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Research Article

PREPARATION AND CHARACTERIZATION OF CHITOSAN SUCCINATE AS COATING POLYMER FOR ENTERIC-COATED TABLET

SILVIA SURINI*, KOKO PRAKOSO

Laboratory of Pharmaceutics and Pharmaceutical Technology Development, Faculty of Pharmacy, Universitas Indonesia, Depok, 16424, Indonesia. Email: silvia@farmasi.ui.ac.id

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ABSTRACT

Objective: This present study was aimed to evaluate the potential of chitosan succinate as a coating polymer.

Methods: In this study, chemical modification of chitosan was performed by substituting a succinate group into chitosan's amine group. This reaction used a water-solvent method to obtain chitosan succinate. Chitosan succinate was characterized and used as a coating agent in enteric-coated tablet dosage forms containing sodium diclofenac as the drug model at concentrations of 3% and 4% and combined it with hydroxypropyl methylcellulose phthalate (HPMCP) in ratios of 3:1 and 2:1 (3%). The obtained tablets were evaluated based on their physical appearance, uniformity of weight and size, thickness film, disintegration time for an hour in acid, and dissolution profile.

Results: Although the enteric-coated tablets with 3% and 4% chitosan succinate dissolved after 1 h in acid, they could not hold drug release in the acid medium under 10%. The enteric-coated tablet combined with chitosan succinate and HPMCP (3:1 and 2:1) at 3% did not dissolve after 1 h in the acid medium and could hold drug release up to 8.53% in acid.

Conclusion: A combination of chitosan succinate and HPMCP (3:1 and 2:1) at 3% has a better ability to hold drug release in acid medium and met the requirement as a coating in enteric-coated tablet dosage forms.

Keywords: Enteric-coated tablet, Chitosan succinate, N-acylation chitosan, Sodium diclofenac.

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INTRODUCTION

Application of coatings to the surface of pharmaceutical solid dosage forms, particularly tablets, has been practised for over 150 years [1]. Enteric-coated tablets are used to prevent stomach irritation and a drug's release into the stomach for the delivery of drugs to the intestine for absorption into the bloodstream [2]. Enteric-coated tablets supported by polymers have good stability in stomach fluids and dissolve well in the intestine [1].

Hydroxypropyl methylcellulose phthalate (HPMCP) and cellulose acetate succinate are common excipients used in enteric-coated tablets [3]. These are prepared from modified cellulose with dicarboxylic acid, such as phthalic or succinic acid. Group of carboxyl was substituted by hydroxyl group to increase its solubility because this group can ionize to become carboxylate ion with high solubility in alkaline [4].

Recently, many researchers attempted to modify chitosan to create a novel enteric-coated polymer. The amine functional group of chitosan can be modified using a substitution reaction under mild conditions, which is an added advantage along with its many other properties, such as biodegradability, non-toxicity, and non-immunogenicity. The amino group can be substituted with a dicarboxylic acid, such as phthalic or succinic acid. Chitosan succinate is created through substitution reaction with succinic acid. Being anionic, chitosan succinate has favorable characteristics for the oral delivery system and has wide solubility in alkaline media and decreased solubility in acid. The change in solubility occurs because of the decreased amount of amino group and substitution with carboxylic groups during the substitution reaction [5-8]. This characteristic indicates that modifying chitosan with succinic acid gives it the potential to be a useful polymer for enteric-coated tablets [9].

Adding a proton to chitosan's amino group (NH_3) changes the amino group to NH_4^+ and makes chitosan as a better solubility in acid medium. The loss of amino groups decreases chitosan solubility in acid and creates better solubility in alkaline [10,11]. In this research, we modified chitosan to create chitosan succinate through substitution reaction using succinic acid. The result was characterized by physical, chemical, and functional changes. Further, we created an enteric-coated tablet of natrium diclofenac to test chitosan's efficacy as an enteric coating polymer.

