Department of Pharmacy, School of Pharmaceutical Chemistry, The University of Antioquia, Medellin, Colombia

Powder and compaction characteristics of pregelatinized starches

J. Rojas[1], Y. Uribe, A. Zuluaga

Received August 8, 2011, accepted September 9, 2011

Prof. Dr. John Rojas, Department of Pharmacy, School of Pharmaceutical Chemistry, The University of Antioquia, 094 Medellin, Colombia
jrojasca@gmail.com

Pharmazie 67: 513–517 (2012) *doi: 10.1691/ph.2012.1118*

Pregelatinized starch is widely used as a pharmaceutical aid, especially as a filler-binder. It is known that the tableting performance of excipients could be affected by their source. The aim of this study was to evaluate the powder and tableting properties of pregelatinized starches obtained from yucca, corn and rice and compare those properties with those of Starch 1500®. This material had the lowest particle size, and porosity and largest density and best flow. However, yucca starch and corn starch showed an irregular granule morphology, better compactibility and compressibility than Starch 1500®. Their onset of plastic deformation and their strain rate sensitivity was comparable to that of Starch 1500®. These two materials showed compact disintegration slower that Starch 1500®. Conversely, rice starch showed a high elasticity, and friability, low compactibility, which are undesirable for direct compression. This study demonstrated the potential use of pregelatinized starches, especially those obtained from yucca and corn as direct compression filler-binders.

1. Introduction

Starch constitutes the major polysaccharide stock in nature. Important sources of starch are corn, rice, yucca, wheat, potatoes, etc. Starch is formed by water insoluble granules of low water hydration ability. The amorphous region of starch is composed of amylose and branching points of amylopectin; whereas, the crystalline regions is comprised of parallel oriented double helices of short and long anhydroglucose chains. Thus, the crystallinity index of native starches ranges from 15 to 45% (Puchongkavarin et al. 2003).

Starch constitutes an important class of adjuvants in tablet and capsule formulations. It can be used as glidant, lubricant and disintegrant in powder form, or as wet binder in semisolid formulations. Corn starch is the most commonly form used in tablet formulations due to the good cohesive properties, inertness, availability and low cost (Shangraw 1996). However, native starches are not employed as a dry filler-binder for direct compression since they have poor flow and the resulting compacts are weak and suffer from lamination and capping.

In order to improve the functional properties of starch, modification of physical properties such as particle size and particle size distribution, shape, crystallinity, hygroscopicity, solubility, compressibility, stability could be accomplished through pregelatinization (Aulton 2002). At the molecular level, pregelatinization causes rearrangement of intra/intermolecular hydrogen bonding between the water and starch molecules resulting in the collapse or disruption of molecular orders within the granule (Odeku et al. 2008).

Pregelatinization leads to a partial and irreversible granule hydrolysis and can be carried out by enzymatic, thermal (extrusion, drum drying and spray drying), and solvent processing, oxidation, hydrolysis, and crosslinking methods (Adedokun and Itiola 2010). During pregelatinization granules precipitate amylose and release amylopectin which is responsible for swelling (Herman et al. 1989). The resulting powder produces softer gels and has improved flowability, higher packing densities, swelling ability, and water absorption capacity than natural starches. Pregelatinized starch also has a high binding capacity due to the increased particle surface area, low crystallinity, high porosity and high roughness (Alebiowu and Itiola 2002).

In contact with waters, pregelatinized starch easily forms a gel. The strength of the gel depends on the amylose component, whereas its cohesiveness depends on the amylopectin component. Swelling and water retention ability depend on the amylopectin content. The gel viscosity is not affected by the ionic strength at a pH range from 3 to 7. At pH >7, viscosity increases due to the reorientation or random coiling of the amylopectin component (Herman et al. 1989).

