Acta Farm. Bonaerense **24** (1): 39-47 (2005)
Recibido el 25 de mayo de 2004
Aceptado el 13 de diciembre de 2004

Development and Evaluation of Amoxicillin Formulations by Direct Compression: Influence of the Adjuvants on Physicomechanical and Biopharmaceutical Properties of the Tablets

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SUMMARY. The amoxicillin 500 mg formulations were developed by direct compression using a 2^3 factorial design. Eight different formulations were carried out and they were analyzed considering three levels: the type of microcrystalline cellulose (Avicel® PH-102 or Avicel® PH-200), the presence or absence of spray-dried lactose, and the presence or absence of the superdisintegrant agent, croscarmellose sodium. Average weight, thickness and diameter, hardness, friability, amoxicillin concentration (iodometric assay), disintegration time, and dissolution profile were the parameters used for the tablets evaluation. Considering all evaluated parameters, a suitable amoxicillin 500 mg tablet formulation should present the microcrystalline cellulose type Avicel® PH-102 and the superdisintegrant agent, croscarmellose sodium (Ac-di-sol® SD-711), in its composition.

RESUMEN. "Desarrollo y evaluación de formulaciones de Amoxicilina por compresión directa: influencia de los adyuvantes sobre las propiedades fisicomecánicas y biofarmacéuicas de los comprimidos". Formulaciones de amoxicilina 500 mg fueron desarrolladas por el método de compresión directa utilizando planeamiento factorial 2^3. Ocho formulaciones diferentes fueron planeadas y analizadas considerando tres niveles: el tipo de celulosa microcristalina (Avicel® PH-102 o Avicel® PH-200), la presencia o ausencia de lactosa liofilizada y la presencia o ausencia de agente superdesintegrante, croscarmelosa sódica. Los parámetros utilizados para la evaluación de los comprimidos fueron: peso medio, espesor y diámetro, friabilidad, concentración de amoxicilina (ensayo iodométrico), tiempo de desintegración y perfil de disolución. Una formulación adecuada de comprimidos de amoxicilina 500 mg deberían conetener en su composición celulosa microcristalina tipo Avicel® PH-102 y el agente superdesintegrante croscarmelosa sódica (Ac-di-sol® SD-711).

INTRODUCTION

Amoxicillin is a semi-synthetic aminopenicillin, with a broad-spectrum bactericidal activity [1-5], used as trihydrate in oral products [3]. Amoxicillin trihydrate is likely a white or almost white crystalline powder [3], and it is well absorbed when given orally, with a bioavailability that appears to be much higher than expected based on its physicomechanical and biopharmaceutical properties, and the pH partition theory [6]. The trihydrate form is slightly soluble in water, and its stability in the solid state is possibly related to the effect of the water content and hygroscopic behavior [3,7]. Because of its poor solubility, amoxicillin trihydrate can be considered as a drug-candidate which may give rise to dissolution-related bioavailability problem [5].

Direct compression technique, besides the

KEY WORDS: Direct compression, Factorial design, Physicochemical properties, Physicomechanical and biopharmaceutical properties, Preformulation, Solid dosage form.
PALABRAS CLAVE: Compresión directa, Forma farmacéutica sólida, Planeamiento factorial, Preformulación, Propiedades físico-mecánicas y biofarmacêuticas, Propiedades físico-químicas.

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economic advantage (time, costs and energy) when compared to the traditional granulation methods, is the suitable process for water-sensitive and termolabile products [8-11] as amoxicillin trihydrate, for example. Another advantage of direct compression is the optimization of tablet disintegration, in which primary drug particle is liberated from the tablet mass and is available for dissolution [12].

The filler-binders must be carefully chosen for the success of a direct compression formulation [12,13], especially when the drug is present in a high dose, and also has some difficulties of compactability and flowability.

Microcrystalline cellulose (Avicel®) shows a relatively free flow, good compressibility and high dilution potential, being also physiologically inert and nontoxic. Its filler-binder-disintegrant properties lead to easy and prompt tablet disintegration, allowing the drug dissolution [8,12,14]. Spray-dried lactose can be used in association with microcrystalline cellulose to reduce formulation costs [14]. According to specifications of the manufacturer, the disintegration time of lactose is dependent on formulations, and some of these formulations need the addition of a disintegrant agent.

