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Effect of binders on 500mg metformin hydrochloride tablets produced by wet granulation

Block, L.C. [1,2],; Schmeling, L.O. [2]; Couto, A.G. [1,3]; Silva, M.A.S. [4]; Tagliari, M.P. [4]; Bresolin, T.M.B. [1,3]; Mourão, S.C. [2, 3]*

[1]*Programa de Mestrado em Ciências Farmacêuticas, Universidade do Vale do Itajaí – UNIVALI, Itajaí,SC, Brazil*
[2]*Centro de Ciências da Saúde, Curso de Farmácia, Laboratório de Produção e Análise de Medicamentos, Universidade do Vale do Itajaí – UNIVALI, Itajaí, SC, Brazil*
[3]*Centro de Ciências da Saúde, Curso de Farmácia, Núcleo de Investigações Químico-Farmacêutica (NIQFAR), Universidade do Vale do Itajaí – UNIVALI, Itajaí, SC, Brazil.*
[4]*Programa de Pós-Graduação em Farmácia, Universidade Federal de Santa Catarina – UFSC, Florianópolis-SC, Brazil.*

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ABSTRACT

Metformin hydrochloride (MH) is an oral hypoglycemic agent and a high-dose drug that has poor flow and compression properties. In this study, the feasibility of developing adequate, low cost 500mg tablets of metformin hydrochloride by wet granulation was tested with several binders (Starch / PVP K30®; Starch 1500® /PVP K30®, PVP K30® and PVP K90®) in a simple tablet press of the type used in small pharmaceutical laboratories. The drug powder was tested for ability to flow, by determining Carr's Index (CI) and the Hausner ratio (HR). Differential scanning calorimetry and thermogravimetric analysis were carried out on isolated MH and 1:1 (w/w) binary mixtures with the excipients. The size distribution, friability, flow properties and drug content of the granules were analyzed, as were the hardness, friability, disintegration, dissolution and uniformity of the dosage form. The drug powder showed CI > 22% and HR > 1.25, characteristic of a poor flow powder, and no significant incompatibilities with the excipients. All the granules showed adequate flow properties and were suitable for pressing into tablets, all of which complied with pharmacopeial specifications. The starch /PVP K30® and starch 1500® /PVP K30® mixtures were best for producing 500 mg MH tablets.

Keywords: Metformin hydrochloride. Tablets. Wet granulation. Binders.

INTRODUCTION

Metformin hydrochloride (MH) is an oral hypoglycemic drug that has long been used in the management of non-insulin-dependent diabetes mellitus. It is taken in tablets of 500 and 850 mg, with low and incomplete absorption by the gastrointestinal tract, the usual dose being 2 g/day and the maximum dose 3 g/day. The absolute bioavailability of a 500mg immediate-release tablet is about 50-60% and the half life is 2-6h; when taken orally, MH reaches a maximum plasma concentration after 2.5 h, being excreted in the urine in unaltered form (Sweetman, 2005). MH is highly soluble in water (Bretnall & Clarke, 1998) and has low permeability to cell membranes, being classified as a BCS class III drug (Nicklin et al., 1996; Chou, 2000).

Several studies have been published on the development of appropriate pharmaceutical forms of MH. Gouldson & Deasy (1997) investigated two excipients containing cellulose, Aquacoat WG and Avicel 955 MCC, for the extrusion-spheronization of MH pellets. Aquacoat WG did not facilitate the spheronization of drug mixtures containing microcrystalline cellulose wetted with an optimal amount of water. However, Avicel 955 MCC, containing 95% microcrystalline cellulose and 5% methylcellulose, did improve the ease of spheronization, enabling an acceptable yield of good spheres with high drug loadings (70%). It also led to a small retardation of drug release, despite the very high solubility of metformin hydrochloride.

Compressed tablets of 10% or 20% metformin in a matrix of pH-sensitive poly (ethylene oxide) (PEO):Eudragit® L-100 (1:2, w/w) were studied by Di Colo et al. (2002), who showed that about 23 and 50% of the drug was released from matrices of 10 and 20% MH, respectively, after 2 h in simulated gastric fluid (pH 1.2). Total drug release was achieved after 2 h in simulated enteric fluid (pH 6.8).

Gohe & Jogani (2003) analyzed the melt granulation technique for the preparation and assessment of coprocessed lactose and microcrystalline cellulose, to develop a multifunctional adjuvant for use in pharmaceuticals, including metformin. The percentage of polymer blend (PVP K 30 plus PEG 4000; 5, 10, or 15%) and the polymer blend ratio (9:1, 1:1, or 1:9) were selected as independent variables in a 32 full factorial design. The batch of cellulose: lactose with 12.5% PVP:PEG (1:9) and 6% crospovidone

Autor correspondente: Samanta Cardozo Mourão - Curso de Farmácia, Laboratório de Produção e Análise de Medicamentos - Universidade do Vale do Itajaí – UNIVALI - Rua Uruguai, 458, CEP 88302-202, Itajaí-SC, Brazil - Tel: 47 3341-7799 - Fax: 47 3341-7798 - e-mail: smourao@univali.br

was selected by means of statistical analysis, as the best directly compressible adjuvant. The authors argued the merits of melt granulation over classical wet granulation and spray-drying.