METHODS

Reagents

Natrium diclofenac (Dipharma Francis, Italy), Primogel® (DMW International, the Netherland), Avicel® PH 102 (Mingtai Chemical, China), glycerol (Brataco, Indonesia), HPMCP (Shin-Etsu Chemical, Japan), PVP (BASF Chemical, German), Talc (Haichin, China), lactose anhydrate (DMW International, Netherland), and other reagents used were of analytical grade.

Chitosan succinate preparation

About 4 g of chitosan (deacetylated degree of 94.2%, Surindo Biotech, Indonesia) was dissolved in 400 ml of 1% acetic acid. Succinic anhydride (Merck, Germany) was dissolved in 400 ml of methanol and added into a beaker with the chitosan solution by dropping method. We increased the pH by adding 1.0 N NaOH until the solution neutralized and prepared the precipitated mixture. This mixture was then filtered to remove the solvent and was then washed with methanol. The precipitate was dialyzed for 24 h and dried at 40°C in an oven (Modena®) for 24 h. Then, the dried material was filtered with 60-mesh sieve.

Characterization

Physical appearance

The products were evaluated based on their shape, color, and odor.

Observation of surface shape and morphology by scanning electron microscopy (SEM)

The shape and morphology of the surface were observed by SEM with the enlargement scales as ×200, ×500, ×1000, and ×5000.

Differential scanning calorimetry

Approximately 5 mg of samples were heated from 30°C to 250°C at a scanning rate of 10°C/min under a stream of nitrogen.

Solubility

Chitosan and chitosan succinate (50 mg) were dissolved into 10 ml of aquadest; 0.1% HCl, pH 1.2; HCl, pH 3; HCl, pH 5; phosphate buffer, pH 6.8; phosphate buffer, pH 7.4; and NaOH, pH 12 for 2 h on a shaker (200 rpm). The aliquots were filtered through a Whatman filter (0.2 µm) and spectrophotometrically assayed at 228 nm.

Degree of substitution (DS)

DS was determined by indirect titration with 1.0 N HCl until the samples showed color change from yellow to orange.

$$DS(mol/g) = \frac{[N_{NaOH}V_{NaOH} - N_{HCl}V_{HCl}]}{\text{Chitosan succinate (g)}}$$

Infrared analysis

IR spectra were obtained with Fourier-Transform Infrared Spectrometer 8400 S (Shimadzu, Jepang) in the range 4000–400 cm^{-1}.

Viscosity

Chitosan succinate was dispersed into 0.03% ammonium solution and made into a polymer concentration of 3% and 4%. Viscosity was measured with a Brookfield viscometer.

Swelling test

Approximately 100 mg of samples were formed as tablets and placed in 20 ml of HCl solution (pH 1.2) and 20 ml of phosphate buffer (pH 6.8) at 37°C±0.5°C. The swelling index was determined after 15, 30, 60, 90, and 120 min. The swelling index was calculated by dividing (Dt–D0) with D0 then times 100%.

Where

D_t = diameter of tablet in t min and D_o = diameter of dried tablet

Preparation of core tablets

Core tablets were prepared by direct compression method with a weight of 300 mg for each tablet (Table 1).

Preformulation testing

Preformulation testing was performed to determine bulk density, tapped density, Hausner's ratio, angle of repose, and compressibility index.

Tablet hardness, diameter, thickness, weight variation, and friability test

These tests were performed according to the Indonesian Pharmacopeia (4th edition). The experiments were conducted with 20 tablets for friability and weight variation and 10 for all other tests. Mean value and standard deviations were calculated.

Table 1: Composition of core tablet formulation

Ingredient	Amount (mg)
Natrium diclofenac	25
Lactose anhydrate	60
Avicel® PH 102	200
Primogel®	9
Talc	6

Disintegration test

One tablet was placed in each of the six tubes, and the disintegration tester was operated for an hour using HCl solution (pH 1.2) as the immersion fluid and maintained at 37°C±2°C.

Dissolution test

This test was performed using the United States Pharmacopeia (USP) type 1 apparatus (basket type) at 50 rpm at 37°C±0.5°C using HCl solution (pH 1.2) for first 2 h and continued 45 min within phosphate buffer (pH 6.8). Dissolution media samples (900 ml and 10 ml) were withdrawn at specific intervals and were analyzed at λ 276 nm [12].

