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The development and characterization of Propranolol Tablets using Tapioca starch as excipient

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Abstract: Tapioca starch (TS) is produced from Cassaca roots and it is differentiated from other starches because it contains about 17–20% amylase and low amount of residual substances. Propranolol (POP) is a non-selective beta-adrenergic blocking agent and it is in the World Health Organization's List of Essential Medicines. The aim of this work was to investigate the potential of TS in the development of POP tablets by means of direct compression. Its evaluation was performed by X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR) relaxometry, scanning electron microscopy (SEM), uniformity of weight, drug content, disintegration, friability, hardness, dissolution test and drug release kinetics. The TS granules were spherical with mean diameter of 10.09 ± 1.85 μm. The XRD, FTIR and NMR suggested physical interaction between TS and POP. The tablets presented average diameter of 1.1 ± 0.0 cm, 0.24 ± 0.02 cm thickness and average weight of 0.544 ± 0.003 g. The hardness of tablets was 10.98 ± 0.31 N and the percentage of friability was 25.74 ± 0.08%. POP was released after 45 min and the release kinetics properly fitted the Hixson-Crowell equation.

Key words: tapioca starch, propranolol, tablet, NMR relaxation.

INTRODUCTION

Starch is one of the most important and abundant natural biopolymers, which has been widely used in pharmaceutical industry, especially in the development of solid oral formulations, as binder, diluent and disintegration agent (Xia et al. 2015, Rowe et al. 2009). The solid oral formulations, such as tablets, are the commonly used pharmaceutical forms, accounting for more than 80% of all administrated formulations, due to its numerous advantages including: easy manufacture and administration, high physical and chemical stability, high patient compliance, convenient packaging, easy storage and the ability to provide an accurate measure of the drug (Adeoye and Alebiowu 2014a, Jivraj et al. 2000).

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In recent decades, there has been an increasing interest on multifunctional excipients for use in tablets and their manufacture by direct compression, aiming to reduce the number of excipients and potential interactions between the excipients in a formulation. The direct compression is an easily controllable method, with low processing time, leading to increased efficiency of the production line; therefore, it is captivating for the pharmaceutical industry. However, the successful production of tablets by direct compression depends almost exclusively on the incorporation of adjuvants in the formulation (Jivraj et al. 2000, Adeoye and Alebiowu 2014b).

Tapioca starch (TS) is produced from *Cassaca roots* and it differs from other starches because it contains about 17–20% amylose, with low level of residual substances, such as proteins, lipids, phosphorous and ash. It is widely used in many products because of its high viscosity, clear appearance, and low production cost when compared to other starches, especially in Southeast Asia and Equatorial region (Pongsawatmanit et al. 2013). The amylose molecule, in TS, is not exclusively linear and it has high molecular weight. Moreover, the amylopectin, in TS, has mostly short side chains, allowing a very densely packed and crystalline organization within the starch granules, resulting in a very strong resistance against disintegration (Russ et al. 2016). However, TS has poor flowability and compressibility, and the latter two parameters have a particular importance for direct compression process (Atichokudomchai and Varavinit 2003). For these reasons, a co-processing in tapioca starch was performed to solve the aforementioned limitations.

In the present investigation, Propranolol hydrochloride (POP) was selected as a model drug to study the TS behavior as tablet matrix. POP is a non-selective beta-adrenergic blocking agent, which is registered in the World Health Organization's (WHO) List of Essential Medicines, as one of the most effective and safe medicines needed in a health system (WHO 2015). POP is still used throughout the world for a number of cardiovascular conditions (e.g. angina pectoris, hypertension, myocardial infarction, cardiac arrhythmias), as well as for a number of others indications, including essential tremor, migraine headaches and hyperthyroidism. It was also shown in controlled double-blinded trials that propranolol has a favorable effect on anxiety management (Areco et al. 2012, Al-Mohrej et al. 2018).

POP is an acid-soluble basic drug, classified as class I, according to the biopharmaceutical classification system (BCS), presenting high permeability and high solubility (Zaharuddin et al. 2014, Wagh and Patel 2010). It is a highly lipophilic drug, reason by which, it is almost completely absorbed after oral administration, nevertheless, it undergoes high first-pass metabolism by the liver in such a way that only about 25% of drug reaches the systemic circulation, therefore high oral dose is necessary. POP has a short half-life of 4 hours, when compared to other beta adrenoceptor antagonists, and requires frequent dosing to maintain a therapeutic effect. Additionally, POP it is a basic drug tightly bound to plasma proteins and widely distributed in all body compartments (Srikanth et al. 2012, Al-Kassas et al. 2016).

Due to the aforementioned factors, POP was selected as a model drug for the tablets development. Especially because it is used in the treatment of different health conditions and requires frequent doses. The development of a single multifunctional excipient can have a major impact in reducing cost and time for the production of POP tablets.