Solid dosage forms, especially tablets, offer many advantages for industrial production. For the manufacture of tablets, good flowability of the blend, i.e., the mixture of excipients and drug, and good compressibility are critical properties. One way to produce tablets of drugs that show bad flow and compression in the pure form is by wet granulation.

Wet granulation involves using liquid binders to provide the adhesion needed to hold the powders together in the form of granules, and improve compressibility. The problem is that the binders can retard disintegration, and their use should be limited (Joneja et al., 1999). The granule properties and performance of tablets should be investigated to ensure a suitable manufacturing process, as well as acceptable drug delivery.

Metformin is an important drug for public health care, as it is used widely in the treatment of diabetes. It is therefore important to develop a feasible, low-cost MH tablet in a low-performance press, of the type found in small-scale pharmaceutical laboratories. However, it is a high dose drug, which makes it difficult to produce the tablets by direct compression, as this results in stress on the tooling machine. Thus, the aim of this study was to produce 500mg metformin hydrochloride tablets by wet granulation and to assess the suitability of low-cost and commercially available binders for compression in a low-performance tablet press.

MATERIAL AND METHODS

All the pharmaceutical grade materials were donated by pharmaceutical and/or pharmochemical companies. Polyvinyl pyrrolidone - PVP K30 (Plasdone K29/32®) and Polyvinyl pyrrolidone - PVP K90 (Plasdone K90®) were obtained from ISP (São Paulo, Brazil) and partially pregelatinized corn starch (Starch 1500®) from Colorcon (São Paulo, Brazil). Starch (Corn Products, Brazil), microcrystalline cellulose - MCC 101 (Blanver Farmacoquímica, Brazil), magnesium stearate (All Chemistry, Brazil), croscarmellose sodium (Mingtai Chemical Co., Valdequimica, Taiwan) and metformin hydrochloride (Idealfarma, China) were provided by UNIVALI-LAPAM (Laboratório de Produção e Análise de Medicamentos da UNIVALI) (Itajaí, Brazil).

Determination of micrometric properties of the drug

Particle Size and Size Distribution

The particle size analysis was carried out on a vibratory sieve shaker (Bertel, N1554) for 10 min, using 850 to 150 μm mesh sieves (Bertel). From the plots of powder weight retained (%) versus mesh size (μm), particle size distribution parameters, such as the mean particle diameter and standard deviation, were determined (Parrot, 2001).

Bulk and Tapped Density

The bulk and tapped densities (d_b and d_t) were measured using a Tap volumeter (Erweka, SMV 12) as a measure of packability of the metformin hydrochloride powder, under standardized conditions, as described in the British Pharmacopoeia (2008). The sample (40 g) was placed in a 100 mL glass graduated cylinder and the unsettled apparent volume (V_0) was measured, giving the bulk powder density, d_0. After tapping the cylinder 10, 500 and 1250 times, the tapped volumes (V_{10}, V_{500} and V_{1250}, respectively) were determined and the final tapped density d1250 calculated. The values given are the means of three measurements. From these data, the Carr index (CI) and Hausner ratio ($HR = d_t / d_b$) were calculated. The packability (P) (mL) was calculated from the following formula:

$$P = V_{10} - V_{500} \qquad (1)$$

Flow Rate

The flow rate of the drug powder was determined in triplicate, as described in the European Pharmacopoeia (2002), using a Granulate Tester (GT, Erweka). A standard stainless steel funnel with an internal diameter of 10 mm and an inner angle of 30º to the vertical axis was selected as the test vessel. A weighed sample (in triplicate) was introduced into the funnel without compaction, and the time (t) needed for the sample to flow completely from the funnel was measured with a chronometer. The flow rate (V_f) in g/s was calculated by the formula:

$$V_f = \frac{M}{t} \qquad (2)$$

Angle of Repose

The angle of repose was measured by a fixed-base cone method, in triplicate, using a device consisting of a mobile cylinder, 4.5 cm in height and 3 cm in diameter, seated on a flat, horizontal, fixed base attached to a motor, which raised the cylinder and separated it from the base. The mobile cylinder was filled with sample, using a spatula, without compaction, and the cylinder was then raised until free of all the sample, whose angle of repose was then calculated by the projection of the shadow formed by the sample cone on a sheet of graph paper, using the formula:

$$\tan\alpha = \frac{H}{R} \qquad (3),$$

where the cone radius (R) was calculated from the base (2R) of the projected triangle, and H is the height of the cone (Banker & Anderson, 1987).

