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Development of Smart Alginate/chitosan Grafted Microcapsules for Colon Site-specific Drug Delivery

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IN THIS study, a smart delivery system for colon site-specific release of diclofenac sodium (DS) was developed based on alginate grafted chitosan (Alg-g-CS) microcapsules. The developed microcapsules were characterized using FTIR and SEM characterization tools, while the present amine content on the alginate microcapsules surface was estimated by ion exchange capacity (IEC) measurements. Besides, both swelling and in vitro drug release profiles were studied at colon pH medium (pH7.4). The results showed an increase in IEC values from 1.1 to 3.6meq/g with increasing CS concentration from 0.1 to 0.5%. Moreover, grafting of alginate microcapsules with chitosan prevented the drug burst release as well as protected alginate microcapsules from the fast disintegration at colon conditions. The gained results clearly suggested that the developed smart Alg-g-CS (0.5%CS) microcapsules could be used effectively for the delivery of diclofenac sodium (DS) to colon tract.

Keywords: Alginate, Chitosan, Drug delivery, Diclofenac sodium.

Introduction

Greatly attention has been given for hydrogel biopolymers over the last fifty years owing to their exceptional properties such as biodegradability, non-toxicity and biocompatibility in addition to their natural abundance [1, 2]. These biopolymers have been widely used for numerous biomedical applications especially as drug delivery systems [3-5]. Indeed, the main objectives for designing controlled and sustained delivery systems are to reduce the required drug dose, increase the drug efficiency by localization at the specific-site of action and provide an acceptable drug release profiles [6]. Alginate is an anionic natural biopolymer extracted from algae and composed of α–L-guluronic acid (G) and the β-D-mannuronic acid (M) [7]. Owing to its excellent and attractive characteristics such as non-toxicity, non-antigenicity, biodegradability, biocompatibility, ease of gelation and exceptional mucoadhesive properties [8] alginate hydrogel biopolymer has found abundant applications in various industrial [9], water treatment [10, 11] and biomedical applications [12]. Therefore, alginate hydrogel has been considered as the most acceptable biopolymer for controlled drug delivery systems [13], since the drug can be incorporated into alginate hydrogel in several forms such as microsphere, beads, tablets and films. In addition, due to its pH-sensitivity under gastrointestinal conditions [14] alginate hydrogel has been effectively used as a smart drug carrier owing. Since, pH sensitivity of alginate can be exploited to alter the drug release profiles. However, fast dissolution of alginate at the higher pH leads to burst release of drug. Therefore, physicochemical modifications of alginate biopolymer such as grafting, coating and crosslinking allow controlling the previous

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properties which are not possible with the native biopolymer as well as improving its mechanical properties, swelling, and drug diffusion/release profiles [15, 16].

Similar to alginate, chitosan biopolymer is also a marine biopolymer obtained by the deacetylation of chitin which is present in shells of marine crustacean [17]. Chitosan consist of a copolymer of β-(1→4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-Dglucopyranose [18, 19]. Due to its excellent physical, chemical and biological properties chitosan-based has been adopted to be effectively used in a vast array of extensively diverse products and applications. Where, it can be applied in food industry [20], cosmetic products [21] and water treatment [22, 23] as well as biomedical fields [24]. Chitosan-based hydrogels have been considered promising materials for tissue engineering, wound healing, bone regeneration and drug delivery applications [25-28].

In this study, chitosan (CS) biopolymer was grafted on the surface of alginate (Alg) microcapsules in order to control the fast dissolution of alginate at colon conditions as well as to promote the drug release profiles. The formulated pH-sensitive (Alg-g-CS) microcapsules were characterized using different characterization tools. Diclofenac sodium (DS) was used as a model of drug and its encapsulation efficiency was estimated. Their swelling as well as in vitro drug release profiles were achieved under simulated colonic conditions.

Experimental

Materials

Sodium alginate (Alg; Medium viscosity) and P-Benzoquinone (PBQ) (purity 99+ %) were obtained from Sigma- Aldrich Chemicals Ltd. (Germany). Chitosan was obtained from across Organics (New Jersey, USA). Diclofenac Sodium (DS) was supplied from Aladdin Chemical Co., Ltd. (Shanghai, China). Calcium chloride (anhydrous Fine GRG 90%) was purchased from Fisher Scientific (Fairlawn, NJ, USA). Acetic acid (99%) and Ethyl alcohol (99%) were obtained from El- Nasr Pharmaceutical Co. for Chemicals. (Egypt).