Currently, Starch 1500® is the most widely used pregelatinized starch in the market. It is used mainly for direct compression and capsule filling. However, it suffers from high sensitivity to magnesium stearate (Bos et al. 1992) and its compacts form a viscose layer in contact with water delaying water penetration and thus, the release of poorly soluble drugs due to gel erosion is enhanced (Mitrevej et al. 1996).

The aim of this study is to evaluate the feasibility of various pregelatinized starches obtained from yucca, corn and rice for direct compression and compare the resulting tableting properties with those of Starch 1500®.

2. Investigations, results and discussion

The FT-IR spectra of pregelatinized starches are shown in Fig. 1. All materials showed four peaks at 3300, 1610, 1350 and 1000 cm^{-1}. The absorption bands at 3300 and 1610 cm^{-1} are due to bound water, while that at 1350 cm^{-1} is due to the bend-

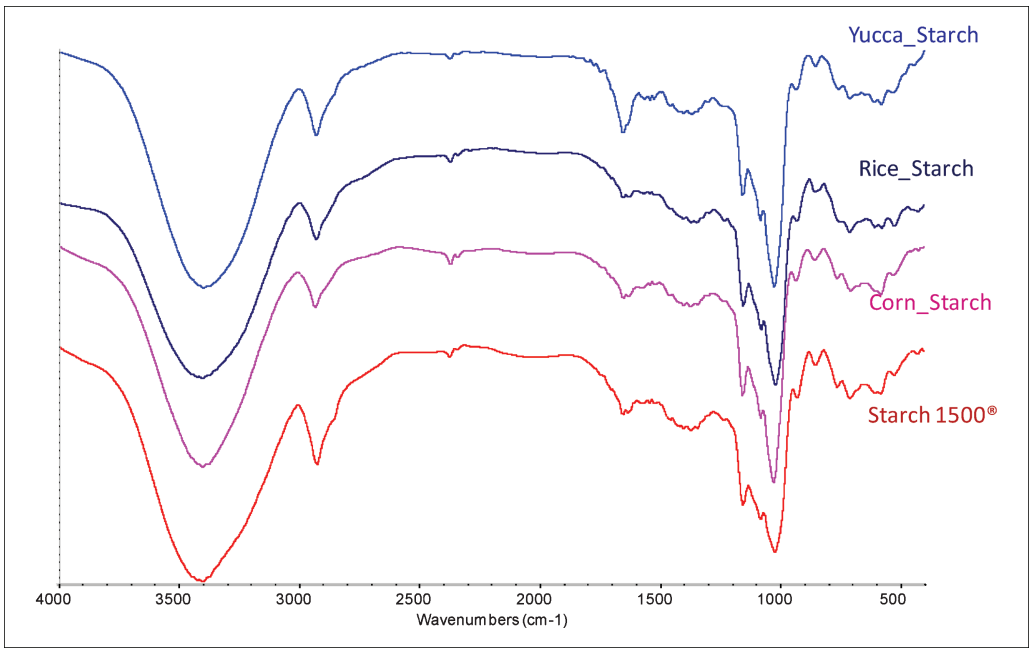

Fig. 1: FT-IR spectra of pregelatinized starches from different native sources

ing vibrational modes of O–C–H, C–C–H, and C–O–H. In the region between 1200 and 900 cm^{-1}, several strong absorption peaks are assigned to C–C and C–O stretching modes (Lizuka and Aishima 1999; Zhbankov 1964).

It has been reported that freshly pregelatinized starch granules retained their shell, but loose their content (Herman et al. 1989). The process of pregelatinization partially breaks the original semispherical starch granules and after milling the granular shape is disrupted and transformed to irregularly-shaped morphology Fig. 2. Thus, the loss of granule structure is due to the pregelatinization and milling process combined. These results agree with those of Odeku et al. (2008).

