Inulin-Niacin Conjugates: Preparation, Characterization, Kinetic and in vitro Release Studies

Showkat Ali Ganie (✉ alishowkat443@gmail.com)

Jamia Millia Islamia

Akbar Ali

Jamia Millia Islamia

Tariq Ahmad Mir

Jamia Millia Islamia

Nasreen Mazumdar

Jamia Millia Islamia

Research Article

Keywords: Inulin, Niacin, Tosylated inulin, Aminated inulin, Inulin Niacin conjugates

Posted Date: April 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-393385/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Journal of Polymers and the Environment on June 24th, 2021. See the published version at <https://doi.org/10.1007/s10924-021-02210-6>.

Abstract

Niacin, an essential B-complex vitamin, used in the treatment of nonalcoholic fatty liver disease is the first perceived lipid regulating medication, inhibits and reverses hepatic steatosis and inflammation in animals and liver cell cultures. Niacin shows beneficial effects on adiposity. Niacin plays an important role in DNA repair, electron transfer, one-carbon metabolism and fatty acid synthesis in cells. Natural polysaccharides with desirable chemical modifications can be combined with vitamins for developing the supplement treatment for vitamin deficiency disorders. Modification of inulin was carried out by tosylation, amination and then conjugated with niacin. Structural elucidation of the derivatives and conjugates was carried out by FT-IR, ^1H NMR and SEM. Thermal behavior was investigated by TGA and DSC techniques. The release and kinetics of niacin, from the conjugate, at different pH was studied. The release was observed to be pH dependent, showing a greater release at higher pH following Korsmeyer-Peppas kinetic model. Polysaccharide based approach was used for the preparation of stable niacin-inulin conjugates with controllable and prolonged release of niacin. These types of conjugates may be useful as vitamin delivery systems for vitamin deficiency disorders.

1. Introduction

Natural polysaccharides-based delivery systems are widely used for anti-inflammatory drugs, antibiotics, proteins, genes, peptides and hormones, because of their extraordinary advantage in biodegradability and biocompatibility [1]. Appropriate modification of polysaccharides allows for an improvement in the properties of natural polymers. The use of biologically active molecules bound in complexes with polysaccharides has several advantages like high physiological activity, low toxicity, etc. compared to common drug forms [2]. Inulin has favorable properties as polymeric carriers for delivery applications, as they tend to form moderately strong intermolecular bonds with various drug molecules, enhancing their bioavailability, reducing the gastrotoxicity, and extending the action of drug substances [3]. It is rationally expected that the inulin-based systems should have great potentials as targeted drug carriers, because of their gellation properties [4]. Biopolymer based drug delivery technology has become a prevalent approach in food industry in recent years for improving stability and delivery of vitamins, nutraceuticals and flavors. The instability of vitamins occurs during product development due to chemical and physical instability leading to product destabilization. Therefore, an approach is required to design the biopolymer-based delivery systems that are suitable for the bioactive compounds like vitamins depending on the physicochemical characteristics. Wu and Lee [5] modified inulin by acetylation reactions with acetic anhydride, succinic anhydride and prepared microspheres from the modified inulin for drug delivery. K. Izawa et al [6] developed inulin scaffold and pendent β -lactosides inulin through sequential chemical modification by the processes of tosylation and azidation as cell/organ-specific drug carriers. Y. Hu et al [7] synthesized inulin derivatives via reaction between inulin, chloroacetyl, pyridine and amino-pyridines and evaluated in vitro antioxidant property of the derivatives against hydroxyl radicals, superoxide radicals and 2,2-diphenyl-1-picrylhydrazyl radicals. Kukovinets et al. [8] prepared stable iodine-containing films and powders based on pectin and pectin-nicotinic acid complex. Powders were elucidated for their

controllable dynamics of iodine release and films based on them were studied for their high bactericidal activity. Chai et al [9] prepared a delivery system comprising of polysaccharide/protein for vitamin E and evaluated vitamin E release profiles in various pH media. M. Licciardi et al [10] synthesized amphiphilic grafted copolymer from inulin, ethylenediamine, succinyl-ceramide and polyethylene glycol. These new inulin grafted copolymers were able to self-assemble into micelles and were loaded with the anticancer drug doxorubicin. The release in different media confirmed that the prepared micelles were able to release doxorubicin in the intact form for a prolonged period and without a burst release. D. Mandracchia et al [11] prepared hydrogel delivery system for glutathione and oxytocin from modified inulin and polyaspartylhydrazide by cross-linking reaction. In vitro studies exhibited that the release of glutathione and oxytocin occurs in simulated intestinal fluid and they suggested potential application of the hybrid hydrogels based on inulin succinic anhydride and polyaspartylhydrazide for the treatment of inflammatory bowel diseases.

