Pre-formulation Study for Preparation of Mucoadhesive Buccal Tablets Containing Nystatin and Cashew Gum by Direct Compression

Ana Paula de Sá Pinto Abrahão Magalhães¹, Flávia Almada do Carmo², Claudia Regina Elias Mansur¹,³

¹. Institute of Macromolecules, Federal University of Rio de Janeiro, Rio de Janeiro 21941-598, Brazil
². Faculty of Pharmacy, Federal University of Rio de Janeiro, Rio de Janeiro 21941-599, Brazil
³. Program of Materials Engineering and Metallurgy, Technology Center, Alberto Luiz Institute of Coimbra, Post-Graduation and Engineering Research - COPPE, Federal University of Rio de Janeiro, Rio de Janeiro 21941-594, Brazil

Abstract: Cashew gum is a branched chain heteropolysaccharide extracted from the cashew tree (Anacardium occidentale L.). Purified cashew gum (PCG) is free of plant contaminants and is highly soluble. Several studies have indicated this polymer can be relevant in the pharmaceutical industry for production of tablets. Recently, our research group reported that PCG can be used as a diluent for tablets produced by direct compression. Nystatin (Nys) is the drug of first choice for treatment of oral candidiasis, in the form of a suspension. The treatment consists of up to six daily doses of a suspension of nys at 500,000 IU, causing low therapeutic adhesion by patients. The objective of this study was to investigate the behavior of PCG together with nys and other excipients (flavoring agents and lubricating agent) for future manufacture of mucoadhesive buccal tablets by direct compression. For that purpose, we performed pre-formulation tests (FTIR, TGA, XRD, solubility, pH, granulometry, swelling degree and powder flow) with physical mixtures of the drug and excipients. The results were excellent, demonstrating that PCG is a polymer with potential for this type of application.

Key words: Purified cashew gum, nystatin, mucoadhesive buccal tablets.

Nomenclature

PCG: Purified cashew gum
Nys: Nystatin

1. Introduction

Cashew gum is a branched heteropolysaccharide acid that after hydrolysis is basically composed of β-D-galactose (72%), D-glucose (14%), arabinose (4.6%), rhamnose (3.2%) and glucuronic acid (4.7%) [1, 2]. According to Cunha and colleagues [3], cashew gum is composed of a main chain of galactose (1 -> 3), with galactose branches (1 -> 6), containing units of rhamnose, glucuronic acid and arabinose as terminal groups. This gum has been widely studied in various areas, especially the pharmaceutical sector, for the development of films, formation of hydrogels, production of micro and nanosystems for controlled drug release, production of tablets and use as a suspension agent, among others [4-9]. From an economic standpoint, since Brazil is the world’s second leading producer of cashew products, the greater use of this raw material in the country can bring economic as well as social benefits, especially in the Northeast region.

Tablets are widely used in the pharmaceutical industry due to the ease of administering one or more drugs. Therefore, tablets are generally made of one or more active substances along with excipients, which facilitate the compression and impart ideal mechanical properties for disintegration, dissolution and release of
the drug(s) [10].

Tablets can be produced by wet or dry granulation or direct compression. In this last method, a mixture of powders is inserted in the compression machine without undergoing a granulation step, thus reducing the number of steps on the production line and decreasing the cost and time. However, the excipients used for this type of compression must have good flow and compressibility properties to assure production of tablets delivering a uniform dose, with constant average weight and hardness and sufficient compactness to remain stable, without cracks or fissures, during production and transport [11-13].

Cashew gum has been studied as an excipient for production of tablets with many functions, such as binding agent, drug release agent, mucoadhesive matrix for oral release, film forming agent for coating, and diluent agent [6, 9, 14-18].

Mucoadhesive systems stand out for delayed drug release applications, due to the possibility of guided release of the drug at the place of action for long periods, a factor that increases the adhesion of patients to treatment. Mucoadhesion basically occurs by the interaction of the polymer matrix with the mucus layer present in the oral mucosa. Among the possible ways of oral administration of drugs, mucoadhesive tablets stand out due to the facility of applying and removing them, the possibility of incorporating more than one drug, and their ease of preparation [19-22].

Candidiasis is an opportunistic disease caused by various species of fungi belonging to the genus Candida. This disease usually appears in cases where the individual’s immunity is compromised, such as in patients suffering from acquired immunodeficiency syndrome (AIDS), cancer patients undergoing chemotherapy and denture wearers (in which case it is called denture-related stomatitis) [23, 24].

