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Acetylation of Starch Extracted from Rejected Fruits of *Musa × paradisiaca L.* to Obtain a Pharmaceutical Disintegrant

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Abstract

There are many natural sources to obtain pharmaceutical grade starch, one of which is banana (*Musa × paradisiaca L.*); nevertheless, the use of native starch has certain disadvantages compared to modified starches, whose disintegrating properties are better. In this study, starch extracted from rejected fruits of *Musa × paradisiaca L.*, was modified by acetylation, under the following optimized experimental conditions: 130 mL acetic anhydride, 3 mL sodium hydroxide 50% p/v for each 15 grams of native starch, at 123˚C during 3 hours. The reaction resulted in a modified green banana starch with twice as much swelling capacity compared to unmodified (native) starch; acetylation was verified by infrared spectroscopy and degree of substitution of acetyl groups by back titration. The dissolution profiles of Ibuprofen tablets made with banana modified starch and commercial disintegrant, have no differences according with their similarity factor, f_2. It is concluded that it is feasible to use green banana starch modified through acetylation as a pharmaceutical disintegrant.

Keywords

Modified Banana Starch, Acetylation, Swelling Capacity, Disintegrant, Dissolution Profile

1. Introduction

In Ecuador the pharmaceutical sector invests only 8% of its profits in research, this low percentage prevents giving added value to locally developed products, in such a way that approximately 90% of the components of a drug product are imported. The lack of research and the almost non-existent national production

of both active ingredients and excipients generate not only technological dependence, but high costs of drug product manufacturing [1].

There are numerous natural resources from which various raw materials can be obtained for use as pharmaceutical excipients; this is the case of bananas and plantains, nationally representative products that are exported in large quantities to different countries [2] [3]. Plantain production has different stages, one of which is the post-harvest of the fruit prior to export, which leaves a series of residual organic by-products, including 81,331 MT defined as rejection per year, which are not used properly [4]. The starch extraction processes are of great interest in the field of the pharmaceutical industry, since starch is a versatile excipient widely used in the manufacture of tablets and other products [5].

There are various studies where starch extracted from natural sources is used as a starting material to obtain raw materials with better characteristics. Native starches are those that have not undergone any type of physical or chemical modification; [6] [7] while modified starches have better mechanical and chemical properties as well as high stability [8].

There are various studies where starch extracted from natural sources is used as a starting material to obtain raw materials with better characteristics [7]. Some ways of modifying starches have been described; one of them is acetylation, a chemical modification that occurs by the esterification of native starch with acetic anhydride in basic medium, where the acetyl groups replace the hydroxyl of positions C2, C3 and C6. Acetylation changes the structure of native starch, as well as the association of amylose and amylopectin, improving the functional, mechanical, and thermal properties of starch [7] [9]. The native starch acetylation reaction produces starch esters with a degree of substitution determined by the reaction conditions. The maximum degree of substitution is 3 because three hydroxyl groups are available per unit of anhydroglucose [6]. Depending on the degree of substitution, the corresponding application is given, esters with medium to low degree of substitution, between 0.5 - 2.5, could have applications such as adhesives, cigarette filters, tabletting, biodegradable plastics and ionic metal adsorbents [7] [10]. Starch as a disintegrant is the most widely used excipient in the manufacture of conventional tablets in concentrations of up to 10% in the formulation, which upon contact with water swells and therefore results in its breakdown [11]. The present study aims to extract starch from rejected fruits of *Musa* × *paradisiaca L.*, and modify it by means of an acetylation reaction, increasing its swelling capacity with respect to the native unmodified starch.

2. Materials and Methods

2.1. Starch Extraction

The selected bananas were washed with water and detergent, then disinfected with a chlorine solution (50 ppm), leaving it there for five minutes. The peels were removed from the fruits, 500 g of cut fruit was weighed and placed in a

0.3% citric acid antioxidant solution, in a fruit/solution ratio of 1:1.5 (w/v) for 5 minutes, wet milling was carried out in a blender at maximum speed for two minutes, sieving was carried out in mesh No. 100. The residue was washed 5 times with 100 mL portions of distilled water. The suspension obtained was left to stand for 24 hours to decant the starch. The supernatant was removed and the pulp was again suspended in distilled water and filtered. The final paste was dried in an oven at 40˚C - 45˚C for 24 hours. Finally, the starch obtained was crushed in a mortar and sieved through mesh No. 140, stored in a closed plastic container at room temperature [5].