Niacin component of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate is water soluble and is very important for human body for several redox mechanisms in various enzymatic processes. Niacin plays a key role in reducing inflammations in Parkinson's disease, since a correlation between niacin and this disease have been found [12]. Niacin in the form of nicotinamide is utilized for the systemic therapy of pellagra, preventing cataracts [13], diabetes [14], antioxidant, anti-inflammatory agent, immunomodulator [15]. Niacin has been extensively used clinically for dyslipidemia as an antihyperlipidemic agent due to its ability to decrease total cholesterol, LDL-C and increase HDL through hindering hepatic production of triglycerides [16]. Li et al [17] have revealed that niacin reduced chronic alcohol-induced fatty liver in rats, therefore extend its potential role in this disorder. Arauz et al [18] explored that niacin evidently decreased liver fibrosis in rats and suggested that niacin by its antioxidant properties and reducing TGF- β expression, prohibited hepatic fibrosis in rats. The aim of this study was to explore the effect of chemical modifications on inulin for the *in vitro* release and kinetics of niacin in different pH environments for which inulin was subjected to tosylation, amination reactions and followed by the complexation with niacin.

2. Experimental

2.1. Materials

Lithium chloride, p-toluenesulfonyl chloride, acetone, triethylamine, dimethyl sulfoxide, hydrochloric acid, sodium chloride, sodium hydroxide, monopotassium phosphate, ethylenediamine and N, N-dimethylacetamide, were purchased from Merck (India) Ltd. Niacin was provided by Central Drug House Pvt Ltd New Delhi, India. Inulin was supplied by Himedia laboratories Mumbai, India. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) was provided by Sisco Research Laboratories Pvt Ltd (SRL), New Delhi, India.

2.2. Tosylation of Inulin (T-In)

Tosylation of inulin was carried out by following the procedure reported by J. Ren et al [19]. 1.62 g inulin and 0.63 g lithium chloride were dissolved in N, N-dimethylacetamide (DMA) at 70°C with stirring under nitrogen atmosphere until there was a homogenous solution. The solution was cooled to 0°C, and 20 ml of Et₃N was added. Then a solution of p-toluenesulfonyl chloride (2.85 g) in DMA (20 ml) was added drop wise. After stirring the mixture at 0°C for 6 h under nitrogen atmosphere, the reaction mixture was poured into 450 ml acetone; the tosylated inulin crystallized easily, which was filtered off and washed carefully with acetone. (Yield = 1.1 grams, 67.9%)

2.3. Amination of Tosylated Inulin (A-In)

Amination of tosylated inulin was carried out by following the procedure of Schmidt et al [20]. To 0.5 g tosylated inulin dissolved in 10 ml DMSO, 2.7 ml (40.5 mmol) ethylene diamine was added at 100°C. The reaction mixture was allowed to react for 6 h at 70°C under stirring. After cooling the reaction mixture at room temperature, the product was precipitated in 300 ml acetone by pouring the reaction mixture in acetone; the precipitate was washed three times with acetone and two times with ethanol and dried at 60°C under vacuum. (Yield = 0.32 grams, 64%)

2.4. Preparation of Niacin-Inulin Conjugate (Ni-In)

The process of conjugation of niacin to aminated inulin molecules was carried out according to a method reported by Yang et al [21]. A solution of niacin (0.5g) and EDC (0.5g) in 20 ml anhydrous DMSO (molar ratio 1:1) was prepared and stirred at room temperature until EDC and niacin were mixed thoroughly and dissolved well. The solution was then added slowly to 0.5% (w/v) aqueous aminated inulin solution and stirred at 30°C in the dark for 16 h to let niacin react with aminated inulin molecules. The solution was brought to pH 9.0 by adding aqueous NaOH solution (1.0 M) and centrifuged at 2500 rpm to separate the niacin-inulin conjugate that was washed with double distilled water and dried at 40 °C in an oven. (Yield = 0.4 grams, 80%)

3. Characterizations

3.1. Determination of Viscosity Average Molecular Weight of Inulin

Viscosity measurements [22] were performed for determining M_v of inulin using Ostwald viscometer at 20°C. 10% stock solution of inulin was prepared in distilled water and the stock solution was diluted to prepare 9%, 8%, 6%, 5 and 3% solutions. Flow times for water (t₀) and the solutions (t) were determined and plots of reduced and inherent viscosity against concentration were plotted. Double extrapolation of the plots to zero concentration was used to determine [η], the intrinsic viscosity from the intercept. From the values of intrinsic viscosity, the viscosity average molecular weight of inulin was calculated using the Mark-Houwink equation;

$$[\eta] = KM^a$$

Where [η] is the intrinsic viscosity, M is molecular weight, K and a are constants.