Adeyoe and Alebiowu (2014) developed new multifunctional excipients by co-fusion method of co-processing TS with mannitol. The study concluded that the novel excipient improved the flowability, packing and compaction properties, furthermore, the powder presented potential to be used in compression. In another study, the same

authors evaluated the co-processed excipients as disintegration agent in paracetamol tablets; the novel disintegration agent enhanced the mechanical properties of tablets, as shown by the decrease in their friability and higher tensile strength. The study concluded that the novel disintegration agent was effective in the development of oral paracetamol tablets (Adeyoe and Alebiowu 2014).

The aim of this work was to investigate the potential of co-processed TS, as a multifunctional excipient in the development of POP tablets by direct compression. The developed tablets were evaluated by X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), NMR relaxometry (NMR), scanning electron microscope (SEM), general appearance, organoleptic properties, uniformity of weight, the drug content, the disintegration, the friability, the hardness, dissolution test and drug release kinetics.

MATERIALS AND METHODS

MATERIALS

The materials used were: tapioca starch from Sarfam Comercial Ltd-Brasil, propranolol from All Chemistry Ltd-Brazil, methanol from All Chemistry Ltd-Brazil, hydrochloric acid from All Chemistry Ltd-Brazil.

METHODS

Co-Processing of Tapioca Starch

The TS was processed by co-fusion, where 50 g of TS were dispersed in distilled water and heated at 60 ºC. The dispersion was stirred during 5 min at the same temperature, until it formed a paste, then it was kept under stirring on a hot plate for 10 min. The paste was dried at 50 ºC in a hot air oven for 24 h, then the dry TS was triturated using a porcelain mortar and pestle for 10 min to ensure the uniform size reduction. The resulting product was sieved using a 420 µm and 150 µm sieve, then stored in a screw capped bottle until used (Adeoye and Alebiowu 2014b).

Determination of Tapioca Starch particle´s shape and size

The size and shape of TS particles was determined by scanning electron microscopy, (SEM) using a Quanta Bruker, 250 FEG model with Server XT microscope program for the evaluation of particle size. The images of TS, POP and tablets were obtained at 1000 and 5000 magnification, with an accelerating voltage of 5.0 kV.

Determination of Tapioca Starch flow properties

The flow properties of the TS were assessed by Hausner's ratio (HR) and Carr's index. The HR was determined from the bulk and tapped volumes, according to Equation 1 (Hausner 1967):

$$HR = \frac{V_b}{V_t} \qquad \text{(Equation 1)}$$

Where, V_t = tapped volume (cm^3), V_b = bulk volume (cm^3).

The Carr's index is a simple method to evaluate the powders flow properties by comparing the bulk and tapped density, according to Equation 2.

Carr`s Index = (tapped density – bulky density) x 100 / tapped density (Equation 2)

The density was measured after weighing and transferring a certain amount of the TS powder to a 100 ml beaker, where the volume of material was registered. The apparent density was calculated from the ratio between the mass and the volume occupied by the powder. The tapped density was measured in a Nova Ética (Brazil) apparatus, using 100 beats per min, and comparing the difference between the initial and final volumes (Guerra et al. 2008).

DEVELOPMENT OF TABLETS

The tablets were prepared by compressing 550 mg of a binary mixture of TS powder and POP. Each of the 550 mg tablets contained POP and the TS powder in ratio of 15:85 wt% and it was homogenized with the aid of a mortar and pestle, using geometric progression, before compression. The tablets were prepared by compressing the mixture, manually filled into the die cavity of 11 mm flat punches, in a single-punch press tablet compression machine Monopress LM1, model CFW 08 (Lemaq/LM). The compression pressure was adjusted manually.

CHARACTERIZATION OF TABLETS

FTIR analysis

FTIR was employed to characterize the possible interaction between POP and TS. The infrared spectra were obtained using an IR Prestige Shimadzu FTIR spectrometer, model 21. The spectra were scanned over a frequency range of 4000-400 cm^{-1}, at 25 °C. The samples were investigated using KBr tablets.

X-ray diffraction

The structure of TS, POP and the tablets were investigated by X-rays diffraction (XRD) using a Lab X Shimadzu diffractometer, model XRD-6100, with nickel-filtered CuKα radiation of wavelength 1.54 Å, at 25 °C. The 2θ scanning range varied from 2° to 80°, with 0.02° steps, operated at 40 KV and 30 mA.

Time-domain nuclear magnetic resonance

The solid-state nuclear magnetic resonance spectroscopy (NMR) is a powerful technique to measure nuclear relaxation times, such as: spin-lattice relaxation time in the laboratory frame and spin-spin relaxation time in the laboratory frame. The first measurement promotes evaluation of the sample in the MHz scale and the second one comes from the loss of phase coherence among nuclei in the *xy* plane, which affects the relaxation of the component perpendicular to B_0. The spin-lattice relaxation parameters involve changes in thermal equilibrium of spin systems and the responses are intrinsically related to the system´s molecular dynamics, which is derived from the morphology of the system (Silva et al. 2016). This way, the relaxation parameters are of great value to understand the drug dispersion in the polymer matrix, the interaction between drug and polymer, the molecular dynamics of drug-polymer and the molecular domains formation in an organic material (Monteiro et al. 2016).