This process rendered particles larger in size (> 90 μm) than those of spray-dried corn starch (Starch 1500®). Spray drying is a well known technique for producing spherical and semispherical particles of small sizes. Powder properties of pregelatinized starches are shown in Table 1. Since Starch 1500® exhibited small particles, it showed the largest bulk and tap densities, lowest porosity, and hence, presented the largest flow as seen by the low value of angle of repose (12.5°). However, all materials had angles of repose < 30°, indicating free flowing properties. Likewise, powder consolidation as shown by the Carr's index was also comparable for all materials. Further, as expected, the pregelatinization process did not change the true density of starch, independent of its source.

Even though the moisture content of all materials was ≤ 8%, the swelling values varied considerably. Yucca starch and rice starch had the largest and lowest swelling values, respectively. This means that the ability of these materials to interact with water via hydrogen bonding is affected by the starch source. Common moisture content of native starches ranges from 10–12%, and values larger than 13% could lead to microbial grow.

Table 2 shows the parameters obtained from the different compaction models used. Except for Rice starch, the yield pressure of all starches was comparable indicating a similar onset of plastic deformation under compression. Rice starch, on the other hand, presented a brittle deforming mechanism. Since in all cases the D_b values were larger than D_0, densification through particle rearrangement was prevalent than die filling at low compaction pressures. Further, rice starch was the material that showed the highest powder densification at low pressures. On the contrary, Starch 1500® showed the least volume reduction at low applied pressures due to its high bulk and tap densities. The Kawakita analysis showed comparable total compressibility values for corn and yucca starches. Furthermore, the "b" parameter showed that rice starch was the material with the least cohesive forces

Table 1: Tablet properties of pregelatinized starches

Property	Corn	Rice	Yucca	Starch 1500®
True density (g/cm^3) n = 3	1.51(0.0)	1.49(0.0)	1.51(0.0)	1.49(0.0)
Geometric mean diameter (μm) n = 1	93.7(7.6)	92.7(10.4)	116.8(8.9)	69.9(8.2)
Bulk density (g/cm^3) n = 3	0.58(0.02)	0.61(0.02)	0.58(0.01)	0.66(0.02)
Tap density (g/cm^3) n = 3	0.72(0.02)	0.78(0.02)	0.74(0.00)	0.82(0.02)
Powder porosity n = 1	0.62	0.59	0.61	0.56
Carr's index n = 3	20.2(2.6)	22.1(3.9)	21.4(1.3)	19.8(2.9)
Swelling values (ml/g) n = 3	4.5(0.0)	2.0(0.2)	5.2(0.1)	3.5(0.1)
Angle of repose (degrees) n = 3	29.0(2.6)	26.5(1.7)	21.8(1.1)	12.5(1.7)
Moisture content (%) n = 1	7.2	7.1	8.0	7.0
Compact friability n = 1	0.05	1.42	0.25	0.57
Lubricant sensitivity n = 1	0.33(0.06)	0.42(0.02)	0.61(0.01)	0.37(0.03)
Strain rate sensitivity (%) n = 1	11.2	33.9	12.0	11.7

