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ORIGINAL PAPER

Synthesis of sodium alginate grafted stearate acid (NaAlg-g-St) and evaluation of the polymer as drug release controlling matrix

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Abstract

Sodium alginate grafted stearic acid (NaAlg-*g*-St) was synthesized via the reaction of stearic acid and sodium alginate (NaAlg) in the presence of diisopropylcarbodiimid (DIC) under the solvent free condition. Sustained release matrix tablets of indomethacin (IM) were developed by employing sodium alginate or the new synthesized polymer. The drug dissolution test and other physicochemical properties were evaluated for each formulation. The results of this study showed that sodium alginate grafted stearic acid, has a good effect on the sustained releasing feature of the tablets and causes the drug to be released gradually; and probably, causes less side effects and more compliance in patients. In the physicochemical tests, the usage of NaAlg or the NaAlg-*g*-St was not effective on the tablet's hardness but in other tests made a significant change statistically.

Keywords Indomethacin · Sustained release tablets · Sodium alginate · Sodium alginate grafted stearic acid

Introduction

Biodegradable polymers are the non-toxic polymers that decompose by biological reactions to the natural byproducts such as H_2O, CO_2, N_2, inorganic salts and biomass [1]. These polymers are often used for drug delivery, where they release drugs slowly into the body [2]. Some of the commonly used types of these polymers are poly(lactide) [3], poly(lactide-co-glycolide) [4], dextran [5] and sodium alginate [6]. Poly (lactide-co-glycolide) is used to make pharmaceutical implants because of the very slow drugs release rate (for years or months) and the high price. While Alginates and their derivatives were used in more prevalent and cheaper dosage forms such as pills and capsules.

Alginic acid, so-called algin, is a biodegradable polysaccharide which is a linear copolymer composed of *D*-mannuronic acid and *L*-guluronic acid monomers. Algin is biodegradable, inexpensive, stable and simply available from the renewable resources. This acidic polymer can be reacted with sodium carbonate to produce sodium alginate salt (Scheme 1) [7].

A wide range of research has been done to use this biopolymer in drug delivery and tissue engineering system. For example: as a suitable carrier for local drug release [8]. Sodium alginate has been studied widely as a suitable substance for controlled drug delivery [9].

Unfortunately regardless of the many benefits of sodium alginate, it is suffering from some problems such as prone to enzymatic degradation and limitations in controlled-release due to rapid dissolution of alginate matrices in the high pH ranges which can cause burst release of active molecules. Chemically modification by grafting method is a well-established way to overcome these problems [10]. For this purpose, several molecules are grafted to the sodium alginate, some of which are: poly(*N,N'*-dimethylacrylamide) [10], polyacrylonitrile [11], poly(methyl methacrylate) [12], and poly(*N*-isopropylacrylamide) [13].

Indomethacin or indometacin (IM) is a water-insoluble nonsteroidal anti-inflammatory drug (NSAID) commonly used to treatment of pain and inflammation caused by rheumatoid arthritis and osteoarthritis [14]. IM has a short biological half-life (2.5 h) and similar to the other NSAIDs, it causes gastric irritation [15]. Preparation of sustain release the matrix

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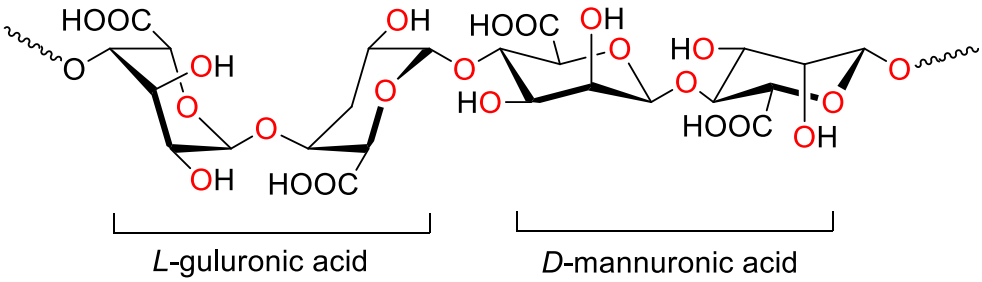
Scheme 1 Structure of alginic acid



tablet from the biodegradable polysaccharides (such as sodium alginate) can enhance patients' compliance, reduce the gastric irritation and improve bioavailability profile of Indomethacin [14].