Thermal Analysis of Drug and Excipients

The possibility of drug-excipient interactions was investigated by differential scanning calorimetry (DSC) and thermogravimetric (TG) analysis.

The MH and each excipient were individually weighed in glass vials, and homogeneous 1:1 (w/w) binary mixtures were obtained by simply mixing with a spatula.

The DSC curves were produced with a Shimadzu DSC-60 cell. Approximately 2 mg of sample was weighed and placed in a sealed aluminum pan. An empty aluminum pan was used as reference. The sample was heated from 25 to 500 °C at a rate of 10 °C.min^{-1} in an atmosphere of nitrogen flowing at 50 mL.min^{-1}. The DSC equipment was calibrated beforehand with a standard reference of indium.

The TG/DTG curves were obtained with a Shimadzu TGA-50 thermobalance. Using a platinum pan, approximately 4 mg of sample was heated from 25 to 800°C at 10°C min^{-1} under nitrogen flowing at 50 mL min^{-1}. The equipment was calibrated beforehand with a standard reference of calcium oxalate.

Preparation of Granules of Metformin

Granules were prepared in 4 formulations (F1 to F4), in the compositions shown in Table 1. A batch of 2 kg of each composition was produced. All the powders (drug and excipients) were brought to a standard particle size by passing through a 1.00 mm sieve, weighed, and mixed for 10 min in a V mixer (Marconi, MA 200, São Paulo, Brazil). Purified water was used as the granulating fluid to form the wetted mass of formulations F3 and F4, while 20% starch was used in F1 and 20% Starch 1500® in F2. Approximately 200 mL of granulating fluid was added from a graduated measuring cylinder to the powder blend as it was mixed in the sigma mixer (MBI-07, Lieme, Brazil) to obtain a mass with a desirable consistency. The wetted mass was then granulated by passing through a 2.5 mm screen of an oscillatory granulator (Lawes, K70, Brazil). The granules were air dried in an oven (Lawes, Brazil) at 40 ºC for 1 h. The moisture content was determined in an infrared moisture analyzer (Mettler LJ16 Greifensee, Switzerland). The dried granules (moisture of 3-5%) were passed through a 1.00 mm screen in the oscillatory granulator. Finally, 1% w/w of the superdisintegrant sodium croscarmellose and 2% w/w of the lubricant magnesium stearate were added, in a V mixer (Marconi, MA200, Brazil), for 5 minutes.

Table 1 - Composition (mg/tablet) of 500 mg metformin HCl tablets

Formulation / Composition	F1	F2	F3	F4
Metformin hydrochloride	500	500	500	500
Starch	31.25	--	--	--
Starch 1500®	--	31.25	--	--
PVP K30®	31.25	31.25	62.5	--
PVP K90®	--	--	--	31.25
Microcrystalline cellulose 101	62.5	62.5	62.5	93.75
Croscarmellose sodium	12.5	12.5	12.5	12.5
Magnesium stearate	6.25	6.25	6.25	6.25

Analysis of Metformin Granules

The batches of granules were analyzed for particle size and size distribution, bulk and tapped density and flow properties (Carr's Index, Hausner ratio, flow rate, angle of repose) as described above for the drug powder. The granular friability, loss on drying, and metformin content were also determined.

Granular Friability

The friability of the granules was measured in an adapted device (Prista et al., 2002). The granules were sieved on a 150 µm screen to eliminate the fine particles. An accurately weighed amount of the sample retained by the screen was placed in a covered graduated 100 mL cylinder. The cylinder was fixed in a friabilator (TA 20, Erweka, Heusenstamm, Germany) and rotated at 20 rpm for 10 min. After the test, the powder was sieved again and the sample retained on the 150 µm screen was weighed. The friability was calculated as the percentage of the material lost through the sieve after the test, which was carried out in triplicate.

Loss on Drying

Loss of weight on drying at 105°C to constant weight was determined in triplicate with an infrared moisture analyzer (Mettler Toledo LJ16, Greifensee, Switzerland).

Assay of Metformin

The MH content was determined spectrophotometrically (UVPC 1601, Shimadzu, Tokyo, Japan) at 233 nm, using water as solvent. A quantity of granules theoretically equivalent to 0.1000 g of MH was dissolved in water and sonicated for 15 min, then diluted to 100 mL with water and filtered. The filtrate was diluted with water and the absorbance at 233 nm was read on analytical curves previously constructed in triplicate in the range 2-25 µg.mL^{-1}, with a typical equation (y = 0.0795x + 0.0004), and r^2 of 0.9999.

Preparation and analysis of metformin HCl tablets

Round, flat-faced tablets with a mass of 650 mg, containing 500 mg of metformin HCl, 12 mm in diameter and with an average hardness of > 45 N, were made in a rotary tablet press (2000 10 PSC, Lawes, São Paulo, Brazil).

