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Evaluation of chitosan succinate and chitosan phthalate as enteric coating polymers for diclofenac sodium tablets

K.M. Aiedeh[1]*, M.O. Taha[2], H. Al-Khatib[1]

[1]Department of Pharmaceutics and Pharmaceutical Technology, [2]Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan, Amman, Jordan
*Correspondence: Aiedeh@ju.edu.jo

This study aims at evaluating the potential of chitosan succinate and chitosan phthalate as enteric coating polymers for diclofenac sodium tablets. The solubility of the new chitosan derivatives was evaluated in different media to check their suitability for enteric applications. Diclofenac sodium core tablets were coated with either derivative and drug release was evaluated according to the USP method for delayed release (enteric) preparations. The effects of storage, elevated temperature and humidity on drug release were also evaluated. The solubility profile of chitosan succinate and chitosan phthalate was completely different from that of chitosan. The new derivatives showed significantly improved solubility in basic media while their solubility in acidic media decreased in comparison to the native polymer. Chitosan phthalate coated tablets complied with USP specifications for delayed release preparations while chitosan succinate coated tablets released a high percentage of the drug in the acid stage but failed to provide the required dissolution criteria for enteric tablets. Storage under ambient conditions as well as under elevated temperature and humidity slowed down the release from tablets coated with these polymers.

Key words: Chitosan succinate – Chitosan phthalate – Enteric film coating – Spray coating – Diclofenac sodium.

Chitosan (poly[-(1,4)-2-amino-2-deoxy-D-glucopyranose]) is a natural polymer obtained by the hydrolysis (deacetylation) of chitin, a native polymer present in shellfish. Together with chitin, chitosan is considered the second most abundant polysaccharide after cellulose [1]. The amine group on the polymer has a pKa in the range of 5.5 to 6.5. At low pH, the polymer is soluble, with the sol-gel transition occurring at an approximate pH value of 7 [2]. The pH sensitivity, coupled with the reactivity of the primary amine groups, make chitosan a unique polymer for drug delivery applications.

Among other applications, chitosan and its derivatives have been used as wound dressings [3], in mucoadhesive drug delivery systems [4], as matrix-forming agents for per-oral sustained drug delivery [5-8] and colonic drug delivery [9, 10].

Enteric polymers are a special class of pharmaceutical excipients designed to resist the acidic nature of the stomach contents yet dissolve readily upon exposure to the higher pH environment of the intestines [11]. Enteric drug delivery systems have been used to deliver drugs to the colon for the treatment of inflammatory diseases; for the protection of the gastric or upper intestinal mucosa from irritating drugs or for protecting peptide drugs from degradation in regions of high enzymatic activity or low pH.

The pH-dependent solubility of these polymers is a function of the ionization of carboxylic acid groups along the polymer chain [12]. The type of the carboxylic acid substitution on the polymer's backbone as well as the total free carboxylic acid content of the polymer are the most influential criteria in determining the dissolution rate and the threshold pH at which the polymer dissolves and releases the drug [13, 14].

Chitosan succinate and chitosan phthalate are chitosan derivatives that were prepared in our laboratory through the acylation of the amino group using succinic and phthalic anhydrides [15]. Converting the polymer from an amine to a succinate or a phthalate amide changes the solubility profile of the modified polymers completely. While the modified polymers are insoluble under acidic conditions, by increasing the pH of the medium the polymers start to dissolve.

Considering this pH-dependent solubility and the good film-forming properties of chitosan, chitosan succinate and chitosan phthalate are expected to have a great potential and perform well as polymeric derivatives for enteric coating.

I. MATERIALS

Chitosan (Mwt 70 KD) was obtained from Aldrich Chemical Company (USA), diclofenac sodium from Fluka (Switzerland), maize starch from National Starch (USA), lactose from Fluka (Switzerland), microcrystalline cellulose (Avicel PH101) from FMC International (Ireland), colloidal silicone dioxide (Aerosil 200) and magnesium stearate from Merck (Germany) and sodium starch glycolate (Primojel) from Avebe (The Netherlands).

