Ars Pharmaceutica

Bran of cassava starch flour and bran of cassava flour as potential tablet excipients

Salvado de harina y salvado de fécula de mandioca como potenciales excipientes para comprimidos

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http://dx.doi.org/10.30827/ars.v60i4.9385

Artículo Original
Original Article

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Financiación
Fundings

No fundings received

Conflicto de interés
Competing interest

The authors report no conflicts of interest whatsoever

Agradecimientos
Acknowledgements

Fundação Dom Aguirre, for finantial support to Valéria Campos Orsi. Project funding by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, São Paulo, Brazil) (FAPESP Ref. No. 2018/05522-9 (Project PsaPhageKill)) in the form of a BPE fellowship granted to Victor M. Balcão is hereby gratefully acknowledged. This work also received support from CNPq, National Council for Scientific and Technological Development Brazil, in the form of Research Productivity (PQ) fellowships granted to Victor M. Balcão (Refs. No. 306113/2014-7 and 308208/2017-0).

Received: 13.05.2019
Accepted: 19.08.2019

ABSTRACT

Objectives: The physicochemical characteristics of bran of cassava starch flour and bran of cassava flour (viz. organoleptic characteristics, pH value, moisture content, total ashes, lipid, protein, starch and fiber contents) and biopharmacotechnical parameters (viz. granulometry, flow capacity, angle at rest, outflow time and apparent density) were evaluated aiming at assessing their potential use as tablet excipients.

Methodos: Three tablet formulations of venlafaxine hydrochloride were proposed, having as excipients bran of cassava flour, bran of cassava starch flour and Starch 1500®. The tablets were produced using two different pressures (98±5 MPa and 32±6 Mpa) and their mechanical (hardness and friability) and dissolubility characteristics were evaluated.

Results and Conclusions: The tablets produced with both cassava flours, using higher pressures, presented similar physicochemical characteristics to those obtained with the excipient Starch1500®, thus indicating that cassava flours possess the potential to be used as disintegrating agents in tablets.

Keywords*:* excipient; tablets; *Manihot esculenta*

RESUMEN

Objetivos: Se evaluaron características físico-químicas del salvado de harina y del salvado de la fécula de mandioca (características organolépticas, pH, humedad, cenizas totales y contenido de lípidos, proteínas, almidones y fibras) y biofarmacotécnicas (granulometría, capacidad de flujo, ángulo en reposo, tiempo de salida y densidad aparente) con el objetivo de evaluar el uso de estos residuos como excipientes para comprimidos.

Métodos: Se propusieron tres formulaciones en comprimidos de venlafaxina teniendo como excipientes salvado de harina de mandioca, salvado de fécula de mandioca y Starch 1500 ®. Las pastillas se produjeron utilizando dos presiones diferentes (98 ± 5 MPa y 32 ± 6 Mpa). Las características mecánicas (dureza y friabilidad) y de disolución de los comprimidos se evaluaron.

Resultados y Conclusiones: Los comprimidos producidos con ambos salvados de mandioca, utilizando las presiones más elevadas, presentaron características físico-químicas similares a las obtenidas con el excipiente Starch1500®, indicando que las harinas de mandioca poseen potencial para ser utilizadas como agentes desintegrantes en comprimidos.

Palabras clave: Excipientes; comprimidos; *Manihot esculenta*

INTRODUCTION

Growing expectations and demands regarding drug quality have been stimulating research and development of new pharmaceutical compounds. In the meantime, drug quality does not solely depend on the characteristics of the active principles and on the production process, but also on both the quality and functionality of the excipients utilized. [1-2] The excipients also influence in a significative fashion the release of the active principle contained in the medicine. [3-4] During the production process, the intrinsic characteristics of the (solid state) excipients as well as of the active principle are reflected in important parameters of the tablets, such as compressibility, fluidity, ability to form uniform mixtures, lubrication, sedimentation and solubility. [5-6] More and more, excipients are gaining increasing prominence within pharmaceutical formulations, assuming now multiple functions critical to the effectiveness, safety and stability of the dosage forms.[7] Over recent years the pharmaceutical industry has been looking over alternative materials from plant origin possessing high starch content [5,8-10] that would, on one hand, allow to overcome certain difficulties inherent to the compression process in the production of tablets and, on the other hand, exhibit economic feasibility. The brans of cassava (*Manihot esculenta*) flour and of cassava starch flour are residues arising from industrial processing of cassava to produce cassava flour and cassava starch flour and are therefore potential candidates for the development of new pharmaceutical materials and excipients to be used in pharmaceutical solid dosage forms aiment at oral administration. These brans possess a large amount of starch in their composition, low levels of impurities, and can be produced in large scale and at a low cost [5,10,11]. Hence, in this research effort the major goal was to characterize both the bran of cassava starch flour (Bsf) and the bran of cassava flour (Bf), and to fully assess their potential as new tablet excipients.