Croscarmellose sodium is a superdisintegrant agent that improves appreciably the disintegration time of tablet formulations. Moreover, it presents an advantage in direct compression, since it can be used in low concentrations, providing suitable dissolution of the formulations [12,15].

In this paper we report the development of amoxicillin 500 mg formulations by direct compression employing a 2^3 factorial design, and the evaluation of adjuvants as microcrystalline cellulose, spray-dried lactose, and croscarmellose sodium, on physicomechanical and biopharmaceutical properties of the resulting compacts.

MATERIALS AND METHODS

Amoxicillin trihydrate compacted (DEG Imp. Prods. Quim. Ltda., Brazil, batch F400090 from DSM Anti-Infectives India Private Ltd.), microcrystalline cellulose (Avicel® PH-102 and Avicel® PH-200, FMC Corporation, Philadelphia, batches 2710 and M709C, respectively), spray-dried lactose (Lactose Super-Tab®, the Lactose Company of New Zealand Limited, batch 7050604), croscarmellose sodium (Ac-di-sol® SD-711, FMC Corporation, Philadelphia, batch T649C), colloidal silica (Cab-O-Sil® M-5, CABOT GmbH, batch 3027D) and magnesium stearate (HENRYFARMA, Brazil).

The product named Amoxicillin Trihydrate Compacted consists of granules obtained by means of dry compaction of the crystalline powder without adding any excipients. These granules present an increased bulk density and improved flowability and compressibility. According specifications of the manufacture, DMS Anti-Infectives [16], this material is suited for developing tablets by the direct compression process, after the addition of the appropriate excipients and lubricants. Amoxicillin trihydrate compacted presents a tapped bulk density (1250 taps), DIN ISO 787, in a range of 0.7 to 0.8 g/mL. The formulations were developed using a 2^3 factorial design [17]. That is, eight different formulations presenting distinctive composition were carried out, as showed in Table 1a. Three factors or levels were analyzed: a) factor 1 = MCC, the type of microcrystalline cellulose; b) factor 2 = MIX, the presence or absence of spray-dried lactose; and, c) factor 3 = DIS, the presence or absence of the superdisintegrant agent. These factors and their respective assignments are presented in Table 1b. The two types of microcrystalline cellulose used as filler-binders were Avicel® PH-102 (100 µm) and Avicel® PH-200 (200 µm), differing one another by particle size. Spray-dried lactose was associated with the two microcrystalline cellulose types to reduce formulation costs. Croscarmellose sodium (Ac-di-sol® SD-711), a superdisintegrant agent, was tested in this study, considering the disintegration time of tablets containing spray-dried lactose depends on the formulation, sometimes requiring a disintegrant agent. Three replicate batches were prepared for each formulation. The formulations present 500 mg of drug, amoxicillin trihydrate compacted, and 200 mg of diluents (Table 1a). These quantities are equivalent to 69% and 27% composition of the tablet weight, respectively. Microcrystalline cellulose alone (200 mg), Avicel® PH-102 or Avicel® PH-200, and a half-to-half mixture of microcrystalline cellulose and spray-dried lactose, Lactose Super-Tab® (100 mg/100 mg) were used as diluents. The glidant (colloidal silica, Cab-O-Sil® M-5) and lubricant (magnesium stearate) quantities were previously determined for all formulations, and their established values were 10.5 mg and 17.5 mg, respectively, which correspond to 1.5% and 2.5% composition of the tablet weight. The superdisintegrant (Ac-di-sol® SD-711) quantity used per tablet formulation was 7 mg or 1% composition

Formulation	Amoxicillin trihydrate	Avicel® PH-102	Avicel® PH-200	Lactose Super-Tab®	Cab-O-Sil®	Magnesium stearate	Ac-di-sol®
I	500 mg	200 mg	-	-	10.5 mg	17.5 mg	-
II	500 mg	-	200 mg	-	10.5 mg	17.5 mg	-
III	500 mg	100 mg	-	100 mg	10.5 mg	17.5 mg	-
IV	500 mg	-	100 mg	100 mg	10.5 mg	17.5 mg	-
V	500 mg	200 mg	-	-	10.5 mg	17.5 mg	7 mg
VI	500 mg	-	200 mg	-	10.5 mg	17.5 mg	7 mg
VII	500 mg	100 mg	-	100 mg	10.5 mg	17.5 mg	7 mg
VIII	500 mg	-	100 mg	100 mg	10.5 mg	17.5 mg	7 mg

Table 1a. Composition of the formulations (I to VIII) developed through a 2^3 factorial design. Total weight of tablets without disintegrant = 728.0 mg; total weight of tablets with disintegrant (*Ac-di-sol* ®) = 735.0 mg.

of the tablet weight. Powders were mixed for 25 min in a twin-shell mixer FABBE of 5Kg capacity. The mixing time was set based on the fluidity and lubricability findings of the powder blend. The direct compression of all formulations was carried out in a Neuberger press, containing a single die, and three pairs of plane punches of 13.6 mm diameter each. About one hundred tablets were produced from each batch of each formulation (I to VIII).