In the majority of cases, oral candidiasis is caused by the species Candida albicans. The treatment of this disease is limited due to the affected region, because of the direct contact with saliva, causing low availability of the drug in the region. Furthermore, therapeutic adhesion by patients tends to be low because of the need for frequent administration, and many patients suffer from underlying immunodeficiency. All these drawbacks can result in chronic recurrence of the disease [23].

The drugs most often prescribed for conventional treatment of oral candidiasis are antifungal antibiotics of the polyene macrolide class, such as nys and amphotericin B [25]. The therapeutic action mechanism of this latter drug involves its binding to the ergosterol molecules present in the fungal cell membrane, leading to the formation of pores in the membrane and allowing leakage of the intracellular content, finally provoking cell lysis (death). Nys has a broader antifungal spectrum than amphotericin B, meaning that some fungal species that are resistant to amphotericin B are susceptible to nys [23, 26-29].

Due to the low solubility of nys, the conventional way of delivering it for treatment of oral candidiasis is in the form of an aqueous suspension. However, this type of formulation often causes undesirable sensations in patients, such as bitter taste and feeling of harshness in the mouth, as well as nausea. The doses must be administered several times daily for an interval of one week. All these factors lead to low treatment adhesion by patients [30].

In the past two decades, there has been growing research interest in developing new drug formulations that are more accepted by patients, by reducing the frequency of doses and improving the organoleptic properties, in particular regarding the use of nys to treat oral candidiasis [18, 31-36].

The objective of this work was to employ pre-formulation tests described in the literature to analyze the possibility of using a physical powder mixture of purified cashew gum together with nys, vanilla, menthol and magnesium stearate, suitable for direct compression to obtain mucoadhesive buccal tablets containing nys for treatment of oral candidiasis.
2. Experimental Setup

The mucoadhesive buccal tablets were prepared with nys (500,000 IU), acquired from Pharma Nostra (lot 4018626); purified cashew gum as the diluent and mucoadhesive agent, collected in the municipality of Severiano Melo, Rio Grande do Norte state, Brazil, according to the method described by Pinto, Silva and Mansur (2018); the flavoring agents vanilla and menthol; and the lubricating agent magnesium stearate (Pharma Nostra, Brazil).

2.1 Preparation of the Physical Mixtures

We prepared 9 mixtures with the components identified above, with the proportions reported in Table 1.

The physical mixtures were prepared by adding each of the excipients in a closed jar, which was then swirled for 3 minutes to homogenize all the components of the formulation.

2.2 Pre-formulation Tests

To study the physico-chemical properties of the components of the formulation, all the excipients and the drug were submitted to pre-formulation tests, employing the techniques identified below.

2.2.1 Fourier-transform Infrared Spectroscopy (FTIR)

Samples of nys and PCG alone and the various physical mixtures of powders were analyzed using KBr pellets. The FTIR spectra were obtained with a spectrometer operating with resolution of 4 cm\(^{-1}\) and scanning range of 4000 to 400 cm\(^{-1}\), at room temperature.

2.2.2 Thermogravimetric Analysis (TGA)

The PCG, nys and physical mixtures 1, 2 and 3 were analyzed under N2 atmosphere in a temperature range of 25 to 700°C and heating rate of 10°C/min.

2.2.3 Crystallinity Analysis by X-ray Diffraction

The diffraction patterns of the samples of nys and the mixtures were acquired at voltage of 40 kV and current of 20 mA, with a scanning range of 5° < 2θ < 80° and step of 0.05°/min.

The crystallinity percentages were obtained by the peak deconvolution method from the diffractograms of the samples, using the Fityk 0.9.8 software, which performs curve fitting by applying Gaussian functions obtained from the shapes and data of the diffractogram peaks. This supplies information about the crystalline and amorphous areas of the material analyzed, after baseline correction. Equation (1) was used to obtain the crystallinity percentage.

\[
\text{% Crystallinity} = \frac{\text{crystalline area} \times 100}{(\text{crystalline area} + \text{amorphous area})}
\] (1)