Reagent grade chemicals were purchased and used as received without further modification: sodium hydroxide from Lonver House (UK), succinic anhydride from Aldrich Chemical Company (USA), phthalic anhydride from Scharlau (EU) and potassium dihydrogen orthophosphate from Rasayan (India).

All solvents used (acetone, ethanol, diethyl ether, pyridine and hydrochloric acid) were of analytical grade and purchased from the Gainland Chemical Company (UK). They were used as received without further purification.

II. METHODS

1. Synthesis of chitosan phthalate and chitosan succinate

Chitosan phthalate (CP) and chitosan succinate (CS) were synthesized according to the method described earlier [15] with slight modifications. To a mechanically stirred solution of chitosan (300 g, equivalent to 186 mmol glucosamine) in aqueous HCl solution (0.37%, 1.5 l) a solution of phthalic anhydride (18.8 g, 187.5 mmol) or succinic anhydride (27.8 g, 187.5 mmol) in pyridine (150 ml) was added dropwise at room temperature. The pH was maintained at 7.0 by intermittent dropwise addition of NaOH solution (1.0 M). Fourty minutes later, the reaction was terminated by precipitating the product with acetone followed by filtration under suction; the resulting semi-synthetic polymer was then washed using acetone and diethyl ether and dried overnight at room temperature.

2. Infrared (IR) spectroscopy

IR spectra of CP and CS were determined between 500-4000 cm^{-1} using the KBr disc method in a Nicolet Impact 400 IR spectrophotometer (Nicolet Technologies, USA).

3. Determination of the degree of substitution

The degree of phthalate or succinate substitution on chitosan was determined as follows: the chitosan conjugates (CS or CP, 0.1 g) were completely hydrolyzed in NaOH solution (3.0 M, 30 ml) over 48 h. The concentrations of phthalic and succinic acids in the hydrolysis solutions were determined by UV spectrophotometry at $\lambda = 232$ nm for phthalic acid and $\lambda = 228$ nm for succinic acid. Unmodified chitosan was treated in the same way and the resulting solution was used as a blank.

The degree of substitution (g %) was defined as the ratio of the measured amount of phthalic or succinic acid in the hydrolysis solution to the amount of the original chitosan conjugate sample.

4. Polymeric solubility

The solubility of chitosan and its conjugates (CS and CP) was determined as follows: the particular polymer (0.1 g) was placed in a 30-ml screw-capped bottle containing either HCl solution (30 ml, 0.1 M, pH 1.0), NaOH solution (30 ml, 0.1 M, pH 13.0) or distilled water (30 ml, pH 5.5).

The polymeric suspension was then shaken using a mechanical shaker (KS 500, Janke and Kunkel-Ika, Germany) at room temperature for 48 h. The suspension was then filtered and left overnight to dry under vacuum. The dissolved amount was then calculated by the difference in weight.

5. Preparation of core tablets

Diclofenac sodium (DS) core tablets (50 mg/tablet) were prepared using the wet granulation method. The formula contents and their corresponding percentages are shown in *Table I*. The drug was dry mixed with starch, lactose and microcrystalline cellulose for 5 min in an FGS granulator (Erweka, Germany). Starch mucilage (5% aqueous paste) was then added gradually to the mixing bowl to produce a damp mass. The resulting mass was then screened through a 1.7-mm stainless steel sieve and dried in a tray oven at 45°C for 30 min to produce the primary granules. Final granules were produced by passing the primary ones through the FGS granulator 0.63 mm sieve and then drying them for 3 h in the oven at 45°C.

Anhydrous silica and sodium starch glycolate were added to a known weight of granules and mixed for 10 min. Magnesium stearate was then added and mixed for an additional 5 min. The final mixture was compressed using a single punch tableting machine (Manesty F3, UK) using a 9-mm shallow concave punch and die set using a compression force of 60-85 N to obtain tablets with a hardness of ~10 Kp and total disintegration time of maximum 15 min.

