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Effects of Filler-Binders and Lubricants on Physicochemical Properties of Tablets Obtained by Direct Compression: A 2^2 Factorial Design

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SUMMARY. The influence of the filler-binder granulometry (Avicel PH 101 or Avicel PH 102) and the type of lubricants (magnesium stearate or stearic acid) by means of a 2^2 factorial design on the physicochemical characteristics of tablets containing high amount of an active substance have been studied. Acetylsalicylic acid (ASA) was used as a model drug. All formulations met pharmacopeial specifications for mean weight, assay, uniformity of content, and disintegration time. Higher hardness and higher percentage of drug dissolved ($p \leq 0.05$) was shown by formulations prepared with stearic acid compared to formulations prepared with magnesium stearate. Tablet friability was significantly higher ($p \leq 0.05$) for formulations prepared with Avicel PH 101 in relation to formulations containing Avicel PH 102. The type of lubricant as well as the filler granulometry showed to have a great influence on the physicochemical and biopharmaceutical characteristics of tablets containing high amount of active substance obtained by direct compression.

RESUMEN. "Efecto de los Excipientes Diluyente-aglutinante y Lubricante sobre las Propiedades Fisicoquímicas de Tabletas Obtenidas por Compresión Directa: un Diseño Factorial 2^2". En el presente trabajo se estudió la influencia de la granulometría del diluyente-aglutinante (Avicel PH 101 o Avicel PH 102) y el tipo de lubricante (estearato de magnesio o ácido esteárico), mediante un diseño factorial 2^2, sobre las características fisicoquímicas de tabletas con un alto contenido de principio activo. El ácido acetilsalicílico (ASA) fue utilizado como fármaco modelo. Todas las formulaciones cumplían con las especificaciones de farmacopea en cuanto al peso promedio, ensayos de uniformidad de contenido y tiempo de desintegración. Mayor dureza y porcentaje disuelto ($p \leq 0,05$) fueron observados en las formulaciones preparadas con ácido esteárico comparadas con aquellas en que se utilizó estearato de magnesio. La friabilidad de las tabletas fue significativamente mayor ($p \leq 0,05$) para aquellas preparadas con Avicel PH 101 en comparación con las que contenían Avicel PH 102. Tanto el tipo de lubricante como la granulometría del diluyente mostraron una gran influencia en las características fisicoquímicas y propiedades biofarmacéuticas de las tabletas obtenidas por compresión directa con un alto contenido de sustancia activa.

INTRODUCTION

Tablets are the most commonly used dosage form. The ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids; tamper-proofness compared to capsules; and safety compared to parenteral dosage forms makes tablets a popular and versatile dosage form [1].

Considering the methods of preparation of tablets, direct compression has important advantages compared to traditional granulation methods, such as lower cost, saving time and energy, fewer unit operations, fewer stability issues for actives that are sensitive to heat or moisture, and the possibility to add fewer excipients to the formula [2,3]. Due to these advantages, tablet manufacturing by direct compression has increased steadily over the last years [4]. However, the rational choice of excipients is essential to obtain tablets with adequate properties.

Filler-binders or diluents, disintegrating agents and lubricants are the major types of excipients and adjuvants used for direct compression of tablets, which are present in almost all tablet formulations [3]. In order to obtain a good tablet formulation by direct compression, filler-binders [5,6] as well as lubricants [7] must be carefully chosen.

KEY WORDS: Acetylsalicylic acid, Adjuvants, Direct compression, Factorial design, Tablets.
PALABRAS CLAVE: Ácido acetilsalicílico, Compresión directa, Diseño factorial, Excipiente, Tabletas.

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Microcrystalline cellulose is a white, crystalline powder composed of agglomerated porous particles [8]. Currently, it is one of the most commonly used direct compression excipient [9]. Part of its popularity can be related to its excellent compatibility at low pressures and high dilution potential, being also chemically inert and compatible with most drugs [2]. It is commercially available in different particle sizes (20-200 µm) and moisture grades (all ≤ 5.0 %), which have different properties and applications [8]. The type of microcrystalline cellulose can influence hardness, friability and percentage of drug released of tablets [4,6,10].

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density. It is widely used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0% [8]. Stearic acid is a hard, white or faintly yellow colored, somewhat glossy powder, also widely used in oral formulations as a tablet and capsule lubricant in a concentration ranged between 0.25-3% [11].