2.2.4 Solubility and pH

Nys’ solubility was determined in distilled water and artificial saliva according to the method described in the Farmacopeia Brasileira [37]. For this purpose, 1 g of each sample was added to a round-bottom flask with capacity of 100 ml, wrapped in aluminum foil and left under magnetic stirring for 24 hours. Then 1 ml of each sample was removed and filtered through a

| Table 1 Components of the formulation. |
|----------------------------------------|
| Physical mixture | Nys (parts) | PCG (parts) | Vanilla (wt.%) | Menthol (wt.%) | Magnesium stearate (wt.%) |
|------------------|-------------|-------------|----------------|---------------|--------------------------|
| 1                | 1           | 1           | -              | -             | -                        |
| 2                | 1           | 2           | -              | -             | -                        |
| 3                | 1           | 3           | -              | -             | -                        |
| 4                | 1           | 1           | 0.25           | 0.25          | -                        |
| 5                | 1           | 2           | 0.25           | 0.25          | -                        |
| 6                | 1           | 3           | 0.25           | 0.25          | -                        |
| 7                | 1           | 1           | 0.25           | 0.25          | 0.5                      |
| 8                | 1           | 2           | 0.25           | 0.25          | 0.5                      |
| 9                | 1           | 3           | 0.25           | 0.25          | 0.5                      |
Poly (vinylidene fluoride) (PVDF) membrane with pore size of 45 µm, after which 3 ml of acetic acid solution (37% v/v) was added to each sample for reading in a UV spectrophotometer at 306 nm, to obtain the concentration of nys in the solvents, water and artificial saliva. The nys was classified according to the solubility presented in the tests, from highly soluble to practically or totally insoluble.

The pH values of the nys samples in distilled water and artificial saliva were measured at the concentration of 1% p/v in each of the solvents.

2.2.5 Determination of the Swelling Degree

The swelling degree of the PCG and physical mixture 9 was ascertained according to the method described in the British Pharmacopoeia [38] with small modifications, as suggested by Gowthamarajan and colleagues [6]. For this purpose, 1.0 g of each sample was separately weighed and added separately in two 50 mL test tubes with cap, one containing only PCG and the other containing the physical mixture. The samples were moistened with 1.0 ml of 96% ethanol and then with 25 ml of distilled water, after which the tubes were closed. Then they were agitated vigorously every 10 minutes for 1 hour, after which the tubes were placed at rest for 3 hours, when the volume of each sample was measured.

2.2.6 Granulometric Analysis of PCG

This analysis was carried out as described in the Farmacopeia Brasileira [37], using a set of sieves chosen previously with different mesh sizes attached to an electromagnetic sieve shaker and 25 g of PCG, for 15 minutes with adequate vibration. After the end of this period, the portion retained in each sieve and the collector was weighed separately to calculate the percentage, using Eq. (2) [37]:

\[
\% \text{ retained by the sieve} = \frac{W_1}{W_2} \times 100
\]  

Where:
- \( W_1 \): Weight of the sample retained in each sieve
- \( W_2 \): Sum of the weights retained in all the sieves plus the collector (in grams);

The sieve sizes were chosen according to the classification of the Brazilian Association of Technical Standards – ABNT (1984) ISO 33101:2000. After this procedure, the average particle size was calculated, using the weight percentages retained in each sieve, and also the average pore sizes (mesh) of the sieves from larger to smaller, according to Eq. (3) and (4):

\[
X_n (\mu m) = \frac{S_x + S_y}{2} \quad (3)
\]

\[
X_n (\mu m) = \sum (X_n \times \% W_n) \quad (4)
\]

Where:
- \( S_y \): pore size of the next smaller sieve to \( S_x \).
- \( X_n = \) average pore size of the particles in each sieve
- \( \% W_n = \) % weight of the particles retained in each sieve used.

2.2.7 Study of the Flow Properties of the Powders

The angle of repose was determined according to the method described by Lachman and colleagues [39]. The test equipment consists of a fixed horizontal base with a support attached to each side, with an adaptor for a glass funnel. Samples of nys, PCG and physical mixture 9 were analyzed. For this purpose, each sample was added in the funnel to create a continuous flow, forming a cone-shaped pile on the fixed base with a determined radius. The angle of repose was calculated according to Eq. (5).

\[
\tan (\alpha) = \frac{\text{Cone height}}{R} \quad (5)
\]

Where:
- Cone height = height of the pile formed by the powder flow
- \( R = \) radius of the fixed base

The Carr index (also called the Carr compressibility index) and the Hausner ratio of the samples of nys, PCG and physical mixture 9 were obtained from the apparent and tapped (or tamped) densities, by Eq. (6) and (7), respectively [38].