Preparation of DS-loaded Alg-g-CS microcapsules

DS-loaded Alg-g-CS microcapsules were prepared via three consequently stages. Firstly, alginate (2%, w/v) was dissolved in hot distilled water under continuous stirring and followed with cooling at room temperature. A known amount of DS-drug was dissolved in distilled water with final concentration 20 % (w/w) to the total weight of native Alg. DS solution was added to the prepared Alg solution under stirring to obtain a homogenous solution, and left for 30 min at room temperature. The mixture was then dripped into a solution of $CaCl_2$ (2%, w/v) as a gelling medium via a syringe needle using an electrostatic pump. The formulated wet microcapsules were left for 15 min at room temperature, then separated and washed by distilled water. Secondly, DS-loaded Alg microcapsules were subsequently soaked in a solution of PBQ (0.04M)/pH 10 at 30 °C for 1 h with continuous gentle stirring for activation of Alg microcapsules surface [29]. The resultant PBQ-activated alginate microcapsules were separated and washed several times with distilled water to remove the excess of PBQ molecules. Finally, the third stage involved surface grafting of microcapsules and was achieved via immersing microcapsules in a solution of chitosan with different concentrations (CS; (0.1, 0.3, 0.5 and1% w/v)) under continuous gentile stirring at 25 °C for 1h. The formed pH-sensitive grafted microcapsules were rinsed and washed several times with distilled water to remove the excess of un-grafted CS molecules, and followed by vacuum drying at 40 °C overnight until constant weight. The developed grafted microcapsules were coded as S0.1, S0.3, S0.5 and S1 based on the used CS concentration, while Alg microcapsules were coded as S0. The proposed mechanism for the preparation of Alg-g-CS microcapsules was investigated in Fig. 1.

Instrumental characterization

The changes in the chemical and morphological structures of the developed microcapsules were investigated using Fourier transform Infrared Spectrophotometer (FT-IR, Model 8400 S, Shimadzu, Japan) and Scanning Electron Microscopy (SEM, Model Jsm 6360 LA, Joel, Japan).

Determination of amine content

Ion exchange capacity (IEC) measurements were conducted to determine the present amine content on the surface of activated alginate microcapsules. Where, a definite amount of the grafted microcapsules was crushed and soaked in a solution of (0.1 M H_2SO_4).and kept for 12 h at room temperature. Thereafter, the mixture was filtered and the aliquot was titrated with a solution of NaOH (0.1M) [30]. IEC values were estimated