Lubricants are pharmaceutical excipients indispensable for improving the quality and manufacturing efficiency of solid preparations, mainly due to their characteristics to improve fluidity, filling properties, as well as to prevent powder adhesion to punch faces, and minimize die-wall friction [12]. In a general way, hydrophobic lubricants are more efficient than hydrophilic lubricants. On the other hand, hydrophobic lubricants can also alter other physicochemical properties of tablets, such as tensile strength (hardness), disintegration time, and drug release [3]. These influences are explained by the formation of a hydrophobic film around host particles giving a molecular coverage [12] which makes the interparticle bound formation [3,13] more difficult. Thus, the lubrication process is a combination of factors involving lubricant material, formulation to be lubricated, and the mechanical process, which results in the final dosage form [12].

In this work we evaluated the influence of filler-binder granulometry (Avicel PH 101 or Avicel PH 102) and the type of hydrophobic lubricant (magnesium stearate and stearic acid) on the physicochemical characteristics of tablets prepared by direct compression and containing high amount of acetylsalicylic acid, as a model drug, chosen due to its good compactability and moderately low solubility in water.

MATERIALS AND METHODS

Materials

Acetylsalicylic acid (ASA) was purchased from Delaware (Porto Alegre, RS, Brazil). Microcrystalline celluloses (Avicel PH 101 and Avicel PH 102) were a gift from FMC Corporation, Philadelphia, USA. Colloidal silica (Cab-O-Sil M-5) was purchased from CABOT GMbH, Germany. Starch, magnesium stearate, and stearic acid were obtained from Henrifarma, São Paulo, SP, Brasil. All other materials and reagents were of analytical or pharmaceutical grade, and used as received.

Preparation of tablets

Firstly, powders were mixed for 10 min in a twin-shell mixer (FABBE, 5 Kg of capacity, São Paulo, SP). The mixing time was set based on the uniformity of the parameter of unitary dose [3]. Flat-faced tablets were prepared by direct compression (3 batches of each formulation) using an eccentric machine (Neuberger Press, São Paulo, Brasil), containing a single die, and three pairs of plane punches of 13 mm diameter each. About 100 tablets from each formulation were produced. The basic quantitative formulation was ASA (500 mg - 77.7%); starch (60 mg - 9.3%); filler (80 mg - 12.5%) and lubricant (3.2 mg - 0.5%). Tablet weight was set to 643 mg. Acetylsalicylic acid employed as drug model, was used as received, showing a mean particle size of 695 ± 27 µm, determined by sieving [6].

Study of the influence of adjuvants

The influence of adjuvants on the physicochemical properties of tablets was evaluated by a 2^2 factorial design. Hardness, friability and percentage of drug dissolved were the physicochemical characteristics chosen for this factorial study. The qualitative factors studied were the filler-binder granulometry and the type of lubricant (Table 1). Table 2 shows the quali-quantitative composition of the formulations prepared according to this factorial design.

Additionally, for comparison and to obtain a better discussion on the results obtained by the 2^2 factorial design, we also prepared tablets similarly, however, without using lubricant or adding a glidant (colloidal silica) to the formulation.

Powder properties

The repose angles of different mixtures were measured according to the fixed-funnel method [14]. Powder was filled into the funnel, so that after releasing it out in a base of know diameter (4 cm), the height of the cone was measured and the angle of repose (α) was determined (n = 3 for each batch) by the following Equation [**1**],

$$\tan \alpha = h/r \qquad [\mathbf{1}]$$

Factors	Levels
A: Filler-binder granulometry	(-) Avicel PH-102: mean size of 100 µm (+) Avicel PH-101: mean size of 50 µm
B: Lubricant	(-) Stearic acid (+) Magnesium stearate

Table 1. Qualitative factors and levels evaluated in the factorial design.

Formulation	ASA	Starch	Avicel PH-102	Avicel PH-101	Stearic acid	Magnesium stearate
I	500 mg	60 mg	80 mg		3.2 mg	
II	500 mg	60 mg	80 mg			3.2 mg
III	500 mg	60 mg		80 mg	3.2 mg	
IV	500 mg	60 mg		80 mg		3.2 mg

Table 2. Quali-quantitative composition of the formulation developed using the 2^2 factorial design. Total weight of tablets: 643.20 mg.

where α is the angle of repose (°), h the height of the cone formed by the powder (mm), and r the radius of the cone (mm).

For the determination of bulk and tap densities, an appropriate amount of sample was poured in a 100 mL tared graduated cylinder. The volume was then read directly from the cylinder and used to calculate bulk density (ρ_{bulk}) according to the mass/volume ratio. For tap density (ρ_{tap}), the cylinder was tapped 1,250 times until volume was constant, using a tap density analyzer (Pharma Test, PT-TD, Hamburg, Germany). The compressibility was calculated [14,15] using the Equation [**2**],

$$\% \text{ of compressibility} = [(\rho_{tap} - \rho_{bulk}) / \rho_{tap}] \times 100 \quad [\mathbf{2}]$$

where ρ_{bulk} is the bulk density ($g.ml^{-1}$) and ρ_{tap} is the tap density ($g.ml^{-1}$).