The hardness and friability of tablets were measured in a Hardness Tester (TBH 20, Erweka, Heusenstamm, Germany) and the TA 20 friabilometer, respectively. The disintegration time was measured in a Disintegrator (306-AC, Nova Ética, Brazil). The drug content of each batch was analysed spectrophotometrically, as described for the granules. All the tests were carried out under standardized conditions, as described in the United States Pharmacopeia (2008).

The dissolution test was carried out in a DT 80 dissolution tester (Erweka, Heusenstamm, Germany) in 6 replicates, using apparatus I, at 100 rpm, 37 ± 0.5 °C, with pH 6.8 phosphate buffer as the dissolution medium (British Pharmacopeia, 2008). After 45 min, the sample was collected and filtered, and the filtrate diluted with the same solvent as that used in the dissolution test. The percentage of MH dissolved was determined spectrophotometrically, as described for the drug assay, from an analytical curve based on standard solutions in the test buffer, previously constructed at the same wavelength in the range of 2-25 µg.mL^{-1}, in triplicate, with a typical equation y = 0.0784x - 0.0065 (r^2 = 0.999).

RESULTS

Thermal Analysis of Drug and Excipients

The DSC curve of pure MH exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237 ºC (T_{onset} = 231.2, T_{peak} = 233.33 and ΔH_{fusion} = -313.51 J/g), which corresponds to pure anhydrous crystalline MH, according to published data (Merck Index, 2001). The TG/DTG curves showed that MH is thermally stable up to 210°C and exhibited four significant mass loss steps in the following temperature ranges: 210 –307 ºC (Δm = 45.8 %), 305 – 356 ºC (Δm = 26.4 %), 356 – 404 ºC (Δm = 7.5 %) and 404 - 800 ºC (Δm = 18.8 %) (Figure 1).

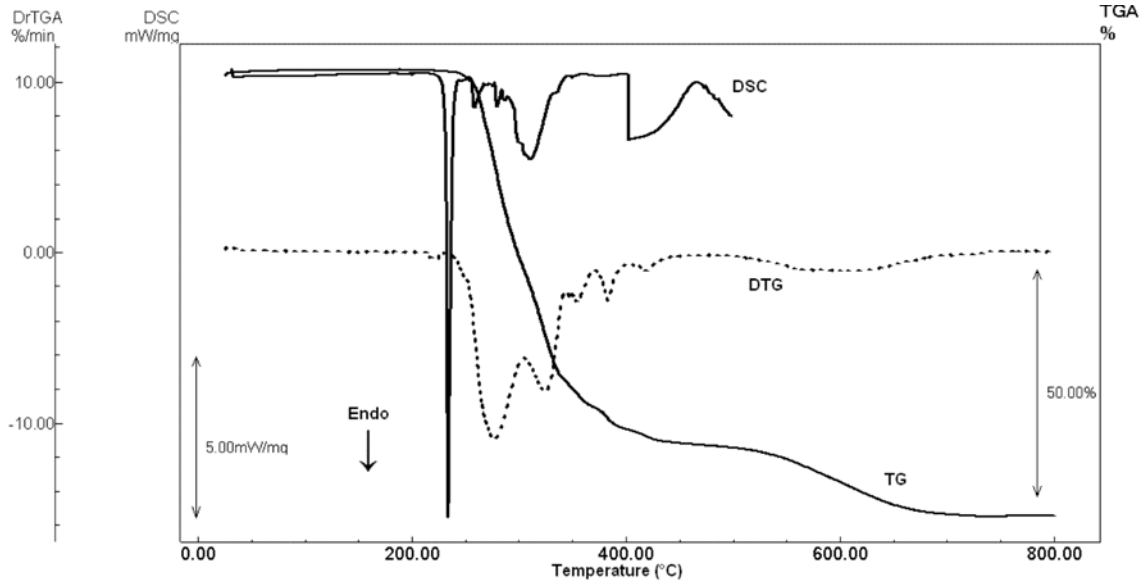

Figure 1 - DSC and TG/DTG curves of metformin hydrochloride heated at 10 ºC.min-1 under nitrogen flowing at 50 mL.min^{-1}.

The DSC and TG curves of the binary mixtures (1:1) of the drug and the excipients (PVPK90, starch, starch 1500® and microcrystalline cellulose 101) are shown in Figures 2a and 2b. The binary mixtures of metformin/starch and metformin/starch 1500® showed a slight depression of the melting point of the drug from 233.4°C to 226°C. Moreover, they produced shorter melting peaks than the isolated drug. The binary mixtures of metformin/MCC 101 and metformin/PVPK90 did not show any significant change in the thermoanalytical behaviour of the drug.

