

Evaluation of the application of cashew gum as an excipient to produce tablets

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Abstract

Cashew gum is extracted from the exudate of the giant cashew tree (*Anacardium occidentale* L.). The objective of this work was to study the extraction and purification of cashew gum through experiments to characterize its structures and physicochemical and thermal properties, and to evaluate its use as a pharmaceutical excipient. The characterization of the materials was performed by infrared spectroscopy, thermogravimetric analysis and rheological studies of powder. Analysis of the material showed that it has reasonable flow characteristics and compressibility, allowing the use as diluent of tablets. Tablets were produced with a cashew gum isolated and purified by the direct compression method, and it was shown that the tablets produced with the purified cashew gum obtained better mechanical properties (hardness and friability) and less disintegration time than tablets made with gum of cashew isolated, suggesting the use of purified cashew gum as a diluent for this type of pharmaceutical form.

Keywords: *cashew gum, pharmaceutical excipient, direct compression, characterization, tablets.*

1. Introduction

The International Pharmaceutical Excipients Council defines excipients as substances composing pharmaceutical preparations that, although therapeutically inert or inactive, are necessary for their manufacture^[1].

Tablets are one of the main forms for oral administration of solid drugs. They are easy to administer and can contain one or multiple drugs. They are prepared with pharmaceutical excipients that facilitate compression during manufacture and guarantee suitable mechanical properties for disintegration and drug release within the body^[2]. They can be produced by compression of powders obtained by wet or dry granulation or by direct compression. In the direct compression method, the mixture of powders is compressed without a prior granulation step, reducing the number of steps on the production line and hence the time and cost^[3].

The cashew gum from Northeastern Brazil is characterized as a branched heteropolysaccharide acid, which after hydrolysis is basically composed of β -D-galactose (72%), D-glucose (14%), arabinose (4.6%), rhamnose (3.2%) and glucuronic acid (4.7%)^[4]. Cashew gum has been studied by various researchers in a wide range of fields, including the pharmaceutical sector. In this respect, this substance has been investigated for the formation of hydrogels, tablet fillers, mucoadhesive properties, micro and nanoparticles for controlled drug release^[5-8].

Specifically, for production of tablets, cashew gum has been studied as a binder, drug release promoter and former of coating films. All the studies reported in the literature have used the wet granulation method to prepare tablets^[6,9-11]. Also, no work has investigated the use of this excipient material as a diluent for tablets.

Another factor that deserves mention is the need to standardize the method to obtain any raw material, to assure its quality and safety, especially for medicinal use^[1]. Previous studies of cashew gum have applied various methods to obtain this material, so there is as yet no standardized method for its extraction. Therefore, the objective of this study was to investigate the variables related to the extraction and purification of cashew gum, as well as the possibility of its use as a diluent excipient for production of tablets by the direct compression method.

2. Materials and Methods

We used the following materials: cashew gum exudate, collected in the municipality of Severiano Melo, Rio Grande do Norte, Brazil; hydrated ethyl alcohol (95.54° GL); sodium chloride (NaCl) reagent grade, sodium hydroxide reagent grade; and spectroscopic potassium bromide (KBr), all acquired from Vetec Química Fina (Brazil).

2.1 Extraction and purification of cashew gum

The following factors were assessed in this respect: sodium chloride (NaCl) concentration; cashew tree exudate concentration in proportion to ethanol 95.54 °GL; and number of purification steps.