Physicochemical characterization of tablets

Characterization of tablets was carried out according to the following parameters: mean weight, thickness, diameter, hardness, friability, drug content, uniformity of content, disintegration time and dissolution test. Mean weight and uniformity of content was determined (n = 20 or 10, respectively) according to the Brazilian Pharmacopoeia [16]. Thickness and diameter were determined using a paquimeter as the measuring instrument (n = 20). The determination of hardness and friability was carried out according to the Brazilian Pharmacopoeia [16], using a Ducom apparatus (Off Tec Galileo, DUCOM, Bangalore, India) and an Etica apparatus (Especial model, Ética, São Paulo, Brazil). ASA content was assayed according to the Brazilian Pharmacopoeia [16] by acidimetry. Disintegration and dissolution test were carried out according to the Brazilian Pharmacopoeia [16] using an Etica apparatus (301 model, Nova Ética, São Paulo, Brazil) and a Pharma Test apparatus (model PTWII, Hamburg, Germany). For the dissolution test, six tablets from each formulation were used. The dissolution test was performed using the USP 24 basket method. Baskets were rotated at 50 rpm. The medium was 500 ml sodium acetate buffer pH 4.5 maintained at 37 °C ± 0.5 °C. After 30 min, sample aliquots were withdrawn, diluted with the dissolution medium and drug absorbance was measured at 256 nm using a UV spectrophotometer (Milton Roy Inc., Spectronic Genesys 2, New York, USA).

Statistical analysis

Formulations were prepared and analyzed in triplicate. Results are expressed as mean ± SD (standard deviation). One-way analysis of variance (ANOVA) or two-way analysis of variance (ANOVA) were employed in the comparison to experimental data. Post-hoc multiple comparisons were done by Tukey test. All analyses were run using the SigmaStat Statistical Program (Version 3.0, Jandel Scientific, USA). The 2^2 factorial design employed in this work is showed in Table 2.

RESULTS AND DISCUSSION

The flowability of a powder is a behavioral characterization of its ability to flow, and its vital importance in the production of tablets is well documented in the literature [2,3]. Flowability characteristics were evaluated by the repose an-

gle and percentage of compressibility. The results of the four different blends prepared according to the factorial design are shown in Table 3. Smaller values of both parameters indicated better flowability. Regarding the repose angle, the blends containing magnesium stearate showed lower values compared to the blends containing stearic acid. This result is according to the better glidant property of magnesium stearate [3]. Although the results from repose angle did not show good flowability properties of the blends (repose angle higher than 40°) [15], the results from the percentage of compressibility demonstrated that they present favourable (18-21%) to good flow properties (12-16%), depending on the granulometry of the filler-binder adjuvant [3]. On the other hand, when stearic acid was used as lubricant, blends prepared with Avicel PH 102 demonstrated a lower percentage of compressibility (16-18%) compared to blends containing Avicel PH 101 (18-21%). At this point, we decided not to add any other adjuvant to improve the flowability of the blends to obtain a better evaluation of the influence of original parameters (granulometry of the filler-binder and type of lubricant) on the properties of tablets.

The physicochemical and biopharmaceutical characteristics of the tablets prepared in this study are presented in Table 4. All formulations presented similar uniform mean weight according to the basic formulation (tablet weight set up to 643 mg), with low variation (DPR% < 2.0) among the different batches. Thickness and diameter values were similar for the different formulations and according to the die and punches used in this work. Disintegration time was lower than 2 min for all formulations. ASA contents were in the range of 95-105%, as well as the uniformity of content presented low relative standard deviation (< 2.0 %). However, the effects of the filler-binder granulometry and the lubricant were clearly observed in the results of hardness, friability and percentage of drug dissolved. Regarding the hardness of all formulations, the factorial study showed a significant influence ($p \leq 0.05$) for both evaluated factors (filler binder granulometry and lubricant) without interaction between them. Formulations containing Avicel PH-102 (Formulations I and II) presented higher hardness compared to those prepared with Avicel PH-101 (Formulations III and IV). Tablets prepared by direct compression with Avicel PH-101 may present higher hardness than those prepared with Avicel-PH 102 explained by some authors due to the higher surface area of the former [6,10,17]. However, according to Rowe [8], particles of Avicel PH 102 have a larger surface area (1.21-1.30 $m^2.g^{-1}$) compared