Preparation of enteric-coated tablets

Core tablets were coated with different concentrations of chitosan succinate coating solution and used in combination with hydroxypropyl methylcellulose to increase their potential as an enteric polymer. The detailed compositions of the natrium diclofenac enteric-coated tablet formulations are given in Table 2.

Evaluation of enteric-coated tablets

Appearance

Color and shape were visually inspected before and following the coating process.

Film thickness

Radius and height of tablets were measured using a micrometer before and after coating. The differences were used to calculate film thickness.

Weight uniformity

Twenty enteric-coated tablets for each formulation were weighed before and after coating, and average weight was calculated. The average weight was used to calculate the increment of weight.

Disintegration test

One tablet was placed in each of the six tubes of the basket, and the disintegration test was operated for an hour using HCl solution (pH 1.2) as the immersion fluid and maintained at 37°C±2°C. After an hour, the basket was lifted from the fluid and each tablet was observed. The test was continued using phosphate buffer (pH 6.8) and operated for 45 min.

In vitro drug release

This test was performed using USP type 1 apparatus (basket type) at 50 rpm at 37°C±0.5°C using HCl solution (pH 1.2) for the first 2 h and continued for 45 min with phosphate buffer pH 6.8. Dissolution media samples (900 ml and 10 ml) were withdrawn at specific intervals and analyzed at λ 276 nm [12].

Table 2: Composition of enteric coating solutions

Ingredients	Formulation (g)				
	Sealing	F1	F2	F3	F4
Chitosan succinate	-	3	4	2.25	2
HPMCP	-	-	-	0.75	1
Glycerol	-	0.9	1.2	0.9	0.9
PVP	3	-	-	-	-
Ethanol 95% ad	100	-	-	-	-
Ammonium solution 0.03% (v/v) ad	-	100	100	100	100

PVP: Polyvinylpyrrolidone, F1: Coating solution chitosan succinate 3%, F2: Coating solution chitosan succinate 4%, F3: Coating solution chitosan succinate HPMCP (3:1) 3%, F4: Coating solution chitosan succinate HPMCP (2:1) 3%, Glycerol was 30% of total concentration of polymer for F1-F4, HPMCP: Hydroxypropyl methylcellulose phthalate

RESULTS AND DISCUSSION

Characterization of chitosan succinate

The product was a odorless granular solid with irregular shape and yellowish-white colour. The surface morphology of the chitosan succinate powder was coarse and rough. SEM image was not shown.

Differential scanning calorimetry measurements were performed to investigate changes in the physical state of the compounds. From the termogram, we concluded that the endothermic peak of chitosan succinate (79°C) differed from its origin polymer (82.4°C), and they also had different melting traces, wherein chitosan succinate was 131.1°C and chitosan 122.7°C.

The obtained DS was 3.65 mol/g after 8 h. DS was influenced by the time needed for synthesis. Further increase of reaction time slightly promoted further succinylation reaction. In another research, 24 h was the optimum reaction time to obtain high DS of the product [10,13].

The materials dissolved in the acidic region at pH 1.2 and alkaline region (from phosphate buffer medium to pH 12 medium), but it did not dissolve in aquadest. The solubility in the acidic region could be caused by the protonation of the *N*-amino groups (–NH2 to –NH3+), and the solubility in the basic region could be caused by the change of the carboxyl groups to carboxylate ions (–COOH to –COO) [4,14,15]. On the other hand, the solubility in aquadest was caused by its lower DS, which was 3.65 mol/g. The greater DS showed the greater solubility in aquadest [6].

The IR spectra of prepared chitosan succinate showed stretching at 1670.41 cm^{-1} for –C=O and 1541.18 cm^{-1} for –NH– in amide bonding, whereas the stretching at 1585.54 cm^{-1} –C=O for amine decreased [16]. The stretching for carboxylic carbonyl was not clearly seen because the DS was too low (3.65 mol/g).