3.2. FT-IR Spectroscopy

FTIR measurements of the samples were performed with a Bruker Tensor 37 spectrometer (MA, USA) equipped with single bounce attenuated total reflectance (ATR) accessory. All the spectra were averaged from 32 scans from 4000 to 600 cm^{-1} with a resolution of 4 cm^{-1} .

3.3. ^1H NMR spectroscopy

The ^1H nuclear magnetic resonance (^1H NMR) spectra were determined by using an AV III 500 NMR spectrometer Bruker (MA, USA) at 500 MHz using D_2O and DMSO-d_6 as solvents. Chemical shift (δ) was reported in ppm using tetramethylsilane (TMS) as an internal reference.

3.4. Thermogravimetry Analysis

TGA was carried out in the nitrogen environment with a TG/DT A6300 instrument (SII Nano Technology Inc. Tokyo, Japan). Samples with an approximate mass of 10 mg were analyzed in the 50–600 $^{\circ}\text{C}$ temperature range at a heating rate of 10 $^{\circ}\text{C}/\text{min}$.

3.5. Differential Scanning Calorimetry Analysis

Thermal characterization of the samples was studied by differential scanning calorimetry using DSC 6220 (SII Nano Technology Inc. Tokyo, Japan). Thermograms were obtained from 5–6 mg samples by heating at 30–200 $^{\circ}\text{C}$ under nitrogen atmosphere at a rate 10 $^{\circ}\text{C}/\text{min}$.

3.6. Scanning Electron Microscopy

Morphological studies of the inulin derivatives and niacin-inulin conjugate was examined by scanning electron microscopy (SEM). Samples for SEM analysis were prepared by sprinkling the sample on one side of a double adhesive stub. The stub was then coated by gold under vacuum and mounted on metal grid and viewed using a microscope (ZEISS EVO 50 Series, Germany).

3.7. In Vitro Niacin Release from Conjugates

The release studies of niacin from the prepared niacin-inulin conjugate were carried out by using USP type II apparatus (Electrolab, Mumbai, India) at 50 rpm in different mediums comprising of water, simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The USP type II apparatus consists of a glass vessel and a coated paddle that reduces turbulence due to stirring. The apparatus is housed in a constant-temperature assembly. The sample is placed within the media in the dissolution vessel and the paddle starts stirring so that the paddle rotates at 50 rpm (in some instances 75 or 100 rpm). The liquid sample solutions are collected from dissolution vessel at various time intervals and are analyzed for release studies by Ultraviolet-visible spectroscopy.

Preparation of simulated gastric fluid [23]: SGF (pH 1.5) was prepared by mixing 2 g of NaCl and 7 mL of HCl, which was then diluted to 1 L using double distilled water.

Preparation of simulated intestinal fluid (pH 4.5) [24]: 6.8 g of monobasic potassium phosphate were dissolved in 250 mL water, and then 77 mL of 0.2 M sodium hydroxide and 500 mL of water were added to obtain simulated intestinal fluid.

4. Results And Discussion

4.1. FT-IR Spectroscopy

FT-IR spectrum of In, T-In, A-In and Ni-In is shown in Fig. 1. In the FT-IR T-In spectra of tosylated inulin (T-In) characteristic peaks at 1619 cm^{-1} , 1390 cm^{-1} , 1171 cm^{-1} and 831 cm^{-1} corresponds to C = C aromatic, SO_2 asymmetric, SO_2 symmetric and S-O-C bonds respectively as shown in Fig. 1 [25][26]. In the spectrum of aminated inulin (A-In), the peaks at 3257 cm^{-1} , 1596 cm^{-1} and 1468 cm^{-1} correspond to the amine vibration resulted by the reaction between ethylenediamine and tosylated inulin and the peak at 1229 cm^{-1} corresponds to C-N stretching [27][28]. In the spectrum of inulin niacin complex (Ni-In) peaks at 1588, 1484 and 1414 cm^{-1} are due to the C-C and C-N stretching of the niacin ring. Characteristic peak at 2990 cm^{-1} is due to the C-H stretching of the pyridine ring. The prominent characteristic peak at 1706 cm^{-1} is because of the C = O group of the niacin molecule [29].