Studies on animal models have shown that co-administration of sodium alginate and IM simultaneously reduces the gastrointestinal tract symptoms. In addition, molecular studies on that were done on the animal's tissue samples also confirm the above statements [16].

In this study, to improve the NaAlg efficacy, hydrophobicity of sodium alginate was augmented through an esterification reaction with the stearic acid to form NaAlg-*g*-St, then it was used as the drug controlled release matrix.

Experimental

Materials

Dimethylaminopyridine (DMAP), and dialysis tube with cut-off 12,000 Da. were purchased from Sigma-Aldrich company (USA) and N,N′-Diisopropylcarbodiimide (DIC) from Merck company (Germany). Sodium alginate, solvents (ethanol, acetone, …) and other chemicals such as HCl, stearic acid, sodium phosphate monobasic, and sodium hydroxide prepared from Samchun Chemical Co. (South Korea). All ingredients that were used in the tablet preparation process were pharmaceutical grade from Boehringer Mannheim (Germany).

Apparatus

Fourier transform infrared (IR) spectra of NaAlg and NaAlg-g-St were recorded in the wavelength region between 400 and 4000 cm^{-1} at the ambient temperature as KBr disks, using a Bruker FT-IR Plus spectrophotometer.

Nuclear magnetic resonance (^{1}H NMR) spectra of NaAlg and NaAlg-g-St was measured using an NMR spectrometer (Avance-500, Bruker, Germany). Chemical shifts are given in the δ unit as part per million (ppm).

Differential scanning calorimetry (DSC) thermograms were recorded on a Mettler-Toledo (USA) calorimeter.

High-performance liquid chromatography (HPLC) analysis was carried out using a system equipped with an LC-20 AD XR pump, an SPD-M20A UV detector (Shimadzu, Japan) and the autosampler.

Methods

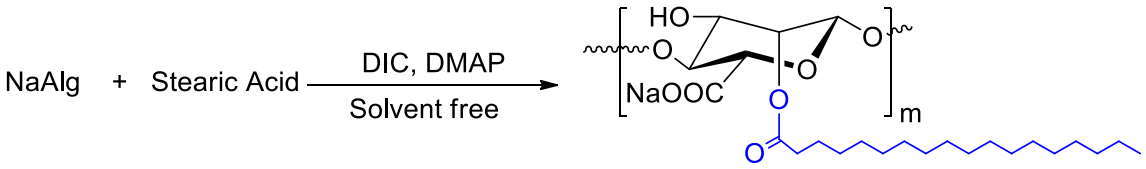
Synthesis of sodium alginate grafted stearic acid (NaAlg-g-St)

Using a mortar and pestle, 5.6 g of stearic acid and 2.05 mL of diisopropylcarbodiimid (DIC) were ground for 3 min. Then 10 g sodium alginate (NaAlg) and 2.54 g of dimethylaminopyridine (DMAP) were added to the mixture and were floured for 90 min. After this, the mixture was washed with ethanol (3 × 20 mL) to prepare a white paste. Further purification was carried out in a dialysis tube with cut-off 12,000 Da. in the 1000 mL distilled water twice. After precipitation and freeze-drying, the pure product was obtained. Characterization of the polymer (NaAlg-g-St) was performed using IR and H-NMR spectra (Scheme 2).

Preparation of indomethacin matrix tablet formulations

To prepare 25 mg indomethacin tablets for two formulations Containing, lactose (filler), NaAlg and NaAlg-g-St (drug controlling polymer), indomethacin (active pharmaceutical ingredient) with magnesium stearate (lubricant) were weighted and blended according to Table 1. Unit dosage weights of all the tablet formulations were set to 0.3 g (Table 1).