The results of the swelling index test of chitosan succinate in the acid medium (126.6%) showed that swelling was lower than that of the origin polymer. In the alkaline medium, chitosan succinate showed swelling ability, but the ability was too low (16.1% after 45 min). However, it was higher than chitosan, which did not have swelling ability in the alkaline medium. Chitosan succinate had a charged carboxyl, which was ionized in phosphate buffer; hence, an osmotic pressure gradient occurred and caused transferal of water and materials into the polymer.

Viscosity measurements were conducted on chitosan succinate using an aqueous solution of ammonium 0.03% (w/v) as a solvent. Flow properties of chitosan did not change much when it was modified into chitosan succinate. Tests were performed on chitosan succinate concentrations of 3% and 4%. Based on the test results, it can be concluded that chitosan succinate showed flow properties of pseudoplastics.

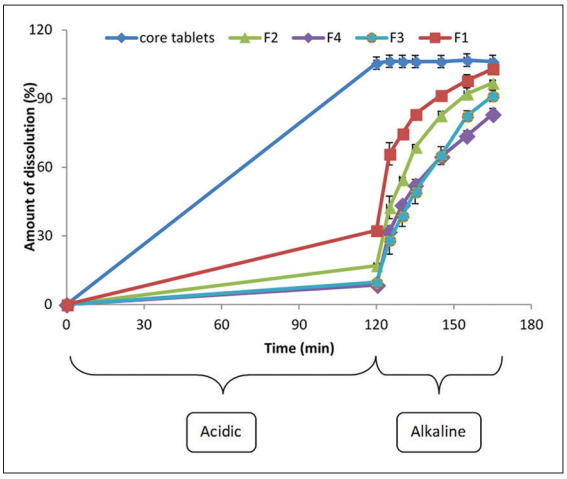

Fig. 1: Dissolution profiles of the core tablets and the enteric-coated tablets of F1–F4 in HCl solution pH 1.2 for 2 h and phosphate buffer solution pH 6.8 for 45 min. Each point represents the mean ± SD (n=3)

An increased concentration of chitosan succinate caused the increased viscosity of the medium. A rheogram is used to show the force per unit area (shearing stress) of the molecules of long-chain materials. With increasing shearing stress, the molecules begin drafting in the direction of flow. This reduces the resistance in the direction of the material, and the resulting differences in terms of velocity (rate of shear) were greater for every subsequent shearing stress [17].

Core tablet evaluation

Core tablet evaluation included appearance, diameter, thickness, weight variation, hardness, friability, and disintegration (Table 3).

Dissolution test of core tablets

The amount of natrium diclofenac released was measured using a calibration curve made of natrium diclofenac with dissolved phosphate buffer (pH 6.8). The calibration curve was calculated using the following equation: y=0.00357+0.02818x with r=0.99992.

The dissolution test was conducted using regression linear method, using phosphate buffer for dilution, causing sodium diclofenac to undergone intramolecular cyclization under acidic conditions, and making it immeasurable. The result of the dissolution test observed was 105.48±2.73%.

Evaluation of preparation coating solution

Medium preparation was performed on six coating formulations of chitosan succinate medium at 3%, 4%, and 5%, and three formulations of chitosan succinate combined with HPMCP were chitosan succinate-HPMCP (3:1) 3%, chitosan succinate-HPMCP (2:1) 3%, and chitosan succinate-HPMCP (3:1) 4%. Each plasticizer formulation used the same percentage as the polymer (30%). The coating solution that was made was further tested for viscosity using a Brookfield viscometer. The succinate chitosan coating solution 3% and 4% and the combination of chitosan succinate-HPMCP (3:1 and 2:1) with the total concentration of 3% showed the following results, respectively: Viscosity 1825.7, 2775.5, 1809.4, and 1491 cps. The coating solution with a concentration of 5% chitosan succinate and chitosan succinate-HPMCP (3:1) 4% could not flow; therefore, no viscosity measurements were taken, and these solutions did not proceed to the coating process. Coating solution with a concentration of 4% chitosan succinate had the highest viscosity compared with other coating solutions. A greater concentration would increase the viscosity of the solution [17]. Coating with a combination solution of chitosan succinate-HPMCP (3:1) of 3% had a greater viscosity than the combination of chitosan succinate (2:1) 3%, indicating that the addition of HPMCP did not increase the viscosity of the coating solution. Based on these preliminary studies, there are several ideal formulations of coating medium, i.e. coating medium made of chitosan succinate 3%, coating medium made of chitosan succinate 4%, coating medium made of combination of chitosan succinate-HPMCP (3:1) 3%, and coating medium made of chitosan succinate-HPMCP (2:1) 3%.

