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Pharmaceutical equivalence of metformin tablets with various binders

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ABSTRACT

Metformin hydrochloride is a high-dose drug widely used as an oral anti-hyperglycemic agent. As it is highly crystalline and has poor compaction properties, it is difficult to form tablets by direct compression. The aim of this study was to develop adequate metformin tablets, pharmaceutically equivalent to the reference product, Glucophage® (marketed as Glifage® in Brazil). Metformin 500mg tablets were produced by wet granulation with various binders (A = starch, B = starch 1500®, C = PVP K30®, D = PVP K90®). The tablets were analyzed for their hardness, friability, disintegration, dissolution, content uniformity and dissolution profile (basket apparatus at 50 rpm, pH 6.8 phosphate buffer). The 4 formulations, F1 (5% A and 5% C), F2 (5% B and 5% C), F3 (10% C) and F4 (5% D), demonstrated adequate uniformity of content, hardness, friability, disintegration and total drug dissolution after 30 minutes (F1, F2 and F4), and after 60 minutes (F3). The drug release time profiles fitted a Higuchi model (F1, F2 and F3), similarly to the pharmaceutical reference, or a zero order model (F4). The dissolution efficiency for all the formulations was 75%, except for F3 (45%). F1 and F2 were thus equivalent to Glifage®.

Keywords: dissolution; metformin; tablet; binder; pharmaceutical equivalence

INTRODUCTION

Metformin hydrochloride is an oral anti-hyperglycemic drug, belonging to the biguanide class. It has long been used in the management of non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus), particularly when the diet itself does not achieve weight and/or glycemia normalization (Sweetman, 2005; Korolkovas, 2006).

Results from the *United Kingdom Prospective Diabetes Study* show that long-term control of blood glucose with the aid of metformin decreases the potentially fatal risks linked to diabetes, such as myocardial infarction and coronary disease in overweight diabetic patients. Since metformin is not associated with weight gain, it is the hypoglycemic agent of choice for the treatment for this kind of diabetic patients (Campbell, 2000).

Metformin, which is slowly and partially absorbed by the gut, is taken in the form of oral tablets of 500 and 850mg, usually at a dose of 2g (maximum of 3g) per day. The absolute bioavailability of a 500mg immediate-release tablet is about 50 to 60%; the half-life is 2 - 6h and the maximum plasma concentration is reached after 2.5h, the drug being excreted through the urinary tract unaltered (Sweetman, 2005). In the Bioavailability Classification System (BCS), metformin is classified as a class III drug, because of its high water solubility, one part metformin dissolving in two parts water (Bretnall & Clarke, 1998), and its low cell membrane permeability and partition coefficient, log P (*n*-octanol/buffer pH 7.4) being –1.43 (Chou, 2000). Metformin solubility is higher than 100 mg/mL in water, in 0.1M hydrochloric acid and in pH 4.5, pH 6.8 and pH 9.5 buffer solutions. The highest metformin dose in tablets (1000mg) is soluble in 250 mL of aqueous medium at any pH from 1 to 7.5. The pKa of metformin is 11.5 and it occurs as a cation at the pH of the gastrointestinal tract (GIT) (Scheen, 1996; Chou, 2000). The hydrophilicity and ionization properties of metformin suggest that its transport through cell membranes could be limited. Studies with Caco-2 cells demonstrate a low rate of transport of metformin (Dimitrijevic et al., 1999) and a permeability coefficient of 5.5 10^{-6} cm/s at pH 7.4 (Nicklin et al., 1996), which is much lower than BCS I reference drugs.

The metformin solution is bioequivalent to the immediate-release (IR) tablet which dissolves completely in 1h (Sambol et al., 1996). Cheng et al. (2004) state that if a pharmaceutical form dissolves quickly, the bioavailability of the active ingredient will not be affected by dissolution and, in this case, there is the possibility of extending biowaivers (relaxing the need for bioavailability tests) to Class III, on the basis of the *in vitro* dissolution profile. These authors carried out an *in vivo* study of two metformin immediate-release pharmaceutical brands of 500mg tablets administered to 12 healthy, adult Chinese volunteers, showing that the two products were bioequivalent, since there were no significant differences between their pharmacokinetic parameters and the results were consistent

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with those reported for metformin IR tablets in other ethnic populations (Cheng et al., 2004).