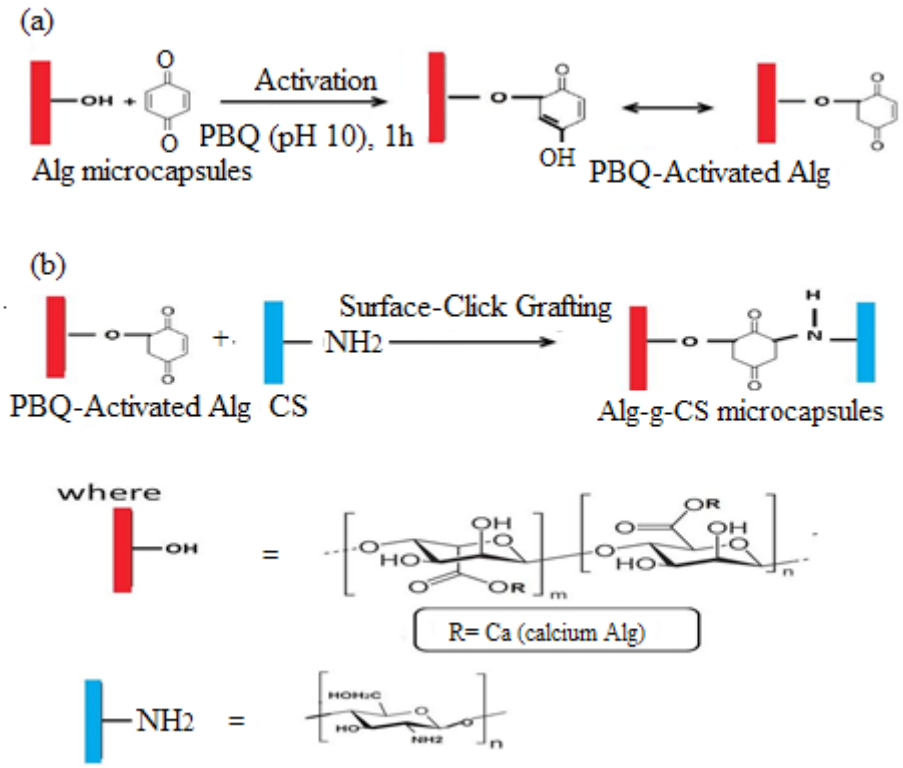

Fig. 1. Preparation of Alg-g-CS microcapsules.

using the following equation:

$$IEC(meq/g) = \frac{(V_2 - V_1)N}{w} \quad (1)$$

Where, V_1 is and V_2 are NaOH volumes required for neutralization of H_2SO_4 in the absence and the presence of the microcapsules sample, N signifies normality of NaOH solution and w is the weight of the microcapsules sample.

Swelling experiments

The swelling profile of the grafted microcapsules was investigated via the immersing method [31]. Accurately weighed 10 mg of dried microcapsules were immersed in 50 mL buffer solution (pH 7.4) and allowed to swell at 37°C. At predetermined time intervals, the swollen samples were rinsed gently the excess surface-adhered water drops were removed by blotting them between two filter papers, and followed with weighing using an accurate electronic balance. The percent of swelling degree (SD%) can be expressed by the following equation:

$$SD\ (\%) = \frac{S_b - S_a}{S_a} \times 100 \quad (2)$$

Where, S_a represents weight of initial dried sample at time zero and S_b signifies weight of the swollen sample at time t.

DS-drug loading studies

DS-drug loading efficiency (%) was estimated via immersing 10mg of crushed DS- loaded microcapsules in 50 mL (pH 7.4) of phosphate-buffered solution (PBS) with shaking for 24 h at 37 °C in a water bath to ensure complete extraction of DS-drug from microcapsules samples. After filtration, an aliquot sample was removed and DS was analyzed using a UV spectrophotometer at a wavelength of 276 nm, and each determination was conducted in triplicate. DS-drug loading efficiency can be calculated as follows:

$$\text{Drug loading efficiency (\%)} = (W_1/W_0) \times 100 \quad (3)$$

Where W_1 is the amount of drug in the weighted amount of microcapsules and W_0 is the initial amount of drug that was first added during the loading stage.

In vitro DS-drug release studies

For studying the in vitro DS-release studies from the grafted microcapsules, 10mg of tested samples were immersed in a simulated colonic fluid (SCF, pH 7.4) at 37 °C under gentle shaking.

At predetermined time intervals, approximately 1 mL of the used buffer solution was removed and replaced with freshly buffer solution. The released amount of DS-drug was analyzed using UV- spectroscopy at 276 nm using a standard curve of known concentrations in the range of (0.05-2.5 mg/mL).

Results and Discussion

IEC measurements

Effect of CS concentration on IEC values of Alg-g-CS microcapsules was studied and the results were depicted in Fig. 2. Where, IEC represents the amine content present on the microcapsules surface. The results clarified that IEC value was increased from 1.1 to 3.6m_{eq}/g with increasing CS concentration from 0.1% (S0.1) to 0.5 % (S0.5). This could be explained by increasing number of the primary amine groups that attached to the available active sites on the PBQ activated alginate. However, further increase of CS concentrations up to 1% (S1) has no significant effect on IEC values as a result of complete grafting of most activated OH groups of alginate with 0.5% of CS, and the left numbers of activated OH groups of alginate were limited.

