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Original Article

ARRACACIA XANTHORRHIZA ACETYLATED STARCH: A NEW EXCIPIENT FOR CONTROLLED DRUG DELIVERY

JUAN J CARRASCAL, GERMÁN MATIZ, YOLIMA BAENA*

Universidad Nacional de Colombia, Sede Bogotá, Science Faculty, Pharmacy Department–Research Group Technology of Natural Products Carrera 304503, Bogotá D. C., (111311), Colombia
Email: ybaenaa@unal.edu.co

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ABSTRACT

Objective: Chemically modify by acetylation, *Arracacia xanthorrhiza* starch, and to physicochemically and pharmacotechnically characterize it, thereby evaluating its potential as a pharmaceutical excipient, in comparison with the native starch of *Arracacia xanthorrhiza.*

Methods: The chemical modification was performed through acetylation with acetic anhydride (AA) on different levels, determining following starch's characteristics: degree of substitution (DS), size and form of particles, its degree of crystallinity through X-ray powder diffraction (XRPD), gelatinization temperature (Tg) through differential scanning calorimetry (DSC), swelling power (SP) and sorption isotherms by means of Enslin method, and its application as excipient in tablet production, using diclofenac as model drug.

Results: On the third level of substitution, the morphology of modified-starch particles presented changes on their surface and all modified starches increased their particle average sizes, in comparison to native starch. Starch crystallinity was not altered by acetylation, and the DS increased as more AA was added to the reaction. This modification caused a decrease of Tg by approx. 9.45 °C for *A. xanthorrhiza* starch modified to level III, in comparison to native starch. SP and water uptake capacity increased with starch modification, being greater to higher DS. Dissolution studies conducted on tablets showed that diclofenac delivery occurs practically immediately when using native starch, while those made of acetylated starch were close-fitting with Korsmeyer-Peppas model, with a release mechanism that suggests an anomalous, non-Fickian transport behaviour, related to a mechanism governed by swelling and diffusion.

Conclusion: The results suggest *A. xanthorrhiza* acetylated starches, as promising materials for the development of controlled-delivery matrix systems.

Keywords: Acetilation, starch, Arracacia xanthorrhiza, controlled delivery

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INTRODUCTION

Additional to requiring higher administration frequencies, conventional drug delivery systems may produce, over time, great fluctuations in the plasmatic levels when administered in multi-dose regimens, which is far from the ideal in pharmacotherapy. Controlled drug delivery formulations tend to offer a better approach to ideal therapy by favoring a more constant plasmatic concentration, maintaining it inside the therapeutic margin and reducing dosage frequency [1]. Among possible ways of controlled dosage, hydrophilic matrix formulations are the most efficient and most employed, given the simplicity and low costs of their manufacturing process [2, 3].

In these matrix formulations mainly hydrophilic polymers are used, especially those cellulose-derived. The possibility of obtaining alternative materials with similar behaviours would represent a valuable contribution to this field. One of these possibilities is using starches obtained from natural sources other than corn (*Zea mayz*) and potatoes (*Solanum tuberosum*), which could serve as excipients in their natural forms or by means of some physical, chemical or enzymatic modifications [4]. Some modified starches are used as excipients in the pharmaceutical industry, for controlling the speed of drug delivery in hydrophilic matrices, mostly [5, 6]. This is mainly due to the increase in swelling capacity, even at low temperatures, allowing for the formation of a gel-like barrier surrounding the particles [7].

Acetylation is among the most common chemical methods used to modify starch. This type of modification is obtained by esterification of native starch [8] and might be achieved with AA, vinyl acetate or acetic acid, and depends on factors such as reagent concentration, reaction time and temperature and pH value, that module the number of acetyl groups incorporated into-OH groups of starch molecules [9].

In order to select starch for industrial use, aside from economic viability considerations, it is necessary to evaluate physicochemical characteristics that depend on the vegetal source, the type of chemical modification and DS achieved. Native starch is normally not adequate for designing controlled drug delivery systems given its very quick release due to low swelling and quick enzymatic degradation in biological systems [10].

The objective of this investigation was to chemically modify *A. xanthorrhiza* native starch (non-traditional starch source), by means of AA on different levels and evaluating it's physicochemical and pharmacotechnical properties, with the aim of determining possible applications in the development of controlled drug delivery systems.