4.2. ^1H -NMR Spectroscopy

Figure 2 represents the proton NMR of T-In, A-In and Ni-In complex. The proton NMR spectrum of tosylated inulin shows peaks at δ 7.1 and 7.5 ppm which correspond to the aromatic protons of the tosyl group. This confirms the formation of the tosylated derivative of inulin. K. Izawa and T. Hasegawa [30] reported the peak of the tosyl group in the range of 7–8 ppm for the tosylated polysaccharide. The peaks resonating at 3.6–2.1 ppm in aminated inulin is observed due to the -CH protons of ethylenediamine. The spectrum showed a signal appearing at 5.0 ppm that is assigned to the -NH protons of ethylenediamine moiety. P. Jana et al [28] reported that the peaks resonating at 3.2–2.4 ppm in the aminated carboxymethyl guar gum is due to protons of ethylenediamine. M. A. R. Ahamed reported that the signal obtained at 5.08 ppm in aminated polymer is assigned to -NH protons of ethylenediamine [31]. In the NMR spectra of niacin inulin complex prominent peaks arise from 9-7.5 ppm because of the protons at ortho, meta and para positions of the aromatic ring of niacin molecule. F. A. Al-Saif and M. S. Refat described the position of protons emerging from the protons of niacin in the range of 9.08–7.67 ppm [32].

4.3. Thermogravimetric Analysis

Thermal decomposition behavior of inulin, tosylated inulin, aminated inulin and niacin-inulin complex is shown in Fig. 3. The major weight loss of tosylated inulin occurred in the temperature range of 170–350°C, within which the weight loss percentage was 58% and the highest decomposition rate was at 270°C. Y. Chen et al suggested that the thermolysis within this range mostly came from the thermal decomposition of the tosyl group present in the derivative. They described that the appearance of the first temperature of degradation at lower temperature and the shift of the other deflection's temperature should be related to the presence of the tosyl groups [33][34]. A-In shows three stages of thermal degradation: the first one starts at 70°C with 15% weight loss, the second decomposition starts at 150°C with 38% weight loss and the final decomposition at 220°C with 20% weight loss. E. C. S. Filho et al suggested that lower thermal stability of aminated inulin is caused by the weight of functional groups coupled with inulin and TGA curves show that aminated inulin starts degrading at lower temperature than

inulin [35]. Niacin-inulin complex shows two stages of thermal decomposition. First one starts at 50°C with 10 % weight loss and the second one starts at 140°C with maximum weight loss of 70%. From the TG thermograms integral procedural decomposition temperature (IPDT) values were calculated according to Doyle [36]. The values were 300°C, 310°C, 385°C and 427°C of In, T-In, A-In and Ni-In complex respectively. From the values of IPDT, it is clear that the thermal stability of the derivatives and the complex increases after the reaction.

4.4. Differential Scanning Calorimetry

In inulin two endothermic peaks are observed. The first broad peak at 109°C is mainly due to water evaporation while the second peak at 185°C is attributed to the melting of inulin. C. Blecker reported similar results who observed two endothermic peaks in the DSC of inulin [37]. In comparison to inulin the thermogram of tosylated inulin was shifted to lower temperature. In tosylated inulin there is a major and a minor endotherm peaks at 90°C and 155°C respectively. It also shows one exothermic peak at 180 °C. B. J. Trask et al suggested in the DSC of tosylated polysaccharide, that the appearance of thermograms at lower-temperature was the first sign of the presence of the tosyl group since the decomposition at low temperatures is produced by the tosyl derivatives [38]. Aminated inulin shows first endotherm peak at 50°C and second endotherm peak at 105°C. G. Kaur et al [39] observed the same pattern in the DSC of aminated polysaccharides. They ascribed these transitions to the introduction of amino groups into inulin. Niacin inulin complex displayed two endotherm peaks one at 125°C and another at 175°C [Figure 4]. It is evident from the DSC results that the thermal stability of niacin inulin complex increases because of the incorporation of additional groups to the inulin structure.

4.5. Scanning Electron Microscope

The SEM image of tosylated inulin shows separated regular and cube like structures with smooth surfaces which are different from that of inulin. Aminated inulin shows a changed surface probably due to the amination reaction involving tosylated inulin. Niacin-inulin complex has similar structures, as aminated inulin with features indicating attachment of molecules resulting into well sintered nature of the complexes with variant grain sizes and shapes. [Figure 5]

4.6 Kinetics and Mechanism of Niacin Release

In order to understand the mechanism of niacin release from inulin niacin conjugates zero order, first order, Higuchi model and Korsmeyer-Peppas model were explored for this study over different time intervals at physiological temperature (37°C), in three different pH media. The simplified form of zero order, first order, Higuchi model and Korsmeyer-Peppas model are given by equations 1–4 respectively.

I. Zero-Order Kinetic Model: It reports the system in which the rate of release is independent of the drug concentration [40];

$$Q_t = Q_0 + K_0 t \quad \text{equation 1}$$

Where Q_t is the niacin release in time t and Q_0 is the initial amount of niacin released in the solution and K_0 is the release rate constant.