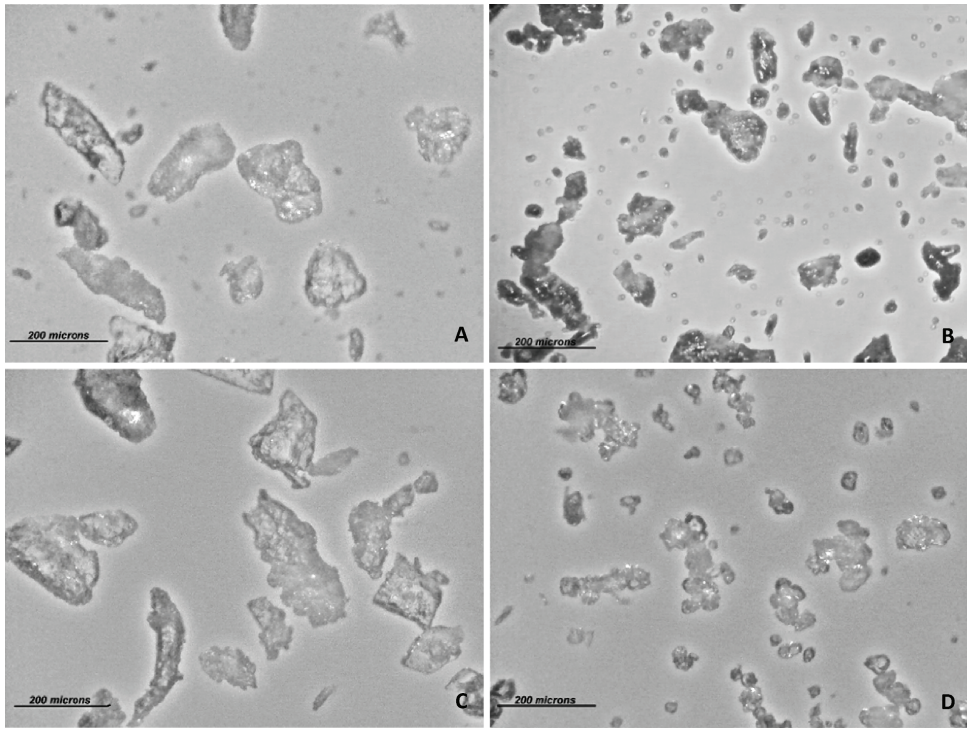

Fig. 2: Optical microphotographs of pregelatinized starches from: (a) Yucca; (b) Corn; (c) Rice; (d) Starch 1500®

to compression. The compactibility graphs of starch compacts made at 1 s and 30 s dwell times is shown in Fig. 3. Compactibility ranged in decreasing order as: corn starch > yucca starch > starch 1500® > rice starch. Even though rice starch had the largest volume reduction, it had the lowest compactibility and theoretical tensile strength. The compact friability was inversely correlated to compactibility and ranged as: corn starch < yucca starch < Starch 1500® < rice starch. Friability of rice starch exceeded 1% making it not appropriate to resist shock and abrasion without chipping/braking during manufacturing, packaging, and transportation processes.

Yucca starch was the most sensitive material to magnesium stearate, probably due to the high ability to hydrogen bonding which is hindered by magnesium stearate. Conversely, corn, Starch 1500® and rice starches had comparable and lower lubricant sensitivity. However, Starch 1500® is known for having high sensitivity to lubricants (Hsu et al. 1997).

Table 2: Parameters obtained from the Heckel, Kawakita and Leuenberger models.

Model	Parameter	Corn	Rice	Yucca	Starch 1500®
	P_y [a]	77.5	256	80	73.5
	D_0 [b]	0.21	0.38	0.22	0.13
Heckel	D_a [c]	0.60	0.79	0.61	0.57
	D_b [d]	0.58	0.61	0.58	0.66
Kawakita	a [e]	0.62	0.55	0.62	0.57
	b [f]	0.22	0.34	0.20	0.13
Leuenberger	T_{max} [g]	2.5	1.1	2.5	3.2
	ρ_c [h]	0.024	0.02	0.019	0.08

[a] Yield pressure found by $P_y = 1/\text{slope}$.
[b] Initial rearrangement as a result of die filling, found by $D_0 = \rho_{bulk}/\rho_{tap}$.
[c] Total powder packing at low pressures found from $D_a = 1\text{-}e^{-\text{intercept}}$
[d] Particle rearrangement/fragmentation at early compression stages found by $D_b = D_a - D_0$.
[e] Compressibility index.
[f] Inverse of resistance to cohesive forces.
[g] Theoretical maximum tensile strength.
[h] Compression susceptibility.