MATERIALS AND METHODS

*A. xanthorrh*iza rhizomes from which starch was derived were acquired in the marketplace of Paloquemao, in Bogotá (Colombia), choosing fresh, whole, bruise-free products presenting adequate organoleptic characteristics (20 kg). A voucher specimen of the plant (COL-602870) was identified and deposited at the Herbario Nacional Colombiano of the Universidad Nacional de Colombia. For starch extraction and acetylation processes, following substances were used: ethanol (EtOH) 96% (supplied by Empresa de Licores de Cundinamarca-Colombia, Pharmaceutical grade), AA ≥ 99.0% (J. T Baker, USA, analytical grade), sodium hydroxide (NaOH) (Merck, Germany, pharmaceutical grade), hydrogen chloride (HCl) (Merck, Germany, analytical grade) and deionized water (obtained by using Merck Millipore Milli-Q water purification equipment, Billerica, MA, USA). To determine the acetylation percentage (AP) and DS, potassium hydroxide (KOH) (Merck, Germany, analytical grade) and phenolphthalein (J. T Baker, USA, analytical grade) were used. In the evaluation of starch's functionality as a diluent in tablet production, following substances were used: sodium diclofenac (Merck, Germany, pharmaceutical grade), disodium phosphate (Sigma-

Aldrich, USA, analytical grade) and sodium phosphate (Sigma-Aldrich, USA, analytical grade).

Native starch isolation

The process of starch extraction started with washing 20 kg of healthy *A. xanthorrhiza* rhizomes which were peeled, washed again, squared and blended with drinking water until a slurry was obtained. The latter was filtered and allowed to settle for one night. The supernatant liquid was eliminated by decantation and the sediment resuspended in distilled water to be washed anew. Finally, the sediment was resuspended in EtOH, vacuum filtered (vacuum pump Cast, DOA-P704-AA; USA) and dried to 40 °C (Mettler Toledo stove, Lindberg blue M, USA) for 12 h. The product was then packed and stored for its later use.

Acetylation, acetyl-group determination and substitution degree

Native starch was acetylated on three levels by varying the quantities of AA added (5, 10 and 15 ml for levels I, II and III, respectively), employing the method described by Mirmoghtadaie *et al.* [11], albeit with some modifications. A suspension consisting of 200 ml of distilled water and 40 g of native starch was prepared, initially adjusting the pH to 8.5 by means of a NaOH solution (3%p/v), stirring at 20 rpm (Talboys, hot plate stirrer, 7x7 USA) and letting the system stabilize for 30 min. After that period, previously defined quantities of AA were added drop by drop. pH was kept between 8.5 and 9.0 (pH meter Mettler Toledo, seven easy, Switzerland) for the whole reaction through little additions of the same NaOH solution. Afterwards, the system was adjusted to pH 5 with HCl solution (0.5N), filtered and the resulting residue washed three times with distilled water and once with EtOH, allowing it to dry at 40 °C for 12 h. The resulting modified-starch was then stored for later study. The reaction was verified through infrared (IR) spectrum of native and acetylated starches (Infrared spectrometer, Perkin Elmer, Spectrum BX, USA), in a wavelength interval ranging between 400-4000 cm^{-1}.

For AP and DS determination the alkaline saponification technique, as described by Sodhi and Singh, with modifications was used [12]. In a 250 ml flask were added 50 ml of EtOH-water solution (70% v/v) and then 50 ml of KOH solution (0.5N). The mixture was agitated at 50 rpm and kept at 50 °C for 30 min (Talboys hot plate stirrer, 7x7 USA) and later kept at room temperature for 72 h, with occasional stirring. Alkali excess was valued through back-titration with HCl solution (0.5N), using phenolphthalein as indicator. Simultaneously, a blank determination was made with a sample of native starch, following the same procedure. All calculations were realized with equation 1.

$$AP = \frac{[(\text{mL blank} - \text{mL sample}) * [\text{HCl}] * 0{,}043] * 100}{\text{sample grams}} \ldots\ldots \text{(Equation 1)}$$

For which: 0.043= acetyl-group milligrams

DS determination, which corresponds to the mean number of hydroxyl groups replaced by CH_3-C=O groups in the anhydro-glucose-unit (UAG), is calculated using equation 2:

$$DS = \frac{(162 * AP)}{((4300 - (42 * AP))} \ldots\ldots. \text{(Equation 2)}$$

For which:

162 = molecular weight of each UAG.

4300 = 100 x molecular weight of CH_3-C=O group

42 = Molecular weight of CH_3-C=O group minus 1.

Morphology, size and particle size distribution

The morphology of each obtained starch was assessed using scanning electron microscopy (SEM, FEI, Quanta 200-r, USA). Particle size was assessed using a particle size analyzer (Mastersizer, Malvern Instruments, 2000S, USA) with a refractive index of 1.494 and±1% accuracy, employing cold water as a vehicle [13].