FTIR analysis

The chemical structure of the used native polymers and the developed grafted microcapsules was investigated by FTIR analysis as shown in Fig. 3 (a-c). IR spectrum of alginate (Alg; Fig. 3a) showed a broad absorption band at 3446.5 cm^{-1} owing to the stretching frequency of –OH groups. Also, a broad asymmetrical band 1630 cm^{-1} was observed and corresponds to the COO- stretching. An even broader absorption band was present at 1062 cm^{-1}which can be attributed to the present COH stretching [14]. IR spectrum of chitosan (CS; Fig. 3b) confirmed the stretching vibration band at 3439 cm^{-1} that attributed stretching vibration of NH_2 and OH groups of CS. Band at 2903 cm^{-1} represent (C-H stretching on methyl) for both CS. In addition, band at 1622 cm^{-1} corresponds to stretching of C=O group of a primary amide (amide I) that present in CS structure [26]. Besides, band at 1400 cm^{-1} corresponds to deformation vibration of C–N in chitosan, and the band at 1066 cm^{-1} corresponds to asymmetric stretching of C–N–C for chitosan. On the other hand, IR spectrum of the grafted microcapsules (Alg-g-CS; Fig. 3c) clarified that both OH and N-H stretching vibration were shifted, and increased significantly

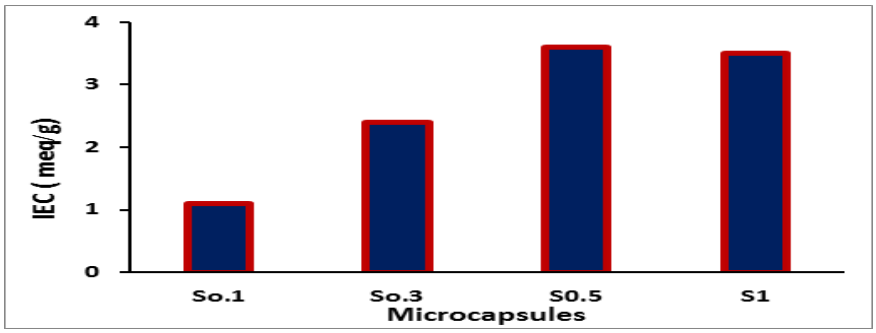

Fig. 2. IEC values of Alg-g-CS microcapsules.

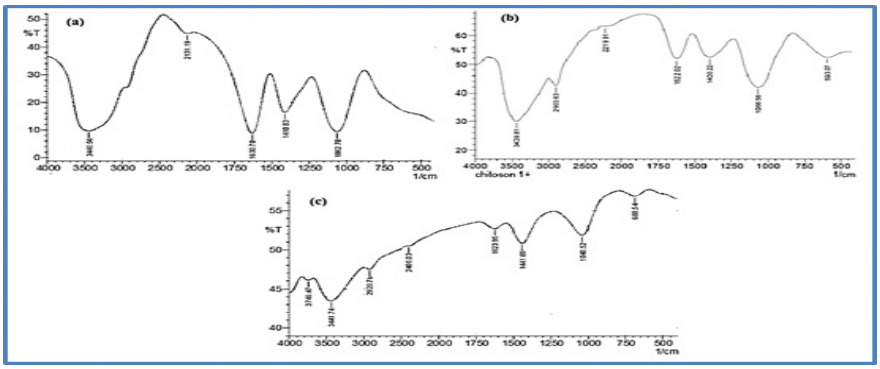

Fig. 3. FT-IR spectra of (a) Alg, (b) CS and (c) Alg-g-CS microcapsules (0.5% CS).

after the grafting process to 3441 cm^{-1}. Where, OH stretching vibration is overlapped by N–H stretching due to the presence of CS molecules on the Alg surface. Also, the asymmetric peak of –COO- group was shifted to 1623 cm^{-1}. The present peak at 1070 cm^{-1} probably as a result of ionic interaction between COO- groups of Alg and NH_3^+ groups of CS [16]. Furthermore, the band at 1441 cm^{-1} could be related to C-N stretching vibrations indicating the tolerable preparation of the grafted alginate microcapsules.

SEM analysis

SEM images of Alg, CS and Alg-g-CS microcapsules were investigated at the same magnification as shown in Fig. 4 (a-c). It was clear that the Alg (Fig. 4a) exhibited a granular surface while a roughly surface was observed in case of CS biopolymer (Fig. 4b). On the other hand, it was detected that the surface morphology of the developed Alg-g-CS microcapsules (Fig. 4c) was significantly changed compared to the native biopolymers. Since, dense and random fibrillar surface has formed after grafting of alginate surface with CS molecules. These results could be ascribed by presence of amine groups on the activated surface of Alg, since they provide more roughly surface.