MATERIALS AND METHODS

Materials

Samples of cassava brans were kindly supplied by Caio Prado Alimentos Ltda (Araras, Brazil), and were produced from cassava (*Manihot esculenta* Crantz*)* cultivar IAC 13. The brans were crushed in a Wiley-type mill (Marconi, model MA340, Piracicaba/SP, Brazil) and sieved (through a sieve with mesh opening of 0.850 mm, from Granutest, São Paulo, Brazil). As a model drug one used venlafaxine hydrochloride 99.32% pure (IdealFarma, Lot VHF 50071109, Anápolis, Goiás, Brazil). The excipient used for comparison purposes was Starch 1500® (Colorcon do Brasil, Lot IN 517075, Cotia/SP, Brazil).

Experimental procedures

Physicochemical characterization of cassava brans

Organoleptic characteristics, appearance, odor and color of samples of brans of cassava starch flour (Bsf) and of cassava flour (Bf) were analyzed according to the Brazilian Pharmacopoeia.[12] The contents in moisture, acidity, total ashes, lipid, protein, starch, fiber, and pH value, were determined according to the standards of the Institute Adolfo Lutz.[13] Bsf and Bf samples were also characterized according to their granulometry utilizing a sieving technique.[14] In order to estimate the flow capacity one used the technique for determination of the angle at rest, the outflow time and apparent density.[14] The percentage compressibility index was determined via correlation between the apparent density and the compacted density (Lachman et al., 2001). For determination of the swelling index one used the specifications of the Brazilian Pharmacopoeia.[12]

Tablet production

The tablet formulations (Table1) were prepared using the technique of moist granulation.

Table 1: Pharmaceutical formulae of the tablets prepared using bran of cassava starch flour (Bsf) bran of cassava flour (Bf) and Starch1500® as excipients

Ingredient	Formulation								
	I			II			III		
	Active content (mg)	mg/ tablet	Contribution (%)	Active content (mg)	mg/ tablet	Contribution (%)	Active content (mg)	mg/ tablet	Contribution (%)
Venlafaxine chlorhydrate	50	50	18.93	50	50	18.64	50	50	18.57
Bf		100	37.85		0	0		0	0
Bsf		0	0		100	37.29		0	0
Starch1500®		0	0		0	0		100	37.15
Tricalcium phosphate		77	29.14		77	28.71		77	28.60
Sodium bicarbonate		10	3.79		10	3.73		10	3.71
Carboxymethylcellulose (aq) 1 % (w/w) *		27	10.22		31	11.56		32	11.89
Magnesium stearate		0.2	0.08		0.2	0.07		0.2	0.07
Total		264	100.00		268	100.00		269	100.00

* sufficient amount to;

The defined granulometry for Bsf was of 0.300 mm, using sieve number 50, and for Bf one has used smaller granules (viz. 0.150 mm) using also sieve number 50. For this, all formulation components were weighed and mixed (except for magnesium stearate and carboxymethylcellulose (CMC)) using the technique for geometric dilution of powders. CMC was dispersed in water (1%, w/v) and added to the mixture of powders, thus producing a malleable mass. The moist mass was then forced to pass through a sieve with mesh size of 3.35 mm. The moist mass was then forced to pass through a sieve with a mesh size of 3.35 mm. The moist granules thus produced were collected and scattered in an uniform fashion on a tray and subsequently dried in a circulation chamber set at 40 °C (Marconi, model MA035, Piracicaba/SP, Brazil). Following drying, the granules were placed in a porcelain mortar and crushed with the aid of a pestle, to reduce the granule size. The granules thus produced were then forced to pass through the mesh surface of a sieve number 40 and further mixed with 0.2% (w/w) of magnesium stearate. The granules retained in the mesh of sieve number 50 were subject to compression in an instrumented hydraulic press, [15] under two different average pressure forces, viz. 98 ± 5 MPa and 32 ± 6 MPa.

Hardness and friability trials of the tablet formulations

Hardness trials were performed in a manual durometer (Nova Ética, model 298, Vargem Grande Paulista /SP, Brazil) and the friability tests were performed using a friabilometer (Nova ética, model NT240, Vargem Grande Paulista, /SP, Brazil) according the Brazilian Pharmacopoeia.[12]

Dissolution tests of the tablet formulations

The dissolutor (American Lab, model AL1000, Charqueada, /SP, Brazil) was used with a type-II apparatus (shaft) employing 900 mL of HCl 100 mM as dissolution medium, 50 rpm of stirring speed and 37 °C.[16] The concentration of venlafaxine hydrochloride was determined via UV-VIS spectrophotometry at 274 nm in a UV-VIS spectrophotometer (Shimadzu, model 1501, Tokyo, Japan).