X-ray powder diffraction (XRPD)

X-ray diffraction analysis was performed on each obtained starch using an X-ray fluorescence spectrometer (Phillips, Magix Pro, Holland), in the range of 10 °-70 ° 2θ/θ, with a scanning speed of 0.066 °2θ/s [14].

Swelling power (SP)

The starch swelling was determined using the method described by González and Pérez [15], albeit with some modifications. The determination was conducted at temperatures between 25 and 70 °C. 4 g of each starch were dispersed in 200 ml water and placed into a 300 ml triple-neck flask which contained a magnetic agitator. A refrigerant was plugged to the central neck, a thermometer to one side, and a glass cap to the remaining opening. Flask was heated and agitated at 30 rpm (Talboys hot plate stirrer, 7x7 USA), with 10 ml samples of the suspension taken each 5 °C. Said samples were placed in previously weighed centrifuge-flasks; the weight of flask and sample was measured and centrifuged at 2200 rpm for 5 min (Centrifuge Hettich, Rotofix32A, Germany). The supernatant was decanted in dry, previously weighed Petri-dishes and the weight of dish and supernatant was noted. Centrifuge tubes with precipitate were again weighed. Determinations were done in triplicate. Equations 3 through 6 were used for corresponding calculations.

$$W_1 = \frac{\text{Starch dry-basis weight (g)}}{\text{Starch dry-basis weight (g)} + 200} * 100\ldots\ldots. \text{(Equation 3)}$$

$$W_2 = A * \frac{W_1}{100}\ldots\ldots. \text{(Equation 4)}$$

$$\%SS = \frac{b}{W_2} * 100\ldots\ldots \text{(Equation 5)}$$

$$SP = \frac{a * 100}{W_2 * (100 - \%SS)} \ldots\ldots. \text{(Equation 6)}$$

A = Sample weight (g), a = Sediment weight in tube (g), b = Weight of residue in Petri dish (solubilized starch, g), W_1 = Percentage of dry-basis starch in suspension, W_2 = Starch in each sample, % SS = Soluble solids percentage (g/starch g) y SP = Swelling power.

Gelatinization temperature

The range for gelatinization temperature was determined by DSC (Mettler Toledo, DSC823, Switzerland), following method by Alves *et al.* [16] with some modifications. 2 µL samples of water suspension (10% p/p) of each starch were placed in previously weighed aluminum capsules. Each capsule was weighed, including the 2 µL sample and then hermetically sealed. An empty aluminum capsule was taken as reference. Samples were then heated from-20 ° to 90 °C, at 10 °C/min.

Sorption isotherms

For each starch, the sorption behavior was analyzed using a design by Enslin-Neff (fig. 1) [17]. On one of its ends, the equipment presents a sample unit, consisting of a glass funnel and a glass frit over which the sample is placed. On the other end, a graded pipette on the horizontal position at the same height as the upper level of the glass frit (to neutralize the effects of hydrostatic pressure). The system is balanced with distilled water (25 °C) using almost the whole pipette; fluid's position in that moment represents the pipette's point zero (starting position). The sample consisting of particulate matter (1 g) is placed uniformly applied on the glass frit. The sample absorbs liquid by capillarity and no other force shall intervene. The volume of absorbed liquid is measured at predetermined time intervals. Determinations were done in triplicate [14].

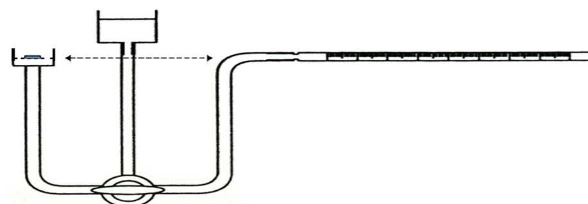

Fig. 1: Schematic representation of Enslin apparatus for water uptake studies

Evaluation of *A. xanthorrhiza* starches functionality as diluents in tablets

These tests were conducted as described in the corresponding chapters of USP 39 [18]. 450 mg tablets were produced by direct compression for this trial, for each one of the starches, using sodium diclofenac (100 mg) as a model drug. Compaction pressure was 188 Mpa, employing a punch of 5/16" 8 mm, (Hydraulic press, Carver Inc, Model C, USA).

Determinations of dissolution profiles were done, in triplicate, under following conditions:

Apparatus 1, medium phosphate buffer pH 6.8 (900 ml), speed 100 rpm, temperature 37 °C and sampling times varied between 1 and 16 h (Automatic dissolution, Distek, Evolution 6100, USA). Sodium diclofenac was quantified by ultraviolet spectroscopy (UV spectrophotometer, Agilent Technologies model 8453, USA), following a previously validated analytical methodology [16].