II. First-Order Kinetic Model: It depicts the system in which the release rate of drug depends on concentration of drug [41];

$$\log Q_t = \log Q_0 + K_1 t / 2.303 \quad \text{equation 2}$$

Where Q_t is the amount of niacin dissolved in time t and Q_0 is the initial amount of niacin in the solution and K_1 is the release constant of first order.

III. Higuachi's Kinetic Model: It reports the system in which the fraction of drug release from matrix is proportional to square root of time [42];

$$M_t / M_\infty = K_H t^{\frac{1}{2}} \quad \text{equation 3}$$

Where M_t and M_∞ are cumulative amount of niacin release at time t and infinite time respectively, and K_H is the Higuchi dissolution constant reflection characteristics.

IV. Korsmeyer-Peppas Kinetic Model: This model explains the fraction of drug released is exponentially related to time by the following equation [43];

$$M_t / M_\infty = K t^n \quad \text{equation 4}$$

Where M_t and M_∞ represents fraction of niacin release during time t and infinite respectively and K is the constant and n is the diffusional exponent.

Drug release data at three different pH's is plotted in figure 7 (d) and the fitting results are summarized in tables 1. Zero order, first order and Higuchi models cannot fit the experimental data well which indicates that the niacin release does not follow the hypothesis of these mechanisms which involves rapid dissolution of niacin molecules. Korsmeyer-Peppas fits the data well, which proves the flexibility of this model. The amount of niacin released was directly proportional to the time and pH until a release efficiency of around 80% of the total released niacin was reached, percent found ideal in Korsmeyer-Peppas model describing the controlled release of niacin. The most suitable model to describe the release of niacin is Korsmeyer-Peppas model due to its coefficient of correlation (0.9996, 0.96372 and 0.8161 in water, SGF and SIF respectively) near to unity as shown in figure 6.

Table 1
Kinetic fitting parameters at different pH

Medias	Zero order coefficient of correlation (R^2)	First order coefficient of correlation (R^2)	Higuchi's model coefficient of correlation (R^2)	Korsmeyer- Peppas model coefficient of correlation (R^2)
Water	0.1591	0.4771	0.4473	0.9996
SIF	0.1491	0.4919	0.4721	0.9637
SGF	0.1368	0.3633	0.4382	0.8161

4.7. *In Vitro* Niacin Release from Inulin Niacin Conjugates

To evaluate the possible influence of pH on the niacin release, inulin-niacin conjugates were incubated under different pH conditions that mimic the pH conditions of stomach and intestine. The amount of niacin released from the prepared inulin niacin conjugates was measured at various time intervals and the percent release versus time was explored which is presented in Table 2.

Table 2
Release percentage of niacin with time in SGF, SIF and Water

Time (Hours)	Percentage Release in SGF	Percentage Release in SIF	Percentage Release in Water
0.5	5.21	6.88	7.6
1	7.88	11.36	14.71
2	19.25	29.07	32.45
4	9.55	12.47	13.04
8	7.39	8.12	8.47
12	3.56	5.02	5.61
24	3.18	3.10	3.75

The release of niacin as investigated by UV-visible spectroscopy shows similar type of release behavior in all the three media (SGF, SIF and water) as is evident from the cumulative release percentage graphs [figure 7 (d)] which corresponds to biphasic release. In all the three media, maximum release takes place in first two hours of time. The cumulative release percentage was highest in water reaching a maximum of 80%, in simulated gastric fluid this percentage reaches 55% whereas in simulated intestinal fluid release is about 70%. D. H. Hanna et al reported release of niacin from cellulose-chitosan hydrogels and revealed that at higher pH the release of niacin was higher as compared to lower pH, because of the

higher solubility of niacin in neutral or alkaline medium [16]. Li et al reported the release of vitamin D₃ from modified alginate vitamin D₃ complex; the release was higher in simulated intestinal fluid as compared to simulated gastric fluid because at higher pH the alginate swells to release vitamin D₃ [44]. In our earlier studies, we observed similar release behavior of folic acid from functionalized inulin in different pH mediums with maximum release at higher pH [45]. In this investigation, niacin loaded inulin was observed to have a controlled niacin delivery which offer several potential benefits. The in vitro release profile of niacin from inulin niacin conjugates shows initial burst release within 2 hours followed by slow and sustained release in an incremental form within 24 hours as is evident from the cumulative release profiles.