\[
\text{Carr index} = 100 \times (\rho \text{ tapped} - \rho \text{ apparent}) / \rho \text{ tapped} \quad (6)
\]

\[
\text{Hausner ratio} = \rho \text{ tapped} / \rho \text{ apparent} \quad (7)
\]

Where:
- \( \rho \text{ tapped} = \) tapped (or tamped) density
- \( \rho \text{ apparent} = \) apparent density

The apparent and tap density values were calculated.
after adding the sample to a 250 mL graduated beaker, noting the volume occupied by the powder at time zero (before subjecting the beaker to taping) and the volume occupied by the powder after subject the beaker to a total of 1250 taps, with an incremental number of taps of 10, 40, 50, 100, 300, 250 and 500 striking movements until there is no variation between the density values in the beat intervals. In this way, it was possible to perform apparent density calculations using the zero-time powder volume and the tap density using the volume occupied by the powder after cessation of the taping movements of the beaker.

Tables 2 and 3 were used to evaluate the angle of repose, Carr index and Hausner ratio. These tables were obtained from the British Pharmacopoeia, containing correlations between the angle of repose, Carr index and Hausner ratio and the flow properties [38].

### 3.3 Fourier-Transform Infrared Spectroscopy (FTIR)

Spectrometry in the infrared region allows vibrational analysis of polymers, and the set of bands contained in the spectrum is specific for each substance, since the isolated bands refer to the vibrations...
of a determined functional group or type of bond of the compound studied.

The structural aspects of the GPC, nys and physical mixtures with the two flavoring agents and the lubricating agent were investigated by FTIR to verify whether an increase of the GPC concentration would cause an increase of the bands present in the structure of each material and to note any alteration of the spectra of these samples, such as the appearance of a new band, indicating structural modification of the molecules. The spectra of the PCG (Fig. 1) and nystatin contained all the bands described in the literature and those of the mixtures showed that a rising concentration of PCG in the mixtures promoted broader bands, causing overlapping of the bands of the nys structure, as well as disappearance of the band of nystatin at 1004 cm\(^{-1}\) due to the widening of the band of PGC at 1070 cm\(^{-1}\) [18, 43]. More importantly, there was no shift of the bands in the spectra, demonstrating the absence of physico-chemical interaction of the PCG, nystatin, flavoring agents and lubricating agent.

3.2 Thermogravimetric Analysis (TGA)

Thermogravimetric analysis is a thermal analysis technique in which the mass variation is determined in function of temperature increase or a constant temperature over time. This technique reveals alterations caused by heat and determines the temperature at which substances start to decompose.

The thermogravimetric analysis of purified cashew gum (Fig. 2A) showed three decomposition peaks, the first one at 46.36°C for water loss, the second and third at 222.73°C and 288.01°C respectively, show that the process of decomposition of the polysaccharides of this gum occurs in two stages, as described in the literature [18, 53].

The thermogram of the nys sample (Fig. 2B) showed three decomposition peaks, starting at 100.4°C, which was related to water loss because it was a hygroscopic drug. The second peak is more intense decomposition at 160.09°C, related to the first decomposition stage of nystatin and the second stage in

![Infrared spectroscopy spectra](image-url)

**Fig. 1** Infrared spectroscopy spectra.
Infrared spectroscopy of PCG, nystatin and physical mixtures 4 (Nys:PCG 1:1 + 0.27% w/w Vanilla + 0.27% w/w Menthol), 6 (Nys:PCG 1:3 + 0.27% w/w Vanilla + 0.27% w/w Menthol), 7 (Nys:PCG 1:1 + 0.27% w/w Vanillin + 0.27% w/w Menthol + 0.54% w/w Magnesium stearate) and 9 (Nys:PCG 1:3 + 0.27% w/w Vanillin + 0.27% w/w Menthol + 0.54% w/w Magnesium stearate).
Fig. 2  Thermogravimetric analysis.
A. PCG. B. Nystatin. C. Physical mixture 3.
a wider range with a peak of 419.83°C, leading to the total decomposition of nys. The obtained profile of loss of mass as a function of the increase in temperature obtained for NYS is very similar to the result obtained by other groups of researchers [54, 55], with other formulations for the same drug and by Koontz and collaborators in an antifungal study natamycin, belonging to the same pharmacological class as the NYS, which demonstrates the behavior characteristic of polyene macrolides [56].

Therefore, when we observe the thermogram of the physical mixture 3 (Fig. 2C), we can conclude that the mixture between PCG and Nys did not cause any type of change in the decomposition temperatures of the polymer and the drug, making it clear that there is no physico-chemical interaction between them.