Different kinetic models such as zero-order, first order and Korsmeyer and Peppas (Equations 7, 8 and 9) were used to analyze drug-release kinetics from the tablets.

$$\frac{M_t}{M_\infty} = K^{'}t \text{ …… Equation 7}$$

$$log\frac{M_t}{M_\infty} = K''t \text{ …… Equation 8}$$

$$\frac{M_t}{M_\infty} = K'''t^n \text{ ……. Equation 9}$$

Where M_t/M_∞, $K^{'}$, $K^{''}yK'''$ represent the fraction of drug released, and the release constants for each model respectively. Similarity factor f2 was used for profile evaluation (equation 10) [19].

$$f_2 = 50log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(Rt-Tt)^2\right]^{-0,5} x\ 100\right\} \text{…… Equation 10}$$

For which Rt y Tt correspond to accumulated drug percentages released on each moment, for the tablets with native starch as a diluent and those with the corresponding modified starch, respectively.

RESULTS AND DISCUSSION

Degree of substitution

In total, four types of starch were obtained: one of native starch, and three with different acetylation levels. Table 1 shows AP and DS achieved for each level. As the volume of AA added increases, a rise on both parameters can be evidenced, although not in directly proportional way.

Table 1: Percentage and substitution degree of *A. xanthorrhiza* starch in different levels of acetylation

Starch type	Acetylation percentage mean±SD	Substitution degree mean±SD
A. xanthorrhiza native	0.00	0.00
A. xanthorrhiza level I	7.9±0.09	0.33±0.004
A. xanthorrhiza level II	13.5±0.12	0.59±0.006
A. xanthorrhiza level III	16.6±1.12	0.74±0.06

SD-Standard deviation; n=10.

This might occur due to tight packaging of amylose chains in amorphous regions, and to the highly organized amylopectin chains, which might affect the efficiency of acetylation reactions on starch's glucose units [12]. Efficiency was considerably lower than one achieved with corn starch under the same conditions (see supplementary material, table S1) because particle size of the corn starch is smaller and percentage of amylose is higher than *A. xanthorrhiza*, aspects that improve the reaction [20]; to increase reaction efficiency, catalysts and more drastic temperatures would be required [21]. Although the efficiency of the reaction can improve, it follows a mechanism of addition-elimination that under equal conditions will depend on the reactivity of the-OH groups of the starch, leading to the reaction not being homogeneous and at high concentrations of AA some glucose units will be inaccessible to react and the-OH groups will remain unacylated, obtaining values of DS far from 3.0 [20].

IR showed starch acetylation in reference to native starch (see supplementary material, fig, S1). When comparing the analysis of IR for the starches that were subjected to the reaction can be observed a decrease (shortening) of vibrations related to stretching or tension (between 3700-2800 cm^{-1}). This is due to the introduction of acetyl groups to the structure of the starch that provides a certain spherical effect to the flexural vibrations indicating changes in the sample analyzed [9].

Likewise, the appearance of a band between 1720-1760 cm^{-1} was observed in the modified starches, this is assigned to the vibration of the C = O bond (carbonyl group), which is clear evidence of the modification [22]. Finally, with acetylation, a decrease was observed in the signals corresponding to the vibrations of stretching (3000-3900 cm^{-1}) and vibrations of flexion of the O-H groups due to the introduction of the acetyl C-O groups to the starch, corroborating that the acetylation reaction was performed on the samples analyzed [23].

Morphology, size and particle size distribution

SEM (fig. 2) showed irregular *A. xanthorrhiza* native starch granules (fig. 2a), with fluted, polyhedral, globular surface, which is in accordance to postulations by Moraes *et al.* [24]. For acetylation level I (fig. 2b), granules show no change on their surfaces, maintaining globular, polyhedral shapes. Level II granules (fig. 2c) show no surface changes, though some loose globular shape and evidence their fusion. Acetylation level III granules (fig. 2d) show light damage on their surfaces and increased irregularity; although they are not high due to the low DS, this could be generated by the fusion of the granules and the formation of hydrogen bonds, being evident also, by other authors, in modifications on starches such as butyrylation and carboxymethylation [25].