The relaxation times of TS, POP and tablets were analyzed in a MARAN Ultra low-field NMR spectrometer (Oxford Instruments, Oxford, UK), using an 18 mm NMR tube, operating at 23 MHz for the hydrogen nucleus. The pulse sequence to obtain the spin lattice relaxation time data was inversion-recovery (recycle delay – 180° – τ – 90° – acquisition data) and the 90° pulse of 7.5 μs was calibrated automatically by the instrument's software. The amplitude of FID was sampled for twenty τ data points, ranging from 0.1 to 40.000 ms, using 40 data points, with 4 scans for each point and 10 s of recycle delay. The pulse sequence used to measure the spin-spin relaxation time was Carr-Purcell-Meiboom-Gil (CPMG) and the 90° pulse of 7.5 μs was calibrated automatically by the instrument´s software, τ was 800 μs; analysis temperature was 25 °C. The relaxation values and relative intensities were obtained by fitting the exponential data with assistance of the WINFIT program. Distribution exponential fitting were performed using the WINDXP software, as a plot of relaxation amplitude versus relaxation time. Both WINFIT and WINDXP are commercial programs and come with low-field NMR spectrometer.

EVALUATION OF TABLETS

Appearance, hardness, friability, weight variation, disintegration, drug content and drug release of TS tablets and TS/POP tablets were evaluated.

General appearance

The general features of the TS tablets and TS/POP tablets, such as: size, shape, diameter, thickness and color, were evaluated. The thickness of ten tablets was determined using a manual caliper gauge, controlled within a ± 5% of the standard value, according to the Brazilian Pharmacopeia (Brazil 2010).

Uniformity of weight

In the weight uniformity test, 20 units of randomly selected TS and TS/POP tablets were weighted to determine their average weight. According to the Brazilian Pharmacopeia, the maximum allowed variation is 10% with respect to weight for tablets containing 130 mg or less of drug (Brazil 2010). The individual weights are compared with the upper and lower limits of the tablets.

Friability Test

Friability was measured by spinning 10 units of TS tablets and TS/POP tablets in a Nova Ética/ Brazil friabilator, model 300/1, set at 100 rpm, 25 rpm for 4 min. The "before" and "after" weights of the tablets were recorded and the mass loss in percentage should be less or equal to 1%. The friability test is used to evaluate the tablet`s ability to withstand abrasion in packaging or during handling or shipping (Brazil 2010).

Disintegration Test

The disintegration test evaluates the time required for the tablet to break into particles. For the disintegration studies, six units of TS tablets and TS/POP tablets were tested using a Nova Ética/ Brazil disintegrator, model 301/AC. The necessary time for each tablet to disintegrate at 37 ± 0.5 ºC in distilled water, to the point where the tablet was small enough to pass through the mesh at the bottom of the basket, was recorded using a stopwatch. The time limit should not exceed 30 minutes (Brazil 2010).

Tablet Hardness

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness (Brazil 2010). The hardness was measured using the tablet hardness tester Nova Ética/Brazil, model 298/ATTS. A mean value was calculated based on the hardness measurements of 10 individual tablets of TS and TS/POP.

Drug Content

The drug content of 10 tablets with POP was evaluated. The tablets were previously pulverized with assistance of a mortar and pestle. Then, 10 mg of this powder was added in a 100 ml volumetric flask with 20 ml of water while stirring for 10 minutes, then the volume was completed with methanol; then, filtration was performed after homogenization of mixture. The absorbance was measured at 290 nm, in a Jasco UV/Visible spectrometer, model V-630; methanol was used as blank. The same procedure was performed with the TS tablets (Khandai et al. 2010).

Dissolution Test

The release study of POP was determined in a Nova Ética/Brazil dissolutor, model 299/3, with apparatus I (basket), at 100 rpm. The dissolution rate was studied using 900 ml of 0.1 N hydrochloric solution (pH 1.2) for 45 minutes. The temperature was maintained at 37 ± 0.2 ºC. Samples of 5 ml each were withdrawn at different time intervals, such as: 5, 10, 15, 30 and 45 minutes, filtered,

diluted and analyzed for POP content, using UV/Visible spectrometer Jasco, model V-630, at 290 nm, and a 0.1 N hydrochloric solution as blank. An equal amount of fresh dissolution medium was replaced (Brazil 2010, Khandai et al. 2010). The release study was conducted in five tablets.

Analysis of release profiles

The rate and mechanism of POP release from the tablets were analyzed by fitting the dissolution data into a zero-order equation (Equation 3) (Costa 2002).

$$Q = K_0 T \quad \text{(Equation 3)}$$

Where Q is the amount of drug released at time t and k_0 is the release rate constant.

First Order equation (Equation 4) (Costa 2002).

$$Ln\ (100 - Q) = \ln 100 - k_1 t \quad \text{(Equation 4)}$$

Where k_1 is the release data constant.

The dissolution data were fitted to the Higuchi s equation (Equation 5) (Higuchi 1963).

$$Q = K_2 t^{1/2} \quad \text{(Equation 5)}$$

Where k_2 is the diffusion rate constant.