The central role of this drug in the treatment of diabetes and the need to resolve public health problems justify increasing its availability in an adequate pharmaceutical form. Metformin is therefore an important drug for public health policy, especially in Brazil, where it is not yet produced by official government laboratories.

Tableting behavior, flowability and the tendency to stick to the punches can be affected by the choice of crystal form (Martino et al., 1996) or the degree of crystallinity (Rasenack & Müller, 2002). For example, monoclinic crystals lead to unstable tablets with a high capping tendency, owing to the rigid molecular structure inside the crystal, whereas orthorhombic crystals show better compression behavior (Martino et al., 1996). Amorphous particles are likely to show plastic deformation upon compaction, substantial lubricant sensitivity (Eissens et al., 2002) and stronger bonding than those in the crystalline form (Hansen et al., 2004), resulting in higher mechanical strength (Bozic et al., 2008). On the other hand, highly crystalline materials mainly fragment, leading to a larger surface area and increased number of contact points suitable for bond formation. In both cases, plastic deformation occurs in the later stages of compression and adequate tablet strength can be obtained (Alderborn & Nyström, 1996).

Therefore, successful compaction depends on a combination of crystallinity-related properties and these should be better known by studying the physics of compaction of each drug. Despite the importance of such information, in the case of metformin hydrochloride, it is only known that its crystallinity is high on account of its poor compactability. However, there are no data on how these properties are related to each other, up to now.

Given that metformin hydrochloride is a high-dose drug that is hard to compress directly into tablets, the objective of this study was to develop formulations that make the process more consistent and therefore feasible for industrial production, while maintaining pharmaceutical equivalence to the Brazilian reference pharmaceutical form.

MATERIAL AND METHODS

Material

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

Methods

Preparation of the Metformin tablets

The tablets were prepared after wet granulation with various binders (Table 1). The metformin was standardized by passing through a 1.00mm sieve. Cellulose, PVP K30 (formulations F1, F2 e F3), PVP K90 (F4), part of the starch (F1) and/or part of the pre-gelatinized Starch 1500® (F2) were mixed for 10 minutes in a V mixer (Marconi®, MA 200, São Paulo, Brazil). Purified water was used as the granulating fluid, to form the wet mass of formulations F3 and F4. For F1 and F2, the granulating fluids were 200mL of 20% starch paste and 20% Starch 1500® paste, respectively (2kg of each formulation). The granulating fluid was added from a graduated measuring cylinder while the powder blend was mixed in a sigma mixer (Lieme® MBI-07, Brazil), to obtain the desirable consistency of the mass. The wetted mass was then granulated by passing through a 2.5mm mesh screen, using an oscillating granulator (Lawes®, Brazil). The granules were dried in a hot-air oven (Lawes®, Brazil) at 40 ºC for 1h. The moisture content was determined with an infrared moisture analyzer (Mettler® LJ16 Greifensee, Switzerland). The dried granules (moisture 3-5%) were passed through a 1.00mm mesh screen, using the oscillating granulator (Lawes®, Brazil). At the end, 1% w/w of the superdisintegrant croscarmellose sodium and 2% w/w of the lubricant magnesium stearate were added and mixed in a V mixer (Marconi®, MA 200, Brazil) for 5 minutes. Tablets of 643mg were made in a rotary tableting machine (Lawes® 10 PSC, Brazil), with 12mm concave punches.

Characteristics of tablet formulations

The tablets were characterized by weight, hardness, disintegration, friability, uniformity of dose and dissolution profile. The average weight was obtained over 20 units, as recommended in United States Pharmacopeia (2006) and the Farmacopéia Brasileira (1988). The hardness was determined in a Hardness Tester (TBH 20, Erweka®), over 10 tablets, and a minimum hardness of 3 kgf (Farmacopéia Brasileira, 1988) was adopted as the acceptance criterion. For each formulation, the friability was evaluated in a friabilator over a sample of 20 tablets and the acceptance criterion was a maximum loss of 1.5% of the initial weight (Farmacopeia Brasileira, 1988).