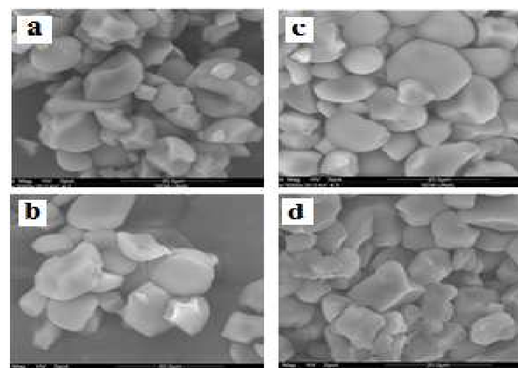

Fig. 2: Microphotographs of *A. xanthorrhiza* starch (5000x): a) Native, b) Acetylation level I, c) acetylation level II, d) acetylation level III

90% of native *A. xanthorrhiza* starch particles had a size smaller than 29.01 µm, with particle size distributions ranging between 2.10 and 35.0 µm. Acetylated particles show an apparent size increase, as readings showed 90% of particles for acetylation levels I, II and III

stood below 100.95, 97.97 and 93.51 µm, respectively (see supplementary material, fig. S2-S5). Contact of acetylated material with water during the obtaining process tends to form a hydrophilic, adherent gel that could promote particle coalescence [26]. This coalescence is explained by the intergranular aggregation, which can be caused by interaction between functional groups due to an increase in the hydrogen bonds and therefore intergranular agglomeration [27].

X-ray powder diffraction

XRPD measurement verified if acetylation altered the starch's degree of crystallinity [10]. Fig. 3. shows signs at 14.9 °, 17.1 °,18.4, 21.7 °, 23.3 °, which coincides with that reported by other authors [27], where the signal at 17 ° and the double peak at 22 ° and 24 ° are characteristics of the starch of *A. Xanthorrizha*. The crystalline pattern was not affected by acetylation in the working conditions (low DS), which agrees with some authors [28].

However, some modifications made to starches for other authors, such as esterification with chloroacetic acid results in a change in the crystalline pattern, enough to destroy the crystallinity of the starch, changing it to an amorphous state [29]. For modifications by acetylation at high levels a decrease in crystallinity may occur due to substitutions of-OH groups by bulky acetyl groups in the starch chain, that reduce the formation of junction zones between starch molecules due to steric hinderances and results in the limited destruction of the ordered crystalline structure [30].

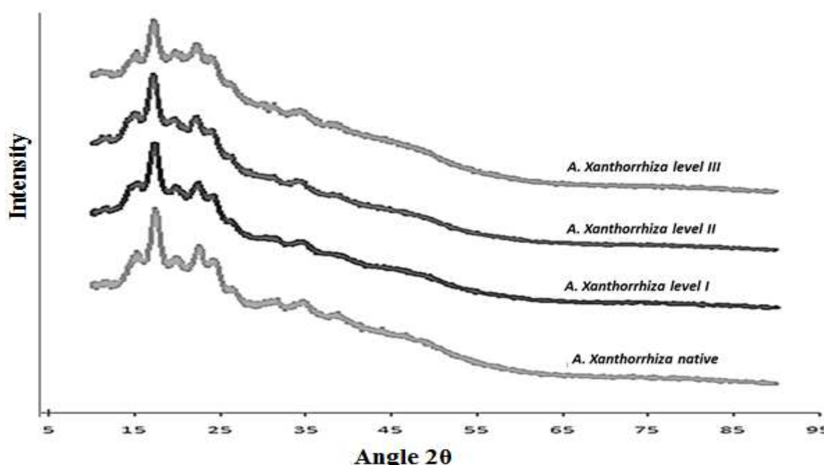

Fig. 3: X ray powder diffraction study of native *A. xanthorrhiza* starch and *A. xanthorrhiza* starch with three levels of acetylation (Levels I, II and III)

Swelling power

Fig. 4 shows that SP increases as the temperature rises which matches postulations of Li and Yeh [31], as it comes closer to gel formation. At this point, native starch can retain 16.20±0.22 times its own weight in water, while starches modified on levels I, II and III, present values of 22.93±2.48, 26.77±0.15 and 24.98±2.67, respectively at 65 °C (These values correspond to mean=3±SD). This increase occurs at the low level of acetylation, because inclusion of acetyl groups in the polymer chains that confirm the starch, causes an intragranular disruption that enables permeation of water to the amorphous region, which is eased by the greater energy supplied. Accordingly, more water is absorbed which translates into greater swelling [20, 32].