3.3 Analysis of Crystallinity by X-ray Diffraction (XRD)

X-ray diffraction is a technique involving the scattering of X-rays caused by organized structures that allows characterizing polymeric materials regarding their crystalline and amorphous states.

The XRD curves obtained in the diffractograms of the samples of nys and the physical mixtures in powdered form are shown in Fig. 3.

This technique was used to evaluate whether the crystallinity degree of the samples would decrease with increasing concentration of PCG and the excipients (flavoring agents and lubricating agent). Analysis of crystallinity is very important in the pre-formulation step, since to make tablets by direct compression it is necessary for the mixture of the drug with the excipients to have good flow properties, and the flow of materials feeding the compressor is related to various parameters, such as crystallinity. Highly regular (i.e., more crystalline) materials tend to have flow property from marginal to poor due to their greater relative surface area, which favors stronger cohesion force among the particles and can cause clogging of the compressor feed apparatus [42].

The crystallinity percentages of the samples reported in Table 4 were obtained by applying equation 1 using the Fityk 0.9.8 software. It can be seen that the increase of PCG concentration and addition of the lubricating agent contributed significantly to diminish the crystallinity of the physical mixtures in relation to the crystallinity of the pure drug.

Nys is a semi-crystalline drug and in its original form it does not have good flow or compressibility properties, preventing its use to produce tablets by the direct compression method. The mixture of PCG with nys, due to the former’s amorphous character, reduced the intensity of the drug’s crystalline peak in the mixture at a proportion of 1:1, and more so at 1:3 (Fig. 3), enabling making tablets by direct compression with a formulation containing only nys and PCG (1:3).

The addition of the flavoring agents (which are necessary to make the tablets more palatable to patients) caused a slight increase of the crystallinity of the mixtures due to the high crystallinity degrees of vanilla and menthol. However, this small increase of crystallinity would not interfere in the possibility of producing tablets by direct compression.

Finally, the analysis of the mixture containing all the excipients (nys, PCG, flavoring agents and lubricating agent) showed that the small particles of the lubricating agent adhered easily to the other components, reducing the friction and thus improving the flow properties of the samples (Liberal, 2008). In this respect, mixture 9, with crystallinity degree of 13.9%, presented the most favorable characteristics for production of tablets via direct compression.

3.4 Solubility and pH

The study of the solubility of a raw material at different pH values, in water and non-aqueous solvents, is one of the first and foremost steps of pre-formulation studies. Such studies reveal significant parameters about the performance of a pharmaceutical product [44].
Table 4  Crystallinity percentage of the samples of nys and physical mixtures.

| Sample         | % Crystallinity |
|----------------|-----------------|
| Nys            | 41.56           |
| Mixture 1      | 28.08           |
| Mixture 3      | 14.12           |
| Mixture 4      | 32.51           |
| Mixture 6      | 20.31           |
| Mixture 7      | 23.58           |
| Mixture 9      | 13.39           |

Fig. 3  Diffractorgrams of the samples obtained by XRD.

Nys was practically insoluble in both solvents tested. In water it had solubility of approximately 15 mg in 100 ml of water, while in artificial saliva the parameters were 64 mg in 100 ml, both with pH equal to 5.

Further regarding solubility, the PCG was tested in an earlier experiment by our research group [18] and was classified as completely soluble in water, acetic acid solution (1% p/v, pH 2.5) and ammonium hydroxide solution (5% p/v, pH 10.5), so there was no need to examine the solubility again.

3.5 Determination of the Swelling Degree

The swelling degree is the volume in milliliters occupied by 1 g of a drug, including any adherent mucilage, after being soaked in an aqueous medium for 4 hours [6, 38].

The swelling degree of physical mixture 9 was 100%, i.e., the high solubility in water and artificial saliva of PCG makes it an excellent excipient for controlled drug release purposes due to the gradual release of the drug [6] when the tablet is in contact with water or saliva (Fig. 4).
3.6 Granulometric Analysis of PCG

During the production of solid forms, the particle size distribution of the materials affects various processes and parameters, such as compressibility, mixture efficiency, particle flow, weight, disintegration time, hardness, friability, dissolution rate and bioavailability. The flow properties of the material are particularly important for the manufacturing processes of solid drug products, such as sifting, mixing, granulating and compacting, while density influences the compressibility, porosity and dissolution of tablets [45-48].

