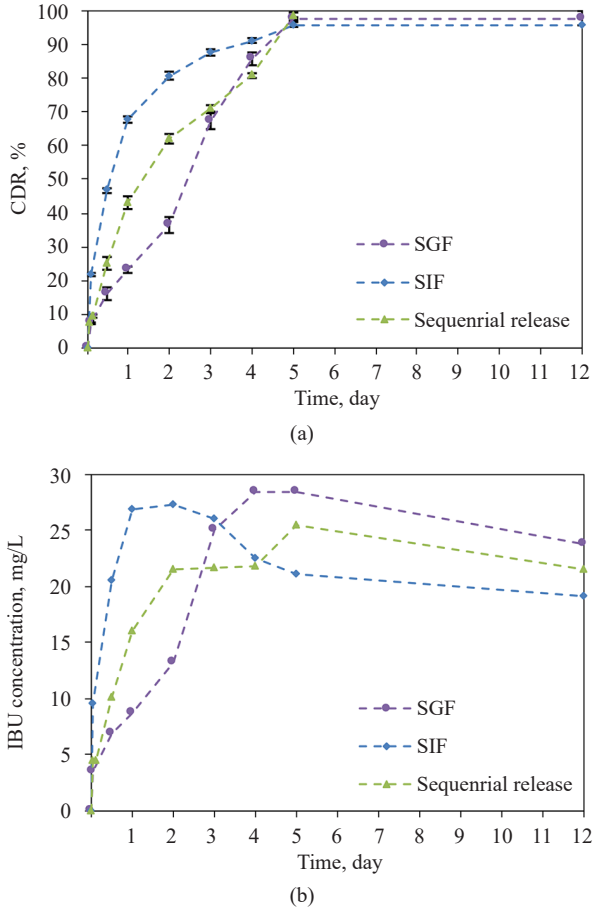


Fig. 7. *In vitro* release of IBU-CSNPs in terms of the CDR (a) and ibuprofen concentration (b) recorded under SGF, SIF, and sequential pH-changing conditions

In the sequential pH condition, the ibuprofen release profile of the IBU-CSNPs is a combination of the release patterns witnessed in SGF and SIF, but at different CDR and ibuprofen concentrations. The release kinetics of the drug-loaded nanoparticles under the sequentially changing pH condition exhibit distinctions starting from the transition of the environment with a slower ibuprofen release rate. In this case, the maximum ibuprofen concentration is reached after 5 days along with the therapeutic drug concentration achieved after 12 h and continuously maintained in the range of 10.05–21.57 mg/L until the 12th day. As depicted in Fig. 7, the findings of this biomimetic evaluation indicate that the higher CDR and ibuprofen concentration in SIF than in SGF enables effective drug delivery to the intestine as well as avoids drug leakage in the stomach.

The release kinetics of IBU-CSNPs in SGF, SIF, and biomimetic conditions are mathematically analyzed by the determined models including zero order, first order, Higuchi, Kormeyer–Peppas, and Kopcha. The results from the analysis are tabulated in Table 2.

Table 2. Analysis of IBU-CSNPs release kinetics by mathematical models

Model	Model coefficient	Experimental condition		
		SGF	SIF	Sequential release
Z-O	k_0	0.196	0.162	0.185
	R^2	0.987	0.750	0.939
F-O	k_1	0.491	0.230	0.456
	R^2	0.908	0.636	0.754
H	k_H	0.171	0.134	0.160
	R^2	0.897	0.563	0.789
K–P	k_{KP}	0.237	0.697	0.416
	n	0.917	0.470	0.622
	R^2	0.983	0.999	0.997
Kopcha	A	0.076	0.494	0.375
	B	0.167	0.000	0.025
	R^2	0.994	0.966	0.995

The release profile of IBU-CSNPs follows the Korsmeyer–Peppas model in SIF (R^2 of 0.999) and the Kopcha model in SGF (R^2 of 0.994). Both models show an extremely high correlation with the ibuprofen release kinetics under the sequentially pH-changing condition. The release exponent of 0.470 determines the anomalous or non-Fickian transport for the release kinetics of IBU-CSNPs governed by the drug diffusion, swelling, and degradation of the nanoparticles. On the contrary, the mechanism of the drug release into the acidic environment is predominantly controlled by the erosion of the nanoparticles according to the greater erosion constant (B) than the diffusion constant (A) in the Kopcha model. For the simulated oral drug delivery by changing pH, the release exponent below 0.85 (Korsmeyer–Peppas model) and A/B ratio above 1 (Kopcha model) confirm that the ibuprofen diffusion is the primary mechanism controlling the drug release from the IBU-CSNPs. This finding is reasonable due to the much longer exposure duration of the nanoparticles encapsulating ibuprofen in SIF than in SGF.

4. CONCLUSIONS

The IBU-CSNPs successfully synthesized following the synthesis procedure with the CS/TPP ratio from 1 : 0.25 to 1 : 1 (mg/mg) show a uniform spherical shape and a particle size of 50–60 nm. The CS/TPP ratio influences the drug entrapment efficiency of the developed nanoparticles. When the ratio decreases below 1 : 1 (mg/mg), there is a failure in the drug loading of the CSNPs as evidenced by a remarkable reduction in both EE and LC. Under the simulated condition of oral drug delivery, the IBU-CSNPs have a degradability of about 50% after 7 days and excellent acid resistance, as well as demonstrating a controlled pH-responsive release. In the first 3 h within the SGF environment, only 9.44% of ibuprofen is released, demonstrating the high efficiency of ibuprofen protection within the CSNPs system. The release gradually increases in the SIF environment to reach 25.07% at the 12-h mark having an ibuprofen concentration of 10.05 mg/mL. The ibuprofen concentration keeps increasing, reaching its peak at 25.50 mg/mL after 5 days of IBU-CSNP exposure to SIF. The erosion of nanochitosan contributes to the slow ibuprofen release in SGF, while the sustained release in SIF follows the non-Fickian process governed by diffusion, swelling, and degradation of the IBU-CSNPs.

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Authors' contributions

All authors contributed equally to the research.

The authors declare no conflicts of interest.

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