The dissolution data were fitted to the Hixson-Crowell equation (Equation 6) (Merchant et al. 2006).

$$Q_0^{1/3} - Qt^{1/3} = K_{HC}\, t \quad \text{(Equation 6)}$$

Where Q_t is the amount of drug release at time t, Q_0 is the initial amount of the drug in the tablet, and K_{HC} is the rate constant for Hixson-Crowell.

The dissolution data were fitted to the Baker-Lonsdale equation (Equation 7) (Costa 2002).

$$\frac{3}{2}[1 - (1 - F)^{2/3}] - F = kt \quad \text{(Equation 7)}$$

Where, F is the fraction of drug release and k is the release rate constant.

RESULTS AND DISCUSSION

SHAPE AND SIZE OF SYNTHESIZED PARTICLES

The TS, POP and tablets were analyzed through SEM to investigate the appearance, shape and size. It was found that TS granules (Figure 1) were spherical, with smooth surfaces and they were aggregated. These results are in agreement with the study of Xia et al. (2015) where the SEM study showed that the TS granules were prone to aggregate with each other. The size distribution of TS granules was measured using Server XT microscope program and they exhibited a mean diameter of 10.09 ± 1.85 µm (Figure S1 - Supplementary Material). Atichokudomchai and Varavinit (2003) also found that the mean diameter of native TS starch granules was 14.7 ± 0.1 µm. Consequently, the average size of TS granules was similar to those found in the literature. SEM microscopy shows the POP crystals dispersed in TS matrix (Figure S2).

The study of granulometry is fundamental in the development of solid pharmaceutical forms and in large scale production. The size, shape and uniformity of the particles determine their flow properties. Very fine particles do not flow freely

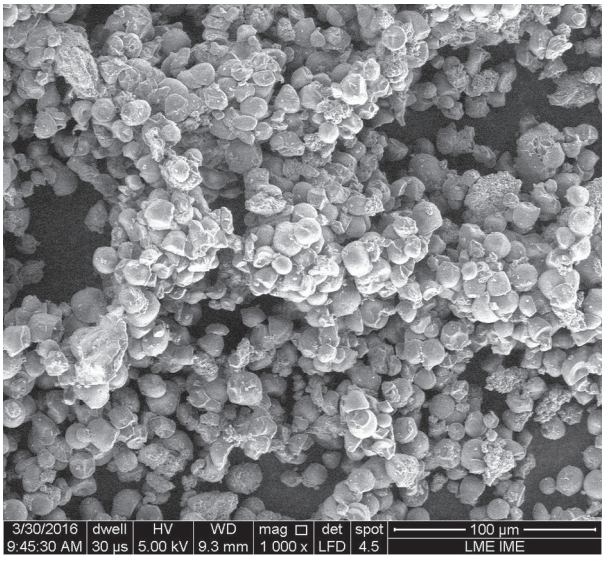

Figure 1 - The scanning electron micrograph (magnificent 1000 x) of tapioca starch granules after co-fusion process.

like larger ones do. In general, particles ranging from 250 to 2,000 μm, flow freely if the shape is propitious. Particles ranging from 75 to 250 μm can either flow freely or present problems, depending on its shape and other factors, such as humidity. When particles are smaller than 100 μm, flow becomes a problem regardless the nature of substance (Staniforth 2005).

The TS particles presented mean diameter of 10.09 ± 1.85 μm, indicating a poor flow.

FLOW PROPERTIES

Staniforth (2005) establishes that a powder can have one tapped density and various apparent densities. Apparent densities depends on the way the particles are packaged as a function of its porosity. The results of the bulky and tapped densities were used to determine the Hausner ratio (HR) and the Carr Index (IC). Consequently, the HR and IC provide indirect results of the powder flow properties, since the more rounded the particles are, the smaller the air spaces within the powder mixtures, facilitating their flow (Garcia et al. 2012). The bulky density of TS was 0.45 ± 0.01 g/cm^3 and the tapped density of TS was 0.64 ± 0.02 g/cm^3. The HR and IC measurements were used to evaluate the flow properties of the TS granules. IC values lower than 10% indicate excellent flow, IC values between 11 to 15% indicate good flow, IC values between 16 to 20% indicate weak flow, IC values between 21 to 31% indicate poor flow and IC values higher than 32% indicate very poor flow. HR values between 1 to 1.1 indicate excellent flow, HR values between 1.12 to 1.18 indicate good flow, HR values between 1.19 to 1.25 indicate weak flow, HR values between 1.26 to 1.45 indicate poor flow; HR values higher than 1.50 indicate very poor flow (Garcia et al. 2012).

The TS granules showed HR value of 1.48 ± 0.03 and IC value of 28.33 ± 1.53%. Thereby, the TS granules presented poor flow, according the HR and IC values. Since the tablets were prepared by direct compression and the mixture was manually filled into the die cavity of tablet compression machine, the feed mechanism was not influenced by the flow properties. One alternative for improving the flow of TS granules is the addition of 0.2 wt% of colloidal silicon dioxide, once a good flow can ensure a reproducible filling and an efficient distribution of the powders in the production of pharmaceutical forms (Staniforth 2005). Moreover, it can be concluded that the HR and IC results are in agreement with the granulometry analysis, confirming that TS granules have poor flow.