The evaluation of the resulting tablets was based on the following parameters: *(a) average weight*, according to the Brazilian Pharmacopoeia [18]. The accepted limits, in this study, were 691.60 to 764.40 mg for the formulations without the superdisintegrant, and 698.25 to 771.75 mg for those containing the superdisintegrant; *(b) thickness and diameter*, using a paquimeter as the measuring instrument, and twenty tablets from each batch were tested; *(c) hardness*, according to the Brazilian Pharmacopoeia [18], using a Ducom apparatus, mod. Off Tec Galileo. The lowest value acceptable is 4.5 kgf or 45 N (manual apparatus with an air pump); *(d) friability*, according to the Brazilian Pharmacopoeia [18], using an Etica apparatus, mod. Special. The friability measure is based on the loss of powder, and it must be less than 1.5%; *(e) amoxicillin concentration* (iodometric assay), according to the FDA [19]. The accepted limits are 90 to 120% of the labeled amount in milligrams. In this study, the labeled amount is 500 mg, thus the accepted limits were 450 to 600 mg; *(f) disintegration time* ($t_{disintegration}$), according to Amoxicillin Tablets/Official Monographs in the USP [20], using an Etica apparatus, mod. 301; and, *(g) dissolution profile*, using a Pharma Test apparatus, mod. PTWII. The conditions of the dissolution profiles were the same as those described for the dissolution test of Amoxicillin Capsules/Official Monographs in the USP [20]. Six tablets from each batch of each formulation (I to VIII) were tested. The dissolution profiles were performed for up to 120 min, and samples were taken every 10 min. Sample aliquots of 5 mL were diluted to 100 mL, and spectrophotometrically analyzed at 272 nm.

The statistical analysis included the following procedures: analysis of variance (ANOVA), F test, and PDIFF test. The SAS statistical package, version 6.08 (SAS/STAT 1992) was used. The experiments were carried out through a randomized sample, in triplicate (batches 1, 2, 3), employing a 2^3 factorial design (Table 1b).

Factor or level	(-)	(+)
MCC	Avicel® PH-102 (100 µm)	Avicel® PH-200 (200 µm)
MIX	absent	present
DIS	absent	present

Table 1b. Factors or levels and their respective assignments in the 2^3 factorial design. MCC = microcrystalline cellulose type; MIX = the presence or absence of spray-dried lactose; DIS = the presence or absence of superdisintegrant.

RESULTS AND DISCUSSION

According to the official methodology used to evaluate the parameters related to physicochemical properties of the resulting tablets, all formulations (I to VIII) were within the specified values, as presented in Table 2.

The hardness was influenced by the type of microcrystalline cellulose (MCC) and level of the superdisintegrant (DIS, Table 3). The hardness of tablets presenting the superdisintegrant de-

Parameters	I	II	III	IV	V	VI	VII	VIII
Average weight (mg)	730.13 (± 3.78)	730.72 (± 3.06)	724.23 (± 8.08)	730.51 (± 0.66)	732.03 (± 13.49)	737.86 (± 12.89)	740.95 (± 4.11)	741.50 (± 7.15)
Thickness (cm)	0.46 (± 0.01)	0.46 (± 0.01)	0.44 (± 0.00)	0.44 (± 0.00)	0.46 (± 0.01)	0.47 (± 0.01)	0.45 (± 0.01)	0.45 (± 0.00)
Diameter (cm)	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36
Hardness (N)	117.8 (± 18.5)	106.7 (± 20.2)	118.3 (± 7.6)	110.2 (± 3.4)	115.2 (± 4.5)	100.5 (± 9.1)	103.0 (± 8.3)	85.3 (± 14.8)
Friability (%)	0.1670 (± 0.0305)	0.1861 (± 0.0311)	0.2045 (± 0.0466)	0.2399 (± 0.0408)	0.1055 (± 0.0051)	0.1344 (± 0.0271)	0.2012 (± 0.0893)	0.3664 (± 0.0486)
$t_{disintegration}$ (min)	less than one	less than one	less than one	less than one	less than one	less than one	less than one	less than one
Iodometric assay (%)	95.50 (± 3.05)	94.92 (± 0.64)	92.86 (± 2.79)	93.54 (± 2.29)	92.01 (± 0.54)	98.02 (± 1.37)	95.85 (± 1.70)	96.43 (± 1.76)