First, NaAlg or NaAlg-g-St were mixed with the drug for 1 h in a Tumbler Mixer (kavosh, I.R.I). Then, the filler material was added to the mixture and mixed again for 30 min. Finally, the blended powderwas lubrified with the lubricant for 2 min. A portion of the powder was stored for testing powder flow and compressibility. Most of the powder was also pressed with a single punch tablet press machine (kavosh, I.R.I).



Scheme 2 Synthesis of sodium alginate grafted stearic acid

Evaluation of matrix tablets

Hardness

The hardness of the tablets was determined by using the Erweka hardness tester apparatus (TBH 325, Germany).

Friability

The Erweka friability test device (Erweka, Germany) was used to determine the friability of the tablets. From each formulation (F1 and F2), 6.5 g tablets were dedusted and weighed. Then they were put in a drum of the friabilator and rotated for 100 times at 25 rpm for 15 min. The tablets were dedusted and were re-weighed. The percentage friability was calculated by the formula [17]:

$$\%\text{friability} = (\text{Initial wt.} - \text{Final wt.}/\text{Initial wt.}) \times 100.$$

Dissolution tests

The dissolution test was performed according to the apparatus II USP dissolution method [18] using a dissolution tester (kavosh, I.R.I). The drug release study is performed in the 900 mL phosphate buffer (pH 7.4) medium and sampling times were 15, 30, 60, 120, 240, and 360 min. 5 mL samples of being withdrawn from the vessels and then the same amount of the fresh buffer was replaced each time. The samples were filtered and analyzed with HPLC. The percent of IM released at various time intervals was calculated and plotted versus time. The dissolution profiles of the formulas are shown in Fig. 4.

It is necessary to state that the dissolution test was negative in the HCl medium (0.1 M) and no detectable drug release was observed in both formulations.

Table 1 The composition of different indomethacin tablets formulations

Ingredient (g)	F1	F2
Indomethacin	0.025	0.025
Sodium alginate	0.060	–
Magnesium stearate	0.003	0.003
Polymer	–	0.060
Lactose	0.212	0.212
Wright of tablet	0.300	0.300

Drug content

IM content in the tablets was measured using the HPLC method. A C18-PerfectSil Target column (ODS-3, Germany) was used. The mobile phase comprised of acetonitrile and solution of 0.01 M monobasic sodium phosphate and 0.01 M dibasic sodium phosphate (40:60). The mobile phase flow rate was adjusted constant (1 mL/min), and the effluent was monitored at 190–800 nm using a photodiode array UV detector, but the standard curve was drawn based on area under the curve absorption at 254 nm vs. time. Analysis and processing of data were done by *LabSolutions* software.

The tablets were powdered in the mortar. The powder was dissolved in 100 ml ethanol. Then sonicated for 10 min in a sonicator bath one hour. One milliliter of the supernatant solution was delivered to a volume of 10 ml. Finally, 20 μL of the diluted solution was injected into the HPLC.

Weight variation

10 tablets were weighed with digital scales and their mean, standard deviation and CV% were determined. According to American Pharmacopoeia, the standard deviation up to 10% of the labeled potency is acceptable (Table 2).

Differential scanning calorimetry

IM, NaAlg-g-St and physical mixture of the drug and NaAlg-g-St were subjected to differential scanning calorimetry (DSC) analysis to understanding the physical state of the indomethacin in the dispersion and any interaction between the drug and NaAlg-g-St. The calorimeter (Mettler-Toledo USA) was used at a scanning rate of 5 °C/min between 25 °C to 200 °C. The samples were sealed in aluminum pans and heated in the Argon as the inert atmosphere at a flow rate of 50 ml/min. Figure 3 shows the thermograms of IM, NaAlg-g-St and physical mixture of IM and NaAlg-g-St.

Statistical analysis

All the results are presented as mean ± SD and analyzed using Excel 2013, and SPSS version 16 software. Statistical analysis of the data was made by two sample independent (t-test). All p-values ≤ 0.05 were considered as a criterion for the significance of the difference.