The disintegration was carried out in a disintegrator (306-AC, Nova Ética®) as specified in United States Pharmacopeia (2006), taking into account the acceptance criterion for immediate-release tablets. The drug content of batches was assayed spectrophotometrically, as described in the British Pharmacopoeia (2005). An amount of powdered sample corresponding to 0.1000g of metformin was dispersed in water and sonicated for 15 minutes, diluted

Table 1 - Composition (mg) of metformin 500 mg tablet formulations

Formulation / Composition	F1	F2	F3	F4
Metformin hydrochloride	500	500	500	500
Starch	31.25	--	--	--
Pre-gelatinized starch (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
TOTAL	643.75	643.75	643.75	643.75

to 100 mL with water and filtered. The filtrate was diluted with water and the absorbance at 233 nm was compared with the analytical curve previously plotted over the range 2-25 $\mu g.mL^{-1}$, in triplicate, that closely followed a linear equation ($y = 0.0795x + 0.0004$), with $r^2 = 0.9999$.

Dissolution assay

The dissolution assay was carried out with an Erweka® DT80 dissolution tester and sample solutions were analyzed in a UV spectrophotometer (UVPC, Shimadzu®).

The dissolution profiles of the metformin tablets (F1, F2, F3, F4), as well as the commercial product (UNIVALI-LAPAM®) and reference tablets (Glifage®, Merck), were determined as specified in the British Pharmacopoeia (2005), using the USP method I (basket), with 900 mL of 0.68% (w/v) phosphate buffer dissolution medium (pH 6.8), at 37 ± 0.5 °C. The dissolution tests were performed at 50 rpm.

Samples of 5 mL were taken after 5, 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 minutes and the medium was replaced to maintain the same volume over 2h (thus ensuring sink conditions). Six tablets of each formulation were analyzed. The samples collected were filtered and diluted in purified water and the metformin dissolved at each time point was determined from an analytical curve by UV spectrophotometry at 233 nm.

Data analysis

The dissolution profiles for each set of six tablets, were compared with each other, using equations derived from mathematical models such as zero order, first order and Higuchi (Higuchi, 1961) to calculate rates of dissolution. Other parameters, such as dissolution efficiency (DE), difference factor (*f1*) and similarity factor (*f2*) were also calculated and analyzed by ANOVA, followed by the Ryan-Einot-Gabriel-Welsch Multiple Range *a posteriori* test. Excel 6.0 software was used, and statistical significance was declared when $p < 0.01$.

RESULTS

The characteristics of the tablets are shown in Table 2.

As shown in Figure 1, 85% of the drug was released within 25 minutes at 50 rpm, for all formulations except F3.

The kinetics of drug release was analyzed from the respective dissolution profiles in order to compare the drug release model of each formulation. The slope (k) and linear regression coefficient (r^2) are presented in Table 3. According to the values of r^2, batch F4 and the commercial product are best represented by zero order kinetics. However, the Higuchi model also gives a high r^2, reflecting the influence of PVP K90, which has a high molecular weight and a high microcrystalline cellulose content, over the drug-release kinetics for both formulations. For all the other formulations, including the reference tablet, the Higuchi diffusion model gives the best fit (Table 3).

The DE was very similar among the formulations, except for F3 (Table 4), which had a lower value. The DE for the formulations followed the sequence: reference > commercial product > F1 > F2 > F4 > F3. ANOVA, followed by the *Ryan-Einot-Gabriel-Welsh Multiple Range* test, showed that F3 was statistically different from the others, while F1, F2, F4, the reference tablet and the commercial product were similar. However, according to the values of *f1* and *f2*, only F1 and F2 and commercial product were similar to the reference tablet (Table 4).

Table 2 - Characteristics of metformin 500mg tablets

Formulation	F1	F2	F3	F4	Commercial product	Reference
Weight average	649.81	637.58	657.16	657.46	684.12	526.46
(mg)[a]	(8.92)	(11.33)	(6.86)	(14.29)	(7.88)	(3.95)
Hardness (N)[a]	111.4	137.4	83.7	65.1	131.6	262.2
	(12.4)	(76.0)	(7.6)	(10.3)	(12.0)	(35.3)
Friability (%)[b]	0.13	0.45	0.14	0.47	0.30	0.00
Disintegration time[c] (min)	9.69	9.55	11.22	8.00	8.00	7.42
Assay (%)[d]	97.38	96.32	99.09	99.93	99.09	98.93
	(0.13)	(0.36)	(0.42)	(0.17)	(0.82)	(0.32)

values represent the average ± (standard deviation), [a] n = 10, [b] n = 1; [c] n = 6, [d] n=3.