Blend	Repose angle (º)	ρ_{bulk} (mg.ml^{-1})	ρ_{tap} (mg.ml^{-1})	Compressibility (%)
I	54.96 ± 0.64 ^{a}	0.769 ± 0.006 ^{b}	0.931 ± 0.008 ^{b}	17.20 ± 1.56 ^{b}
II	46.55 ± 0.47 ^{d}	0.812 ± 0.005 ^{a}	0.971 ± 0.015 ^{a}	16.58 ± 1.56 ^{b}
III	52.78 ± 0.64 ^{b}	0.773 ± 0.008 ^{b}	0.970 ± 0.007 ^{a}	20.25 ± 1.41 ^{a}
IV	48.12 ± 0.51 ^{c}	0.812 ± 0.005 ^{a}	0.991 ± 0.015 ^{a}	18.09 ± 2.69 ^{a,b}

Table 3. Experimental values (n = 3) of repose angle, bulk density (ρ_{bulk}), tap density (ρ_{tap}) and compressibility of the different blends prepared according to the factorial design. Mean ± standard deviation. Means, in column, with the same letter are not significantly different (Two way ANOVA, $p \leq 0.05$, Tukey test).

Parameter	Formulation			
	I	II	III	IV
Mean weight (mg)	626.34 (± 12.21)	641.75 (± 2.50)	631.23 (± 2.05)	639.91 (± 4.70)
Thickness (cm)	4.62 (± 0.07)	4.70 (± 0.02)	4.71 (± 0.07)	4.76 (± 0.02)
Diameter (cm)	12.61 (± 0.01)	12.60 (± 0.01)	12.60 (± 0.01)	12.63 (± 0.01)
Hardness (N)	6.75 ^{a} (± 1.15)	3.98 ^{c} (± 0.08)	4.94 ^{b} (± 0.38)	3.11 ^{c} (± 0.22)
Friability (%)	0.79 ^{c} (± 0.33)	2.40 ^{b} (± 1.82)	12.71 ^{a} (± 12.78)	17.08 ^{a} (± 10.03)
Disintegration time (min)	0.09 (± 0.03)	0.15 (± 0.02)	0.13 (± 0.13)	1.48 (± 0.47)
Uniformity of content (mg)	495.67 (± 5.12)	477.95 (± 3.61)	502.30 (± 9.89)	485.89 (± 6.79)
ASA content (mg)	495.45 (± 5.70)	478.47 (± 3.00)	502.06 (± 9.37)	486.48 (± 9.05)
Drug dissolved (%)	33.69 ^{b} (± 6.30)	21.59 ^{c} (± 3.81)	49.35 ^{a} (±.19.98)	16.31 ^{c} (± 4.70)

Table 4. Characteristics of ASA tablets obtained by direct compression according to the 22 factorial design. Mean ± standard deviation (3 batches). Means, in line, with the same letter are not statistically different (Two way ANOVA, $p \leq 0.05$, Tukey test).

to the particles of Avicel PH 101 (1.06-1.12 $m^2.g^{-1}$), probably because of the higher porosity of the former. On the other hand, Zhang *et al.* [18] showed no difference between true density of Avicel PH 101 and Avicel PH 102 (1.64 ± 0.01 $m^2.g^{-1}$ and 1.62 ± 0.01 $m^2.g^{-1}$). These previous reports can justify the higher hardness of tablets prepared with Avicel PH 102 than those prepared with Avicel PH 101 not only due to the higher surface area of the latter but also by the higher particle size of the ASA crystals leading to a negative effect on hardness when filler-binders with low granulometry were employed. In a similar way, tablets prepared with stearic acid (Formulations I and III) showed a higher hardness compared to tablets prepared with magnesium stearate (Formulations II and IV). This lower hardness of tablets prepared with magnesium stearate, as lubricant, could be explained by the formation of a hydrophobic film around host particles giving a molecular coverage [12] which makes interparticle bounds formation [13,19,20] more difficult.

On the other hand, regarding the evaluation of the friability of tablets, the factorial study showed a significant influence only of the filler-binder granulometry ($p \leq 0.05$). Formulations prepared with cellulose microcrystalline with higher granulometry (Avicel PH-102) presented a lower friability, which agrees to the result from hardness previously discussed.