Swelling evaluation

Swelling of the dried microcapsules is generally attributed to the hydration of the hydrophilic groups of alginate and chitosan. Figure 5 showed the swelling profiles of Alg and Alg-g-CS microcapsules at pH 7.4. The results clarified that Alg microcapsules exhibited higher swelling degree values with increasing the swelling time up to 4h compared with the grafted alginate microcapsules. However, disintegration of Alg took place beyond 4h from the initial swelling time. The instability of Alg microcapsules at pH7.4 could be attributed to disruption of calcium-alginate microcapsules occurred in saline phosphate buffer solution (PBS). Thus, the chelating action of phosphate ions occurred, and the affinity of phosphate ions for calcium ions was higher than that of Alg matrix [32], thus, large disintegration occurred for Alg microcapsules. On the other hand, the grafted microcapsules were enhanced their stability at pH 7.4 with increasing CS concentration. Where, Alg microcapsules that grafted with 0.1 and 0.3% CS (S0.1 and S0.3) were found to be stable up to 6 h from the initial swelling time and recorded maximum swelling values 3150 and 3200%. Further increasing CS concentration up to 1% clearly enhanced the stability of Alg microcapsules and protects them from fast disruption at pH 7.4 with further increasing time of swelling up to 8 h. Sensitivity of the grafted microcapsules at pH 7.4 could be explained by decreasing the ionization of amine groups of CS, since most of amino groups' chitosan were deprotonated. As a result,

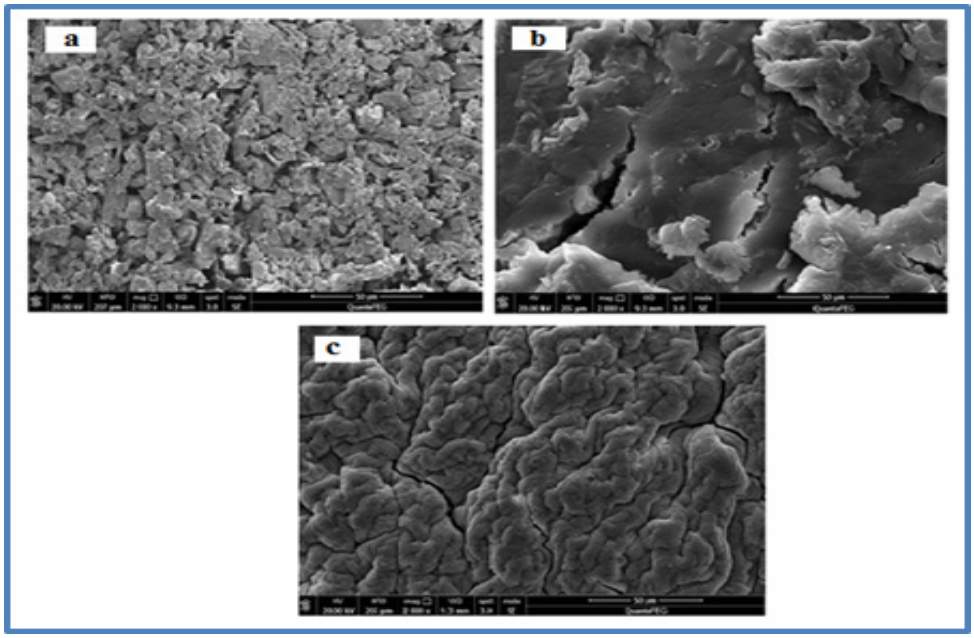

Fig. 4. SEM images of (a) Alg, (b) CS and (c) Alg-g-CS microcapsules (0.5% CS).