XRD ANALYSIS

The XRD diffractograms of TS granules, POP and tablets are presented in Figure 2. TS can be classified into three types (A, B or C) based on their diffraction patterns. Polymorphous "A" exhibit strong diffraction peaks at 15°, 17°, 18° and 23°; type "B" usually display peaks at 5.6°, 17°, 22°, and 24°; the mixture of "A" and "B" patterns correspond to type "C" (Xia et al. 2015, Atichokudomchai and Varavinit 2003). The XRD pattern of TS granules showed the polymorph type A with strong peaks at 15°, 23°, and a doublet at 17° and 18°. From the

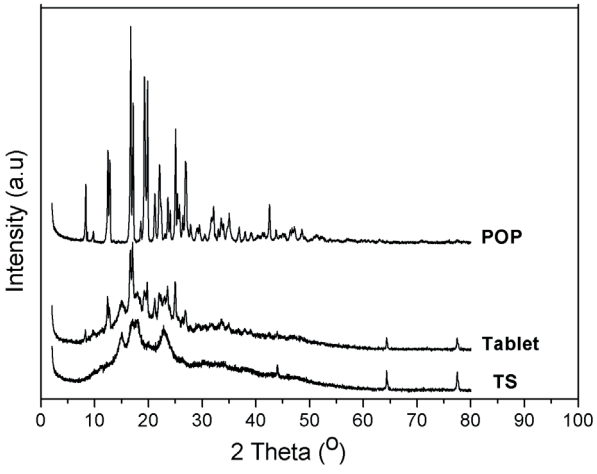

Figure 2 - X-ray diffraction pattern of tapioca starch granules, propranolol and tablets developed.

XRD analysis of POP, it was possible to observe its crystalline nature, with strong peaks at 8.2º, 14º, 18º, doublets at 22º, 23º and 25º. This result is in agreement with the study of Roberts and Rowe (1994), who confirmed a single crystal nature of propranolol hydrochloride. The XRD analysis of the tablets demonstrated some characteristics peaks of TS at 15º, 17º, 18º and 23º, and some characteristics peaks of POP at 14º, 18º and 25º, indicating that a homogeneous mixture was achieved.

FTIR ANALYSIS

The drug-polymer interaction was verified by comparing the FTIR spectrum of the tablets with the TS and POP FTIR spectra. The FTIR spectra of TS, POP and tablets are showed in Figure 3. The FTIR of TS granules shows peaks at 3550 – 3200 cm^{-1}, which are related to the O-H stretching; at 2930 cm^{-1}, which is related to the C-H stretching, an intense band at 1640 cm^{-1}, which is related to the deformation vibrations of the hydroxyl groups, and the peaks at 1158 cm^{-1} and 1081 cm^{-1}, which are associated to a C-O stretch in a hydroglucose ring of C-O-H starch group. The band at 1020 cm^{-1} can be associated to the amorphous part of TS (Xia et al. 2015). The FTIR spectrum of POP hydrochloride shows peaks at 2965 cm^{-1}, which correspond to a secondary amine group, at 3300 cm^{1}, due to hydroxyl group (secondary), at 1267 cm^{-1}, due to the aryl alkyl ether stretching band and a peak at 798 cm^{-1}, due to a substituted naphthalene (Chaturvedi et al. 2010). The FTIR spectrum of the tablets shows peaks at 3400 cm^{-1}, which are attributed to the O-H stretching of TS, at 1158 cm^{-1} and 1081 cm^{-1}, which are associated to a C-O stretch in a hydroglucose ring of C-O-H starch group; at 2965 cm^{-1}, which are associated to the presence of a POP secondary amine group; at 1267 cm^{-1}, which are associated to a stretching of the aryl alkyl ether and at 798 cm^{-1}, due to a substituted naphthalene. Some peaks corresponding to functional groups of the drug remained in the same wavenumber after its incorporation into the tablets; hence, there were no major interactions between POP and TS granules.

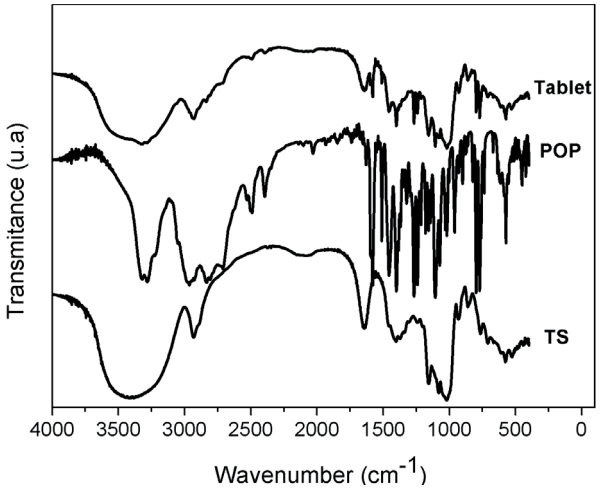

Figure 3 - FTIR of tapioca starch granules, propranolol and tablets developed.