2.1.1 Determination of the best NaCl concentration

Initially the best salt content was evaluated for subsequent use in planning the experiments to evaluate the other factors (concentrations of gum and ethanol). To assess the influence of NaCl concentration, four aqueous solutions were prepared containing 10%w/v of unprocessed (in natura) gum (exudate), which were submitted to magnetic stirring for 24 hours. After this period, the pH of each solution was adjusted to pH 7 with sodium hydroxide 1 M (NaOH). Then, in each 100 mL of gum solution, varied quantities of NaCl were added (3, 5, 7 and 9 g), to obtain solutions called gum-NaCl 3%, 5%, 7% and 9%w/v. These were stirred until the salt was completely dissolved. Then the solutions were centrifuged to remove sand and other solids. The resulting solutions were filtered through a sintered disk funnel with porosity 1. The gum was extracted by precipitation using ethanol 95.54 °GL as non-solvent agent, in the ratio of 4:1 (ethanol:gum solution). After precipitation, the mixture was again centrifuged to separate the precipitate from the hydroalcoholic solution.

The precipitate was frozen and lyophilized and then ground with a mortar to obtain a powder. The isolated cashew gum (ICG) was then purified, by repeating the same routine as in the first step, but without adjusting the pH and adding salt. The amount of salt that will be used in the next steps will be chosen according to the evaluation of the yield obtained at the end of the purification process verified in this topic.

After the purification, the cashew gum (CG) was washed to remove a possible excess salt, as described below (performed in duplicate).

In each centrifuge tube (1, 2 and 3), 2 g of sample (ground CG) and 20 mL of ethanol were added. The tubes were shaken to assure contact of the ethanol with the gum particles. Then the tubes were spun at 4,000 rpm for 5 min. For tube 1 this process was performed once only. For tube 2, the ethanol was discarded and 20 mL of fresh ethanol was added, followed by the same centrifuging, for two washing steps. For tube 3, the same process was repeated a third time, to complete three washing steps. At the end of the process, the remaining material in each tube after discarding the ethanol (supernatant) was frozen with liquid nitrogen and lyophilized until complete drying of the sample (24 hours). All the samples were ground, and identified as: tube 1- PCGW1, with one washing; tube 2- PCGW2, with two washings; and tube 3- PCGW3, with three washings.

At the end, each sample was ground in an analytic mill (model IKA®-WORKS A11 basic) for 2 minutes. The resulting isolated and purified gum powders were analyzed by thermogravimetry (TGA) in a TA Instruments TGA Q500 analyzer, using a heating rate of 10 °C/min in a range between 0° and 700 °C, under an inert nitrogen atmosphere.

2.1.2 2² Factorial design with center point repetitions to study the extraction of cashew gum

The influence of the exudate and ethanol concentrations on the extraction yield was studied using a 2² factorial design. For this purpose, cashew tree exudate solutions were prepared in distilled water at concentrations of 5, 7.5 and 10%w/v (low, level and high level, respectively) at pH 7. Then NaCl was added to reach a salt concentration of 7%w/v in the samples, which were centrifuged and then filtered through a sintered glass disk funnel. The filtrate was submitted to precipitation with ethanol at proportions of ethanol:CG solution of 4:1, 6:1 and 8:1 (low, level and high level, respectively).

Based on the results of the tests described above, it was necessary to perform complementary experiments, varying the exudate concentration (4.0 to 10.0%w/v) while keeping the ethanol proportion constant (4:1), to try to obtain the best results.

2.1.3 Obtaining purified cashew gum

The purified cashew gum (PCG), used in the other steps, was obtained under the following extraction and purification conditions, selected based on the factorial experiments described above: NaCl concentration of 7% p/v; exudate concentration in solution of 7.0% p/v; ethanol:exudate solution ratio of 4:1; and three extraction steps, one for isolation and two for purification.

To check whether the number of extraction steps had an influence on the removal of impurities from the gum, a second purification step was performed with the gum sample obtained after the first purification step, following the same procedures as in the first step.

2.2 Fourier-Transform Infrared absorption spectroscopic analysis

The chemical structure of the cashew gum was characterized by spectroscopy in the mid-infrared region of 4000 to 400 cm⁻¹, in a Varian Excalibur spectroscope. The spectra were obtained by mixing the material with potassium bromide (KBr) in pellet form, using 50 scans and resolution of 2 cm⁻¹.