Table 2 Physicochemical features of different indomethacin tablets

Formulation	Hardness(N)	Friability%	Drug content	Weight(mg)	Diameter(mm)
F1	63.41 ± 12.5	0.30	22.3 ± 0.2	300 ± 0.700	10.04 ± 0.01
F2	58.88 ± 6.21	0.15	23.00 ± 0.4	300 ± 1.050	10.02 ± 0.19

Results and discussion

Ft-IR study

The FT-IR spectrum of NaAlg-*g*-St is shown in Fig. 1. Broad-band peak between 3000 and 3800 cm^{-1} was attributed to O–H stretching vibrations. Two peaks which appeared in 2916 and 2850 cm^{-1} indicate the stretching vibrations aliphatic C–H, and in 1619 cm^{-1} shows the absorption band of the COO^{-}. Compared to NaAlg spectrum, a new weak band in 1736 cm^{-1} (highlighted in the red box) was assigned to the carbonyl group of stearate, which confirmed the grafting of stearate group to the polymer. This is in good harmony with the results reported papers [19–21]. Of course, it should be noted that in a polymeric chain, there are numerous hydroxyl groups, that some of which may be esterified. Therefore, the peak of carbonyl group if carboxylic acid and ester are commonly appeared together in FT-IR spectrums such grafted polymers[22].

^{1}H-NMR study

Another confirmation of the grafting is the ^{1}H-NMR spectrum of the NaAlg-g-St (Fig. 2). The absorption peak at δ = 0.84 ppm was assigned to the group of the stearate. Methylene groups of St appeared in δ = 1.27–1.32 ppm as a multiple peak. A single peak was recorded at δ = 2.88 ppm which indicates the nearest protons to the carbonyl group of the St the area ratio of 1 to 3 peaks has been calculated to confirm the successfully grafting. The ratio was about 3 to 2.

Given that these peaks did not exist in the NaAlg's H-NMR spectrum [13, 23, 24] and the area ratio of 1 to 3 peaks all proved the grafting of NaAlg to the St. Other peaks at δ = 3.74–5.02 belong to the NaAlg.

Differential scanning calorimetriy

The thermograms of IM, NaAlg-g-St and the IM-polymer dispersion are shown in Fig. 3. The thermogram of pure indomethacin (Fig. 3a) showed a sharp peak at 161.5 °C which is related to the melting point of the drug. NaAlg-g-St showed an endothermic peak at 60 °C. Since the peak extends up to 100 °C, it is probably attributing to the loss of the water absorbed by the polymer from the atmosphere.

It can be seen in Fig. 3c that due to Wonder Wallis interactions between the drug and the NaAlg-g-St hydrophobic branches (stearate), a peak that assigned to the drug crystalline