2.2. Starch Acetylation

A factorial design 2^3 with 3 central points was applied. 15 g of starch (dry basis) were weighed and mixed with acetic anhydride (120 mL; 125 mL; 130 mL) in a three-necked 250 mL flask with a refrigerant. The suspension was stirred at 350 rpm for 5 min, then 50% p/v NaOH (0.10 mL; 0.15 mL; 0.20 mL) was added per each gram of starch. The balloon was heated to 123˚C in an oil bath with magnetic stirring. The reaction time elapses since the system reaches this temperature. Samples were taken at different times (2 h; 2.5 h and 3 h). At the end of the reaction time, the system was cooled to 50˚C and 100 mL of 96% ethanol was added to stop the reaction. The resulting suspension was added to 500 mL of distilled water to precipitate the starch. It was vacuum filtered by washing the solid residue with 500 mL of water until most of the acetic anhydride was removed. The obtained starch paste was oven dried at 50˚C for 24 h. Finally, the modified starch was crushed and sieved through a mesh No. 140, to homogenize the particle size [6].

2.3. Acetyl Groups and Degree of Substitution

1 g of acetylated starch (dry base) was weighed into a 250 mL Erlenmeyer flask and 50 mL of 75% ethanol was added. The system was heated to 50˚C with magnetic stirring for 30 min. It was cooled to room temperature and then 40 mL of 0.5 N KOH and four drops of phenolphthalein were added with constant stirring. The flask was capped and allowed to stir for 72 h. The saponified sample was then titrated with 0.2 N HCl, then the system was left to stand for 2 h and the alkali that could have leached from the sample was titrated [6]. The same procedure was applied in the native starches used as reference. The percentage of CH_3-C-O-groups was calculated with the following formula:

$$\%\text{Acetyl} = \frac{B - M \times N \times 0.043}{PM} \times 100 \quad (1)$$

B = mL of HCl used in the blank;
S = mL of HCl used in the sample;
N = HCl Normality;
mw = molecular weight in grams;
0.043 = miliequivalents of CH_3-CO-group.

The degree of substitution (DS) in the acetylated starch is equivalent to the average number of hydroxyl groups that were replaced by CH_3-CO-groups in the anhydrous glucose unit (AGU). It was calculated with the following formula:

$$DS = \frac{162 \times \%Acetyl}{4300 - (42 \times \%Acetyl)} \quad (2)$$

162 = molecular weight of AGU;
4300 = 100 × molecular weight of CH_3-CO-;
42 = (molecular weight of CH_3-CO-.

2.4. Swelling Capacity

Based on previous research [12], 1.4 grams of starch were weighed into a 10 mL cylinder. Then distilled water at room temperature was added up to 9 mL, the cylinder was capped and the system was stirred for 4 minutes. Finally, it was left to rest for 40 minutes and the swelling volume of the starch was measured.

2.5. Infrared Spectroscopy

The samples were analyzed at a range of 600 to 4000 cm^{-1} on a Perkin Elmer spectrometer [12].

2.6. Tablet Manufacturing

To obtain tablets, the Direct Compression Method was chosen, adapting from [13], the tablets were made according to **Table 1**.

2.7. Dissolution Profile

This test was carried out according to the methodology proposed in the pharmacopoeia [14], using 900 mL of dissolution medium (phosphate buffer pH 7.2) and apparatus II at 50 rpm for 1 hour. Samples were taken at: 5, 10, 15, 20, 30, 45 and 60 minutes. Dilutions were made to reach a concentration of 0.0081 mg/mL, and quantified by UV spectrophotometry at a maximum absorption length of 221 nm. Specification: Not less than 80% of the indicated amount of Ibuprofen dissolves in 60 minutes.

Table 1. Ibuprofeno 200 mg tablets formulation.

Component	Quantity (mg)	%	Function
Ibuprofen	200.0	40.0	Active Ingredient
Modified Starch[a]	50.0	10.0	Disintegrant
Microcrystalline cellulose	242.5	48.5	Filler
Colloidal silicon dioxide	2.5	0.5	Glidant
Magnesium stearate	5.0	1.0	Lubricant
TOTAL	500	100.0	

a. Modified corn starch or acetylated banana starch.

3. Results

Swelling capacity tests were performed by triplicate on each sample of modified starch. The results for acetylated banana starches, native banana starch and modified (commercial) corn starch are detailed in Table 2.

Figure 1 shows the effect of the study factors that are statistically significant on the swelling capacity of the modified starch.