NMR MEASUREMENTS

In this work, proton NMR relaxometry was used to measure the behavior of spin-lattice relaxation time with T_1H as time constant, and also a spin-spin relaxation time with T_2H as time constant. The relaxometry parameters were determined to better understand the changes in the tablets main structures. The spin-lattice (or longitudinal) relaxation time, T_1H, quantifies the rate of transfer energy from the nuclear spin system to the neighboring molecules (the lattice). The T_1H values are relatively long due to the lack of means to transfer energy from NMR transitions into thermal energy. In T_2H relaxation, no energy is transferred from the nuclei to their surroundings and the process is an entropy-driven one. Such an entropy-driven process is the exchange of spins between neighboring nuclei and thus the T_2H relaxation is often called spin-spin relaxation (Monteiro et al. 2013, Sebastião et al. 2016, Iulianelli et al. 2016, Tavares et al. 2017).

One of the objectives of this work was to perform hydrogen spin-lattice relaxation time

measurements to obtain more information on the samples homogeneity, the drug dispersion and the interaction process. The MSE-FID pulse sequence was applied to determine the rigid and amorphous fraction of the TS granules and the tablets developed. It is clear that the T_1H and T_2*H values characterize two different process and therefore, in the common case, T_1H is different from T_2*H.

TD-NMR allowed the determination of spin-lattice relaxation times and domain distribution curves for TS, POP and tablets (Table I and Figure 4). The TS presented two domains: T_1H at 4.4 ms is related to less rigid domain and with higher mobility, corresponding to the water hydrogen nuclei present in the sample; T_1H at 90 ms is related to more rigid domain, with lower molecular mobility, corresponding to a more restricted region, attributed to the relaxation of polysaccharide hydrogen nuclei (Lima et al. 2012). The domain with greater intensity, T_1H of 90 ms, controls the relaxation process, which can be verified by the larger area under the distribution curve (Tavares et al. 2017).

POP showed one relaxation time, T_1H, at 2252 ms, corresponding to its crystalline domain, also confirmed in the XRD analysis. This result was expected, since POP is a small molecule, which has a high organization in its crystalline form.

For the tablets, three molecular domains with distinct T_1H values at 5.1 ms, 86 ms and 1627 ms were observed. The T_1H values at 5.1 ms and 86 ms correspond to TS and the T_1H value at 1627 ms corresponds to POP. The domain at 86 ms presented a higher intensity compared to the other domains. Moreover, the domains were separated and it was possible to conclude that there was no chemical interaction between TS granules and POP. However, there was dispersion between components; cause T_1H value of POP nuclei was shifted to lower value, showing a changing of the T_1H pattern. This result corroborated the XRD and FTIR data, showing a physical dispersion. Further, a difference in the

TABLE I
Spin-lattice relaxation time (T_1H), spin-spin lattice relaxation time (T_2H) attributed to rigid (T_2H_r*) and mobile (T_2H_m*) domains, including its respective percentage values and residual second moment of the dipolar interaction (M_2) for TS, POP and tablets.

Sample	T_1H (ms)	T_2H_r* (us)/ percentual (%)	T_2H_m* (us) / percentual (%)
TS	4.4 90	26 / 61	394 / 39
POP	2252	13.64 / 100	-
Tablets	5.1 86 1627	22 / 68	645 / 32

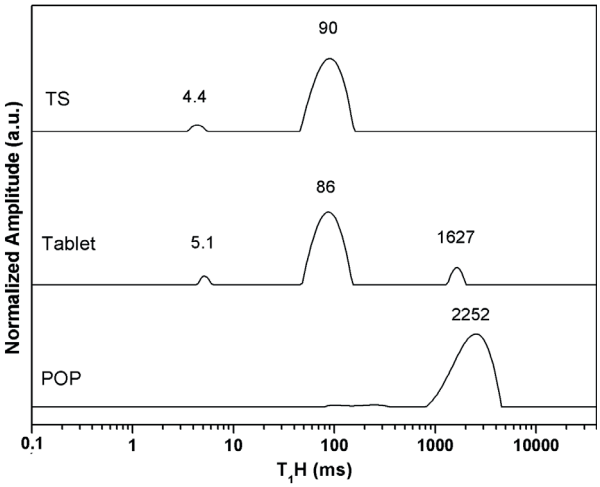

Figure 4 - Distribution curves obtained by low-field nuclear magnetic resonance of tapioca starch, propranolol and tablets.

T_1H value of POP was observed when it was mixed with TS, in the tablets, compared to the pure drug. The mixture of POP with TS promoted a change in the drug organization, making the packing of POP molecules more difficult, reducing its T_1H value in the tablets (Tavares et al. 2007, Tavares et al. 2017).