Table 2. Evaluation of the amoxicillin tablets obtained by direct compression for the eight formulations (I to VIII). $t_{disintegration}$ = disintegration time. The parameters resulting are presented as the mean from the three batches of each formulation (I to VIII).

Formulations	MCC	MIX	DIS	Hardness means (N)
I	-	-	-	117.8^{a} (± 18.5)
II	+	-	-	106.7^{a} (± 20.2)
III	-	+	-	118.3^{a} (± 7.6)
IV	+	+	-	110.2^{a} (± 3.4)
V	-	-	+	115.2^{a} (± 4.5)
VI	+	-	+	100.3^{a} (± 9.1)
VII	-	+	+	103.0^{b} (± 8.3)
VIII	+	+	+	85.3^{b} (± 14.8)
I to VIII	-			113.6^{A}
I to VIII	+			100.7^{B}
I to VIII			-	113.3^{a}
I to VIII			+	100.9^{b}

Table 3. Hardness (N) of the amoxicillin tablets formulations developed (I to VIII). CV = 15.44 %; A, B, a,b: the means followed by different capital letters and different small letters indicate significant differences between the levels of microcrystalline cellulose (types) [MCC] and disintegrant [DIS], respectively, for the F test ($P < 0.05$).

creased significantly. The formulations containing the microcrystalline cellulose of larger mean particle size, Avicel® PH-200 [MCC (+)], presented even lower values of hardness. Otherwise, for formulations containing Avicel® PH-102 [MCC (-)], the hardness was significant decreased only when the superdisintegrant and lactose were present [DIS (+) and MIX (+), respectively].

Regarding both microcrystalline cellulose types were part of the developed formulations in the same proportion, the lower values of hardness for tablets containing Avicel® PH-200 [MCC (+)] could be explained by its larger mean particle size. The larger mean particle size is responsible for providing a smaller superficial area and, consequently, the particle contact area for bonding also becomes smaller, as reported by Doelker [14] and Doelker *et al.* [21]. The larger mean particle size of Avicel® PH-200 would be impairing the interactions or bonds between particles of the same material [cohesion], such as microcrystalline cellulose particles; or, between particles of different components on formulation [adhesion] during the compaction procedure, such as mixture of the microcrystalline cellulose, lactose, and superdisintegrant particles. Moreover, formulations containing the superdisintegrant plus two insoluble direct compression systems (diluent/drug) can present a decrease in breaking force (hardness), as observed by Khan and Rhodes (1973) apud Ferrero *et al.* [15].

According to the data showed in Table 4, the

Formulations	MCC	MIX	DIS	Friability (%)
I	-	-	-	0.1670^{a} (± 0.0305)
II	+	-	-	0.1866^{b} (± 0.0311)
III	-	+	-	0.2044^{b} (± 0.0466)
IV	+	+	-	0.3990^{c} (± 0.0408)
V	-	-	+	0.1055^{a} (± 0.0051)
VI	+	-	+	0.1344^{a} (± 0.0271)
VII	-	+	+	0.2012^{b} (± 0.803)
VIII	+	+	+	0.3664^{d} (± 0.0486)
I to VIII	-			0.1696^{A}
I to VII	+			0.2317^{B}
I to VIII		-	-	0.1765^{b}
I to VIII		+	-	0.2221^{b}
I to VIII		-	+	0.1199^{c}
I to VIII		+	+	0.2838^{a}

Table 4. Friability (%) of the amoxicillin tablets formulations developed (I to VIII). CV = 22.87 %; a,b,c, A, B: the means followed by different capital letters indicate the differences between the microcrystalline cellulose types [MCC]; the means followed by different small letters indicate the differences between the interaction of lactose [MIX] and disintegrant [DIS] levels (P< 0.05) through the PDIFF test.

microcrystalline cellulose Avicel® PH-200 [MCC (+)] significantly increased the friability of resulting tablets. The presence of lactose [MIX (+)] and the superdisintegrant [DIS (+)] also contributed to the significant increase of friability, and formulations containing Avicel® PH-200 [MCC(+)], lactose [MIX(+)] and the superdisintegrant [DIS(+)] presented even higher values. On the other hand, for formulations containing Avicel® PH-102 [MCC (-)], the friability significantly increased only when lactose was present [MIX (+)].