5. Conclusions

Tosyl and amine derivatives of inulin and niacin-modified inulin conjugates were successfully synthesized. Inulin was first modified by tosylation and amination reactions and then niacin was conjugated to the aminated inulin derivative. FT-IR, NMR, SEM characterizations showed the changes of chemical modifications. Thermal degradation behavior was elucidated by TGA and DSC which shows increased thermal stability of the chemically modified derivatives. The release of niacin from the conjugate was studied by using UV-Visible spectroscopy. The release and kinetic of niacin, from the matrices, at different pH was studied. The release was observed to be pH dependent, showing a greater release of the vitamin from the conjugate in water than in SIF and SGF. Kinetics of niacin release revealed that the inulin niacin conjugates follow Korsmeyer-Peppas model. Natural polymer-based approach was used for the preparation of stable niacin-inulin conjugates with controllable and prolonged release of niacin. These types of conjugates may be useful as vitamin delivery systems for vitamin deficiency disorders.

Declarations

Acknowledgement

SAG and AA would like to thank University Grants Commission, New Delhi, India for awarding SRF fellowships.

References

1. Chauvierre C, Manchanda R, Labarre D, et al (2010) Artificial oxygen carrier based on polysaccharides–poly(alkylcyanoacrylates) nanoparticle templates. *Biomaterials* 31:6069–6074. <https://doi.org/10.1016/j.biomaterials.2010.04.039>
2. Khakamov TS, Feoktistov D V., Badykova LA, et al (2013) Development and study of modified film coatings with controlled transport properties. *Russ J Appl Chem* 86:1417–1422. <https://doi.org/10.1134/S1070427213090175>

3. Kulterer MR, Reichel VE, Kargl R, et al (2012) Functional Polysaccharide Composite Nanoparticles from Cellulose Acetate and Potential Applications. *Adv Funct Mater* 22:1749–1758.
<https://doi.org/10.1002/adfm.201102350>
4. Stevens C V., Meriggi A, Booten K (2001) Chemical Modification of Inulin, a Valuable Renewable Resource, and Its Industrial Applications. *Biomacromolecules* 2:1–16.
<https://doi.org/10.1021/bm005642t>
5. Wu XY, Lee PI (2000) Preparation and characterization of inulin ester microspheres as drug carriers. *J Appl Polym Sci* 77:833–840. [https://doi.org/10.1002/\(SICI\)1097-4628\(20000725\)77:4<833::AID-APP17>3.0.CO;2-4](https://doi.org/10.1002/(SICI)1097-4628(20000725)77:4<833::AID-APP17>3.0.CO;2-4)
6. Izawa K, Akiyama K, Abe H, et al (2013) Inulin-based glycopolymer: Its preparation, lectin-affinity and gellation property. *Bioorg Med Chem* 21:2895–2902. <https://doi.org/10.1016/j.bmc.2013.03.066>
7. Hu Y, Zhang J, Yu C, et al (2014) Synthesis, characterization, and antioxidant properties of novel inulin derivatives with amino-pyridine group. *Int J Biol Macromol* 70:44–49.
<https://doi.org/10.1016/j.ijbiomac.2014.06.024>
8. Kukovinets OS, Mudarisova RK, Plekhanova DF, et al (2014) Pectin-nicotinic acid-iodine complexes as a base of new materials with high bactericidal activity. *Russ J Appl Chem* 87:1524–1528.
<https://doi.org/10.1134/S1070427214100206>
9. Chai Z, Li Y, Liu F, et al (2013) Outer Eggshell Membrane as Delivery Vehicle for Polysaccharide/Protein Microcapsules Incorporated with Vitamin E. *J Agric Food Chem* 61:589–595.
<https://doi.org/10.1021/jf3040572>
10. Licciardi M, Scialabba C, Sardo C, et al (2014) Amphiphilic inulin graft co-polymers as self-assembling micelles for doxorubicin delivery. *J Mater Chem B* 2:4262–4271.
<https://doi.org/10.1039/C4TB00235K>
11. Mandracchia D, Denora N, Franco M, et al (2011) New Biodegradable Hydrogels Based on Inulin and α,β -Polyaspartylhydrazide Designed for Colonic Drug Delivery: In Vitro Release of Glutathione and Oxytocin. *J Biomater Sci Polym Ed* 22:313–328.
<https://doi.org/10.1163/092050609X12609582084086>
12. Sole R Del, Lazzoi MR, Vasapollo G (2010) Synthesis of nicotinamide-based molecularly imprinted microspheres and in vitro controlled release studies. *Drug Deliv* 17:130–137.
<https://doi.org/10.3109/10717541003587418>
13. Cumming RG, Mitchell P, Smith W (2000) Diet and cataract. *Ophthalmology* 107:450–456.
[https://doi.org/10.1016/S0161-6420\(99\)00024-X](https://doi.org/10.1016/S0161-6420(99)00024-X)
14. Knip M, Douek IF, Moore WPT, et al (2000) Safety of high-dose nicotinamide: a review. *Diabetologia* 43:1337–1345. <https://doi.org/10.1007/s001250051536>
15. Otte N, Borelli C, Korting HC (2005) Nicotinamide - biologic actions of an emerging cosmetic ingredient. *Int J Cosmet Sci* 27:255–261. <https://doi.org/10.1111/j.1467-2494.2005.00266.x>
16. Hanna DH, Lotfy VF, Basta AH, Saad GR (2020) Comparative evaluation for controlling release of niacin from protein- and cellulose-chitosan based hydrogels. *Int J Biol Macromol*.