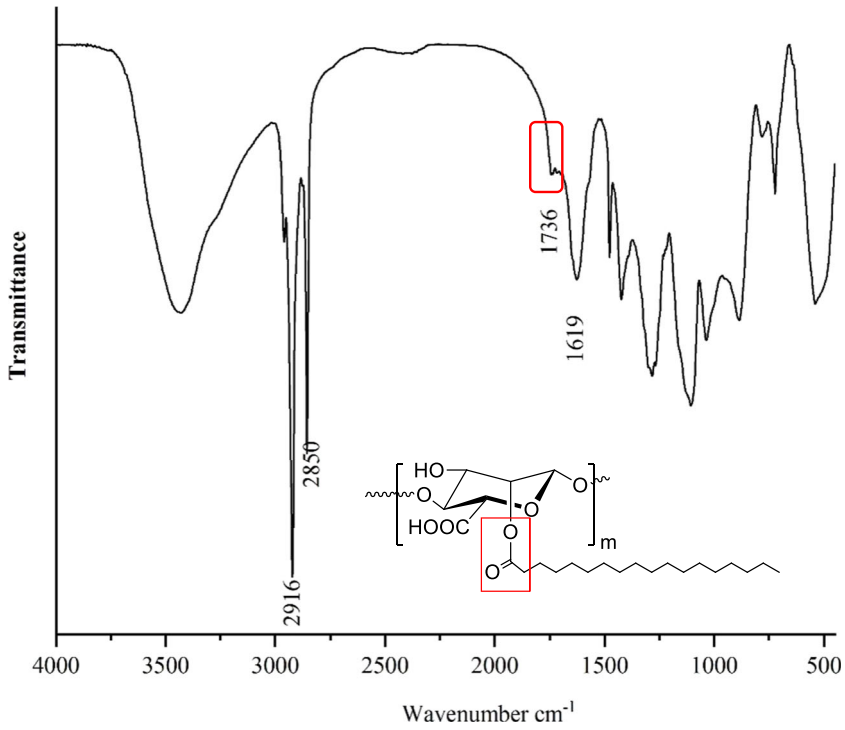


Fig. 1 The FT-IR spectrum of NaAlg-*g*-St as KBr disk

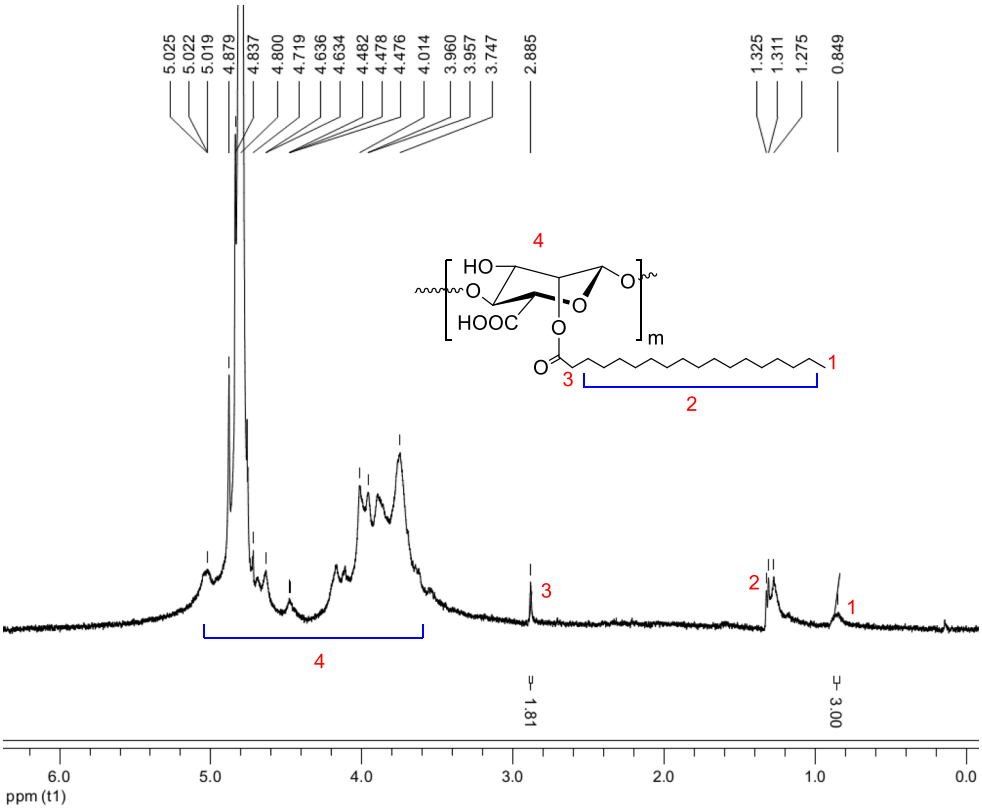


Fig. 2 ^{1}H-NMR spectrum of the NaAlg-g-St in D_2O

structure heat of the fusion, changes from 160.5 (Fig. 3a) to 157 degrees Celsius. In other studies on indomethacin thermogram changes due to the mixing with pharmaceutical ingredients, the reduction in the fusion temperature of indomethacin crystals or total disappearance of the peak has been observed[25, 26].