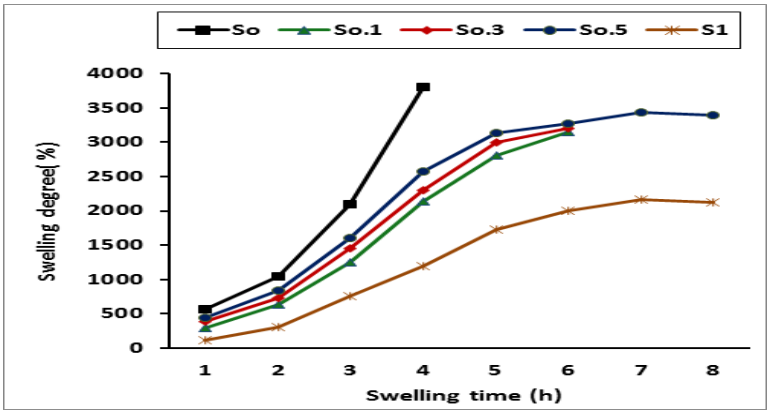

Fig. 5. Swelling profiles at pH 7.4 for Alg and the grafted Alg microcapsules with different concentrations of CS.

the electrostatic interaction between chitosan and alginate become weak. Most of COOH groups of Alg become ionized at pH7.4 and the concentration of negatively charged groups of alginate increases, as a result, the electrostatic repulsion between the COO^- groups in Alg causes the further swelling of the grafted microcapsule network. The result demonstrated also that the swelling degree values of sample S1 (1% CS) were less than values of S0.5 (0.5% CS). This could be explained by increasing the density of network chains with increasing CS concentration from 0.5% to 1% which conversely affects the swelling degree of microcapsules.

From the ion exchange capacity and swelling studies, it was clarified that the grafted microcapsules with 0.5%CS showed the maximum values. As a result, sample S0.5 was selected for the drug loading and release studies as well as the native Alg microcapsules (S0).

Drug loading evaluation

Herein, Diclofinac sodium (DS) was used as a drug model and its loading efficiency was investigated as shown in Fig. 6. The obtained results showed that values of DS- loading efficiency for Alg microcapsules values were slightly higher than values of the grafted microcapsules (S0.5) as a result of the possible drug leaching in the grafting medium during the formation of grafted microcapsules. In all cases DS- loading efficiency exceeded 89% regardless of the initial amount of DS used at the loading process. Thus, the applied loading technique for the SD- loading step proves the successful loading process for DS into Alg and Alg-g-CS microcapsules.

Drug release evaluation

Figure 7 investigated the cumulative DS-release profiles for Alg and the grafted Alg microcapsules with CS (0.5% CS) at pH 7.4 as a simulated colon fluid. It was observed that Alg

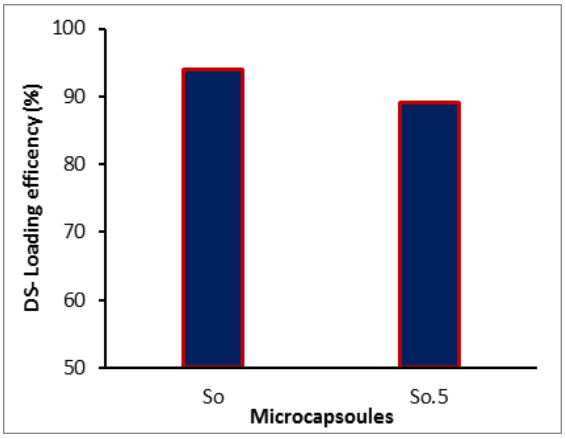

Fig. 6. DS-loading efficiency values for Alg and the grafted Alg microcapsules with CS (0.5% CS).