<https://doi.org/10.1016/j.ijbiomac.2020.02.056>

17. Li Q, Xie G, Zhang W, et al (2014) Dietary Nicotinic Acid Supplementation Ameliorates Chronic Alcohol-Induced Fatty Liver in Rats. *Alcohol Clin Exp Res* 38:1982–1992.
<https://doi.org/10.1111/acer.12396>
18. Arauz J, Rivera-Espinoza Y, Shibayama M, et al (2015) Nicotinic acid prevents experimental liver fibrosis by attenuating the prooxidant process. *Int Immunopharmacol* 28:244–251.
<https://doi.org/10.1016/j.intimp.2015.05.045>
19. Ren J, Liu J, Dong F, Guo Z (2011) Synthesis and hydroxyl radicals scavenging activity of N-(aminoethyl)inulin. *Carbohydr Polym* 85:268–271. <https://doi.org/10.1016/j.carbpol.2011.01.041>
20. Schmidt S, Liebert T, Heinze T (2014) Synthesis of soluble cellulose tosylates in an eco-friendly medium. *Green Chem* 16:1941–1946. <https://doi.org/10.1039/C3GC41994K>
21. Yang S-J, Lin F-H, Tsai K-C, et al (2010) Folic Acid-Conjugated Chitosan Nanoparticles Enhanced Protoporphyrin IX Accumulation in Colorectal Cancer Cells. *Bioconjug Chem* 21:679–689.
<https://doi.org/10.1021/bc9004798>
22. Masuelli MA (2013) Hydrodynamic Properties of Whole Arabic Gum. *World J Agric Res* 1:60–66.
<https://doi.org/10.12691/ajfst-1-3-9>
23. Zhang Z, Jung K-J, Zhang R, et al (2019) In situ monitoring of lipid droplet release from biopolymer microgels under simulated gastric conditions using magnetic resonance imaging and spectroscopy. *Food Res Int* 123:181–188. <https://doi.org/10.1016/j.foodres.2019.04.063>
24. Raviolo MA, Esteve-Romero J, Briñón MC (2011) Stability-indicating micellar liquid chromatography method for three novel derivatives of zidovudine in aqueous and simulated gastric and intestinal fluids matrices. *J Chromatogr A* 1218:2540–2545. <https://doi.org/10.1016/j.chroma.2011.02.018>
25. Gericke M, Schaller J, Liebert T, et al (2012) Studies on the tosylation of cellulose in mixtures of ionic liquids and a co-solvent. *Carbohydr Polym* 89:526–536.
<https://doi.org/10.1016/j.carbpol.2012.03.040>
26. Elchinger P-H, Faugeras P-A, Zerrouki C, et al (2012) Tosylcellulose synthesis in aqueous medium. *Green Chem* 14:3126. <https://doi.org/10.1039/c2gc35592b>
27. Ibn Yaich A, Edlund U, Albertsson A-C (2015) Enhanced formability and mechanical performance of wood hydrolysate films through reductive amination chain extension. *Carbohydr Polym* 117:346–354. <https://doi.org/10.1016/j.carbpol.2014.09.067>
28. Jana P, Mitra T, Selvaraj TKR, et al (2016) Preparation of guar gum scaffold film grafted with ethylenediamine and fish scale collagen, cross-linked with ceftazidime for wound healing application. *Carbohydr Polym* 153:573–581. <https://doi.org/10.1016/j.carbpol.2016.07.053>
29. Käll P-O, Grins J, Fahlman M, Söderlind F (2001) Synthesis, structure determination and X-ray photoelectron spectroscopy characterisation of a novel polymeric silver(I) nicotinic acid complex, H[Ag(py-3-CO₂)₂]. *Polyhedron* 20:2747–2753. [https://doi.org/10.1016/S0277-5387\(01\)00883-X](https://doi.org/10.1016/S0277-5387(01)00883-X)
30. Izawa K, Hasegawa T (2012) Tosylated and azidated inulins as key substrates for further chemical modifications to access inulin-based advanced materials: An inulin-based glycocluster. *Bioorg Med*