Since starch is a plastic deforming material and has a viscoelastic component, it suffers from sensitivity to compaction speed due to stress relaxation of the compacts (Maarschalk et al. 1997). The susceptibility of these materials to compaction speed was measured by the strain rate sensitivity (SRS). Highly plastic deforming materials such as corn starch, yucca starch and Starch 1500® showed a low and comparable strain rate sensitivity (11–12%). Conversely, rice starch which was a more brittle deforming material had the highest sensitivity (∼34%). This result is contradictory to spray-dried rice starch which is reported to have a low elasticity (Mitrevej et al. 1996). The above results are lower compared to reported SRS of native starches such as corn starch (49.3%) (Ching et al. 2005).

Fig. 4 depicts the compact disintegration profiles of pregelatinized starches. All compacts made up to 80 MPa of compression pressure had disintegration times < 30 min. Further increase in the compression pressure did not show major changes in disintegration times. Rice starch and Starch 1500® had comparable and fast disintegration times, independent of the compression pressure used. The low particle size of Starch 1500® and the low strength of rice starch compacts might be responsible for their fast disintegration. It has been reported that spray-dried starch from rice have a fast disintegration time (Puchongkavarin et al. 2003).

This study demonstrated the potential use of pregelatinized starch obtained from yucca and corn as a direct compression agents. They showed an irregular granule morphology, better compactibility and compressibility than Starch 1500®. Their onset of plastic deformation and their strain rate sensitivity was comparable to that of Starch 1500®. These two materials showed slower compact disintegration than Starch 1500®.

3. Experimental

3.1. Materials

Corn, yucca and rice starches were obtained from Corn industries (Cali, Colombia), pregelatinized starch (Starch 1500®, lot IN504089) was obtained from Colorcon (Harleysville, PA).

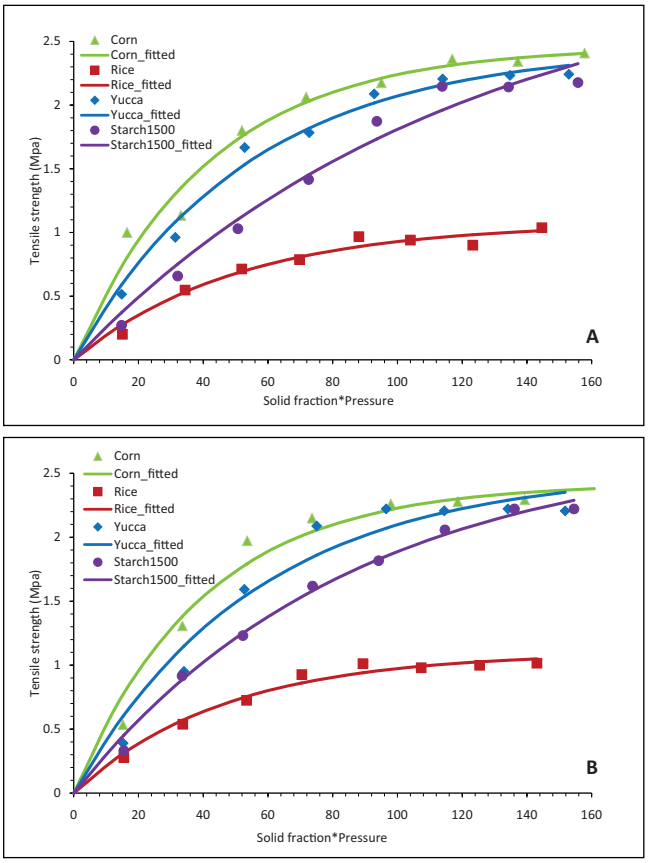

Fig. 3: Compact tensile strength of pregelatinized starches made at a dwell time of (a) 1 sec and (b) 30 sec, respectively

3.2. Starch pregelatinization

A 20% w/v starch slurry was prepared from native starches and heated at 80 °C with constant stirring for ~8 min. The resulting paste was tray-dried in a convection oven (ED115 UL, Binder GmbH, Tuttlingen, Germany) at 80 °C for 24 h and powdered using a ball mill at 60 Hz (Morse Bross Machinery, Denver, CO). The resulting powder was passed through a 150 µm sieve.