The results found for the hardness and friability tests in this study are remarkably related to those reported by Gordon *et al.* [22]. The tablet formulation presenting the lower hardness values will have the higher friability values. Once again, the smaller superficial area of the microcrystalline cellulose type Avicel® PH-200 [MCC (+)] would be impairing the interactions between the particles [cohesion and adhesion] due to the smaller contact area for bonding during the compaction step, producing tablets less resistant to crushing, and crumbling. Doelker [14] emphasized the importance of the particle size in the interparticular bonds of diluents with the other components of the formulation, indicating that in some cases the dilution potential of Avicel® PH-200 may not be as good as that found using Avicel® PH-102.

Additionally, the lactose [MIX (+)] is included under the brittle materials category by the Wiederkehr - von Vincenz classification [14], which is based on the compaction properties of materials. That is, the lactose generally gives a lower mechanical strength and decreases the resistance of tablets to fragmentation [23].

Considering the methodology used for the dissolution profiles, the amount of drug dissolved during a period of 90 min should not be less than 80% of the amount labeled (500 mg). The results are presented in Table 5, and they showed more than 80% of amoxicillin dissolved in 60 min for all developed formulations (I to VIII), suggesting the method of direct compression improved the drug availability.

The Hixson-Crowell model [$W_0^{1/3} - W^{1/3} = K(t-t_1)$] [24] was applied to visualize the linearization of the drug dissolution data found during the first hour of experimentation (Figs. 1 to 4). The cubic root mathematical model considers Wo as the initial theoric amount of drug in the tablets submitted to dissolution. In this study, we considered Wo equal to 500 mg ($W_0^{1/3}$ = 7.93701), t_1 as 1 min, and t varying from 10 to 60 min.

As reported in Table 6, the type of microcrystalline cellulose [MCC (-) or (+)] and the presence of lactose [MIX (+)] and superdisintegrant [DIS (+)] caused changes on the amount of amoxicillin dissolved ($W_0^{1/3} - W^{1/3}$).

Regarding the first hour of experimentation (Table 6), the presence of the superdisintegrant [DIS (+)] increased significantly the amount of amoxicillin dissolved in formulations containing the microcrystalline cellulose type Avicel® PH-102 [MCC (-)], but without lactose [MIX (-)]. Formulation I [MCC (-); MIX (-); DIS (-)] presented the mean value of amoxicillin dissolved equal to 3.4838 whereas that value for formulation V [MCC (-); MIX (-); DIS (+)] was 4.7651 (see Table 6). However, the presence or absence of the superdisintegrant did not significantly change the amount of amoxicillin dissolved for those formulations containing Avicel(PH-200 [MCC (+)] without lactose [MIX (-)]. Formulation II [MCC (+); MIX (-); DIS (-)] had the mean value of amoxicillin dissolved equal to 3.7655, and formulation VI [MCC (+); MIX (-); DIS (+)] presented that value equal to 3.7053. The improved

Time (min)	I (mg%)	II (mg%)	III (mg%)	IV (mg%)	V (mg%)	VI (mg%)	VII (mg%)	VIII (mg%)
10	65.83	68.00	61.93	60.97	71.80	67.87	65.13	57.30
20	72.30	76.50	72.13	70.97	82.70	76.77	75.23	68.17
30	78.90	82.73	79.83	78.83	89.57	83.47	80.40	73.70
40	84.33	87.50	85.97	84.37	94.60	86.77	84.50	76.87
50	88.33	90.83	91.07	88.03	97.23	90.43	87.17	78.90
60	**93.43**	**93.60**	**94.73**	**91.57**	**99.40**	**92.90**	**90.33**	**82.03**
70	93.93	95.33	97.50	94.03	100.57	94.50	91.30	84.73
80	96.67	97.33	99.07	95.60	100.60	94.87	92.33	87.47
90	98.23	99.17	100.83	96.90	101.80	95.93	92.83	89.20
100	99.50	100.37	101.47	98.47	101.67	97.20	93.17	89.37
110	100.93	100.50	102.23	99.07	102.03	97.97	93.77	90.23
120	101.37	102.23	103.40	100.33	102.23	98.60	94.27	91.80

Table 5. Results of the dissolution profiles for the eight developed formulations: mean[a] of amoxicillin dissolved (mg%) *versus* time. [a] Six tablets from each batch (1,2,3).