Chem Lett 22:1189–1193. <https://doi.org/10.1016/j.bmcl.2011.11.094>

31. Riswan Ahamed MA, Azarudeen RS, Kani NM (2014) Antimicrobial Applications of Transition Metal Complexes of Benzothiazole Based Terpolymer: Synthesis, Characterization, and Effect on Bacterial and Fungal Strains. *Bioinorg Chem Appl* 2014:1–16. <https://doi.org/10.1155/2014/764085>
32. Al-Saif FA, Refat MS (2012) Ten metal complexes of vitamin B3/niacin: Spectroscopic, thermal, antibacterial, antifungal, cytotoxicity and antitumor studies of Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Pd(II), Cd(II), Pt(IV) and Au(III) complexes. *J Mol Struct* 1021:40–52. <https://doi.org/10.1016/j.molstruc.2012.04.057>
33. Chen Y, Ye Y, Jing Y, et al (2015) The Synthesis of the Locating Substitution Derivatives of Chitosan by Click Reaction at the 6-Position of Chitin. *Int J Polym Sci* 2015:1–9. <https://doi.org/10.1155/2015/419506>
34. Awada H, Daneault C (2015) Chemical Modification of Poly(Vinyl Alcohol) in Water. *Appl Sci* 5:840–850. <https://doi.org/10.3390/app5040840>
35. Silva Filho EC, Lima LCB, Silva FC, et al (2013) Immobilization of ethylene sulfide in aminated cellulose for removal of the divalent cations. *Carbohydr Polym* 92:1203–1210. <https://doi.org/10.1016/j.carbpol.2012.10.031>
36. Doyle CD (1961) Estimating Thermal Stability of Experimental Polymers by Empirical Thermogravimetric Analysis. *Anal Chem* 33:77–79. <https://doi.org/10.1021/ac60169a022>
37. Blecker C, J.-P. Chevalier CF, Herck J-C Van, Paquot CD and M (2003) CHARACTERISATION OF DIFFERENT INULIN SAMPLES BY DSC. *J Therm Anal Calorimetry*, Vol 71 215–224 71:215–224. <https://doi.org/10.1023/A:1022238905962>
38. Trask BJ, Drake GL, Margavio MF (1987) Thermal properties of tritylated and tosylated cellulose. *J Appl Polym Sci* 33:2317–2331. <https://doi.org/10.1002/app.1987.070330705>
39. Kaur G, Mahajan M, Bassi P (2013) Derivatized Polysaccharides: Preparation, Characterization, and Application as Bioadhesive Polymer for Drug Delivery. *Int J Polym Mater* 62:475–481. <https://doi.org/10.1080/00914037.2012.734348>
40. DONBROW M, SAMUELOV Y (1980) Zero order drug delivery from double-layered porous films: release rate profiles from ethyl cellulose, hydroxypropyl cellulose and polyethylene glycol mixtures. *J Pharm Pharmacol* 32:463–470. <https://doi.org/10.1111/j.2042-7158.1980.tb12970.x>
41. Gibaldi M, Feldman S (1967) Establishment of sink conditions in dissolution rate determinations. Theoretical considerations and application to nondisintegrating dosage forms. *J Pharm Sci* 56:1238–1242. <https://doi.org/10.1002/jps.2600561005>
42. Higuchi T (1961) Rate of Release of Medicaments from Ointment Bases Containing Drugs in Suspension. *J Pharm Sci* 50:874–875. <https://doi.org/10.1002/jps.2600501018>
43. Korsmeyer RW, Gurny R, Doelker E, et al (1983) Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm* 15:25–35. [https://doi.org/10.1016/0378-5173\(83\)90064-9](https://doi.org/10.1016/0378-5173(83)90064-9)
44. Li Q, Liu C-G, Huang Z-H, Xue F-F (2011) Preparation and Characterization of Nanoparticles Based on Hydrophobic Alginate Derivative as Carriers for Sustained Release of Vitamin D 3. *J Agric Food*

45. Ganie SA, Ali A, Mir TA, Mazumdar N (2019) Preparation, characterization and release studies of folic acid from inulin conjugates. *Int J Biol Macromol*. <https://doi.org/10.1016/j.ijbiomac.2019.10.244>

Figures

Figure 1

FTIR spectra of Inulin (In), tosylated inulin (T-In), aminated inulin (A-In) and Niacin-Inulin (Ni-In) complex

Figure 2

^1H NMR of T-In, A-In and Ni-In Complex

Figure 3

TGA Thermograms of In, T-In, A-In and Ni-In complex

Figure 4

DSC Thermograms of In, T-In, A-In and Ni-In complex

Figure 5

SEM images of (a) In, (b) T-In, (c) A-In and (d) Ni-In Complex

Figure 6

Krosmeier-Peppas Kinetic model in water, SIF and SGF

Figure 7

Release of niacin in (a) water, (b) simulated intestinal fluid, (c) simulated gastric fluid (d) Cumulative release percentage of niacin in simulated gastric fluid, simulated intestinal fluid and water