The compatibility tests of the physical mixtures (1:1) of the drug and the excipients croscarmellose sodium, magnesium stearate and PVPK30 are shown in Figures 3a and 3b. The thermal profiles of the mixture can be considered a superposition of the curves of MH and excipients. The DSC curve showed an endothermic peak corresponding to the melting point of MH followed by exothermic events characteristic of the decomposition process, which were confirmed by mass losses observed in the TG data.

Drug assay and moisture content of granules

Initially the granules were assayed for drug and moisture contents. All the granules showed drug assays close to 100% of the theoretical content (F1 = 97.9± 0.2, F2 = 97.07± 0.2, F3 = 97.0± 0.5 and F4 = 99.3± 0.2). The residual moisture contents were 4.4%, 4.3%, 2.4% and 2.2% in F1, F2, F3 and F4, respectively.

Micrometric properties of drug powder and granules

Table 2 shows the mean particle size, bulk and tapped densities, friability and flow properties (Carr's Index, Hausner ratio, flow rate and angle of repose) of the drug powder and granules.

Table 2 - Micrometric properties of metformin and granules

Sample	Mean particle size (mm)	Friability (%)	Bd (g/mL)	Td (g/mL)	P (mL)	CI (%)	HR	V_f (s^{-1})	Angle of repouse (°)
Drug	366.76	nd	0.632 (0,009)	0.828 (0,024)	16.7 (0,00)	23.7 (1,13)	1.31 (0,01)	nd	nd
F1	392.79	2.81 (0,70)	0.526 (0,000)	0.6383 (0,000)	13.33 (0,00)	17.54 (0,00)	1213 (0,000)	6.88 (0,07)	38.70 (0,20)
F2	373.99	3.34 (1,18)	0.514 (0,005)	0.6383 (0,000)	16.67 (0,00)	19.42 (0,79)	1.241 (0,012)	6.49 (0,08)	38.10 (0,70)
F3	400.99	6.13 (0,57)	0.556 (0,000)	0.720 (0,010)	16.67 (0,00)	22.84 (1,07)	1.296 (0,018)	5.10 (0,06)	39.40 (0,40)
F4	359.06	7.98 (1,81)	0.517 (0,000)	0.6977 (0,000)	23.33 (0,00)	25.86 (0,00)	1.349 (0,000)	4.90 (0,04)	37.90 (0,80)

Bd = bulk density;
Td = tapped density;
P= packability;
CI = Carr's index;
HR = Hausner ratio;
V_f = flow rate.
All values are means with SD in bracke (n = 3)