Formulations	MCC	MIX	DIS	$(W_o^{1/3} - W^{1/3})$
I	-	-	-	3.4838 bc
II	+	-	-	3.7655 b
III	-	+	-	3.5675 b
IV	+	+	-	3.3609 bc
V	-	-	+	4.7651 a
VI	+	-	+	3.7053 b
VII	-	+	+	3.4447 bc
VIII	+	+	+	2.8502 c

Table 6. Interactions between the three factors: microcrystalline cellulose type (MCC), level of lactose (MIX) and level of disintegrant (DIS), on the amount of amoxicillin dissolved ($W_o^{1/3} - W^{1/3}$) during the first hour of experimentation. CV = 8.01%; a,b,c: the means followed by different letters indicate differences between the combination of the three factors: microcrystalline cellulose type [MCC], level of lactose [MIX] and level of disintegrant [DIS] through the PDIFF test ($P < 0.05$).

performance of the superdisintegrant agent for the formulations presenting Avicel® PH-102 [MCC (-)] could be explained due to the larger interparticular contact area for bonding of this type of microcrystalline cellulose, since it has a smaller mean particle size [14,21].

Furthermore, the presence of lactose [MIX (+)] significantly decreased the amount of amoxicillin dissolved for formulations containing the superdisintegrant [DIS (+)] and both types of microcrystalline celluloses [MCC (-) and (+)] (Table 6). As already seen above, the mean value of amoxicillin dissolved found for formulation V [MCC (-); MIX (-); DIS (+)] was 4.7651, whereas formulation VII [MCC (-); MIX (+); DIS (+)] presented a value of 3.4447. The same situation occurred for formulations containing Avicel® PH-200 [MCC (+)]. The mean value of amoxicillin dissolved found for formulation VI [MCC (+); MIX (-); DIS (+)] was 3.7053, whereas for formulation VIII [MCC (+); MIX (+); DIS (+)] that value was 2.8502. The competition between the particles of lactose and superdisintegrant for bonding particles of microcrystalline cellulose could be impairing the superdisintegrant action, reflecting on the drug dissolution.

Otherwise, the absence of lactose [MIX (-)] and superdisintegrant [DIS (-)] did not provide significant changes in the amount of drug dissolved ($W_o^{1/3} - W^{1/3}$) for formulations I and II whose differences were only in the type of microcrystalline cellulose (MCC).

As reported by Hassan *et al.* [25], most of the insoluble excipients decrease the dissolution rate of amoxicillin trihydrate, and different grades of microcrystalline cellulose decrease the dissolution rate of the drug to a different level. They also observed that the microcrystalline cellulose type presenting a large surface area (smaller particle size) increases the dispersability of the drug in the dissolution medium.

In the present study, despite of differences in particle size between the two types of microcrystalline celluloses, the drug dissolution was not influenced.

According to the linear regression analysis of

the dissolution data during the first hour of experimentation, the correlation values (r) found for formulations I and II were 0.9958 and 0.9983, respectively. These findings indicate that the dissolution data can follow the cubic root law. The slopes resulting for the formulations I and II were 0.0465 and 0.0485, respectively (Fig. 1). That means, there is no significant difference in the drug dissolution rate by using the both types of microcrystalline celluloses, Avicel® PH-102 or Avicel® PH-200. Additionally, the amount of amoxicillin dissolved ($W_0^{1/3}$ - $W^{1/3}$) was not significantly different for the formulations I (3.4838) and II (3.7655) (Table 6).

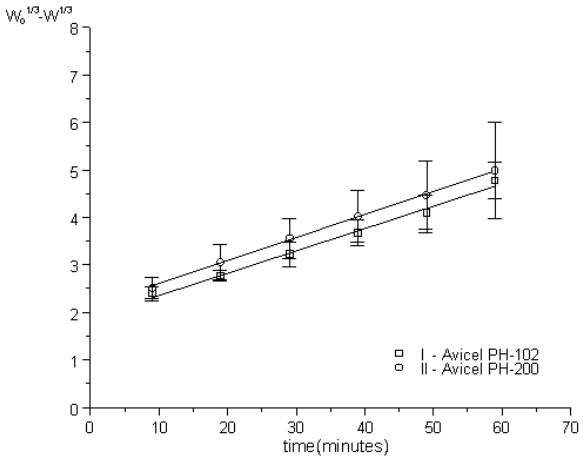

Figure 1. Linearization of resulting dissolution data found for the formulations I and II [MIX (-) and DIS (-)] during the first hour of experimentation, applying the Hixson-Crowell model. The slope values were 0.0465 (I) and 0.0485 (II).