3.3. FT-IR Characterization

Approximately, 1.0 mg of sample was mixed with ~100 mg of dry KBr (dried at 110 °C for 4 h before use). The sample powder was compressed into pellets using a manual press at a dwell time of five minutes. Spectra were collected between 650 and 4000 cm^{-1} on a Perkin Elmer FT-IR spectrophotometer (Spectrum BX, PerkinElmer, CA) equipped with the Ommic® software (Nicolet Corp., Madison, WI).

3.4. Powder properties

Micropictures were obtained on an optical microscope (BM-180, Boeco, Germany) at a 210× magnification, coupled with a digital camera (S8000fd, Fujifilm Corp., Japan). The Carr's index was obtained on ~20 g of sample using an AUTO-TAP shaker (Model AT-2, Quantachrome Instruments, USA) operated for 1000 taps. The angle of repose was determined on ~20 g of sample using a glass funnel (with an orifice diameter and a base diameter of 6.5 mm and 7.5 cm, respectively). The moisture content was determined by heating the samples at 105 °C for 3 h on a convection oven (ED115 UL, Binder GmbH, Tuttlingen, Germany). True density was obtained on a helium picnometer (Accupyc II 1340, Micrometrics, USA) with ~4 g of sample. Porosity was obtained by the expression:

$$[1 - (\rho bulk/\rho true)] \times 100 \quad (1)$$

where ρ_{bulk} and ρ_{true} correspond to the bulk and true densities, respectively. Particle size was determined on a Ro-Tap sieve shaker (Model RX-29, WAS Tyler, Mentor, OH, USA) equipped with size 400, 325, 200, 140, 120, 100, 60 screens stacked in the order mentioned. Approximately 50 g of sample was added to the shaker and operated for 20 min. Particle size was plotted on log-probability scales. The geometric mean diameter (d_g) was calculated from the graphs corresponding to 50% cumulative percentage weight using the Minitab software (Minitab, Inc. State College, PA).

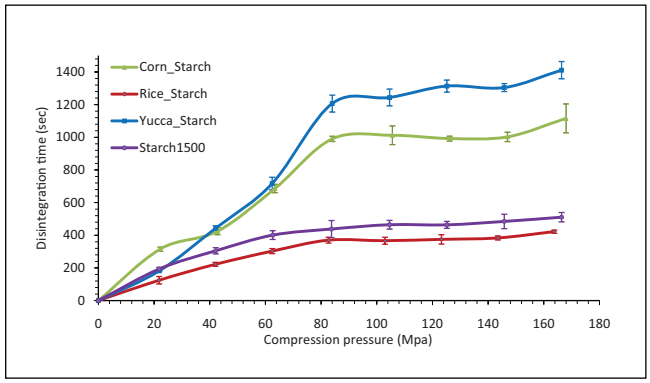

Fig. 4: Compact disintegration of pregelatinized starches

Swelling value was measured on ~0.5 g of sample which was added to a 10 ml graduate cylinder. Distilled water was then added to q.s. and shaken. The cylinder was placed on a flat surface and the increase in volume was measured after 24 h. The swelling value was calculated by dividing the sediment volume by the sample weight.

3.5. Compact preparation

Approximately 500 mg of powder was placed on a 13 mm flat-faced punch and die tooling and compressed on a single punch tablet press (Model 060804 Compac, Indemec Ltda, Itagüí-Colombia) at pressures from ~20 to 160 MPa at 1 and 30 s dwell times.