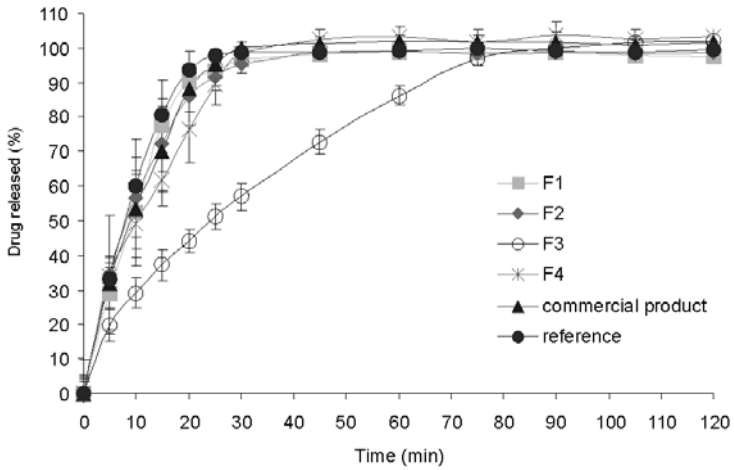

Figure 1. Dissolution profiles of developed formulations, commercial product and pharmaceutical reference of metformin 500 mg tablets, at 50 rpm (basket apparatus), with dissolution medium pH 6.8 phosphate buffer, at 37 ± 0.5°C

Table 3 - Kinetic parameters of metformin 500mg tablet formulations, commercial product and pharmaceutical reference

Formulation	Zero Order		First order		Higuchi	
	r^2	K_0	r^2	K_1	r^2	K_H
F1	0.9829	4.1643	0.9368	0.0755	**0.9937**	28.08
F2	0.9878	3.3882	0.943	0.0594	**0.9997**	22.86
F3	0.9826	1.1886	0.8776	0.0246	**0.9982**	12.198
F4	**0.9996**	2.7654	0.9762	0.0475	**0.9892**	19.986
Pharmaceutical reference	0.9769	4.0278	0.9206	0.0678	**0.9966**	27.283
Commercial product	**0.9978**	3.7183	0.9631	0.0664	**0.9962**	24.916

r^2 = coefficient of determination; K = slope

Table 4 - Percent DE, *f1* and *f2* for metformin 500mg tablet formulations, commercial product and pharmaceutical reference

Formulation	DE (%)	*f1*	*f2*
F1	75.88[a]	6.79	65.23
F2	75.46[a]	7.89	60.49
F3	44.93[b]	39.98	22.32
F4	73.44[a]	15.42	44.17
Commercial product	76.72[a]	8.91	58.13
Pharmaceutical reference	79.01[a]	-----	-----

DE = Dissolution Efficiency; *f1* = difference factor; *f2* = similarity factor (n = 6).
Means with different letters within the same column are significantly differerent ($p< 0.0001$) according to the Ryan-Einot-Gabriel-Welsch Multiple Range Test

DISCUSSION

Drug dissolution testing is an integral part of drug product development and manufacturing and is also used as a quality control tool, to monitor batch-to-batch consistency of the drug release from a product (Qureshi & McGilveray, 1999). It is desirable to have an *in vitro* method of testing dissolution that is sensitive to formulation factors that affect the dissolution process and thus bioavailability. As a result, the reliability and discriminatory capabilities of dissolution tests for IR products has attracted much attention in recent years (Dumont et al., 2007).

The most widely used dissolution tests for IR products use 900mL of an aqueous medium with USP apparatus I (basket) or apparatus II (paddle) at stirring rates of 100 or 50 rpm, respectively (Dumont et al., 2007). For metformin tablets of 500 mg, the United States Pharmacopeia (2006) specifies 1000 mL of dissolution medium and a choice of two tests: apparatus I at 100 rpm in test 1, and apparatus II at 50 rpm in test 2. However, the British Pharmacopoeia (2005) specifies 900 mL and apparatus I at 100 rpm.

The dissolution rate is proportional to the stirring rate, since the higher this rate is, the thinner the surface diffusion layer becomes (Banakar, 1992). Therefore, the dissolution profiles were produced and compared at a stirring rate of 50 rpm, using the basket method.

According to Graffner (2006), when a dissolution test method is developed for the market, the official standards of the Pharmacopoeia should be adopted. Alternative methods will be approved only when official methods are shown to be unsatisfactory and the discriminatory power and ability of the alternative is justified and proved capable of distinguishing between batches with acceptable and unacceptable performance.