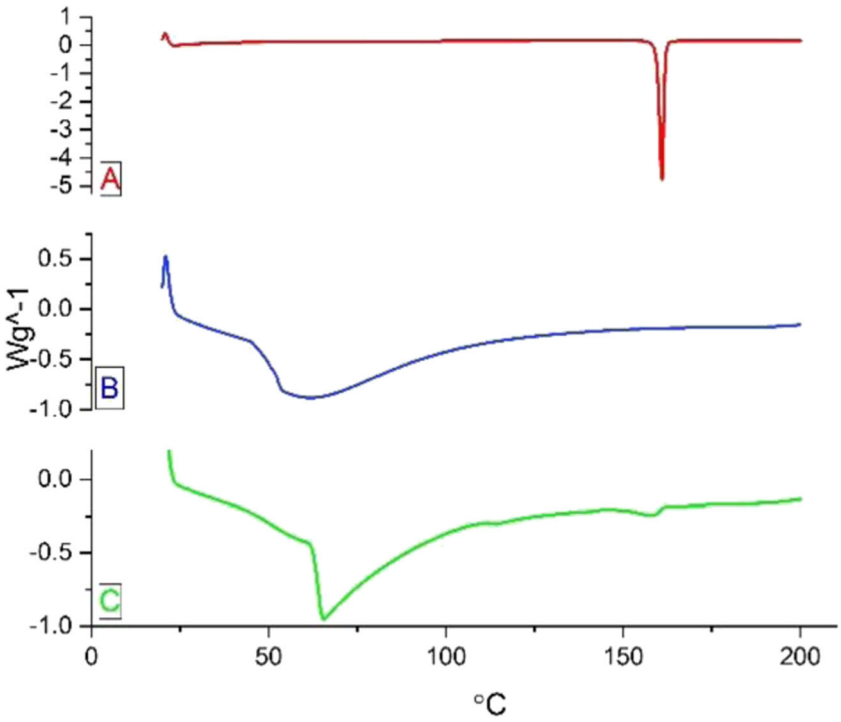


Fig. 3 DSC thermograms of indomethacin (**a**), NaAlg-g-St (**b**) and and IM-loaded NaAlg-g-St (**c**)

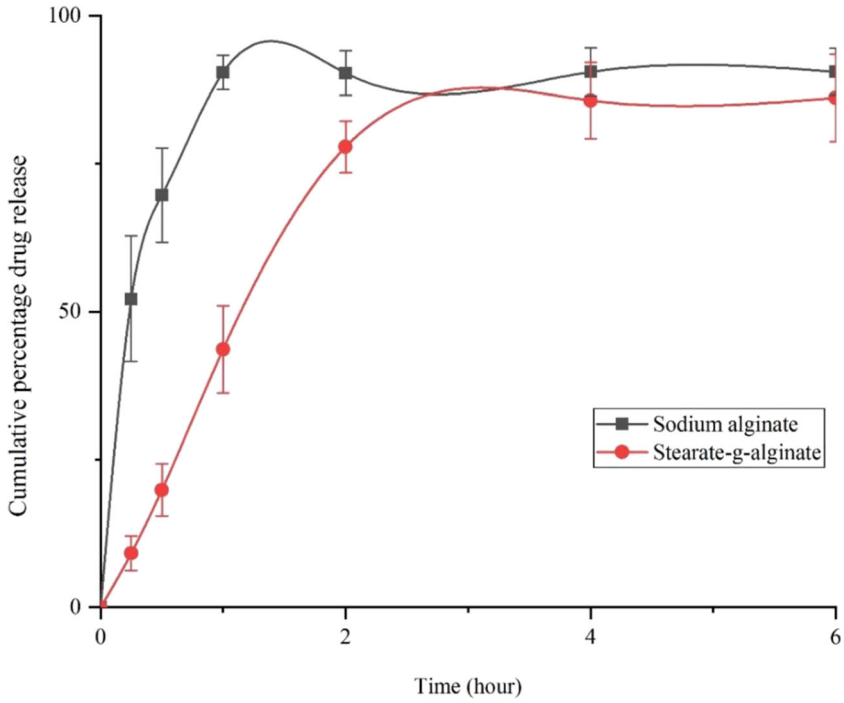


Fig. 4 Indomethacin release from two formulations of matrix tablets

Drug release

Releasing of IM from two formulations of the matrix tablets is determined by HPLC technique (Fig. 4). The formulations containing sodium alginate have the highest degree of drug release over a short period of time. As at the first hour, more than 90% of the drug has been released from the formulation. While in the formulation containing NaAlg-g-St, the drug released much slower so even after 6 h it did not reach 90%.