3.6. Compressibility analysis

The natural logarithm of the inverse of compact porosity, $\ln(1/\varepsilon)$, was plotted against compression pressure to construct the Heckel plots (Heckel 1961a, b). The slope (m) of the linear region of this curve is inversely related to the yield pressure (P_y), which is a measure of the plasticity of the material (Alderborn 1996):

$$\mathrm{Ln}(1/\varepsilon) = \mathrm{mP}(+\mathrm{A}) \quad (2)$$

where A is the intercept obtained by extrapolating the straight line to zero pressure. Other parameters useful in assessing compressibility are D_o, D_a, and D_b, which are related to initial powder packing/densification, total compact densification, and particle rearrangement/fragmentation at the initial compaction stage, respectively (Chowhan 1980). D_o was calculated dividing the bulk density by the true density (York 1992). D_a was obtained (A) by the expression: D_a: 1- $\exp^{-A}$, and D_b was calculated by subtracting D_o from D_a. The strain rate sensitivity was found from the P_y values obtained at 1 s and 30 s dwell times according to the expression:

$$\mathrm{SRS} = 100 \bullet \left[\frac{P_{y2} - P_{y1}}{P_{y2}}\right] \quad (3)$$

where Py_2 and Py_1 are the powder yield pressures at 30 s and 1 s, respectively. The Kawakita model describes the relationship between the degree of volume reduction of the powder and the applied pressure (Kawakita and Ludde 1971). The Kawakita model is given by:

$$\mathrm{P/C} = \mathrm{P/a} + 1/\mathrm{ab} \qquad \mathrm{C} = 1 - (\rho_0/\rho_a) \quad (4)$$

where, ρ_a, ρ_0, C, and P are the compact apparent density, powder bulk density, degree of volume reduction and compression pressure, respectively. The constant "a" is the compressibility index, which is related to the total volume reduction for the powder bed, and the constant "b" is related to the resistant forces (friction/cohesion) to compression (Hedden et al. 2006).

3.7. Compact tensile strength

Crushing strength was determined on a Hardness tester (Model 24041869, Stokes, USA). The tensile strength (TS) was obtained from the crushing strength values by the expression (Fell and Newton 1968):

$$\mathrm{TS} = \left[\frac{2\mathrm{F}}{\pi \times \mathrm{D} \times \mathrm{t}}\right] \quad (5)$$

where F is the crushing force needed to break the compact into two halves, D is the diameter of the compact (mm), and t is the compact thickness (mm). The data of tensile strength versus the product of the solid fraction and the

compression pressure was fitted according to the Leuenberger model (Lanz 2005):

$$TS = T_{max} * \left[1 - e^{(-\gamma_c * P * \rho_r)}\right] \quad (6)$$

where TS is the tensile strength, T_{max} is the theoretical tensile strength at infinite compression pressure, γ_c is the compression susceptibility parameter, ρ_r is the compact relative density and P is the compression pressure. Data fitting was performed employing the Statgraphic® software (StatPoint Technologies, Warrenton, VA).

3.8. Lubricant sensitivity

It was assessed by mixing powders with magnesium stearate at 99:1weight ratios in a V-blender (Riddhi Pharma Machinery, RiddhiState, Gulabnagar, India) for 15 min. Lubricant sensitivity was expressed as the lubricant sensitivity ratio (LSR):

$$LSR = \left[\frac{H_0 - H_{lub}}{H_0}\right] \quad (7)$$

where H_o and H_{lub} is the crushing strength of compacts prepared without and with lubricant, respectively. Samples were analyzed in triplicates.

3.9. Compact friability

Compact friability was determined on 13 compacts using a friabilizador (Model FAB- 25, Logan Instruments Corp., USA) for 4 min at 25 rpm. After the test, compacts were dedusted and reweighed. The percentage weight loss was taken as friability.

3.10. Compact disintegration

It was performed in distilled water at 37 °C employing a disintegration apparatus (231 39-133-115, Hanson Research Corporation, Northridge, California, USA) at 30 strokes/min.

Acknowledgements: We thank the pharmacy department and the unit operations laboratory for providing us with the resources needed to carry out this project.