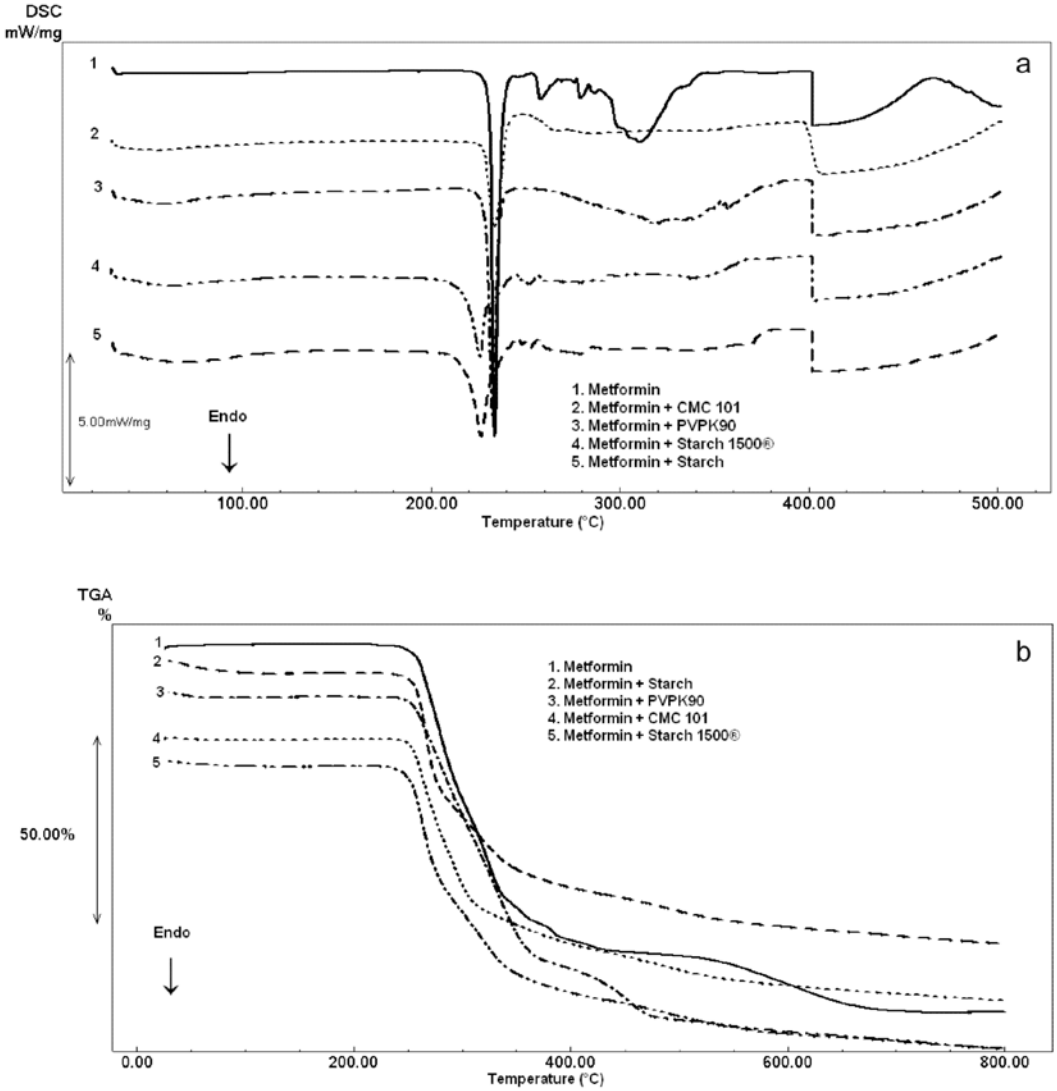

Figure 2 - Stacked overlays of (a) DSC and (b) TGA curves of 1:1 (w:w) metformin/excipient physical mixtures: (1) metformin; (2) metformin/microcrystalline cellulose 101; (3) metformin/polyvinyl pyrrolidone - PVP K90; (4) metformin/starch 1500®; (5) metformin/starch.

Metformin Tablet Analysis

All the granules formulated were successfully compressed, resulting in flat, white, uniform tablets, 12 mm in diameter and 5-6 mm in height.

The tablets were tested in relation to drug content, average mass, uniformity of dosage form, hardness, friability, disintegration time and dissolution. The results are shown in Table 3.

The four formulations showed similar average tablet masses. The hardness of all formulations was > 30 N, as required (United State Pharmacopeia, 2008), in the following order: F4<F3<F1<F2. The friability and disintegration time were within pharmacopeial specifications in all batches, being respectively < 1.5% and < 30 min. The assay of MH content of the tablets showed 97.4, 96.3, 99.1 and 99.9 % in F1, F2, F3 and F4, respectively, which are all within the pharmacopeial specification of 95 to 105 % (United States Pharmacopeia, 2008).

The uniformity of dosage forms of the formulation tablets was determined by the Mass Variation method (Table 3). All the formulations were approved, with RSD < 6% and assay between 85 and 115% (Farmacopéia Brasileira, 1988).

All the formulations passed the dissolution test, complying with a pharmacopeial specification of 70% dissolved in 45 min (British Pharmacopeia, 2008).

Table 3 - Physical tests results for 500 mg metformin tablets

Sample	Average mass (mg)[a]	Hardness (N)[a]	Friability (%)[b]	Disintegration (min)[c]	Dissolution (%)[c]	Assay (%)[d]
	649.8	111.4				97.39
F1			0.13	9.7	Approved	
	(8.9)	(12.4)				(0.13)
	637.6	137.4				96.32
F2			0.45	9.6	Approved	
	(11.3)	(76.0)				(0.36)
	657.2	83.7				99.09
F3			0.14	11.2	Approved	
	(6.9)	(7.6)				(0.42)
	657.5	65.1				99.93
F4			0.47	8.00	Approved	
	(14.3)	(10.3)				(0.17)

Values are means (SD in brackets), a n = 10, b n = 20; c n = 6
(Approved corresponds to > 75% of dissolution after 45 min); d n = 3