Evaluation of enteric-coated tablets

Evaluation included the appearance of coated tablets, thickness of film, weight uniformity, disintegration, and dissolution tests. All the tablets

Table 3: Evaluation of core tablets

Parameter	Result
Appearance	Biconvex, white, glossy surface, and shiny
Weight	302.7±1.34 mg
Diameter	9.0±0 mm
Thickness	4.403±0.126 mm
Friability	0.11%
Hardness	13.752±1.57 Kp
Disintegration	5.49±0.41 min (5 min 30 s)

were coated with the coating solution. F1–F4 coated surface results were smooth and not shiny. Smooth-coated surfaces may be obtained with a good drying process. The color-coated tablet was different from the white F1. F2–F4 were brown because of the resulting polymers' different colors.

Uniformity of size results showed that the F2 coated tablet was 4.478 mm thick and 9.063 mm in diameter. The F2 coated tablet was greater than F1, F3, and F4, with thicknesses of 4.453, 4.449, and 4.439 mm, respectively, and diameters of 9.048, 9.038, and 9.031 mm, respectively. The coated tablets F1, F3, and F4 had the same sodium diclofenac concentration (3%) and showed differences in terms of diameter and thick-coated tablets. F1's diameter and thickness were greater than the tablets coated with F3 and F4. The combination of coated tablet formulations F3 and F4 showed that F3 had a thickness and a diameter greater than those of F4. F1–F4 coated tablets had a value of the coefficient of variation below 2% and met the parameters of uniformity.

Differences in terms of thickness and diameter of coated tablets can be caused by the concentration and viscosity of the coating medium. The greater the concentration of the polymer coating used, the greater the viscosity of the coating medium [18]. The F2 coated tablet had a greater concentration, resulting in a much greater thickness and diameter. The greatest viscosity was shown in F2 medium (2775.5 cps). Coated tablets F1, F3, and F4 had the same concentration but different viscosities. The medium viscosity coating, F1, has a value greater than F3 and F4 (1825.7 cps). The medium viscosity coating F3 was 1809.4 cps and F4 was 1491 cps. Viscosity is influenced by diameter and thickness of coated tablets. This is evident from the difference in terms of viscosity formulations with the same polymer concentration in F1, F3, and F4. Viscosity difference is caused by a reduction in the amount of chitosan succinate that is replaced HPMCP. The results are shown in Table 4.

Coating thickness was measured using data uniformity, coated tablet thickness, and diameter of each formulation. Table 3 shows the thickness of the coated tablets in each coated tablet formulation.

The F2 coated tablet had the largest thickness interval among all the coated tablets, caused by the concentration of chitosan succinate used (4%). Meanwhile, the combination of chitosan succinate tablets coated with HPMCP showed that the F3 coated tablets produced a greater thickness than the F4 tablets. The F1 coated tablet had a coating thickness greater than F3 and F4 tablets. Coating thickness is influenced by the concentration of polymer used and the viscosity of the coating solution [19].

The F2 coated tablet demonstrated the greatest weight increment (5.87%). F1, F3, and F4 demonstrated a similar weight increment (4.31%, 4.96%, and 4.54%, respectively). Coated tablet weight gain can increase the containment of drug release in acidic conditions, and an increase in weight of >5% is not eligible for coated tablets. F2 coated tablets did not qualify as a coated layer tablet due to their increase in weight (exceeding 5%).