2.3 Thermogravimetric analysis

The TGA of the purified gum was performed with a TA Instruments TGA Q500 analyzer, using a heating rate of 10 °C/min in the range from 0 °C to 700 °C under an inert nitrogen atmosphere.

2.4 Rheological testing of the powder

The rheological tests of the purified cashew gum powder involved measuring the average particle size, along with the angle of repose and the bulk (or apparent) and tapped (or compacted) densities, to determine the flow properties. These density values were used to determine the Carr index and Hausner ratio.

2.4.1 Determination of the average particle size

For the verification of the average particle size, the apparatus "Bertel electromagnetic stirrer 110/220v with 6 screens" was used by means of the granulometric analysis described in Agência Nacional de Vigilância Sanitária^[12].

2.4.2 Angle of repose, Carr index and Hausner ratio and Flow properties

The angle of repose was determined according to the method described by Aulton^[13]. The Carr index and the Hausner ratio were obtained by using the density values of the gum samples, following the method described by British Pharmacopeia^[14]. These parameters for the purified gum powder were compared with those values published in British Pharmacopeia^[14] to indicate the flow properties.

2.5 Production of tablets

After the tests of the purified powers, tablets were produced and their properties were evaluated by the method described below.

2.5.1 Preparation of the tablets

The tablets were prepared by direct compression of the purified powder. For each tablet, a powder mass of approximately 350 mg was weighed and compressed manually in a Lemaq LM-1 Monopress, with single punch and using a spherical matrix having diameter of 13 mm, applying 3 metric tons of pressure.

2.5.2 Evaluation of average weight and mechanical strength

The tests to determine the average weight and mechanical strength (hardness and friability) and disintegration period were performed according to the method described Agência Nacional de Vigilância Sanitária^[12].

3. Results and Discussions

3.1 Extraction and purification of cashew gum

The purpose of studying the method of extraction and purification of the cashew gum was to ascertain the factors that influence the yield and degree of purity. These factors were chosen due to their relevance, as presented in previous articles^[4,15-17], according to which it is necessary to establish a reproducible method of extraction and purification of this material.

Initially, it was analyzed the effect of the concentration of NaCl in the aqueous solution prepared to dissolve the cashew tree exudate. Besides, the experiments was conduced to assess the influence of initial exudate mass and proportion of ethanol used to extract and purify the gum.

3.1.1 Determination of the best NaCl concentration

According to Costa et al.^[15], the addition of NaCl in excess in a previously neutralized aqueous solution of cashew gum enables the substitution of the cations possibly contained in the exudate (K⁺, Ca²⁺, Mg²⁺, Fe³⁺) by Na⁺, favoring its transformation into sodium salt. This transformation is reflected in an increase of the gum's solubility in aqueous solutions: at NaCl concentrations of 3, 5, 7 and 9% the final yield was 58.16, 63.93, 75.56 and 76.10%, respectively. As can be seen, higher NaCl concentrations promoted increased solubility of the solutions containing the exudate, leading to higher final yield of the process.

To validade the method of extracting the cashew gum (CG) was employed the NaCl concentration of 7% w/v to

obtain a gum with higher solubility, particle size uniformity and high degree of purity.

3.1.2 2² factorial experiments to evaluate the cashew gum extraction conditions

Table 1 shows the yields in the 2² factorial experiments, with three repetitions at the center point.

As shown by Table 1, the highest yields were obtained in experiments 1 and 3, where the exudate concentration was low level and the ethanol concentration was at both levels. This suggests that the gum concentration has a significant influence on the extraction yield. To corroborate this hypothesis, we performed statistical analysis using the Statisca 7.0 program to analyze the results shown in Table 2.

Table 2 and Figure 1 report the values of the coefficients associated with the two independent variables, along with their interaction. Only the exudate concentration had a significant influence, since the *p*-value obtained is lower than 0.05.

Table 1. Results of the factorial design 2².