The comparative analyses of the *in vitro* performance of the formulations were based on the kinetic parameters calculated from dissolution profiles. A quantitative understanding of the dissolution results was facilitated by mathematical model-based equations (Costa & Lobo, 2001).

In this study, the Higuchi model was the one that best represented almost all the formulations, yielding a high r^2. The slopes were related to dissolution rate constants. Thus, considering the K values from the Higuchi model (K_H), it is observed that F1 and the reference tablet showed a faster dissolution rate. On the other hand, F3 showed a slower dissolution rate and was significantly different from the reference tablet. The analysis of the other constants agrees with these observations.

The dissolution efficiency (DE) of F3 was significantly lower than that of the others, including the reference tablet. A decrease in DE for metformin tablets containing PVP K30 was also reported by Pinho (1999), who found that increasing the polymer content decreases the DE in the modified release tablets.

Starch 1500® is a pre-gelatinized starch that can be used as a binder, diluent and disintegrant. It has suitable flow and compression characteristics that allow it to be used as a tablet binder in dry compression (Rowe et al., 2006). No difference in dissolution profile was observed between starch and Starch 1500®.

The use of DE to compare formulations has been defended by some authors, since bioavailability is also determined by calculating the area under the curve. In an article comparing Cefalexin® dissolution profiles, the author observed differences between formulations that could not be detected through the application of *f1* and *f2* (Serra & Storpirtis, 2007). However, the Brazilian National Sanitary Inspectorate (ANVISA) recommends using these factors as an acceptance criteria (Brasil, 2004)

The methods used in the dissolution study and the comparison parameters can be used to compare and

identify the differences between formulations, in order to establish acceptance criteria and preview how alterations in manufacturing would affect bioavailability. When apparatus I (basket) was used at 50 rpm, in 900 mL of dissolution medium, the comparison of dissolution profiles in terms of *f1* and *f2* proved to be more discriminatory. According to *f1* and *f2*, only F3 and F4 were different from the reference tablet. The values for the other formulations indicated pharmaceutical equivalence to the reference tablet.

The results reported here for the immediate-release dosage form of metformin, a drug which is highly soluble and belongs to class III of BCS, contribute to the discussion on extending biowaivers to these drug formulations (Cheng et al., 2004).

According to official and regulatory guidelines, F1 and F2, as well as the commercial similar tablet, are pharmaceutically equivalent to the reference dosage form, and could be adopted as an alternative tablet for production in official laboratories, in order to fulfill the objectives of public health policies that seek to provide ready access to rational dosage forms of adequate quality.

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RESUMO

Equivalência farmacêutica de comprimidos de metformina obtidos com diferentes aglutinantes

O cloridrato de metformina é um agente oral anti-hiperglicemiante largamente utilizado e caracteriza-se por apresentar dose elevada, alta cristalinidade e baixa compressibilidade, dificultando a produção de comprimidos por compressão direta. O objetivo deste estudo foi desenvolver comprimidos de metformina 500mg através de granulação em via úmida, utilizando diferentes agentes aglutinantes (A = amido, B = amido pré-gelatinizado, C = povidona K30 e D = povidona K90) com equivalência farmacêutica ao medicamento de referência (Glifage®). Os comprimidos foram analisados quanto ao aspecto, dureza, friabilidade, desintegração, dissolução, teor médio, uniformidade de dose e perfil de dissolução (aparato cesto, em 50 rpm, com tampão fosfato pH 6,8). As formulações obtidas F1 (5% de A e 5% de C), F2 (5% de B e 5% de C), F3 (10% de C) e F4 (5% de D) resultaram em adequada uniformidade de dose, dureza, friabilidade e desintegração, com liberação total do fármaco após 30 minutos (F1, F2 e F4), e após 60 minutos (F3). A liberação do fármaco ocorreu segundo cinética de Higuchi (F1, F2 e F3), semelhante ao medicamento de referência ou ordem zero (F4). A eficiência de dissolução foi de 75% para todas as formulações analisadas, exceto F3 (45%). F1 e F2 apresentaram equivalência farmacêutica com o medicamento de referência.

*Palavras-chave***:** dissolução; metformina; comprimidos; aglutinante; equivalência farmacêutica

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