6. Evaluation of core tablets

6.1. Content uniformity

Ten tablets were crushed and transferred into a 1.0-l volumetric flask. NaOH aqueous solution (0.1 M) was then added up to volume to digest and extract the tablets. The resulting solution was examined using UV spectrophotometry at $\lambda = 275$ nm.

Table I - Formula of diclofenac sodium core tablets.

Material	Weight (%)
Diclofenac sodium (DS)	20
Starch	37
Lactose	30
Microcrystalline cellulose (Avicel 101)	8
Colloidal silicon dioxide (Aerosil 200)	0.50
Starch mucilage 5%w/v (maize starch)	1.70
Anhydrous silica (Aerosil)	0.50
Magnesium stearate	0.80
Sodium starch glycolate (Primojel)	1.50

6.2. Physical properties of core tablets

The thickness and diameter of 25 tablets was determined using a micrometer. Ten more tablets were used for the hardness testing using a 2E Irmeco-Schoenfeld hardness tester (Germany) and the mean and standard deviations were calculated.

The disintegration time of five tablets in 1 l of purified water USP at 37 ± 1°C was determined in a ZT3-3 Erweka Tablet Disintegration Unit (Germany). The media temperature was maintained at 37 ± 1°C. Five tablets from each batch were placed in five Perspex tubes, which were placed in five baskets, then the stirring motor was switched on. The disintegration was considered to have terminated when the last tablet particle passed through the screen. The mean disintegration time and standard deviation were calculated.

6.3. Dissolution of core tablets

Drug release was tested in a USP Apparatus #2 (Vankel VK7000, USA). The stirring rate and temperature were adjusted to 50 ± 1 rpm and 37 ±0.5°C, respectively. Nine hundred millilitres phosphate buffer (pH = 6.8) was used as a dissolution medium, the stirring rate and media temperature were maintained at 50 ± 1 rpm and 37 ± 0.5°C, respectively.

Dissolution was carried out in triplicate and 5-ml samples were taken at specific times and replaced by fresh media and the content of DS in the samples was determined using UV absorption at 276 nm.

7. Preparation of coating solutions

The solutions of CP and CS were prepared as follows: the particular polymer, i.e. CP or CS (15.0 g), was dissolved in ammonia solution (275 ml, 3.0% v/v) to produce a final polymer solution with a concentration of 5.4% w/v. The polymer solution was used as such without other additives.

8. Tablet coating

One hundred and fifty grams of core tablets was coated with CS or CP using a simple conventional Erweka coating pan (inner diameter 30 cm) to the target weight gain. Application of the coating dispersion was performed using a hand-held, air gravity spray gun fitted with a 0.8-mm spray nozzle. Drying was achieved through application of heated air from a heat gun. The process was continued until a weight gain of ~2.5% for CP-coated tablets and ~ 6.0% for CS-coated tablets was achieved. The process parameters used in the tablet coating are summarized in *Table II*.

9. Disintegration testing of coated tablets

Testing was performed using a ZT3-3 Erweka tablet disintegration unit as described above. However, instead of purified water USP, freshly prepared 0.1 M HCl was used as the disintegration medium for 120 min, and then replaced with phosphate buffer pH 6.8.

10. Drug release from coated tablets

Drug release was tested in a USP Apparatus #2 according to the USP 24 method. The stirring rate and temperature were adjusted to 50 ± 1 rpm and 37 ± 0.5°C, respectively. Nine hundred millilitres

Table II - Process parameters for tablet coating.

Control setting	
Production feed pump	25 rpm
Pan speed	25 rpm
Spraying	continuous
Spray air pressure	3 bars
Agitation speed of the dispersion	low speed
Dispersion temperature	20-25°C
Inlet temperature	60-70°C
Outlet temperature	40-50°C