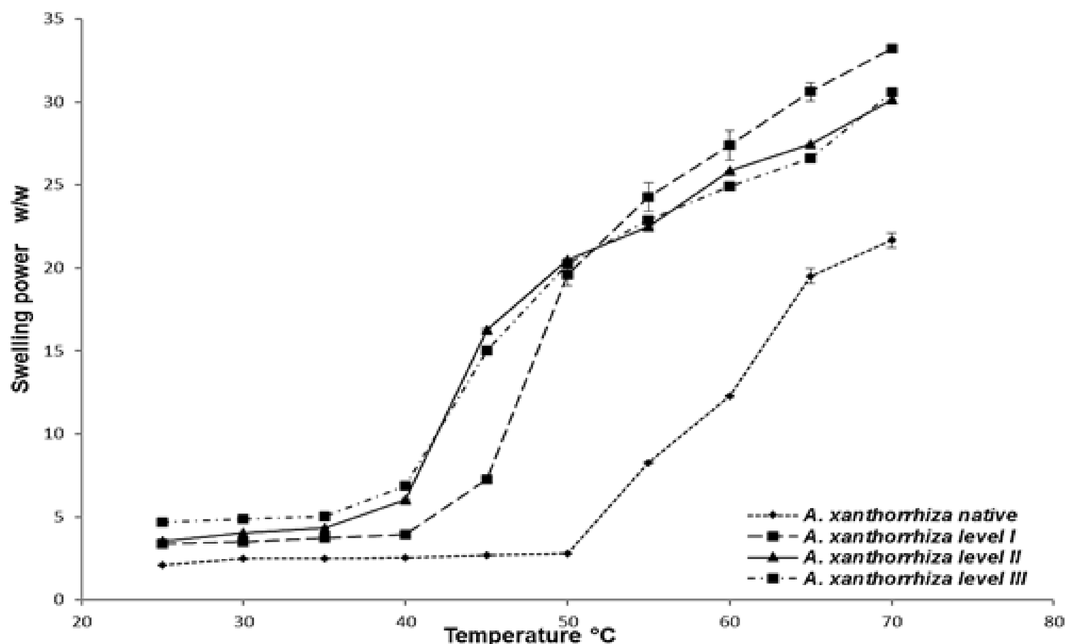

Fig. 4: Swelling power of *A. xanthorrhiza* native starch and *A. xanthorrhiza* acetylated starch with three levels of acetylation (Levels I, II and III). All the values were calculated as mean±standard deviation (n=3)

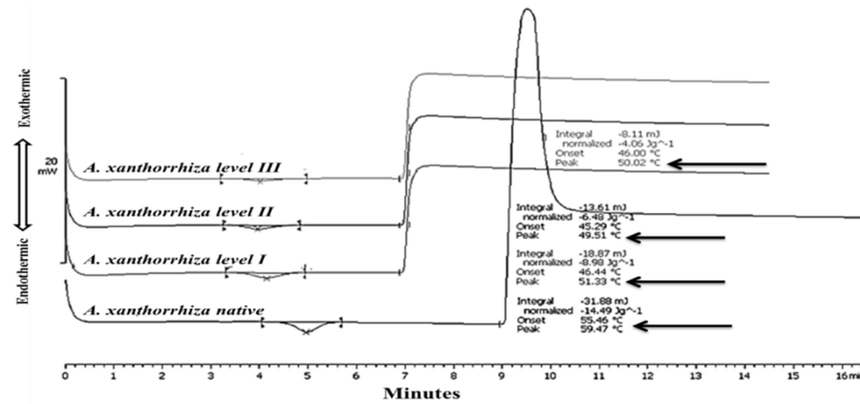

Fig. 5: Thermograms of native *A. xanthorrhiza* starch and *A. xanthorrhiza* starch with three levels of acetylation (Levels I, II and III)

Gelatinization temperature

Thermograms obtained through DSC, with Tg of native and modified starches are presented on fig. 5.

Tg for *A. xanthorrhiza* native starch was 59.5 °C, consistent with values found on literature [33, 34]. This value is lower than those of corn and potato starches, for which gelatinization temperatures are 76.27 °C and 73.66 °C respectively [35, 36]. This behavior is related to a shoulder on the amylopectin branched-chain length of *A. xanthorrizha* starch, which is known as a crystalline structural defect and contributes to the starch's low gelatinization temperatures [37]. Tg diminishes progressively as the modification increases, reaching 51.33 °C, 50.02 °C and 49.51 °C for acetylation levels I, II and III, respectively. These results could be associated with loss of molecular order in the granule [12]. Introduction of acetyl groups causes a disruption in the internal granule structure by disconnecting hydrogen bonds, both intra-and intermolecular. That way, less energy would be necessary for breaching chains and allowing water absorption, thus causing gelatinization [32, 38].

Sorption isotherms

Fig. 6 shows water-sorption profiles in terms of time and table 2, sorption velocity constants associated to each stage of the process.