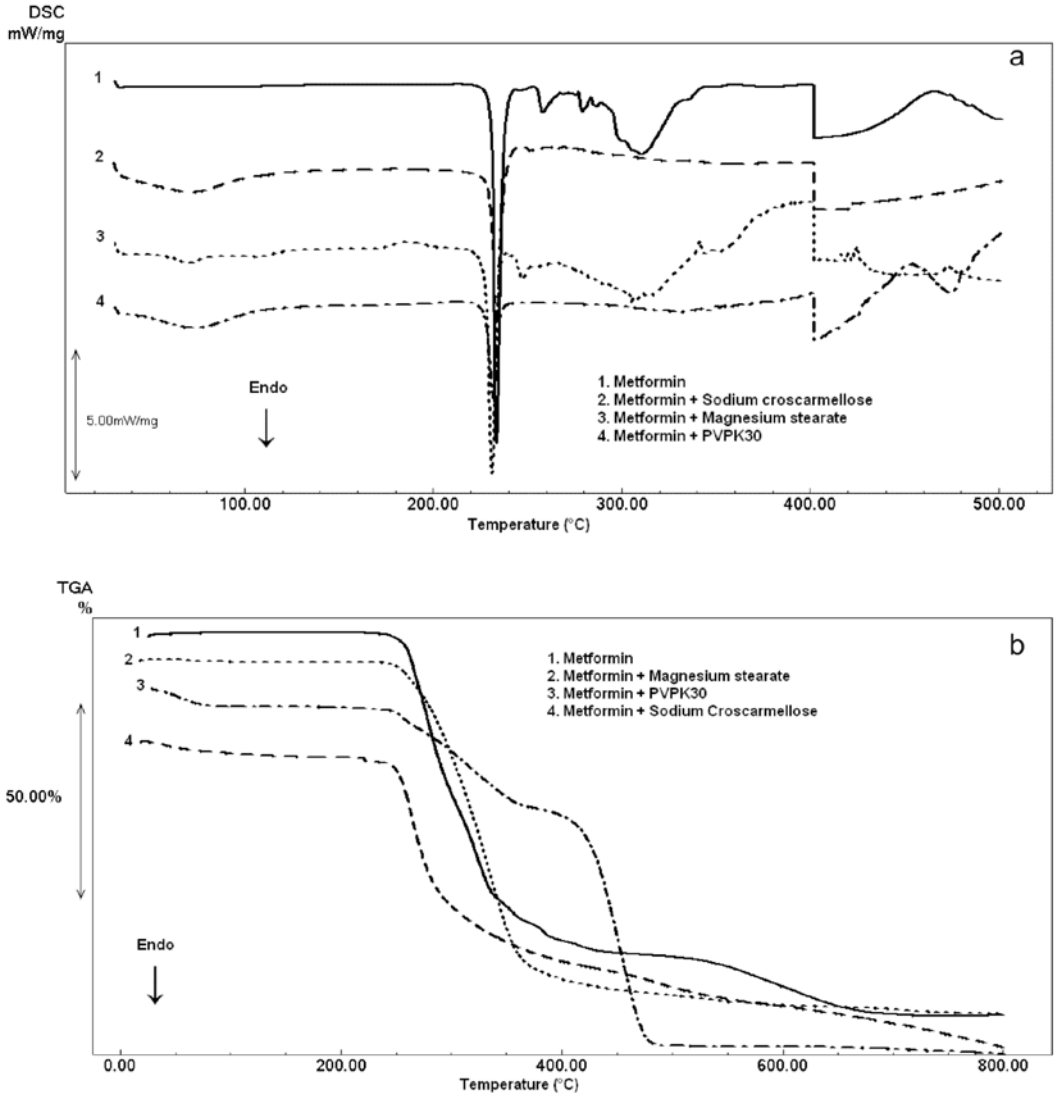

Figure 3 - Stacked overlays of (a) DSC and (b) TGA curves of 1:1 (w:w) metformin/excipient physical mixtures: (1) metformin; (2) metformin/sodium croscarmellose; (3) metformin/magnesium stearate; (4) metformin/polyvinyl pyrrolidone - PVP K30.

DISCUSSION

The choice of excipient in a tablet formulation can affect the performance of the dosage form. The analysis of possible interactions between the drug and excipients and also characterization of the intermediate product can provide information leading to a better choice of excipient.

By thermal analysis it is possible to detect potential drug-excipient interactions. A slight lowering of the melting point and a shorter melting peak were observed when the DSC curves of the binary mixtures of starch (or starch 1500) were compared with those of the isolated drug (Figures 1, 2a and 2b). Pinho (1999) reported similar results for metformin in mixtures with these excipients, and also with lactose and mannitol. These results suggest a possible, but not significant, interaction between the drug and these excipients. Joshi et al. (2002) argue that the stretched peaks in DSC may lead to changes at the onset and peak temperatures, which merely reflect the physical mixing of the components, without indicating any significant chemical interaction.

The thermal behaviour of MH was not modified in the binary mixtures with MCC 101, PVPK90, PVPK30, sodium croscarmellose or magnesium stearate, suggesting no interaction with the excipient.

The granules were produced and analysed in terms of flow properties, friability, loss on drying and metformin assay. It was observed that the higher percentage of fines and higher friability of F3 and F4 may influence the flow properties of these granules, which were poor compared to F1 and F2. Also, the lower residual moisture of F3 and F4 may have enhanced their friability. However, all four types of granule were less than 10 % friable and thus were classified as low friability granules.

The angle of repose gives a qualitative assessment of internal and cohesive frictional forces. An angle $< 30°$ indicates good flow potential, while an angle of $> 40°$ exhibits poor or absent flow (Banker & Anderson, 1987). All batches of granules showed an angle of repose $< 40°$ (Table 2) and were therefore classified as material with reasonable flow potential. However, this was better than the MH powder, since there was no free flow with this powder.