Samples	Concentration exudate(%)	Ethanol:Solution exudate	Yield (%)
1	-1	-1	75.64
2	1	-1	66.61
3	-1	1	76.48
4	1	1	64.54
5	0	0	71.68
6	0	0	70.69
7	0	0	70.59

Table 2. Regression coefficients.

Regression Coefficient	β_0	β_1	β_2	β_{12}	Model adjustment missing
value	70.89	-5.24	-0.31	-0.73	-
<i>P</i>	0.00001	0.003289	0.411646	0.137846	0.744946

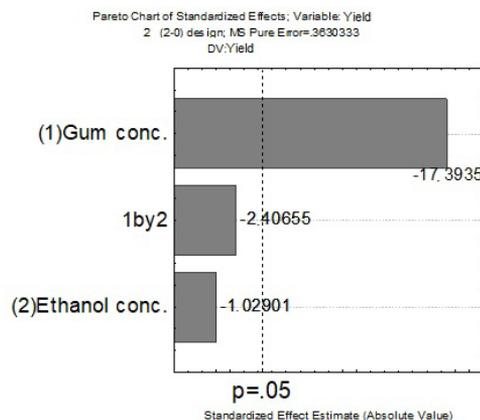


Figure 1. Diagram of Pareto for each independent factor and interaction in factorial design 2². According to the figure, only the concentration of the gum is a significant factor to the process.

As shown in Table 2, of the variables analyzed, only gum concentration presented a statistically significant influence. The negative value of the associated regression coefficient (β_1) indicates it is best to work with the lowest concentration and that neither the ethanol concentration nor the interaction between the resin and ethanol concentrations was statistically significant. However, the value near zero of the regression coefficient (β_2) associated with the ethanol concentration also indicates it is better to work with the medium ethanol concentration or with the lowest concentration value.

Based on the general mathematical model represented in Equation 1 for the 2² factorial design, it is possible to write a predictive model obtained from analysis of the experimental results, as presented in Equation 2.

$$Y = \beta_0 - \beta_1 X_1 - \beta_2 X_2 - \beta_{12} X_1 X_2 \quad (1)$$

$$Y = 70.89 - 5.24 X_1 \quad (2)$$

After verifying the significant influence of gum concentration, we performed complementary experiments varying this concentration and keeping the ethanol:solution ratio constant at 4:1. Figure 2 shows the results with gum concentrations from 4% to 10% w/v.

The results shown in Figure 2 indicate that the greatest purified gum yield was obtained at an exudate concentration in the solution of 7% w/v. The inflection point of the curve of concentration vs. yield represented in Figure 2 is 7%. As of this concentration, the yield of the CG extraction process started to decline, indicating a saturation point of the system exists.

3.2 Fourier -Transform Infrared Spectroscopy (FTIR)

The FTIR spectrum presented in Figure 3 has two cashew gum bands, as described in the literature Silva et al.^[17]. The following bands can be observed: an intense band in the range from 3398 to 3392 cm⁻¹, which can be attributed to the stretching vibration of the hydroxyl – OH group, typical of polysaccharides; a small band from 2927 to 2928 cm⁻¹, referring to the stretching vibration of the C-H groups, related to the monosaccharide galactose; a band from 1643 to 1613 cm⁻¹, which can be attributed to the O-H group from the scissoring vibration of water molecules of residual carboxyl groups of glucuronic acid; and a broad and intense band from 1078 to 1080 cm⁻¹, referring to the stretching of the C-O-C group from the glycosidic bonds of the sugars and stretching and bending vibrations of the O-H bond of the pyranoside sugars present in the chain of this gum.