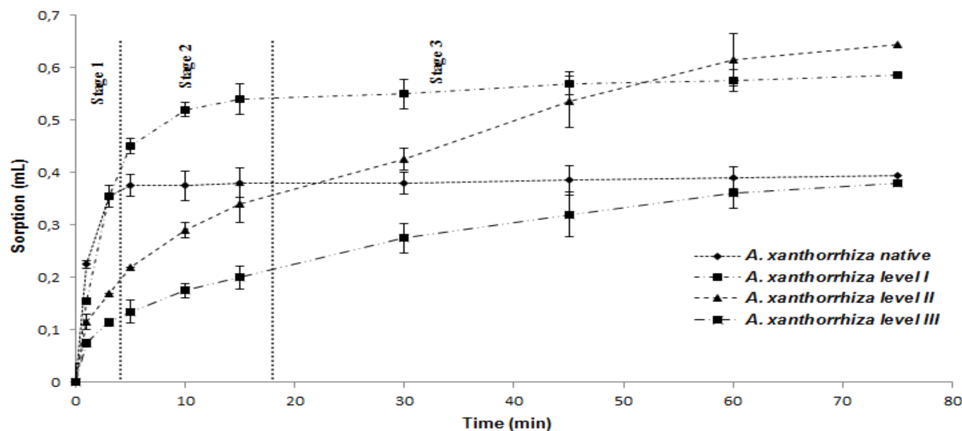

Fig. 6: Sorption isotherms of native *A. xanthorrhiza* starch and *A. xanthorrhiza* starch with three levels of acetylation (Levels I, II and III) (25 °C). All the values were calculated as mean±standard deviation (n=2)

Table 2: Water uptake behavior of modified *A. xanthorrhiza* starch matrices

Starch type	Stage 1 *K*(mL/mg. min) (R^2)	Stage 2 *K*(mL/mg. min) (R^2)	Stage 3 *K*(mL/mg. min) (R^2)
A. xanthorrhiza native	0.107 (0.8866)	0.0005 (0.7500)	0.0003 (1.0000)
A. xanthorrhiza level I	0.1157 (0.9864)	0.0090 (0.9067)	0.0007 (0.9308)
A. xanthorrhiza level II	0.0399 (0.8779)	0.0065 (0.9826)	0.0037 (0.9356)
A. xanthorrhiza level III	0.0357 (0.8732)	0.0054 (0.9900)	0.0020 (0.9643)

K= velocity constants (mL/mg. min); R^2 = Coefficient of correlation of each state

The sorption graphs show that *A. xanthorrhiza* native and acetylation level I starches both present a two-phase behavior characterized by high-speed on the first stage that decreases over time. For level I starch, sorption velocity constants are greater than those of native starch, which means a more hydrophilic material, albeit with less capacity to increase its surroundings viscosity. Acetylation levels II and III starches presented higher water sorption, albeit slower than native and level I starches. It could be because, at neutral or high pH values, the ionization of carboxyl groups and the consequent repulsion between chains with network dilation, which favors the entry of water [39]. This outcome is attributed to material's observed tendency of forming a superficial

hydrophilic gel on the first stages of the process, which hinders water entry. This is associated to greater water sorption capacity as the acetylation degree increases when substitution degree is low [20]. Different behavior occurs at high levels of acetylation, as it has been reported by other authors [20].

Evaluation of *A. xanthorrhiza* starches functionality as diluents in tablets

Tablets were produced to test the functionality of *A. xanthorrhiza* starch as a hydrophilic matrix, using sodium diclofenac as a model drug. *A. xanthorrhiza* acetylated starches presented good compression capacity, without evidence of lamination or adhesion to punches during production. These characteristics would show that it could be used as a diluent for direct compression [40].

Fig. 7 presents release profiles for evaluated formulations, using native and acetylated starch as diluents. With native starch, 89% of sodium diclofenac is released on the first hour, while this same value is achieved near the 14th hour with modified starches.

As tablets came in touch with dissolution medium at 37 °C, a gelatinous coat was formed around them. This coat's thickness was greater as the starch's DS increased. Tablets made of native starch disintegrated after about an hour, which didn't happen on tablets made of modified starches.