The overlaid Infrared spectrum of modified green banana starch, native banana starch and modified corn starch, a commercial sample, is showed in Figure 3.

The degree of substitution was analyzed only in the starch obtained by the best treatment, the one that produced the greatest swelling capacity; Table 3 shows the results obtained below:

The comparison of dissolution profiles allows evaluating certain parameters, in the present case, the influence of the type of disintegrant in the formulation. Table 4 and Figure 2 present this information.

Table 2. Swelling capacity of native and modified starches.

Treatment	Time of reaction (minutes)	Volume of NaOH (mL/g)	Volume of acetic anhydride (mL/g)	Swelling capacity (%)
Native	-	-	-	125.76
1	2.5	0.15	125	200.30
2	2.5	0.15	125	199.75
3	2.5	0.15	125	210.75
4	2.0	0.10	120	150.00
5	2.0	0.20	120	176.67
6	2.0	0.10	130	183.33
7	2.0	0.20	130	196.97
8	3.0	0.10	120	187.27
9	3.0	0.20	120	197.27
10	3.0	0.10	130	212.42
11	3.0	0.20	130	231.21
Modified corn starch[a]	-	-	-	364.55

a. Commercial.

Table 3. Degree of substitution of modified banana starch.

Sample	% acetylation	Degree of substitution
1	18.73	0.86
2	19.23	0.89
3	18.96	0.87
Average	18.97	0.88
RSD[a]	1.33	1.60

a. Relative standard deviation (%).

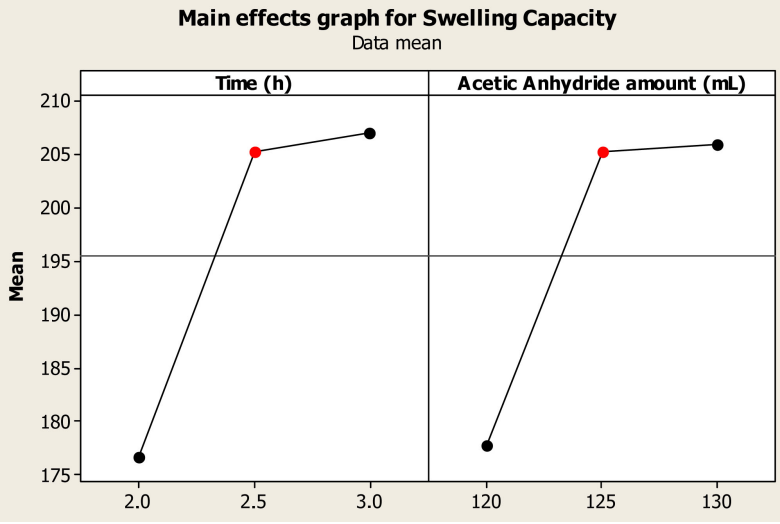

Figure 1. Main effect plot for swelling capacity.

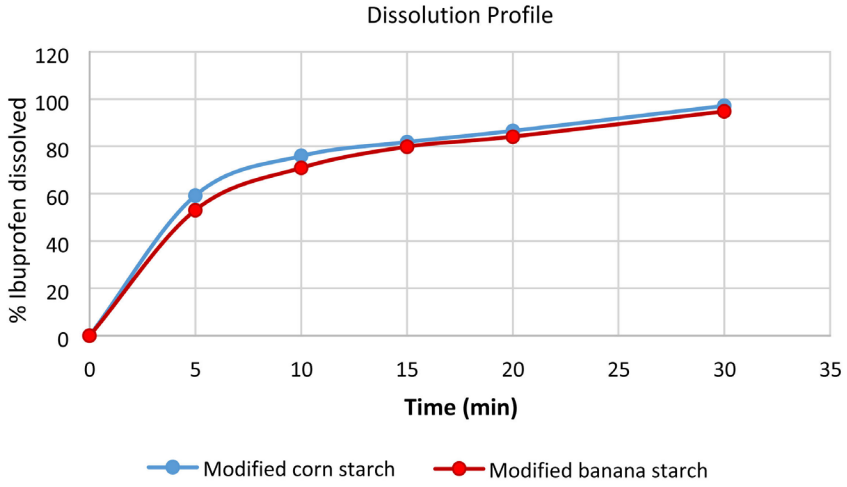

Figure 2. Comparison of dissolution profiles of tablets made with modified banana starch and modified corn starch.

Table 4. Dissolution profile. Reference and test.