3.3 Thermogravimetric analysis

Table 3 presents the temperatures of each degradation stage of the samples: isolated cashew gum (ICG), purified cashew gum (PCG), purified cashew gum with one washing step (PCGW1), purified cashew gum with two washing steps (PCGW2), and purified cashew gum with three washing steps (PCGW3); as well as the percentage of residual mass of each sample. According to this table, sample ICG had one degradation stage more than the other samples, at a temperature of 180.85 °C. The existence of this additional degradation stage shows that the method used to purify the CG was effective, by removing contamination by plant matter from the gum's sugars, Mothé and Rao^[18]. The thermographs of the purified CG samples contain three degradation peaks, the first at 48.23 °C, referring to the loss of water, and the second and third, at 232.29 °C and 295.85 °C, respectively, showing that the decomposition of the polysaccharides of this gum occurs in two stages, confirming the finding reported by Mothé and Rao^[18].

To check whether sample PCG was free of possible excess NaCl added during the purification process, we performed

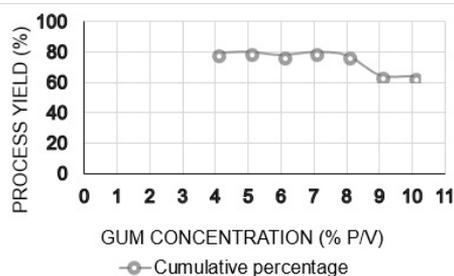


Figure 2. Study the yield of cashew gum. The 7% concentration is inflection point, where the maximum yield of the curve occurs.

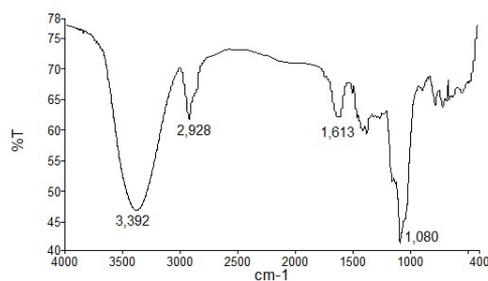


Figure 3. FTIR (KBr) spectrum GC purified.

Table 3. Thermogravimetric analysis.

Samples	Temperature of the first degradation stage (°C)	Temperature in the second degradation stage (°C)	Temperature of the third degradation stage (°C)	Temperature of the fourth degradation stage (°C)	Residual percentage (%)
ICG	53.81	180.85	227.36	292.51	19.56
PCG	48.23	-	232.29	295.85	21.02
PCGW1	49.25	-	228.29	292.81	20.57
PCGW2	50.55	-	227.92	292.28	19.93
PCGW3	48.05	-	228.99	291.20	19.78

three washing steps of the PCG. The thermographs referring to samples PCGW1, PCGW2 and PCGW3 show that it is not necessary to perform washing steps of the PCG, since there were no significant changes in the residual mass percentages at the end for each sample.

3.4 Rheological properties of the powder

The following rheological properties of the cashew gum samples were evaluated: average particle size, by granulometry; and compressibility and flow of the isolated and purified gum samples, by measuring the bulk (or apparent) density, tapped (or compacted) density and angle of repose.

3.4.1 Determination of the average particle size

The results of this experiment showed that the purified CG sample has varied particle size distribution, as can be observed in Figure 4, which reports the percentages of mass retained in the sieves with different mesh sizes. According to Agência Nacional de Vigilância Sanitária^[12], the powder samples had semi-fine profile, because all the particles passed through the 355 μm mesh sieve and at most 40% passed through the 180 μm mesh. We found that the average size of the purified CG particles was 253.64 μm , which can be considered a relatively small size.

3.4.2 Angle of repose

Another parameter of the flow behavior of a powder is the angle of repose, which is a measure of the powder's ability of flow through an orifice in a flat surface. It is considered a direct measure^[19-21]. This is an easy flow measure to obtain because it only requires determining the angle formed between the side of a stationary pile of powdered material and the horizontal. The higher the angle of repose, the more cohesive the powder is.