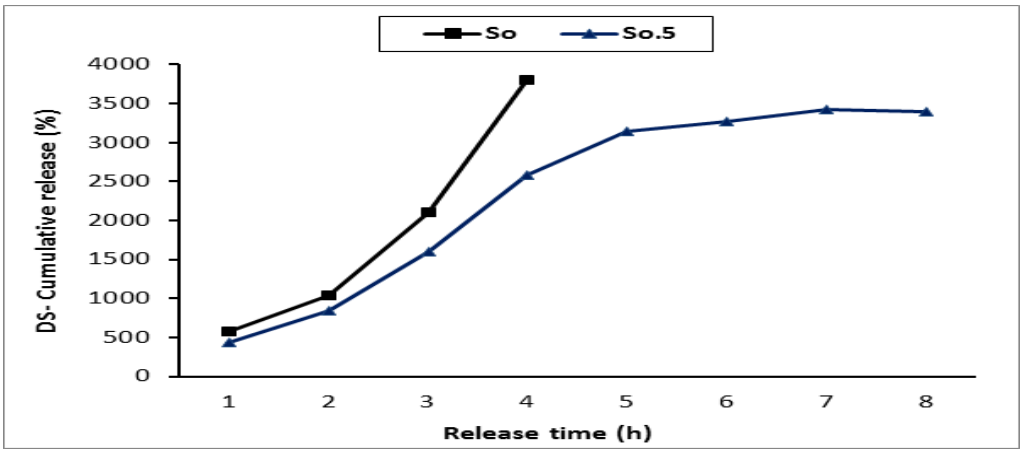

Fig. 7. DS-cumulative release values for Alg and the grafted Alg microcapsules with CS (0.5% CS) at pH 7.4.

microcapsules showed increasing the DS release with increasing release time up to 4 h, and then burst release occurred as a result of disintegration of Alg microcapsules at pH 7.4. These results agreed with the obtained swelling profiles at the same pH. On the other hand the release profile of the grafted Alg microcapsules with CS (0.5% CS) was clearly enhanced with time, where a continuous DS- release was noticed with increasing the release time. Where a maximum cumulative release was recorded after 6h from the initial release time and then the value was nearly constant with increasing time up to 8h. Besides, increasing the release values could be as a result of increasing the swelling degree of the grafted microcapsules resultant from hydrophilic COOH and NH2 groups of Alg and chitosan biopolymer. This obviously reflects positively on the drug release behavior. These observations indicated that CS layer clearly protected Alg microcapsules from fast disintegration as well as prevent the drug burst release at colon site.

Conclusion

Alginate grafted chitosan microcapsules were prepared via surface grafting technique for the delivery of diclofenac sodium to colon specific-site. The developed microcapsules were verified their chemical structures using FTIR analysis, while the changes in their surface morphologies were verified using SEM analysis. Ion exchange capacity measurements indicated the increase of IEC values with increasing chitosan content on the activated alginate surface. In addition, the swelling degree values of the grafted microcapsules were significantly increased with increasing time of swelling up to 8 h. Besides, the stability of alginate microcapsules at pH 7.4 was enhanced with increasing chitosan concentration up to 1%. Drug loading efficency of the grafted microcapsules was 89% while the cumulative drug release profile was improved after CS grafting on alginate microcapsules surface. Finally, it can be concluded that the developed grafted microcapsules could act as a smart caareier for colon specific release of diclofenac sodium.

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تطوير كبسولات الالجينات/ الكيتوزان المطعمة الذكية لتوصيل الدواء إلى القولون

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[٢]قسم بحوث المواد البوليمرية- معهد بحوث التكنولوجيا المتقدمة والمواد الجديدة- مدينة الأبحاث العلمية والتطبيقات التكنولوجية- مدينة برج العرب الجديدة- ص ب ٢١٩٣٤- الأسكندرية - مصر.

فى هذه الدراسة تم تطوير نظام ذكى لتوصيل دواء ديكلوفيناك الصوديوم إلى منطقة القولون مكون من كبسولات الألجينات المطعمة بالكيتوزان. الكبسولات المطورة تم توصيفها بأجهزة الأشعة تحت الحمراء والميكروسكوب الماسح الإلكترونى بينما تم تقدير كمية الأمين الموجودة على سطح كبسولات الالجينات بواسطة قياس سعة المبادلة الأيونية. بجانب ذلك تم التعرف على خاصية امتصاص الماء وخروج الدواء من الكبسولات المحضرة فى القولون. وأظهرت النتائج زيادة سعة المبادلة الأيونية من ١,١الى ٣,٦ مل مكافىء لكل جرام مع زيادة تركيز الكيتوزان من ١, الى ٥, ٪ .إضافة إلى ذلك تطعيم كبسولات الألجينات بالكيتوزان منع الخروج الفورى للدواء وحمى الكبسولات من التدمير السريع فى القولون. النتائج التى تم الحصول عليها تقترح ان الكبسولات المطعمة الذكية يمكن استخدامها بكفائة فى توصيل دواء ديكلوفيناك الصوديوم إلى القولون.