The density of the material depends on the shape and size of the particles. The density is normally proportional to the number of spherical particles present in the bulk, and inversely proportional to the size of particles (Banker & Anderson, 1987). Notwithstanding this, out of all four granule formulations, F3 had the largest granules, as well as the highest bulk and tapped densities (Table 2). These granules were probably more regular in shape, producing a more uniform distribution, with smaller void spaces between the particles.

Carr's index (CI) may be indicative of flowability and degree of packing of the material, which are relevant properties when filling the matrices of the tablet press. A CI of < 15 % indicates an adequate flow of granules and stable packing, while values of > 25 % are characteristic of poor flow properties (Marshall, 2001). The Hausner ratio may be related to the compressibility of powder and values of < 1.25 are indicative of good compressibility (Wells, 2005). The packability, calculated from the bulk volume, is another parameter used to characterize the rheological properties of powders, and values of < 20 mL indicate easily compressible materials (Wells, 2005).

F1 showed the best flow and compressibility properties, with packability < 20 mL, HR < 1.25, CI 17.54 % and the highest flow rate (Table 2), being characterized as material with good flow properties (United States Pharmacopeia, 2008).

All the tablets complied with pharmacopeial specifications regarding the average mass, hardness, friability, disintegration and dissolution testing. In a previous study, Block et al. (2008) evaluated the pharmaceutical equivalence of these formulations and showed showed that F1 (starch / PVP K30®) and F2 (starch 1500® / PVP K30®) are pharmaceutically equivalent to the innovator brand-name drug, and are potential formulations for bioequivalence and registration as a generic medicine.

The binders used in this study are commonly used in the granulation process to obtain tablets. In a comparative study of binders in sulfamethoxazole tablets, it was observed that granules prepared with PVP showed the best flow properties and compressibility, while tablets with starch as binder also had advantageous features (Agrawal & Prakasam, 1988).

Starch is a well-known excipient in tablet manufacturing, being used as a diluent with disintegrant properties and, in paste form, as a binder. Polyvinyl pyrrolidone is a synthetic polymer binding agent with excellent adhesive properties (Rowe et al., 2006). Starch 1500® is a partially pregelatinized starch that has both binder and disintegrant properties (Rahman et al., 2008).

All these binders are commercially available and are widely used in tablet formulation. By consulting the suppliers, it was confirmed that the costs of the excipients in F1 and F2 are suitable, as they represent about 3.5% of the price of commercial available metformin tablets.

In conclusion, a wet granulation technique can be successfully used to overcome the poor compression properties of metformin powder and produce high-dose tablets. In this study, this was achieved with low-cost and compatible excipients, resulting in granules with suitable flow properties and enabling tablets to be produced with a small-scale press that exhibited high hardness, low friability and acceptable disintegration and dissolution, according to the pharmacopeial specifications. These formulations can readily be manufactured by small laboratories and thus help increase the availability of this drug dosage form.

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RESUMO

Efeito de aglutinantes na produção de comprimidos de cloridrato de metformina 500 mg por granulação via úmida

Cloridrato de metformina é um fármaco hipoglicemiante oral que apresenta propriedades pobres de fluxo e compressibilidade. Este trabalho teve como objetivo o desenvolvimento de comprimidos de baixo custo, após granulação por via úmida, contendo 500 mg de cloridrato de metformina e diferentes aglutinantes (F1- amido / PVP K30®; F2- Starch 1500® / PVP K30®, F3- PVP K30®, F4- PVP K90®) em máquinas de compressão de baixo desempenho usadas em laboratórios farmacêuticos de pequeno porte. As propriedades de fluxo do fármaco foram analisadas através do índice de Carr (IC) e fator de Hausner (FH). Cloridrato de metformina e suas misturas binárias com os excipientes na relação 1:1 (m/m) foram analisadas por calorimetria diferencial por varredura e análise termogravimétrica. Os granulados foram analisados quanto a distribuição granulométrica, friabilidade, propriedades de fluxo e teor e os comprimidos em relação à dureza, friabilidade, desintegração, dissolução e uniformidade de conteúdo. O cloridrato de metformina apresentou IC > 22% e FH > 1,25, característicos de fluxo pobre e não apresentou incompatibilidades com os outros excipientes. Todos os granulados demonstraram adequadas propriedades de fluxo e facilidade no processo de compressão. Os comprimidos apresentaram conformidade com as especificações farmacopeicas. As misturas amido / PVP K30® e Starch 1500® / PVP K30® foram mais adequadas para produzir comprimidos de cloridrato de metformina 500 mg.

Palavras-chave: Cloridrato de metformina. Comprimidos. Granulação por via úmida. Aglutinantes.

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