The static angle of repose was 38° (base radius= 7 cm and height= 5.5 cm) for the purified gum. This value suggests the sample in question has a reasonable flow property, as described in Hausner^[22]. The better angle of the purified gum can be related to its smaller average particle size, resulting

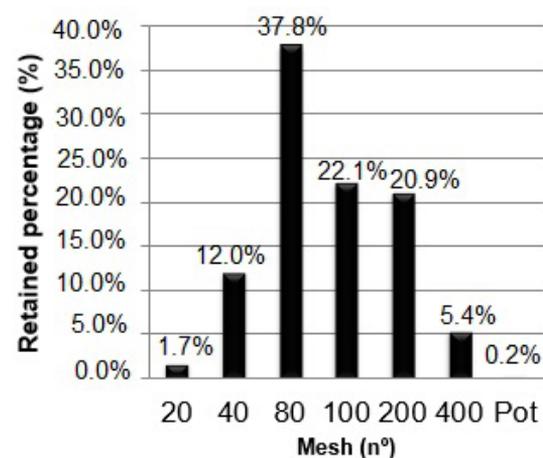


Figure 4. Percentage of mass Purified CG retained in different sizes of mesh sieves. The powder samples had semi-fine profile.

in a greater surface area and commensurately stronger cohesion among the particles.

3.4.3 Carr index and Hausner ratio

The Carr index and Hausner ratio are similar parameters, also used to assess the flow properties of powdered materials, related to the degree of particle interaction and the compressibility of the sample. They are both based on measurement of the bulk (or apparent) density and tapped (or compacted) density^[14,22-24].

The Carr index and Hausner ratio were found by applying the formulas mentioned previously. The values were 19.69 and 1.24 for the Carr index and Hausner ratio of the purified CG, respectively.

3.4.4 Flow properties of the cashew gum powders

Knowledge of the flow properties of powders is one of the main objectives of the pre-formulation tests conducted during the development of a product, since this parameter affects the quality of solid pharmaceutical preparations, such as tablets and capsules. This parameter is generally determined before testing the compression of tablets or filling of gelatin capsules. Low fluidity of the raw material can negatively affect hardness, friability and content uniformity of tablets^[15].

The flow characteristics of powders can be determined by various techniques, such as measuring the angle of repose and calculating the Carr index and Hausner ratio. These tests allow assessing the interactions of the particles, since their size, size distribution and morphology affect the flow parameters of the material. Particles with large surface areas in relation to volume (smaller particles) and those with irregular surfaces interact more readily due to electrostatic and friction forces, increasing the flow resistance and diminishing the flow. Small particles with low density and irregular morphology generally have worse flow properties than larger spherical particles with high density^[25,26].

Based on the Carr index and Hausner ratio values in correlation with the flow characteristics stipulated in British Pharmacopeia^[14], the purified cashew gum has intermediate flow resistance, so it might or might not impair the feed to the compression machine and negatively affect the average weight and hardness of the tablets. However, the angle of repose results showed that the flow characteristics were reasonable. Taken together, the Hausner ratio, Carr index and angle of repose values show that the only negative aspect of the purified cashew gum powder is the relatively high cohesion between particles, suggesting the use of slip agents to improve the flow in the compression machine feeders.

Sliding and lubricating agents are normally used when producing tablets, even for materials with good flow properties, so this is not a limiting factor of the use of cashew gum as a diluent for tablets produced by direct compression.

3.5 Tablets

Cashew gum has been investigated by several researchers as an excipient for production of tablets by the wet granulation method. In these works, the cashew gum served as a binding agent of the excipients of the active ingredients, as well as to form films to coat tablets^[6,10-13].

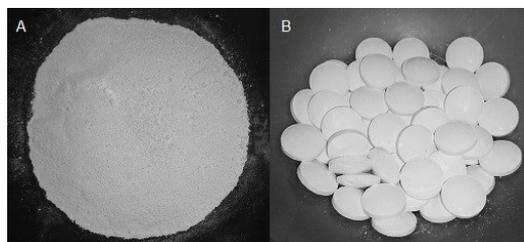


Figure 5. Tablets of purified cashew gum. (A) Powder purified gum; (B) Purified gum tablet.