MSE-FID pulse sequence was used to investigate the spin-spin relaxation time (T_2H) and percentage of each fraction. Thus, it was possible to evaluate each individual fraction (Table I). The signal obtained for TS was composed of two distinct regions: the first one related to rigid nuclear region ($T_2H_r^*$), at 26 μs, which corresponds to the

polymer crystalline phase, equivalent to 61% of the material, following an Abragamian function behavior; the second region with the highest molecular mobility of the hydrogen nucleus ($T_2H_m^*$), at 394 μs, corresponds to the amorphous phase, equivalent to 39% of the material. In the crystalline phase the polymer chains are more rigid or restricted, thus the hydrogen atoms of the polymeric chains have lower T_2H values. It was also observed that the rigid component has the higher contribution to the T_2H values, according to the percentage of domains intensity, showing that the TS relaxation mechanism is controlled by its rigid phase (Iulianelli et al. 2016, Tavares et al. 2017). POP presents only one T_2H^* value at 13.64 μs, which corresponds to its crystalline phase. Since a lower value of T_2H corresponds a higher crystallinity, this data corroborates XRD and T_1H studies.

The tablets presented two T_2H* values: one at 22 μs, which corresponds to the crystalline domain, equivalent to 68% of the material; and another at 645 μs, which corresponds to the most amorphous domain, equivalent to 32% of the material. Consequently, POP interacted with both crystalline and amorphous phase of TS. Nevertheless, in the amorphous part of TS granules there was a major interaction with POP because there was a significant increase in the $T_2H_m^*$ value, indicating that the drug increased the mobility of the polymer chains in the amorphous part. Besides, it was found that the rigid component has the higher contribution to the T_2H values, according to the percentage of domains intensity, showing that the TS relaxation mechanism is controlled by its rigid phase. The spin-spin relaxation times confirmed the spin lattice relaxation time results (Tavares et al. 2017).

In our previous work, the low-field nuclear magnetic resonance was used to investigate nevirapine (NVP) dispersion into PCL hybrids. It was observed that when nanoparticles and NVP were added in the PCL hybrids the T_1H values increased, suggesting that its addition produced a new material, with less molecular mobility, due to the formation of new intermolecular interactions (Monteiro et al. 2016).

TABLET TESTING

The general appearance of the tablets is essential for consumer acceptance, for controlling lot-to-lot uniformity and tablet-to-tablet uniformity (Brazil 2010). The tablets were white, odorless and uniform with no mottling, as can be seen in Figure S3. Tablets containing only TS were developed to be a control in tablet characterization tests. The TS tablets, without POP, had a mean diameter of 1.1 ± 0.02 cm and thickness of 0.25 ± 0.0 cm, while the TS/POP tablets had a mean diameter of 1.1 ± 0.0 cm and thickness of 0.24 ± 0.02 cm. The developed tablets were uniform, with adequate diameter and thickness.

Weight Variation

The average weight of TS tablets was 0.550 ± 0.002 g and the average weight of TS/POP tablets was 0.544 ± 0.003 g. The individual weight of the TS tablets was between 99% and 100.7% and the individual weight of TP/Propranolol tablets was between 97.81% and 99.8%. Therefore, the developed tablets presented proper weight uniformity, according to Brazilian Pharmacopeia (Brazil 2010).

Crushing strength testing

The hardness of TS tablets and TS/POP tablets were 57.07 ± 1.17 N and 10.98 ± 0.31 N, respectively. According to the Brazilian Pharmacopeia, an acceptable hardness is approximately 44.15 N (Brazil 2010). Consequently, the TS/POP tablets presented less hardness than recommended. The hardness can affect the disintegration; consequently, if the tablet is too hard, it may not disintegrate in the required period of time and if the

tablet is too soft, it will not withstand the handling during subsequent processing, such as coating or packaging (Staniforth 2005).

Atichokudomchai and Varavinit (2003) also developed tablets with native tapioca starch and cross-linked tapioca starches by direct compression. It was observed that both compounds produced tablets with very low crushing strength. They attributed this result to the poor compressibility of the powder and it could only be compressed with magnesium stearate into tablets.

However, in our study the TS tablets had a high hardness, probably because when a compression force is applied to the starch granules, its crystalline regions could be forcedly joined. The stronger packing structure resulted in an increase of the crushing strength of the tablets (Atichokudomchai et al. 2001).

The TS/POP tablets showed a low hardness and it can be attributed to the drug mixture into the polymeric matrix, which influenced its compression. So, the drug incorporation reduced the stronger packing structure of TS starch. This result corroborates the NMR data, which shows POP interaction with amorphous and crystalline regions of TS starch.

Friability Test

The friability is the tendency of tablets to powder, chip or fragment. It affects their appearance, consumer acceptance, weight variance or content uniformity (Staniforth 2005). The percentage of friability of TS tablets and TS/POP tablets were 0.55 ± 0.06% and 25.74 ± 0.08%, respectively. Beyond that, the TS/POP tablets were broken, chipped or crumbled after friability test. This result is in accordance with the Crushing strength testing, showing that the TS tablets presented a good handling property and the TS/POP tablets did not. One of the strategies used to improve the tablets hardness is to modify the starch with graft copolymers (Casas et al. 2011).