References

Alderborn G, Nyström C (1996) Pharmaceutical Powder Compaction Technology. Marcel Dekker, New York, USA.

Alebiowu G, Itiola OA (2002) Compressional characteristics of native and pregelatinized forms of sorghum, plantain, and corn starches and the mechanical properties of their tablets. Drug Dev Ind Pharm 28: 663–672.

Aulton ME (2002) Pharmaceutics: The Science of Dosage Form Design, 2nd ed., Churchill Livingstone, United Kingdom, pp. 528–531.

Boss CE, Bolhuis GK, Lerk CF, Duineveld CAA (1992) Evaluation of modified rice starch, a new excipient for direct compression. Drug Dev Ind Pharm 18: 93–106.

Fell JT, Newton JM (1968) The tensile strength of lactose tablets. J Pharm Pharmacol 20: 657–758.

Heckel RW (1961b) Density-pressure relationship in powder compaction. Trans Met Soc AIME 221, 671–675.

Heckel RW (1961a) An analysis of powder compaction phenomena. Trans Met Soc AIME 221: 1001–1008.

Hedden DB, Brone DL, Clement S, McCall M, Olsofsky A, Patel PJ, Prescott J, Hancock BC (2006) Development of an improved fluidization segregation tester for use with pharmaceutical powders. Pharm Technol 30: 54–64.

Herman J, Remon JP, De Vilder J (1989) Modified starches as hydrophilic matrices for controlled oral delivery. I. Production and characterization of thermally modified starches. Int J Pharma 56: 51–63.

Hsu SH, Tsai TR, Chuo WH, Cham TM (1997) Evaluation of Era-Tab as a direct compression excipient. Drug Dev Ind Pharm 23: 711–716.

Kawakita K, Ludde KH (1971) Some considerations on powder compression equations. Powder Technol 4: 61–68.

Lanz M (2005). Pharmaceutical powder technology: Towards a science based understanding of the behavior of powder systems. University of Basel. PhD dissertation, pp. 1–162.

Mitrevej A, Sinchaipanid N, Faroongsarng D (1996) Spray-dried rice starch: comparative evaluation of direct compression fillers. Drug Dev Ind Pharm 22: 587–594.

Musiliu OA, Oludele A, Itiola (2010) Material properties and compaction characteristics of natural and pregelatinized forms of four starches. Carbohydr Polym 79: 818–824.

Oluwatoyin AO, Wolfgang S, Katharina MP (2008) Material and tablet properties of pregelatinized (thermally modified) *Dioscorea* starches. Eur J Pharm Biopharm 70: 357–371.

Pharmacopoeial Convention and the National Formulary (2009)"United States Pharmacopoeia The Standard of Quality", USP32/NF27, United States Pharmacopoeial Convention, New York.

Pradeepkumar P, Sanghvi C, Collins C, Atul JS (1993) Evaluation of Preflo® modified starches as new direct compression excipients. I. Tableting characteristics. Pharm Res 10: 1597–1603.

Puchongkavarin H, Berthaller W, Shobsngob S, Varavinit S (2003) Characterization and utilization of acid-modified rice starches for use in pharmaceutical tablet compression. Starch 55: 464–475.

Shangraw RF (1992) International harmonization of compendia standards for pharmaceutical excipients, in: Crommelin DJA, Midha K (Eds.) Topics in Pharmaceutical Sciences, Medpharm, Stuttgart, 205–223.

Tye CK, Sun C, Amidon GE (2005) Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. J Pharm Sci 94: 465–472.

Van der Voort K, Herman M, Willem V, Gerad KB, Coenraad FL (1997) Effect of water on deformation and bonding of pregelatinzed starch compacts. Eur J Pharm Biopharm 44: 253–260.

York P (1992) Crystal engineering and particle design for the powder compaction process. Drug Dev Ind Pharm 18: 677–721.