Figure 5 contains an image of the tablets produced in this study from the purified cashew gum. It is noteworthy that this material in the experimental condition used was suitable for compression.

The tablet pre-formulation tests recommended by the Brazilian Pharmacopoeia are summarized next.

3.5.1 Evaluation of average weight

According to Agência Nacional de Vigilância Sanitária^[12], the acceptable limits of variation for uncoated tablets with average weight of 250 mg or more is $\pm 5\%$. The tablets were prepared aiming to obtain a final lot with average weight of 350 mg. The results obtained showed that the average weight was well within the acceptable tolerance, since it was 352 mg, a positive variation of approximately 0.6%.

3.5.2 Determination of the mechanical strength of the tablets

The mechanical strength of the tablets prepared with the isolated and purified cashew gum samples was determined by measuring the hardness and friability.

3.5.2.1 Hardness test

This test is applied mainly to uncoated tablets, allowing assessment of the resistance to crushing or breakage by radial pressure, by simulating falls during manufacture, packaging or transport. The hardness of a tablet is proportional to its compression strength and inversely proportional to its porosity.

According to Agência Nacional de Vigilância Sanitária^[12], the minimum hardness acceptable for a tablet is 30 N, or approximately 3 kgf. In this study, we evaluated the hardness of 10 tablets made from isolated and purified cashew gum, finding an average hardness of 6.4 kgf and 6.8 kgf respectively, higher than the minimum threshold set by Agência Nacional de Vigilância Sanitária^[12]. It should be stressed that the hardness must be sufficiently high to keep the tablets from breaking during production and transport (3kgf), but not so high as to impair their disintegration in the gastrointestinal tract.

3.5.2.2 Friability test

This test is only applied to uncoated tablets, to determine the resistance to abrasion when subjected to the mechanical action of the measurement device. The percentage of mass loss of the purified gum tablets (0.17%) and isolated gum tablets (0.75%) was far below the maximum limit stipulated by Agência Nacional de Vigilância Sanitária^[12] of 1.5%. None of the tablets cracked or presented fissures at the end of this test.

3.5.2.3 Disintegration test

According to Agência Nacional de Vigilância Sanitária^[12], a material in this test should disintegrate 30 minutes, meaning that after this interval, no residue of the units tested (capsules or tablets) should remain in the device's metal screen, except insoluble fragments of tablet coatings or capsule films. Units that are transformed into a pasty mass are also considered disintegrated, provided they do not have a palpable core.

The disintegration process of the isolated cashew gum occurred in 30 minutes, limited maximum estimated by Agência Nacional de Vigilância Sanitária^[12]. It is possible to notice that part of the material was soluble in the disintegration water and a large amount of particles was dispersed in the medium, confirming the not complete solubility of all the material isolated in the method of obtaining the cashew gum. However, the disintegration time of the CGP was 10 minutes, ie, three times less than the gum disintegration of the ICG, showing that the purification process favors a solubility of the material and removes insoluble particles from the disintegration process.

Based on the results of this study, we can recommend the use of purified cashew gum as a diluent to make tablets, due to its high solubility in water and low disintegration time.

4. Conclusions

To obtain higher yields in the cashew gum extraction process, it was established: exudate concentration in water of 7%, ethanol ratio: 4: 1, 7 g NaCl solution in 100 ml 7% gum solution and two extraction steps (isolation and purification). The result of the FTIR proved the characteristic bands of cashew gum and the thermograms proved the purity of the material. The flow properties of purified cashew gum were found to be reasonable, providing suitable conditions for the use of such material as a diluent of tablets obtained by direct compression, as evidenced by the pharmacopoeial tests performed on tablets in this work.

Therefore, the characterization tests take as a whole show that this gum can be a promising source of raw material in Brazil, especially in light of the abundance of *Anacardium occidentale* trees. Therefore, new studies should be conducted to adjust the properties of the gum, to add further support to the hypothesis that this gum can be used industrially in the pharmaceutical, food and cosmetics sectors.

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