Disintegration Test

In the disintegration test, the TS tablets disintegrated in 15 min, while the TS/POP tablets disintegrated in 10 min. Both tablets did not exceed 30 min, according to Brazilian Pharmacopeia (Brazil 2010).

Drug Content

The drug content uniformity of the TS/POP tablets was within the range from 95 ± 2.7 to 99 ± 1.2 %. The average amount of POP in the tablets was within the recommended values by the Brazilian Pharmacopeia, which suggests that the drug concentration should be between 90% and 110% (Brazil 2010).

Dissolution Test

The *in vitro* drug release study was shown in Figure 5. It was observed that the developed tablets released 100% of POP after 45 minutes. The propranolol formulations available on the market come in short-acting and long-acting versions. In short acting tablets, POP appears in the blood after 30 minutes and has a maximum effect between 60 and 90 minutes (ASHP 2018). The tablets released 100% of the drug after 45 minutes. Consequently, it was possible develop short-acting tablets with TS and POP.

For the Class I drugs, such as POP, formulated as immediate release products, dissolution rate generally exceed gastric emptying. Therefore, nearly 100% absorption can be expected if at least 85% of a product dissolves within 30 min of *in vitro* dissolution test (Zaharuddin et al. 2014).

Yamini et al. (2011) developed tablets with TS, as a binder agent, and diclofenac as active principle. It was observed that the formulation containing TS showed good dissolution, within the Pharmacopoeial limits and comparable to potato

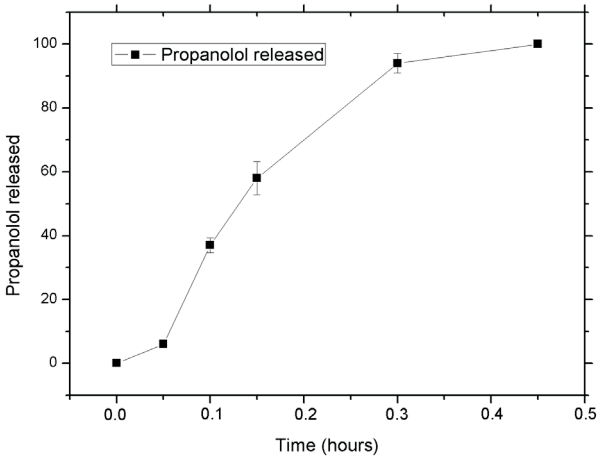

Figure 5 - Propranolol fraction released versus time (mean ± standard deviation, n = 5).

TABLE II
Mathematical modeling and drug release kinetics from TS/POP tablets.

Mathematical Models	(r^2) Values
	TS/POP tablets
Zero-Order	0.898
First-Order	0.0969
Higuchi	0.9172
Hixson-Crowell	0.9902
Baker –Lonsdade	0.9552

and maize starch. Kadoli et al. (2012) also used TS, as a binder, in different concentrations to develop loraxicam tablets. After one hour, tablets with 2 w/v% of starch reached their maximum drug release (97.05%) and tablets with 10 w/v% of starch showed their minimum drug release (79.98%).

The release kinetics data is showed in Table II and the correlation coefficient (r^2) was used to test the applicability of the release models. The kinetics data showed a suitable fit in Hixson-Crowell equation, which indicated that dissolution occurs in planes which are parallel to the drug surface. The Hixson-Crowell model is applied to different pharmaceutical dosage form, where the dimensions of the tablet decrease proportionally, keeping the initial geometry constant (Ramteke et al. 2014).

CONCLUSION

The interest of pharmaceutical industry in the tablet production by direct compression has increased during recent years, especially because it is an easily controllable and less time consuming production method, leading to higher efficiency of the production line. However, the successful production of tablets by direct compression relies almost exclusively of adjuvants inside the formulation and the use of multifunctional adjuvants has shown to be a relevant alternative. POP is on the World Health Organization's List of Essential Medicines, as one of the most effective and safe medicines needed in a health system. In this work, it was possible to develop tablets with only TS and POP by direct compression, and they released the drug after 45 min. Thus, the release kinetics data showed a suitable fit in Hixson-Crowell equation, which indicated that dissolution occurs in planes which are parallel to the drug surface. TS can be used as a multifunctional excipient, binder, filler and disintegrating agent in pharmaceutical tablets and have a major impact in reducing cost and time in the production of POP tablets.

AUTHOR CONTRIBUTIONS

Julyane B.M. Fernandes carried out the major part of experiments, Maísa T. Celestino carried out the tablets development experiment, Maria Inês B. Tavares carried out the NMR analysis, Zaida Maria F. Freitas and Elisabete P. dos Santos carried out the tablets characterizations experiments, Eduardo R. Júnior helped supervisor the project and Mariana S.S.B Monteiro carried out the SEM, FTIR and XRD experiments, wrote the manuscript, supervised the project.

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SUPPLEMENTARY MATERIAL

Figure S1 - Particle size distribution of tapioca starch granules (magnificent 5000 x), using Server XT microscope program.

Figure S2 - The scanning electron micrograph (magnificent 1000 X) of tapioca starch granules with propranolol.

Figure S3 - Tapioca Starch/Propranolol Tablets.