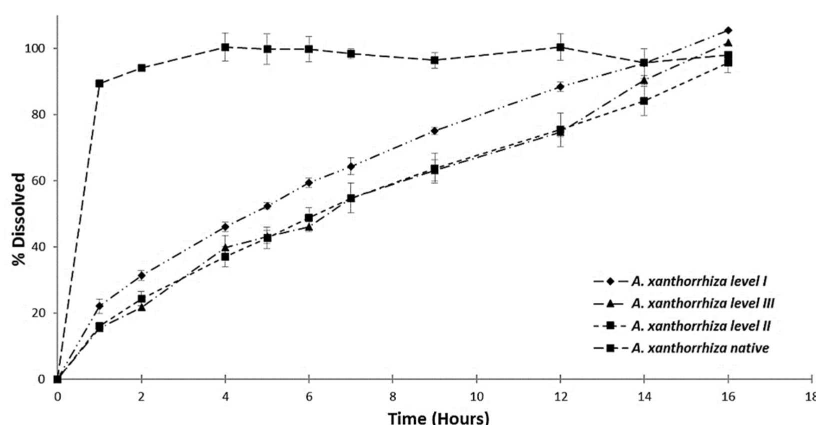

Fig. 7: *In vitro* release profiles of diclofenac from matrices of native *A. xanthorrhiza* starch and *A. xanthorrhiza* starch with three levels of acetylation (Levels I, II and III). All the values were calculated as mean±standard deviation (n=3)

As previously shown, acetylation of *A. xanthorrhiza* starch significantly improves water sorption and retention capacities and drops its gelatinization point. This behaviour has been observed on other starch sources, although not in the same magnitudes [9].

This behaviour suggests that, upon contact with dissolution medium, it acts as a plasticizer, thereby improving the mobility of polymer chains, capturing water and swelling, which in turn contributes to drug delivery control, depending on its modification level. This behavior is similar to cellulose polymers like hydroxypropyl methylcellulose (HPMC) [41].

Table 3 shows results for kinetic behavior determination of sodium diclofenac release from matrices made of *A. xanthorrhiza* starch.

Table 3: Release kinetics of diclofenac from *A. xanthorrhiza* starch matrices with different degrees of acetylation

Starch type	Release kinetic		
	Korsmeyer–peppas n (R^2)	First order K(h^{-1}) (R^2)	Zero-order K(% released/h) (R^2)
A. xanthorrhiza level I	0.5676 (0.9990)	0.2031 (0.9419)	5.9187 (0.9500)
A. xanthorrhiza level II	0.6388 (0.9987)	0.1663 (0.8772)	5.4421 (0.9714)
A. xanthorrhiza level III	0.6797 (0.9924)	0.1465 (0.9063)	5.8158 (0.9792)

Release exponent = n, velocity constants = K, correlation coefficient = R^2

Korsmeyer-Peppas is the model that most closely aligns to results obtained when using modified *A. xanthorrhiza* starch (correlation coefficient approaching 1), with R^2 between 0.9990-0,9924 and values for n between 0.5676-0.6797. This n value, associated to the release mechanism, suggests an anomalous, non-Fickian transport behavior, related to a mechanism governed by swelling and diffusion [42]. Swelling would be related to capacity of modified starch to improve the mobility of the polymer chains due to decrease in Tg in presence of water and increase of medium temperature, similar to explained for some authors for materials like HPMC [41]. Diffusion presented in delivery process would be associated to physico-chemical properties of sodium diclofenac as its solubility and facilitated for the fluid ingress into the matrix [43]. Native starch matrices present a behavior similar to an immediate-release system, characterized by disintegration and active dissolution stages.

Release profiles for varied formulations were compared by similarity factor (f_2), with results being shown on table 4.

Table 4: Dissolution profiles comparison of diclofenac from *A. Xanthorrhiza* starch matrices

Dissolution profiles comparison	Similarity factor f_2
Native vs Level I	30
Native vs Level II	17
Native vs Level III	17
Level I vs Level II	46
Level I vs Level III	47
Level II vs Level III	57

Given that profiles are deemed similar when f_2 ranges between 50 and 100 [44], profiles for acetylation levels II and III are found inside the range, and their comparison with other levels shows no similarity between them. These results clearly evidence that acetylation of *A. xanthorrhiza* starch alters the physicochemical behaviour of native starch, generating a new material capable of controlling drug release, as shown in drug-release profiles with statistically-significative differences in comparison to native starch. Similarity shown for levels II and III implies that a low level of acetylation be enough for controlling drug release.

Results suggest acetylated starch, on different levels, is able to module drug delivery, in contrast to what happens with native starch.

CONCLUSION

A. xanthorrhiza starch proved having great potential for the production of solid oral modified-release pharmaceutical forms. *A. xanthorrhiza* native starch modified by acetylation showed as DS increased, augmented swelling capacity, associated to a drop in gelatinization temperatures. This drop, in turn, promotes the formation of a hydrogel, a gelatinous coat around the tablets when put in contact with dissolution medium at 37 °C. This gelatinous coat prevents water from pouring-in into the tablet and interfering with drug release; hence being kept longer in the matrix and delivered according to the kinetic model of Korsmeyer-Peppas. In general, the favorable pharmacotechnical behaviour of modified *A. xanthorrhiza* starches enables their application as excipients in designing controlled-release solid pharmaceutical forms.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest

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