RESULTS AND DISCUSSION

Venlafaxine hydrochloride is selective serotonin reuptake inhibitor used in the treatment of depression; it was selected as model drug for investigation because Venlafaxine hydrochloride is selective serotonin reuptake inhibitor used in the treatment of depression; it was selected as model drug for investigation because it was selected as model drug for investigation because it was selected as model drug for investigation because

The results of the physicochemical analyses performed to Bsf and Bf cassava bran samples are displayed in Table 2. The results obtained are compatible with the reference values [17-19] except for the lipid and ash contents.

Table 2: Experimental results gathered from the physicochemical analyses performed to cassava starch flour (Bsf) and bran of cassava flour (Bf) samples

Parameter	Reference value	Bsf (%)	Bf (%)
Moisture content*	≤ 16 %	12.92 ± 0.06	12.90 ± 0.09
pH*	4.5 a 7.0	5.54 ± 0.01	5.96 ± 0.01
Acidity*	≤ 2 %	1.973 ± 0.005	1.98 ± 0.01
Ashes*	≤ 0.6 %	0.87 ± 0.01	1.02 ± 0.02
Proteins*	≤ 0.3 %	0.35 ± 0.01	0.40 ± 0.12
Lipids**	< 0.1 %	0.35 ± 0.02	0.45 ± 0.01
Fiber	-----	8.73 ± 0.68	5.50 ± 0.13
Starch	-----	74.46 ± 0.36	79.78 ± 0.43

Note: * USP 30 (2007); Portuguese Pharmacopoeia (2008); Rowe et al. (2009); ** Cereda, 1994.

The two cassava bran types possess enough concentrations in starch so that they can be utilized as tablet disintegrants. The observed indices of ash and lipid, above the standards established by USP 30[17] and Cereda [20] were probably due to several factors, namely the source of the raw material (vegetable origin), agronomic practices, milling procedures, and chemical modifications that starch are prone to. The average size of particles obtained in cassava brans Bsf and Bf were determined after sieving because granule shape and granule size determine powder fluidity (Table 3). In general, particles whose size varies between 0.25 mm and 2.0 mm do flow freely. With particles smaller in size than 0.1 mm, flow is a problem in most materials.[14]

Table 3: Results gathered from the granulometric analyses performed to cassava starch flour (Bsf) and, bran of cassava flour (Bf) samples

Average particle diameter (mm)		Bsf		Bf	
	0.31			0.25	
Sieve mesh	Opening (mm)	Bsf(100 g)	% retained	Bf (100 g)	% retained
20	0.850	0.40	0.41	0.84	0.90
30	0.600	8.04	8.31	13.91	15.00
40	0.425	19.91	20.59	2.39	2.55
50	0.300	26.86	27.77	10.11	10.90
60	0.250	16.66	17.23	6.62	7.00
70	0.212	6.71	6.94	2.62	2.80
80	0.180	6.69	9.92	15.81	17.00
100	0.150	3.72	3.85	7.10	7.67
F < 100	0.125	7.72	7.98	33.34	36.18
	Total	96.71	100	92.74	100

The results obtained for other physicochemical, characteristics of the cassava bran (Bsf and Bf) granules are displayed in Table 4.

Table 4: Physicochemical characteristics of cassava starch flour (Bsf) and bran of cassava flour (Bf) samples with respect to outflow time, angle at rest, apparent density, compacted density, and percent compactness index

Parameter	Bsf			Bf		
Sieve number / (mesh opening, mm)	40/ (0.425)	50/ (0.30)	60/ (0.25)	80/ (0.18)	100/ (0.15)	Botton <0.15
OFT (min)	0.085 ± 0.007	0.113 ± 0.002	0.111 ± 0.001	0.570 ± 0.010	1.45 ± 0.56	1.48 ± 0.05
Â (°)	29.39 ± 0.20	29.39 ± 3.19	30.61 ± 0.61	34.67 ± 0.56	40.57 ± 0.94	40.42 ± 0.42
d_{app} (g mL^{-1})	0.474 ± 0.003	0.509 ± 0.008	0.492 ± 0.006	0.338 ± 0.004	0.370 ± 0.020	0.437 ± 0.005
d_{comp} (g mL^{-1})	0.554± 0.003	0.574 ± 0.009	0.559 ± 0.007	0.470 ± 0.005	0.540 ± 0.001	0.697 ± 0.004
CI (%)	16.273 ± 0.005	13.630 ± 0.010	13.637 ± 0.005	38.890 ± 0.001	51.510 ± 0.010	61.400 ± 5.210

Note: OFT – Outflow time; Â – Angle at rest; d_{app} – Apparent density; d_{comp} – Compacted density; CI – percent compactness index.