The statistical analysis of the percentage of drug dissolved from different formulations showed a significant influence of the lubricant on this parameter ($p \leq 0.05$). The influence of the filler-binder granulometry was dependent on the level of lubricant. Magnesium stearate showed a negative influence on the dissolution of ASA from tablets prepared both with Avicel-PH 101 and Avicel-PH 102 (21.59 ± 3.81 % and 16.31 ± 4.70%, respectively) compared to those formulations prepared with stearic acid (33.69 ± 6.30% and 49.35 ± 19.98, respectively). Magnesium stearate is a hydrophobic material and hence has a negative effect on drug release from formulations [7,12,20,21]. In relation to the filler-binder granulometry, the formulation lubricated by stearic acid and prepared with Avicel-PH 101 instead of Avicel-PH 102 demonstrated a higher drug release after 30 minutes (49.35 ± 19.98% and 33.69 ± 6.30, respectively). This result could be related to the lower hardness of tablets prepared with stearic acid and different cellulose microcrystalline (67.5 and 49.4 N for formulations prepared with Avicel-PH 102 and Avicel-PH 101, respectively). Higher hardness corresponds to a higher interaction among the particles, which could lead to the slow release of the drug [3]. However, the formulation which presented the highest mean drug release 49.35% (Avicel-PH 101 and stearic acid) also presented a higher friability due to its low hardness value. All these formulations presented a lower amount of drug released compared to the drug dissolved after 30 minutes of the ASA raw material, under the same conditions (66.79 ± 6.22%).

In order to confirm the influence of the lubricant on the hardness and drug release from tablets, we additionally prepared formulations without any lubricant and also adding colloidal silicon dioxide (0.5%), as a glidant. Colloidal silicon dioxide is widely used as a glidant in the manufacture of powders, capsules and tablets [21]. Its use has been reported by some authors as a factor that decreases the negative effect of lubricants on the hardness and drug release from tablets [22-24]. For these comparisons, we chose formulations containing Avicel-PH 102 due to their higher hardness and lower friability compared to those prepared with Avicel-PH 101. The formulations prepared without lubricants presented a higher hardness (7.8 ± 0.41 N) and a higher drug release (51.37 ± 5.17) compared to the formulation prepared with stearic acid or magnesium stearate, demonstrating the influence of lubricants on the physicochemical characteristics of tablets developed in this study. However, these tablets showed strong friction between the particles and the die wall during compression.

Regarding the addition of colloidal silicon dioxide to the tablets, the results are according to the previous reports in the literature. The addition of silicon dioxide improved the flowability properties of the blends (repose angle: 27.41 ± 1.08), increased the hardness of the tablets (9.23 ± 1.44 N) as well as the amount of drug released after 30 minutes (63.35 ± 4.50%) in comparison to the same formulation prepared without it (Formulation I; hardness: 6.75 ± 1.15 N; drug released: 33.69 ± 6.30). The decrease in the repose angle of the blend with colloidal silicon dioxide is according to previous reports in the literature [16,21]. In addition, the increase in hardness and amount of drug released could be explained by the greater interaction between cellulose microcrystalline and colloidal silicon dioxide than between the lubricant and cellulose microcrystalline [24]. Considering that the colloidal silicone dioxide and stearic acid are both smaller than microcrystalline cellulose, it can be

assumed that microcrystalline cellulose particles are preferentially coated by colloidal silicon dioxide. In order to demonstrate this stronger interaction between cellulose microcrystalline and colloidal silicon dioxide, we prepared tablets containing colloidal silicon dioxide and without lubricants. These tablets presented the highest hardness value (13.43 ± 0.85 N) and the highest amount of drug release after 30 min (84.22 ± 6.04), showing the great interaction forces between cellulose microcrystalline and colloidal silicon dioxide particles, increasing the drug release of ASA in comparison to its percentage of dissolution from raw material crystals (66.79 ± 6.22 %), as previously commented.

In addition, the low percentage of dissolved drug obtained in our results could be explained by the higher particle size presented by ASA crystals (695 ± 27 µm). To prove our hypothesis we carried out dissolution tests of ASA crystals presenting mean diameter less than 500 µm, obtained by sieving, under the same test conditions previously presented. After 30 minutes, the amount of ASA dissolved was 88.26 ± 5.31%, showing the influence of the crystal mean size on its dissolution.

CONCLUSIONS

The granulometry of filler-binder (microcrystalline cellulose) has significant influence on hardness and friability of ASA tablets. Tablets prepared with microcrystalline cellulose with the largest mean particle size (100 µm; Avicel PH-102) presented higher hardness, lower friability and higher amount of drug released than those prepared with Avicel PH-101 (mean particle size of 50 µm). Regarding tablet lubrication, the use of stearic acid led to the obtaining of tablets with higher hardness and amount of drug dissolved after 30 min compared to magnesium stearate. The overall results of this study show the influence of the type of lubricant as well as the filler granulometry on the physicochemical and biopharmaceutical characteristics of tablets containing high amount of ASA obtained by direct compression.

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