Increase in weight is influenced by the concentration of polymer and plasticizer used. Increasing the concentration of the polymer affects the viscosity of the coating solution to increase its viscosity. The increase in weight of a coated tablet may also be affected by the spraying technique and the amount of coating solution. The amount of coating may vary in each spray.

Disintegration test

Based on the results of the disintegration test, the F1 coated tablet could not be used as a coating polymer because tablets were softened after an hour in HCl solution (pH 1.2). F2–F4 coated tablets were better able to survive in a physical form in the acidic fluid for 1 h. This result is due to the presence of enteric polymer HPMCP, which allows the coated layer to survive well in acidic conditions.

Second, coated tablets were tested in an alkaline medium for 45 min. F2 coated tablets were disintegrated in alkaline after 20 min 57 s and longer than F3 (19 min 7 s) and F4 (17 min 45 s) coated tablets.

Dissolution test

Based on the dissolution profiles of sodium diclofenac-coated tablets in Fig. 1, F1 and F2 coated tablets were not able to resist drug release in the acidic media because the release of the acid was above 10%, which is approximately 32.37% and 17%, respectively. According to Indonesia Pharmacopeia 4th, enteric coated preparations meet the requirements if the drug release in pH 1.2 HCl medium is under 10%. Coated tablets F3 and F4 showed better results with the release of diclofenac sodium in the acidic medium under 10%: 8.53% and 6.74%, respectively. The chitosan succinate enteric coating in these tablets was combined with the enteric polymer HPMCP to improve the quality of the coated tablets.

The results of the drug release of tablets F1 and F2 after dissolution for 45 min in pH 6.8 phosphate medium show that the cumulative amount of dissolved drug reaches 102.99% and 96.80%, respectively. On the other hand, F3 and F4 obtained a cumulative total of 93.48% and 91.97%, respectively. The release of diclofenac sodium in phosphate medium (pH 6.8) cannot be separated from the increase of chitosan succinate solubility in alkali. The F3 and F4 coated tablets met the requirements of cumulative release in alkaline medium, because they released the drug more than 80% in alkaline medium.

Based on this study, chitosan succinate was successfully synthesized using the aquaeous method. DS of chitosan succinate obtained was 3.65 mol/g with the expansion of solubility in the alkaline medium. Chitosan succinate was subsequently used as a coating with four formulations, namely F1–F4. Formulations F1 and F2 could not be used as a coating material on enteric-coated tablets, because they could not resist drug release in acid medium lower than 10%. However, formulation F3 and F4, which were combined with HPMCP 25% and 33% of coating polymers, could resist drug release in acidic medium, subsequently release the drug more than 80% in alkaline medium.

CONCLUSION

The produced chitosan succinate had DS value of 3.65 mol/g and enhanced solubility in alkaline conditions. The enteric-coated tablets, which had been coated with a mixed polymers of chitosan succinate

Table 4: Evaluation of the enteric-coated tablets

Evaluations	*Sealing* (PVP 3%)	F1	F2	F3	F4
Thickness (mm)	4.423±0.001	4.453±0.001	4.478±0.0016	4.449±0.0002	4.439±0.002
Diameter (mm)	9.015±0.0022	9.048±0.002	9.063±0.001	9.038±0.002	9.031±0.001
Weight (mg)	309.3±0.32	322.1±0.86	327.6±0.59	322.8±1.02	322.4±1.12
Increase in weight (%)	2.19%	4.31%	5.87%	4.96%	4.54%
Disintegration time in acidic medium (min)	Dissolved	Dissolved	Undissolved	Undissolved	Undissolved
Disintegration time in alkaline medium (min)	-		20.95±1.88	19.11±0.12	17.75±1.29
% Dissolution in acidic medium for 2 h	-	32.39±0.61	17.00±1.08	8.53±0.89	6.74±1.16
% Dissolution in alkaline medium for 45 min	-	102.99±1.20	96.80±2.45	93.48±3.55	91.97±2.97

and HPMCP (3:1) and (2:1), could withstand drug release <10% in acid medium and extend the drug released in alkaline medium >80%, so it meets the requirements of an enteric-coated tablet.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest in this research.

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