The formulations III and IV are contained of Avicel® PH-102 [MCC (-)] plus lactose [MIX (+)], and Avicel® PH-200 [MCC (+)] plus lactose [MIX (+)], respectively. During the first hour of experimentation, the mean value of amoxicillin dissolved for formulation III (3.5675) was a little bit higher than for formulation IV (3.3609, Table 6). That could be related to the larger superficial area of cellulose type Avicel® PH-102 [14,21], allowing an improved interaction between the particles of diluent and the other components of formulation.

The correlation values (r) found for the formulations III and IV were 0.9999 and 0.9973, respectively, according to the linear regression analysis of the dissolution data in the first hour of experimentation. The respective slopes obtained for the formulations III and IV were 0.0554 and 0.0459, meaning that formulation III presented a slightly faster dissolution rate than formulation IV (Fig. 2). However, the amount of amoxicillin dissolved ($W_0^{1/3}$ - $W^{1/3}$) was not significantly different comparing those formulations (Table 6).

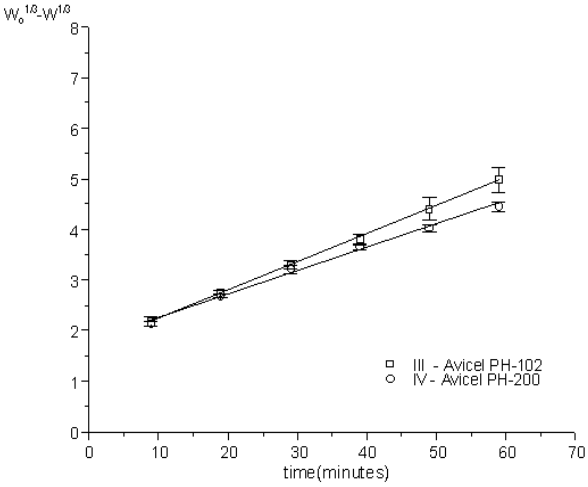

Figure 2. Linearization of resulting dissolution data found for the formulations III and IV [MIX (+) and DIS (-)] during the first hour of experimentation, applying the Hixson-Crowell model. The slope values were 0.0554 (III) and 0.0459 (IV).

Regarding formulations V [MCC (-); MIX (-); DIS (+)] and VI [MCC (+); MIX (-); DIS (+)], the presence of superdisintegrant significantly increased the amount of amoxicillin dissolved for the formulation containing the microcrystalline cellulose Avicel® PH-102 (Table 6). As already mentioned, the smaller mean particle size seems to be the responsible factor [14,21].

Considering the linear regression analysis of the dissolution data during the first hour of experimentation, the correlation values (r) found for the formulations V and VI were 0.9985 and 0.9946, respectively. The respective slopes were 0.0825 and 0.0464, indicating that formulation V presented a faster dissolution rate than formulation VI (Fig. 3). Additionally, the mean value of amoxicillin dissolved was significantly different for those formulations (Table 6).

Through the analysis of resulting dissolution data found for the formulations VII [MCC (-); MIX (+); DIS (+)] and VIII [MCC (+); MIX (+); DIS (+)] we can verify that the presence of lactose did not significantly influence the amount of drug dissolved when the superdisintegrant was present (Table 6).