This experiment revealed that the PCG sample has varied particle size distribution and average value of 269.82 µm (Table 5 and Fig. 5, respectively, which show the percentages of the particles by mass retained in the sieves with different mesh sizes). According to the Farmacopeia Brasileira [37], the samples are classified as semi-fine powders, because all the particles passed through the sieve with 355 µm mesh and up to 40% through the sieve with 180 µm mesh.

3.7 Analysis of Flow Properties

In particulate systems, the set of particles can present different shapes, which will generate different processing characteristics during the manufacture of pharmaceutical products such as tablets, capsules and suspensions. Therefore, it is necessary to study the behavior of raw materials in powdered form to understand how they will affect the quality of the medicament. In this respect, knowledge of the flow properties of powders is very important in pre-formulation tests, to allow predicting the behavior of the particles and optimize the production process with consequent reduction of operating costs [49, 50].

The flow of particles can be analyzed by various techniques, such as measurement of the angle of repose, Carr index and Hausner ratio. These parameters permit predicting the interactions between the particles, since their size, size distribution and morphology can cause alterations in the flow of the powdered material. Particles with larger specific surface area, and thus more contact area to interact with each other through electrostatic forces, will be more resistant to flowing. Generally, small particles with low density and irregular morphology flow worse than larger spherical particles with higher density [51]. Low fluidity of the raw material can affect the average weight, hardness, friability and uniformity of the
content of tablets [51, 52].

The Carr index and Hausner ratio values (Table 4) of both the PCG and nys were in the range considered good to reasonable according to the parameters of the British Pharmacopoeia [38] (Table 5). Moreover, these parameters of physical mixtures 6 and 9 were also in the good to reasonable range, demonstrating they can be compressed to make tablets.

The measurement of the angle of repose is a direct way to evaluate the flow behavior of raw materials inside a compression machine. Based on the parameters described in the British Pharmacopoeia [38]

Table 5  Average size distribution of PCG particles.

| Average mesh size (µm) | Average mesh size x percentage retained |
|------------------------|----------------------------------------|
| 630                    | 127.80                                 |
| 298.5                  | 99.12                                  |
| 163                    | 13.01                                  |
| 118.5                  | 16.18                                  |
| 75                     | 11.40                                  |
| 53                     | 1.70                                   |
| 22                     | 0.61                                   |
| Average particle size (µm) | 269.81                               |

Fig. 5  Distribution of particles of PCG.
Correlation between percentage retained and mesh sizes.

Table 6  Flow parameters of the powders.

| Parameters                | PCG (g) | Nys (g) | Physical mixture 6 | Physical mixture 9 |
|---------------------------|---------|---------|-------------------|-------------------|
| Mass (g)                  | 30      | 20      | 30.42             | 32.34             |
| Apparent volume (ml)      | 57.5    | 58.5    | 62                | 71                |
| Tapped volume (ml)        | 49.5    | 47.5    | 48                | 58                |
| Apparent density (g/ml)   | 0.52    | 0.34    | 0.48              | 0.46              |
| Tapped density (g/ml)     | 0.61    | 0.42    | 0.63              | 0.56              |
| Carr index                | 13.9    | 18.8    | 22.6              | 18.31             |
| Hausner ratio             | 1.16    | 1.23    | 1.29              | 1.22              |
| Angle of repose (degrees) | 37      | 45      | 35                | 31                |
(Table 6), the PCG presented reasonable flow and nys had marginal flow when studied individually (Table 4). The reasonable flow is related to the cohesion force between the particles, whereby the greater the cohesion force, the harder it will be for the powdered substance to flow into the compression machine, possibly impairing the compression process, average tablet weight and hardness. Therefore, the angle of repose should be as suitable as possible to maintain the uniformity of the production lots of tablets. The angle of repose indicated that the addition of the lubricating agent in physical mixtures 6 and 9 significantly improved their flow, from reasonable to good, especially in mixture 9.

Based on the results of the crystallinity test (XRD) and the flow parameters, mixtures 6 and 9 can be used to make tablets by direct compression, because they have adequate flow properties and compressibility.

4. Conclusions

The results of pre-formulation tests indicated that PCG is a highly promising material to produce mucoadhesive buccal tablets containing nys, because due to the properties of this gum, both the mixtures with just the gum and those with the flavoring agents and lubricating agent are adequate for production of tablets by direct compression. The best results were obtained with mixtures 6 and 9, so they will be used in future tests for development of tablets to assure the best organoleptic, flow and compressibility properties of the tablets produced.

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