Time minutes	% Dissolved Tablets with modified corn starch[a] (Reference)	% Dissolved Tablets with modified banana starch (Test)
5	59.31	53.10
10	71.76	69.63
15	81.87	79.88
20	86.64	84.21
30	97.23	94.87

a. Commercial.

The numerical comparison of the dissolution profiles was performed by calculating the similarity factor (f_2):

$$f_2 = 50\log\left\{\frac{1}{\sqrt{1+\sum\left(\frac{[R-T]^2}{n}\right)}}\times 100\right\} \quad (3)$$

$$= 50\log\left\{\frac{1}{\sqrt{1+\frac{58.5356}{5}}}\times 100\right\} = 72.40$$

4. Discussion

Table 2 shows that the swelling capacity for the modified starch increases to higher amount of acetic anhydride, higher amount of sodium hydroxide and longer reaction time. However, none of the treatments carried out to modify banana starch achieves a swelling capacity equal to that of commercial modified corn starch. Two of the factors were statistically significant for the acetylation reaction: the higher the amount of acetic anhydride (acetylating reagent) and the longer the reaction time, the swelling capacity of the modified banana starch increases.

As can be seen in the IR spectrum, Figure 3, for the modified banana starch there is an increase in the signal close to 1724 cm^{-1}, which is characteristic of the carboxyl groups introduced in the acetylated starch molecules and which are similar to those who were found in previous study [12]. Additionally, signals were presented in the range of 900 - 1250 cm^{-1}, corresponding to the C-O stretch of the acetyl group; the signal at 1241.1 cm^{-1} corresponds specifically to the C-O stretch of the acetyl groups.

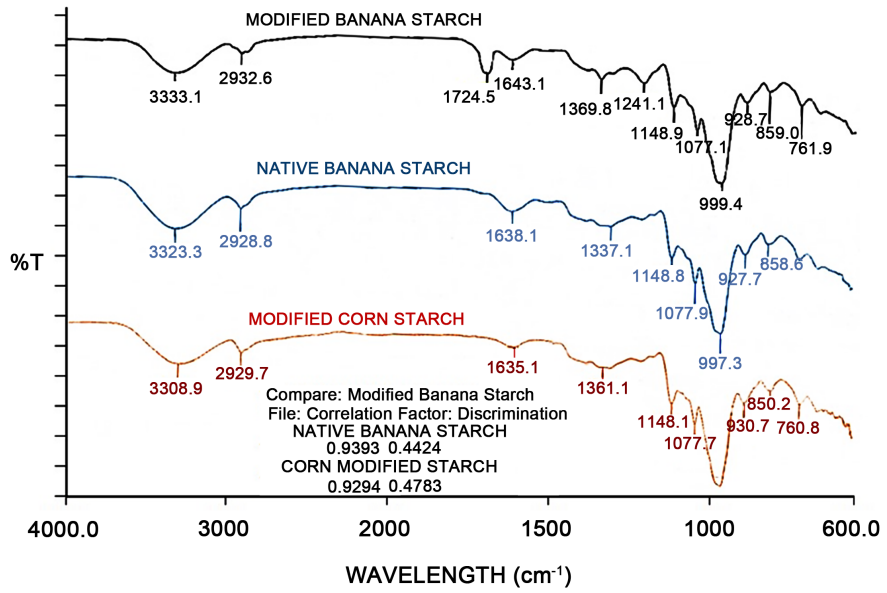

Figure 3. Infrared spectrum of different starches.

The average degree of substitution for the best treatment was 0.88, which is higher than the results obtained by [6]. In such study, after three hours of reaction, a degree of substitution of approximately 0.75 was obtained, notably lower, presumably because a lower amount of acetic anhydride was used compared to the present work. Consequently, the higher the degree of substitution, the disintegrating power of the starch improves, since its swelling capacity is greater compared to the native starch.

The calculated similarity factor, 72.40, is within the range of 50 - 100, which implies that there is no difference in the behavior during the dissolution test of the modified corn starch and the acetylated banana starch.

5. Conclusion

The best condition for acetylation of the starch extracted from rejected banana uses 130 mL of acetic anhydride and 3 mL of sodium hydroxide 50% p/v for each 15 grams of native starch, with three hours of reaction at 123˚C. Acetylation was confirmed by the degree of substitution and infrared spectroscopy. This modification allows obtaining a starch with better disintegrating properties than the native starch, with a twice greater swelling capacity. Despite the better swelling capacity of commercial modified corn starch, the dissolution profiles of tablets made from modified banana starch and commercial disintegrant are similar.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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