Powders with a low angle at rest, typically close to 25°, do flow freely, while those with high angles at rest, typically higher than 50°, display a bad flow.[4] A compressibility index (CI) with values smaller than 15% usually reflects an easy outflow of the sample particles, while values higher than 25% indicate a difficult flow of the particles.[21] Considering the aspects evaluated, the use of particles of Bsf resulting from sieves 40, 50, and 60 is not critical in the performance of the tablet manufacturing process, and all have good flow characteristics, with CI between 13.63 and 16.27 % (Table 4). However, the granules of Bf from sieve 80 may facilitate the manufacturing process due to a better flow of the particles, resulting in tablets with lower resistance to disintegration (CI of 38 %), although being bulkier (d_{comp} = 0.47 g mL^{-1}). In spite of the fact that Bf particles resulting from sieve 80 displayed better flow characteristics and less resistance to disintegration, one opted to use the Bf particles from sieve 100, a powder defined as being semi-fine[12]. Even though not presenting the best flow, the compacted density with a higher value (d_{comp} = 0.697 g mL^{-1}) indicates a more cohesive material, favoring the process of compaction (CI of 61.40%). For the Bsf particles, one opted to use in the pharmaceutical formulation the particles from sieve 50, a powder defined as being moderately coarse[12]. In the granulometric distribution of Bsf the higher retention of particles occurred in mesh with size 0.3 mm (sieve 50), while for Bf the higher retention of particles was produced in the mesh with size lower than 150.0 µm. Therefore, the Bsf particle size in sieve 50 was higher than the Bf particle size in sieve with mesh the sizes smaller than 100. This is due to the greater amount of fiber present in Bsf bran, providing a more heterogeneous mixture where the starch is adhered to the fiber. Bsf has better flow characteristics due to both a low cohesion between the particles and their larger size, while Bf presents a worse fluidity due not only to the better cohesion between particles but also to their smaller size.

Experimental tests with cassava brans and with Starch1500® produced a higher swelling index of Bsf (360 ± 34%) when compared to that of Bf (180 ± 16 %). Starch1500® presented the highest swelling index (420 ± 5%). Inspite of the differences in the swelling profile, the results obtained in this study indicate that cassava brans possess a high potential as disaggregating agents for pharmaceutical formulations.[22,23]Venlafaxine hydrochloride was selected as model drug for this study due to its high aqueous solubility.[24] The other components employed in the formulations are commonly employed in the production of tablets.[4] The tablets of the three formulations produced with higher compression forces (160-200 MPa) resulted in tablets with a better appearance. The results obtained in the physical tests performed are displayed in Table 5. The values of disintegration time of a tablet are related to the processes of dissolution/absorption and, hence, to the bioavailability of the drug, while the hardness and friability of a tablet will define their physical stability.[24]

Table 5: Results from physicochemical assays performed to tablet formulations I, II and III

Parameter	*Reference values	Tablet formulation		
		I	II	III
Pressure (MPa)	-----	98 ± 5	98 ± 5	98 ± 5
Weight (g)	-----	0. 263 ± 0.001	0. 270 ± 0.001	0.270 ± 0.001
Thickness (mm)	-----	1.76 ± 0.02	1.89 ± 0.07	1.763 ± 0.005
Friability %	≤ 1.5%	0.01	0.14	0.12
Hardness (N)	≥ 30N	90 ± 1	61.7 ± 0.6	70 ± 1

Note: * – acceptable limit, Brazilian Pharmacopoeia (2010).

The physical tests performed indicated a slightly different behavior for Formulation I, higher hardness and null friability, compared to the other formulations. The tablets from formulation I made with Bf presented a better physical stability, providing them with a better appearance and resistance. The results of the desintegration tests were the same for both forces employed. In all samples, after a time period of 30 min, 100 % of the venlafaxine chlorhydrate was released. One can also infer that, being the disintegration of a tablet an action usually prior to the dissolution process, Bf and Bsf produced a fast disintegration time thus confirming the potential of cassava brans as tablet disintegrants.

CONCLUSIONS

Formulation I presented better physical stability, physicochemical and pharmacotechnical characteristics as compared to formulations II and III. The tests performed on the tablets produced using Bsf and Bf cassava brans revealed that these brans exhibit physicochemical characteristics very similar to those presented by Starch1500®. It can be concluded that the cassava by-products Bf and Bsf could replace with advantage the excipients traditionally used by the pharmaceutical industry to produce tablets.

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