Since only 20% of the formula total weight is NaAlg-g-St, these results show that NaAlg-g-St may be a suitable polymer for the preparation of sustained release tablets of containing IM. as previously, for the production of microparticles, nanoparticles and carbon dioxide sensitive particles, hydrophobic derivatives of alginate have been made by different method and materials, which They also have the sustained release property[27, 28]. Of course, it should be kept in mind that many amid derivatives that are easily prepared from alginates can be bonded to lipids in the gastrointestinal tract and themselves have a pharmacological effect [29, 30].

Conclusions

Due to the lack of proper solvent other than water to dissolve the alginate in the reaction environment, the solvent free method was used to react stearic acid with alginate. Thermal analysis and FT-IR studies showed that there are physical interactions between indomethacin and the fatty acid chains that was added to polysaccharide. The drug release studies showed that these interactions could increase the drug release controlling properties of the polymer.

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References

1. Lendlein A, Sisson A (2011) Handbook of biodegradable polymers: isolation, synthesis, characterization and applications. John Wiley & Sons, Hoboken
2. Ottenbrite RM, Kim SW (2019) Polymeric drugs and drug delivery systems. CRC Press, Boca Raton
3. Kang Y, Wang C, Qiao Y et al (2019). Biomacromolecules 20: 1765–1776
4. Zhao W, Li J, Jin K et al (2016). Mater Sci Eng C 59:1181–1194
5. Bachelder EM, Pino EN, Ainslie KM (2016). Chem Rev 117:1915–1926
6. Hu Y, Peng J, Ke L et al (2016). J Polym Res 23:129
7. Rodrigues D, Freitas AC, Pereira L et al (2015). Food Chem 183: 197–207
8. Abedini F, Ebrahimi M, Roozbehani AH et al (2018). Polym Adv Technol 29:2564–2573
9. Hu Y, Zhang S, Han D et al (2018). J Polym Res 25:148
10. Akın A, Işıklan N (2016). Int J Biol Macromol 82:530–540
11. Kumar D, Pandey J, Raj V et al (2017). Open Med Chem J 11:109
12. Ali U, KJBA K, Buang NA (2015). Polym Rev 55:678–705
13. Işıklan N, Küçükbalcı G (2012). Eur J Pharm Biopharm 82:316–331
14. Ramesh KS (2015). Asian J Pharm 9:234–242
15. Brunton LL (2014) Goodman and Gilman's manual of pharmacology and therapeutics. McGraw-Hill, New York

16. Horibe S, Tanahashi T, Kawauchi S et al (2016). Int J Med Sci 13: 653–663
17. Nawale R, Mohite K (2013). Int J Pharm Sci Res 4:3670–3677
18. Pharmacopeia U (2014) Rockville: US Pharmacopeia
19. Işıklan N, Kurşun F, İnal M (2010). Carbohydrate polym 79:665–672
20. Varshosaz J, Hassanzadeh F, Sadeghi H et al (2012). J Nanomater 2012 Article ID:265657
21. Varshosaz J, Hassanzadeh F, Sadeghi-Aliabadi H et al (2014). BioMed Res Int 2014 Article ID:708593
22. Anwar H, Ahmad M, Minhas MU et al (2017). Carbohydr Polym 166:183–194
23. Youssouf L, Lallemand L, Giraud P et al (2017). Carbohydr Polym 166:55–63
24. Elsayed NH, Monier M, RAS A (2016). Carbohydr Polym 145: 121–131
25. Badri W, Miladi K, Robin S et al (2017). Pharm Res 34:1773–1783
26. Padrela L, Rodrigues MA, Velaga SP et al (2009). Eur J Pharm Sci 38:9–17
27. Choudhary S, Reck JM, Carr AJ et al (2018). Polym Adv Technol 29:198–204
28. Yang J, Dong H (2016). Carbohydr Polym 153:1–6
29. Marounek M, Volek Z, Taubner T et al (2019). Int J Biol Macromol 122:499–502
30. Taubner T, Marounek M, Synytsya A (2017). Int J Biol Macromol 103:202–207