Gordon & Chowhan [26] reported that hygroscopic ingredients decrease the effectiveness of superdisintegrants, like croscarmellose sodium, in promoting *in vitro* dissolution. They also sug-

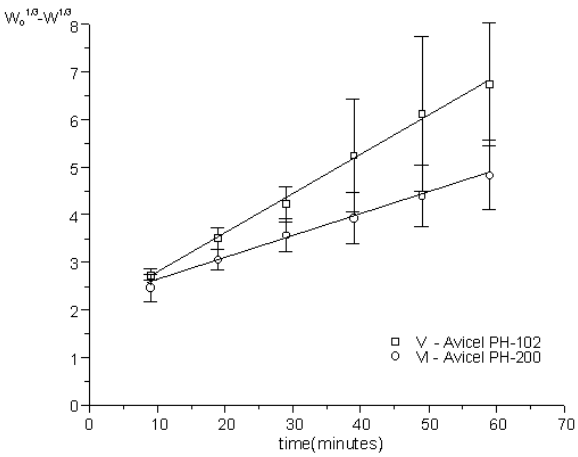

Figure 3. Linearization of resulting dissolution data found for the formulations V and VI [MIX (-) and DIS (+)] during the first hour of experimentation, applying the Hixson-Crowell model. The slope values were 0.0825 (V) and 0.04644 (VI).

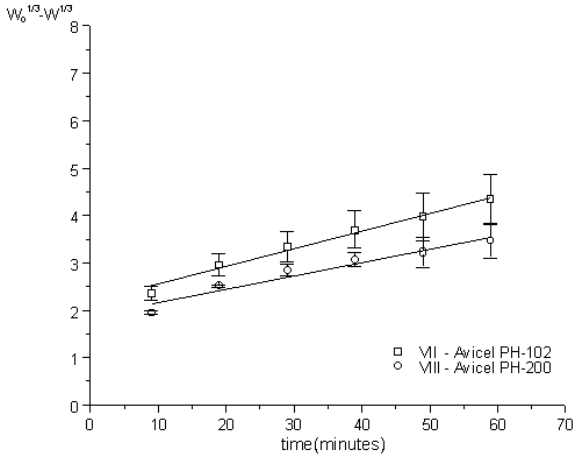

Figure 4. Linearization of resulting dissolution data found for the formulations VII and VIII [MIX (+) and DIS (+)] during the first hour of experimentation, applying the Hixson-Crowell model. The slope values were 0.0382 (VII) and 0.0283 (VIII).

gested that the decrease in tablet dissolution rate may be due to a competitive inhibition of the disintegrant by the other tablet components competing for the locally available water. The extent of the decrease in superdisintegrant efficiency depends on the specific combination of drug and excipients and their composite hygroscopicity, and the amount of superdisintegrant inhibition will increase as the composite hygroscopicity of the formulation increases.

However, in this study, the capacity of water uptake generally presented by the drug, amoxicillin trihydrate, and the diluent, microcrystalline cellulose, did not influence either the superdisintegrant efficiency or the dissolution profiles of tablet formulations.

The presence of lactose [MIX (+)] in formulations containing Avicel® PH-200 [MCC (+)] and the superdisintegrant [DIS (+)] impaired the tablets dissolution. The dissolution rate is proportional to the superficial area of the particles exposed to solvents [13,25], thus formulations containing Avicel® PH-200, which has a smaller superficial particle area than Avicel® PH-102, should present a slower dissolution rate as consequence of a decrease on drug dispersability in the dissolution medium. Moreover, lactose alone or in combination with other diluents provides varied degrees of solubility and hygroscopicity for the direct compression tablet formulation, as suggested by Gordon & Chowhan [26].

The linear regression analysis of the dissolution data in the first hour of experimentation produced the following correlation values (r) for the formulations VII and VIII: 0.9907 and 0.9716, respectively. The respective slopes were 0.0382 and 0.0283, indicating that formulation VII presented a slightly faster dissolution rate than formulation VIII (Fig. 4). However, the mean value of amoxicillin dissolved was not significantly different (Table 6).

CONCLUSIONS

The type of microcrystalline cellulose has significant influence on hardness, friability and dissolution profiles of the resulting amoxicillin 500 mg tablets. These physical properties are negatively affected by using the microcrystalline cellulose with a larger mean particle size (Avicel® PH-200).

The presence of lactose and superdisintegrant lead to an interaction with the two microcrystalline cellulose types, influencing negatively the superdisintegrant efficiency, as demonstrated through the drug dissolution during the first hour of experimentation (Hixson-Crowell model).

Considering all evaluated parameters in this study, a suitable amoxicillin 500 mg formulation by direct compression should present the microcrystalline cellulose type Avicel® PH-102 and the superdisintegrant agent, croscarmellose sodium (Ac-di-sol® SD-711), in its composition.

Acknowledgements. K.F.M.P. is grateful to the CAPES Foundation, a federal scientific agency of Brazil, for scholarship support, and to the FMC Corporation for supplying the raw materials used in this study.

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